

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH**

**NATIONAL ADVISORY COUNCIL FOR  
BIOMEDICAL IMAGING AND BIOENGINEERING**

**Summary of Meeting<sup>1</sup>  
September 16, 2014**

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBID) was convened for its 36<sup>th</sup> meeting on September 16, 2014, at the Bolger Center in Potomac, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), resided as Council chairperson. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 12:50 p.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 2:10 p.m. to 3:00 p.m. for consideration of grant applications.

**Council members present:**

Dr. Kristi Anseth, University of Colorado, Boulder, CO  
Dr. John C. Gore, Vanderbilt University Medical Center, Nashville, TN  
Dr. Karen Hirschi, Yale University, New Haven, CT  
Dr. Cato T. Laurencin, University of Connecticut, Farmington, CT  
Dr. Raphael Lee, University of Chicago, Chicago, IL  
Dr. Mark Musen, Stanford University, Stanford, CA  
Dr. A. Gregory Sorensen, Siemens Healthcare North America, Malvern, PA  
Dr. Daniel Sullivan, Duke University Medical Center, Durham, NC  
Dr. James Thrall, Massachusetts General Hospital, Harvard Medical School, Boston, MA  
Dr. Bruce Tromberg, University of California, Irvine, CA  
Dr. Sheldon Weinbaum, The City College of New York, New York, NY

**Ex officio members present:**

Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH  
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD  
Dr. Sohi Rastegar, National Science Foundation, Arlington, VA

**Ex officio members absent:**

Ms. Sylvia Mathews Burwell, U.S. Department of Health and Human Services, Washington, DC  
Dr. Francis Collins, National Institutes of Health, Bethesda, MD  
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

**Chairperson:**

Dr. Roderic I. Pettigrew

**Acting Executive Secretary:**

Dr. William Heetderks

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<sup>1</sup> For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a conflict of interest may occur. This procedure applies only to applications that are discussed individually, not to "en bloc" actions.

Also present:

NIBIB staff present for portions of the meeting:

Ms. Holly Atherton

Mr. Ryan Aziz

Dr. Richard A. Baird

Ms. Shirley Coney-Johnson

Ms. Christine Cooper

Ms. Zoe Ann Copeland

Dr. Anthony Demsey

Mr. Jeff Domanski

Dr. Henry Eden

Ms. Kate Egan

Ms. Shirley Finney

Mr. Anthony Fransella

Dr. David George

Ms. Pam Glikman

Dr. Ruth Grossman

Dr. John Hayes

Ms. Eunica Haynes

Ms. Alisha Hopkins

Mr. Tom Izzard

Dr. Chris Kelley

Ms. Margot Kern

Dr. Peter Kirschner

Dr. Steven Krosnick

Dr. Tiffani Bailey Lash

Dr. Richard Leapman

Dr. Christina Liu

Dr. Guoying Liu

Dr. Xiao-Zhong (James) Luo

Dr. Shadi Mamaghani

Ms. Jessica Meade

Mr. Todd Merchak

Mr. Joe Mosimann

Dr. Peter Moy

Dr. Vinay Pai

Dr. Grace Peng

Dr. Karen Peterson

Mr. Mohammed Rahamatullah

Ms. Mew Rattanawatkul

Dr. Antonio Sastre

Mr. Shaun Sims

Dr. Manana Sukhareva

Dr. Jessica Tucker

Ms. Li-Yin Xi

Dr. Ruixia Zhou

Dr. Steven Zullo

Non-NIBIB National Institutes of Health (NIH) employees:

Dr. Marie-Jose Belanger, Center for Scientific Review

Members of the public present for portions of the meeting:

Ms. Renee L. Cruea, Academy of Radiology Research

Ms. Erica Froyd, Lewis Burke Associates

Mr. Michael Kalutkiewicz, Academy of Radiology Research

Mr. Damon Kelly, Bolger Center

Dr. Cynthia McCollough, Mayo Clinic, Rochester, MN

Mr. Josh Narotsky, National Capitol Captioning, LLC

Mr. Michael Peters, American College of Radiology

Ms. Kathy Sedgwick, NOVA Research Company

I. Call to Order: Dr. William Heetderks

Dr. William Heetderks called to order the 36th meeting of the National Advisory Council for Biomedical Imaging and Bioengineering. He reminded attendees that the morning session of the meeting was open to the public, welcomed attendees, and introduced Dr. Roderic Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic I. Pettigrew

A. Incoming Council Members

Dr. Pettigrew introduced three new Council members: Drs. Karen Hirschi, Gregory Sorensen, and Daniel Sullivan. He highlighted their career achievements and the expertise they bring to the Council.

## B. Lopez Lecture

Dr. Hector Lopez, program director for the NIBIB Division of Applied Science and Technology, passed away suddenly on June 21, 2014. In remembrance of Dr. Lopez and his outstanding contribution to advancing health care, NIBIB established the Lopez Lecture, to be presented at the September Council Meeting each year by a distinguished scientist who is consistent with the high level of professional performance that Dr. Lopez himself exhibited. The first Lopez Lecture, "Risk, Benefit and New Developments in CT Imaging," was presented by Dr. Cynthia McCollough. At the end of the lecture a commemorative plaque was given to the presenter.

## C. NIBIB Awards and Honors

Two members of the NIBIB family have received distinguished honors and awards.

Dr. Sangeeta Bhatia has been awarded the Lemelson-MIT Prize. This \$500,000 cash prize is one of the most distinguished for bioengineers.

Dr. Richard Ehman received the Mayo Clinic's highest honor, the Distinguished Mayo Clinic Investigator Award, for his research career of great distinction, high scholarship, and creative achievement. Dr. Ehman is a former NIBIB Council Member and represented NIBIB on the NIH Council of Councils.

## D. NIBIB Extramural Program Overview

NIBIB administers 860 active extramural grants totaling \$305 million. NIBIB has leveraged funds available via NIH Common Fund grants. NIBIB contributes about 1 percent to this fund but administers 2.6 percent of the funds, a net positive impact on the Institute.

## E. NIBIB Fiscal Year (FY) 2014 Budget and Legislation

Since 2009, NIBIB has seen an 80 percent increase in the number of high-scoring grants. This has occurred at a time when the budget has been flat and actually has declined due to sequestration. As a result, NIBIB's payline has fallen from the 19th percentile in 2009 to the 9th percentile.

Following Council discussions of alternative funding approaches, NIBIB is piloting a new "Payline Plus" approach. Under this plan, NIBIB awards the preponderance of grants in the stated top 9<sup>th</sup> percentile and selects additional applications from an expanded opportunity zone (EOZ) of those that score between the 10<sup>th</sup> and 18<sup>th</sup> percentile. Applications in the EOZ are selected based on their likelihood to exert a sustained powerful influence in the field, their highly innovative status, and their ability to address a scientific and demographic program priority.

## F. NIH Activities

### *Bill and Melinda Gates Foundation*

In July, Dr. Pettigrew co-moderated the Leapfrog Technologies in Global Health workshop with Dr. Daniel Hartman, who is in charge of new and emerging technologies at the Bill and Melinda Gates Foundation (BMGF). The overarching goal is to establish a more coordinated partnership between NIH and BMGF to address challenges and improve global health. A specific NIBIB-BMGF project has been identified focusing on point of care (POC) systems for low- and middle-income countries. A coordinating meeting for the project is scheduled for October in Seattle.

### *Common Fund Initiatives*

The Big Data to Knowledge (BD2K) initiative focuses on developing technologies for sharing, integrating, and analyzing big data. NIBIB will manage 4 of 11 Centers of Excellence and Training Awards and 4 of 11 Research and Education Activity awards to be announced in October.

The Stimulating Peripheral Activity to Relieve Conditions (SPARC) program is designed to bridge knowledge gaps by studying the underlying mechanisms of electrical control of organ systems. Along with the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Center for Advancing Translational Sciences, NIBIB

is co-leading the initiative. Over the next 6.5 years, \$248 million will be invested in four areas: biology/anatomic and functional mapping; next-generation tools; off-label use of existing market-approved technology for small market indications, and data coordination.

The NIH Single Cell Analysis Challenge "Follow That Cell" is designed to accelerate development of technologies that enable investigators to observe individual cells over time, for example, monitoring a single cell as it mutates from a normal to a neoplastic state. NIBIB and the National Institute of Mental Health co-lead this activity. Up to six prizes totaling \$500,000 will be awarded in the spring.

#### *Brain Research Through Advancing Innovative Technologies (BRAIN)*

The President's BRAIN Initiative, supported by NIH, the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF), focuses on understanding how the brain works. Recommendations of the Advisory Committee to the NIH Director (ACD) formed the basis of funding opportunities, with 58 awards totaling \$46 million to be announced in September 2014. Dr. Pettigrew's editorial, "BRAIN Initiative to Transform Human Imaging" in the July issue of *Science Translational Medicine*, emphasized how this work will benefit all human imaging.

#### *Human Placenta Project*

The Human Placenta Project focuses on understanding the structure and function of the least understood organ in the body. The National Institute of Child Health and Human Development has adopted NIBIB's Design by Biomedical Undergraduate Teams (DEBUT) challenge approach to stimulate scientists to take on this task. NIBIB is expected to play a pivotal role in supporting development of new technologies required to observe the placenta *in utero*.

### **G. NIBIB Activities**

#### *Reverse Paralysis Consortium*

In June, the American Association for the Advancement of Science hosted a congressional briefing on "Rethinking Spinal Cord Injury." Dr. Pettigrew participated in the panel that discussed a range of technologies to address paralysis, including assistive robotics, functional electrical stimulation, and neuromodulation technology pioneered by NIBIB grantees Drs. Reggie Edgerton and Susan Harkema.

Patient response to recent publications about advancements in this area has led to collaboration of many U.S. organizations to accelerate deployment of current spinal cord stimulation technology to patients, while research to advance understanding and systems continues. NIBIB is taking the lead in this effort, including preliminary discussions with the U.S. Food and Drug Administration, foundations, device manufacturers, and scientific experts. A stakeholders' workshop entitled "Addressing Paralysis through Spinal Stimulation Technologies" is planned for November.

#### *Meetings*

NIBIB hosted the second annual Edward C. Nagy New Investigator Symposium in July, with Dr. Bruce Tromberg providing the keynote address. The Symposium featured emerging and early-stage-career NIBIB investigators.

Led by NIBIB's Dr. Grace Peng, the Interagency Modeling and Analysis Group (IMAG) organized a Multiscale Modeling Consortium Meeting held in September. NIBIB grantee and BRAIN ACD committee member Terry Sejnowski was the keynote speaker. IMAG focuses on developing models of disease, including spread of infectious diseases such as Ebola.

#### *Indo-US Initiative on Hypertension*

The goal of the Indo-US initiative on hypertension is to transform detection of hypertension. To date, NIBIB has funded the work of Dr. Rama Mukkamala at Michigan State, and the Request for Applications (RFA) has been re-released as RFA-EB-14-002, with applications due September 26. India's Department

(RFA) has been re-released as RFA-EB-14-002, with applications due September 26. India's Department of Science and Technology has funded three applications. A mini-symposium entitled "Towards Cuff Less Blood Pressure Monitoring via Pulse Transmit Time" was presented to a packed room at the IEEE Engineering in Medicine and Biology Society meeting in August. Speakers included Dr. Mukkamala and NIBIB's Dr. Vinay Pai. A videoconference between the U.S. and Indian teams is planned for late 2014.

#### *DEBUT Challenge Winners*

Winners of the DEBUT challenge have been announced. A first place prize of \$20,000 was awarded to a team at Johns Hopkins University for their AccuSpine device, which assists with proper placement of screws during spinal fusion surgeries. According to the group, nearly one in five screws is improperly positioned during surgery, causing severe damage that leads to chronic pain.

The second place \$15,000 prize was awarded to a team at Boston University for the Sensory Substitution Glove to aid the blind. The glove uses ultrasound and infrared sensors to detect steep drop-offs and head-height obstacles.

Two third place prizes of \$10,000 each were awarded to teams at University of California, Riverside (UCR), and Rice University. The UCR team developed the Diaper-Based System for Neonatal Urine Collection, which can be used to assess hydration state and detect bacterial infections of neonates. The Rice team developed the Nutriflow system to improve delivery of the essential nutrients in milk during tube feeding.

#### H. Science Highlights

Based on an interview with Dr. Rosemarie Hunziker, program director of NIBIB's Division of Discovery Science & Technology, *The New York Times* published an article that describes a three-dimensional brain model. The model exhibits typical tissue function in response to electrical stimulation, treatment with neurotoxins, and trauma.

A second highlight was presented by a Nagy grantee who has developed an all-optical method for stimulating neurons and recording electrical activity without using electrical probes. The method uses rhodopsin, archaerhodopsin, and a charge-coupled device camera and can be accomplished at the microsecond level.

#### III. NIBIB's Future Utilization of Resources: Dr. William Heetderks

Dr. Heetderks noted that, following the May 2014 Council meeting, a task force was formed to explore ways to address concerns about NIBIB's payline and the best use of the Institute's resources. Council member Bruce Tromberg reported task force recommendations to the Council: (1) bring new resources (i.e., more money) into NIBIB; and (2) increase the number of awards.

The first approach involves finding new partners-additional foundations, government agencies, and industry-and increasing NIBIB budget appropriations. The task force recommends approaching foundations that underwrite the level of excellence that NIBIB supports; seeking opportunities to work with other government agencies, particularly nontraditional agencies such as the Department of Commerce and the Centers for Medicare & Medicaid Services that have initiatives that align with or complement NIBIB's mission; and building industry partnerships, a mechanism that other institutes are implementing with some success. To win increased budget appropriations, the task force recommends employing a strategy that will increase awareness and visibility of NIBIB in medical innovation and demonstrate its impact on other NIH institutes.

The second approach-increasing the number of NIBIB awards-will require re-examining the Institute's fiscal management and administrative practices to see whether new resources can be squeezed out and creating new programs, particularly those that support people. K awards make up a small slice of NIBIB's portfolio. With an additional \$1 million, NIBIB could support ten more people, a 25 percent

increase. Such awards would be transformational for their careers at a critical stage, encouraging the growth of investigators as they move from junior investigator or postdoc into faculty positions.

The task force also noted that a few NIBIB grantees who have a lot of resources could be encouraged to seek more career-oriented awards, which might free up funds to support junior and mid-career investigators. By partnering closely with universities and carefully wording RFAs, NIBIB could encourage university investment in salaries of investigators who receive career awards.

There is a lot of national interest in encouraging innovation and stimulating economic growth, which aligns well with NIBIB's mission. As we inform the public about what NIBIB does, we can show how knowledge converts into jobs and growth in the medical innovation economy.

## **Discussion**

Dr. Thrall noted that the Bayh-Dole Act of 1980 was designed to protect intellectual property and make it attractive for commercial development. Capitol Hill will be interested in seeing how that legislation has played out in national commerce.

Dr. Sorensen remarked that it is difficult for Congress and the public to see how they benefit from what NIBIB is doing. Dr. Lee noted that NIBIB's share of the NIH budget does not reflect that technology is a major contributor to advances throughout biomedical research. One way to fix that problem is to identify important areas that are uniquely related to the NIBIB mission, for example, systems science.

Dr. Sullivan stated that increasing the number of K awards would increase the number of people in the research pipeline. He asked whether there are jobs for an increased number of people in the field. Dr. Gore added that without K awards, only a limited number of new faculty positions will be created. An investigator with a K award is relatively cost-free for five years. Continuing that career development for longer would be helpful. Renewing K awards at a slightly higher level would be an effective way to maintain an active research population. Dr. Anseth commented that expansion of K awards into a new mechanism that invests in people could spur innovation. Innovation and risk come early in one's career.

Dr. Weinbaum remarked that the funding crisis disproportionately affects women and minorities. He added that the dollar value of a typical National Science Foundation award is \$300,000 for three years, much less than typical NIH ROIs. By making smaller, more numerous awards, NIBIB can bring new people into the community.

According to Dr. Laurencin, other countries have made funding science a higher priority than has the United States. He commented that Congress and the public should be made aware of the high-impact, important applications that are not being funded because they fall outside the payline. He proposed putting those applications on a sort of "kickstarter" website and asking the public to invest in them.

Dr. Thrall encouraged NIBIB staff to look at the legal implications of a crowdsourcing approach.

Dr. Rastegar expressed excitement about the possibility that NIH and others would adopt a crowdsourcing process if it proved successful. He recommended getting great ideas funded and then moving to those with broader implications. He added that the Smithsonian has very successful funding partnerships that could serve as a model for Nibble.

Dr. Gore expressed concern about the credibility of this strategy and urged sticking to traditional means.

Dr. Tromberg noted that universities expect to bring in foundation or philanthropic contributions at the level of \$12 million per year, the amount of money required to move NIBIB's payline to the 12<sup>th</sup> percentile. NIBIB's mission is more impressive and impactful than that of a single university, so it seems possible to obtain unrestricted contributions from foundations whose goals align with NIBIB.

Dr. Tromberg reported that the National Heart, Lung, and Blood Institute has succeeded in bringing its payline from a low 6<sup>th</sup> percentile to the 12<sup>th</sup> percentile. NIBIB could target the 12<sup>th</sup> percentile with an additional \$12 million. The task force will focus on what available resources could help the Institute achieve this goal.

Dr. Pettigrew summarized the challenge NIBIB faces in light of growth in the number of high-quality applications submitted, following the tremendous growth in the bioengineering field. National Institute of General Medical Sciences (NIGMS) data indicate that the optimal funding level per investigator averages between \$500,000 and \$750,000; returns diminish above this amount. He asked the task force to consider implementing a program that induces applicants to accept awards at a lower level for a longer period of time.

#### IV. Review of Council Procedures and Regulations: Dr. William Heetderks

Dr. Heetderks welcomed visitors and members of the science press and scientific society constituencies. He noted for the record that a quorum was present for this Council meeting. Dr. Heetderks thanked Ms. Pam Glikman, Ms. Alisha Hopkins, and Dr. Anthony Demsey for planning the meeting.

##### A. Council Regulations, Policies, and Procedures

Dr. Heetderks reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

##### B. Future NACBIB Meeting Dates

The next NACBIB meeting is set for Friday, January 23, 2015. Dr. Heetderks asked Council members to inform him about conflicts with any of the upcoming meeting dates listed at the bottom of the agenda.

##### C. Approval of the May 20, 2014, NACBIB Meeting Minutes

A motion to approve minutes of the May 20, 2014, NACBIB meeting was forwarded, seconded, and approved unanimously.

#### V. Patents as Proxies-NIH Hubs of Innovation: Mr. Michael J. Kalutkiewicz

Mr. Kalutkiewicz described a study designed to stimulate further discussion about U.S. science policy and the ways public funds are used in research and development (R&D). A paper he coauthored with former NIBIB Council member Dr. Richard Ehman appeared in the June 2014 issue of *Nature Biotechnology*.

Patents are viewed as critical to moving forward the innovation economy. They are associated with increased productivity, reduced unemployment, and the establishment of more publicly traded companies. The Obama Administration's efforts to push federal agencies to provide an evidence base for their funding priorities were reflected in the President's 2014 budget proposal.

American Recovery and Reinvestment Act (ARRA) funds were used to create the Science of Science Innovation Policy program at the National Science Foundation to develop methodology for projecting outputs of R&D to support funding decisions.

For the study, Mr. Kalutkiewicz and his team pulled data for 2003 to 2012 from the NIH Research Portfolio Online Reporting Tools (RePORT) website, which allows users to sort patents by years, Study Section, and Institute. They searched the United States Patent and Trademark Office (USPTO) website to establish patent frequency per 100 million research dollars for each Institute and looked at the number of forward citations for these patents.

Forward citations are downstream patents spurred by the original patent or for which the original patent was an integral part of development. The citations offer a way to measure the quality or value of a patent; patents with more future citations often led toward transformative new lines of R&D, often in the private sector. Thus, evaluators can identify areas of science that catalyze downstream innovation from original publicly funded patents and therefore are sustainable beyond the initial taxpayer investment.

NIH represents a significant piece of the federal R&D portfolio. For NIH, the average number of patents per \$100 million is just over four; in other words, it takes about \$25 million in NIH grant funding to produce a new piece of intellectual property. Among federal agencies and individual NIH Institutes, NIBIB had the highest number of patents per \$100 million (around 25) and was among those with the most forward citations per patent.

Mr. Kalutkiewicz noted that of the Nobel Prize-winning teams NIH has supported over the past 25 years, 85 percent created and filed new intellectual property.

Taking budget size into account, NIBIB's FY15 budget authority is relatively small compared with other high performers (e.g., Department of Energy, National Aeronautics and Space Administration, and the NSF). Other NIH Institutes with relatively small budgets are performing well in generating patents, such as the National Human Genome Research Institute, the National Eye Institute, and the National Institute of Dental and Craniofacial Research.

Mr. Kalutkiewicz displayed the data using forward citations per patent as the X axis measuring fundamental pursuit of knowledge (basic science) versus consideration for usefulness (applied science). The Y axis showed patents per \$100 million. Three quadrants of interest became apparent: Edison's Quadrant (i.e., high frequency, low forward citations); Bohr's Quadrant (i.e., low frequency, high forward citations); and Pasteur's Quadrant (high frequency, high forward citations). Pasteur never undertook an experiment where he wasn't seeking fundamental new knowledge but didn't have a clear endgame in mind. DARPA attributes its innovation success to Pasteur's Quadrant: "It entails pushing the frontiers of basic science to solve a well-defined, use-inspired need." NIBIB is firmly positioned in that quadrant.

If Pasteur's Quadrant is seen as desirable, a few NIH programs can be targeted as models for Pasteur's-type research and the economic impact that its patents tend to have in the private sector. In turn, this aligns with the Administration's goal of identifying and scaling programs that are more effective with the same amount of dollars. Although further research would be welcome, patent quality and quantity metrics could be useful in the short term, given the strong differences among programs and the empirical connection to job production.

This is a positive message for public health and NIH and all science programs that are publicly supported to be talking about. Preliminary thinking is that scaling up those programs by \$1 billion could increase patent output by 47 percent.

## **Discussion**

Dr. Gore asked whether the study had looked at the Biomedical Technology Research Resource Center grants (P41s) focused on developing new technology. Mr. Kalutkiewicz responded that P41s appear to be very productive at generating intellectual property, producing many patents per \$100 million. He has not compiled downstream patents for P41s but would expect to see a lot of them. He explained that patents arising from National Center for Research Resources (NCRR) funding had been credited to the NIBIB and NIGMS portfolios to which those grants were transferred when NCRR was dissolved.

Dr. Musen commented that it is exciting to see NIBIB as an outlier. He noted that this will be particularly advantageous for those who develop devices; however, intellectual property is very problematic for those who work in the informatics arena, particularly software development.

Dr. Weinbaum asked whether any international comparisons of patent activity have been undertaken. Mr. Kalutkiewicz indicated that he has not explored international patent activity.

Dr. Lee remarked that the average U.S. taxpayer probably does not see how public investment in basic research influences the economy. Technology dominates a major portion of the world economy. These measures of the impact of research investments will strengthen our position with policymakers.

Dr. Pettigrew asked about the strength of the correlation between patents and economic activity. Mr. Kalutkiewicz responded that there is strong evidence in the literature that supports the notion of causation. Metropolitan areas that have a lot of patent activity have lower unemployment, higher wages, more exports, and more company startups. That is the kind of news Congress wants to hear.

Dr. Lee asked how well downstream citations per patent correlate to positive return on investment. Mr. Kalutkiewicz indicated that this is a subject of some debate.



Dr. Tromberg asked how the Council could help support communication of this message to policymakers. Mr. Kalutkiewicz responded that the visuals of imaging and engineering science are extremely compelling on Capitol Hill. Journal articles can help raise awareness, but it is important to let the data speak for itself so the audience begins to recognize that there are important innovation hubs at NIH.

#### **VI. Risk, Benefit, and New Developments in CT Imaging: Dr. Cynthia McCollough**

Dr. Antonio Sastre introduced the first annual Hector Lopez lecturer, Dr. Cynthia McCollough, a Career Scientist at the Mayo Clinic Center for Advanced Imaging Research. Dr. McCollough noted that she had the pleasure and honor of working with Dr. Lopez since 2006; he was program director for all of her grants.

Dr. McCollough noted that it is not feasible to quantify the benefits of computed tomography (CT) via prospective blinded randomized trials. Instead, we rely on expert panels and consensus guidelines generated by societies such as the American College of Radiology (ACR). ACR has developed in-depth appropriateness criteria for 180 topics with over 850 variants.

Having surveyed ACR guidelines that list CT among the most appropriate exams, Dr. McCollough presented examples of clinical scenarios for which ACR expert panels listed CT as the most appropriate, or among the most appropriate, imaging modalities. Scenarios included neurological, thoracic, cardiac, vascular, gastrointestinal, and urologic applications.

In an aortic dissection example, Dr. McCollough noted that CT gives exquisite detail in a rapid timeframe; efficacy studies have shown high sensitivities and specificities. CT is the most appropriate exam for presurgical planning and follow-up for abdominal aortic aneurisms, where surgeons rely on high-quality images to determine stent dimensions and placement.

Dr. McCollough provided data from the literature that support CT's superiority over ultrasound for evaluating patients without a clear clinical diagnosis of acute appendicitis. CT demonstrated superior sensitivity (91% versus 78%) and specificity (90% versus 83%). Literature also provides evidence that CT improves appendicitis outcomes; for example, one study showed that using CT decreased the negative appendectomy rate from 42.9 percent to 7.1 percent among women aged 18-45 years.

Several studies have also shown that CT scans can reduce health care costs. By getting answers faster, costs per patient were reduced almost \$500.

Ultimately, the decision to perform a CT scan is driven by patient benefit. Once justified, the exam should be optimized. Optimization may mean dose increase.

With funding from NIBIB, the Mayo Clinic Center for Advanced Imaging Research is evaluating techniques for dose reduction as part of the sub-millisievert initiative called Critical Resources to Evaluate CT Scan Techniques and Dose Reduction Approaches. The project is developing data, metrics, and software to help investigators in the field achieve widespread dose reduction without compromising diagnostic performance; developing software tools for efficiently conducting observer performance studies; determining the correlation between model and human observers or linear and nonlinear image reconstruction approaches; and developing tools to efficiently and quantitatively optimize CT scanning protocols for each specific diagnostic task studied.

Dr. McCollough described the case of a patient with suspected pancreatic cancer. Images resulting from a low-dose scan were insufficient for a diagnosis, so the patient had to return two days later for repeat CTs. In this case, reducing the dose compromised diagnostic performance.

Dr. McCollough's team is producing reference patient data sets with known pathology or clinical validation of disease and simulating lower-dose exams. They are also developing mathematical model observers, with the goal of correlating optimal dosage—the dosage that produces the correct answer most of the time—to what the model observer predicts should produce the best answer. Ultimately, users will

be able to submit materials and receive guidance as to where their dosage should be on the optimization curve.

The big question is: Should we reduce CT dose? The answer is yes, but not too much, and not because it causes cancer but because people fear it will cause cancer. Fear has consequences: missed or delayed diagnoses or treatment, higher health care costs, and anxiety and emotional distress. After the *New England Journal of Medicine (NEJM)* reported that up to 2 percent of future cancers might be caused by CT, a lot of frightened patients cancelled their CT scans. This and other alarmist media messages are having serious negative consequences on patient care. For example, an 84-year-old male patient with an aortic aneurysm insisted on having an ultrasound instead of the angiogram the surgeon had ordered. As a result, the surgeon did not have the quality information required to perform the surgery well.

Dr. McCullough contends that these fears are inappropriate if the assessment of risk is accurate. She outlined a 2009 paper published in *Archives of Internal Medicine*, which calculated potential cancers using published radiation risk data. The authors concluded that 29,000 future cancers could be related to CT scans performed in the United States in 2007, and these could translate into about 14,500 cancer deaths. The authors assumed that risk is linearly proportional to dose. Dr. McCullough contends that this reasoning is flawed, and there is universal agreement among international experts that risk is not linearly proportional to dose. Radiation protection organizations including the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Commission on Radiation Protection, the National Council on Radiation Protection, the Health Physics Society, the American Association of Physicists in Medicine, and the Academie Nationale de Medicine have issued policy statements to this effect.

Studies of medically and occupationally exposed individuals, those living in high-background-radiation areas, and survivors of the atomic bombings in Japan have demonstrated increased risk of cancer only for doses above 100-250 millisievert. Such doses are far greater than dose levels used in medical imaging.

Two recent observational studies of children who received CT scans suggested that these patients are at higher risk for subsequent cancer. One study found increased risk of cancers in the chest, abdomen, and pelvis in children who only had a head CT; there was no correlation between where the radiation was deposited and where the cancer occurred. These studies lacked a control cohort and did not determine patient-specific doses. They did not evaluate the clinical symptoms and comorbidities that led to an imaging study for associations with cancer. Their results were highly inconsistent with prior literature.

Dr. McCullough cited a recent example of negative consequences of fear of low-dose radiation. A 2-year-old child fell five feet out of a window. In the emergency room, the child was pale, crying, and vomiting. The American Academy of Pediatrics recommends performing a CT scan if the child loses consciousness, but no one had witnessed the fall or knew if the child had lost consciousness. The doctor discharged the child after a physical exam; the child died hours later from a subdural hematoma.

In summary, the benefits of CT scans have been clearly demonstrated. The risks from radiation doses used in medical imaging have not been demonstrated. The fear is real, even if it is unwarranted, and fear has an impact on quality of care, so we must take steps to maintain quality of care. These steps include optimizing doses, lowering them when possible, and using the correct dose all the time; countering flawed literature and media reporting; and developing and translating new applications that bring new types of benefits.

New applications include dual- and multi-energy CT. These approaches make it possible to distinguish between materials that have the same CT number and, consequently, would have the same brightness on a standard CT image. Dual-energy CT allows separate determination of density and atomic number, can provide material composition information, and does not increase radiation dose. Dual-energy CT images include low-/high-energy source images; mixed or blended images that combine low and high energy

images and blend linear and nonlinear; and energy-selective or virtual monochromatic (monoenergetic) images.

Virtual monoenergetic imaging improves iodine contrast and reduces metal artifacts. With energy domain noise reduction, the technique can be used to improve iodine contrast to noise ratio (CNR) (e.g., increases conspicuity of subtle lesions, allows use of less iodinated contrast media, and compensates for poor venous access resulting in slow injection rates).

Material-specific applications represent another very exciting new approach. These applications enable material characterization or classification (e.g., distinguishing between a breast mass or silicone implant leakage). These techniques can be used to differentiate between kidney stone composition, which is useful for determining optimal treatment. These applications can also be used to digitally suppress materials (e.g., bone or plaque) that obscure a view of soft tissue.

These methods offer great potential for solving diagnostic dilemmas in a noninvasive way. They enable disease quantitation: accurate assessment of disease burden; pre- and post-treatment comparisons for early identification of nonresponders and subsequent alteration of treatment; and provision of definitive outcome measures for therapeutic regimens.

These new techniques push the benefits of CT forward. To date, their greatest impact has been with material classification. As technology continues to improve, more applications (and more quantitative applications) can be expected.

## **Discussion**

Dr. Sorensen noted that the press is citing articles from *NEJM*, which presumably has competent scientist reviewers. Dr. McCullough replied that few reviewers in general medical journals have the background to evaluate these papers. The *Journal of the American Medical Association (JAMA)* invited her to review a paper, which *JAMA* eventually rejected; however, the paper was published elsewhere later. There is an urgent need to publish well-balanced papers that answer questions and fears about medical radiation. The problem has been getting strong papers into the big journals.

Dr. Sorensen suggested that it is important to conduct research that generates data to support this position. Dr. McCullough responded that such an investigation would require studying 10 billion people (i.e., 5 billion people in the exposed arm plus 5 billion in the control arm) for their entire lives and account for confounding factors. Such a study is undoable.

Dr. Lee applauded Dr. McCullough's efforts. He noted that humans have 128 genes specifically designed to repair DNA, and these genes can be upregulated by past exposure. Within the World Health Organization (WHO), people are publishing linear dose rate models predicting 60,000 excess deaths in Western Europe in response to Chernobyl. At the same time, WHO's expert advisor group on Chernobyl could not document more than 246 related deaths in the highly exposed zone in Belarus, Ukraine, and Russia.

Dr. Gore pointed out that *Scientific American* published an article entitled "Perception of Risk from Radiation" over 40 years ago, so these are not new issues. However, the field of radiology has been guilty of ignoring concerns and has failed to emphasize the importance of quantifying actual radiation used and the related risks.

Dr. McCullough described a phosphorescence study on double-strand break markers. Blood samples were collected prior to a CT, immediately after the CT, and every hour for 24 hours. The number of double-strand breaks jumped tremendously immediately after the CT, but after 24 hours the number was below baseline.

Dr. Sullivan commented that papers written by groups perceived as radiology advocates would be viewed as biased. He asked whether any neutral parties have issued papers. Dr. McCullough responded that UNSCEAR would be considered a neutral body. The International Commission on Radiological

Protection and the National Council on Radiation Protection & Measurements are hardcore radiation protection groups that might be perceived as hostile to radiology, and they report that CTs are very safe.

Dr. Thrall commented that the radiation issue is not unique. Biases are seen throughout society. For example, there currently seems to be an antiscreening bias among some components of the health services research community. People at the U.S. Preventive Services Task Force look at the same data and interpret it very differently. There will always be issues and controversy.

Dr. McCullough added that the genius of NIBIB's approach is to take the issue off the table by reducing radiation doses to a background level.

At this point, Dr. Sastre presented the Hector Lopez Lecture award to Dr. McCullough.

## VII. Adjournment

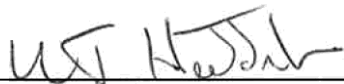
The open session of the NACBIB meeting was adjourned at 12:50 p.m.

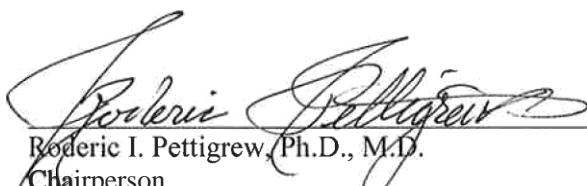
## VIII. Closed Session

The grant application review portion of the meeting was closed to the public in accordance with provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and IO(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2). The closed session was adjourned at 3:00 p.m.

Certification:

We certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.<sup>2</sup>

  
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William Heetderks, M.D., Ph.D.  
Acting Executive Secretary  
National Advisory Council for Biomedical Imaging and Bioengineering  
Acting Director,  
Office of Research Administration  
National Institute of Biomedical Imaging and Bioengineering

  
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Roderic I. Pettigrew, Ph.D., M.D.  
Chairperson  
National Advisory Council for Biomedical Imaging and Bioengineering  
Director,  
National Institute of Biomedical Imaging and Bioengineering

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<sup>2</sup> These minutes will be approved formally by the Council at the next meeting on January 23, 2015, and corrections or notations will be stated in the minutes of that meeting.