

**MEETING SUMMARY**  
**PRESIDENT'S CANCER PANEL**  
**THE FUTURE OF CANCER RESEARCH: ACCELERATING SCIENTIFIC  
INNOVATION**

December 14, 2010  
Bethesda, Maryland

**OVERVIEW**

This meeting was the third in the President's Cancer Panel's (PCP, the Panel) 2010-2011 series, *The Future of Cancer Research: Accelerating Scientific Innovation*. During this meeting, the Panel heard expert testimony from innovators who are engineering and evaluating new technologies, models of research, collaborations, funding strategies, and ways of communicating. The agenda for the meeting was organized into two discussion panels.

**PARTICIPANTS**

***President's Cancer Panel***

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair

Margaret Kripke, Ph.D.

***National Cancer Institute (NCI), National Institutes of Health (NIH)***

Abby Sandler, Ph.D., Executive Secretary, PCP

***Speakers***

Donald A. Berry, Ph.D., Head, Division of Quantitative Sciences, Chair, Department of Biostatistics, The University of Texas MD Anderson Cancer Center

Arthur L. Caplan, Ph.D., Emmanuel and Robert Hart Director of the Center for Bioethics and Sydney D. Caplan Professor of Bioethics, University of Pennsylvania

Jonathon N. Cummings, Ph.D., Associate Professor, The Fuqua School of Business, Duke University

Susannah Fox, Associate Director, Digital Strategy, Pew Internet & American Life Project

Julia I. Lane, Ph.D., Program Director, Science of Science and Innovation Policy, National Science Foundation

Bradley Malin, Ph.D., Assistant Professor, Department of Biomedical Informatics, Director, Health Information Privacy Lab, Vanderbilt University School of Medicine

Raj K. Puri, M.D., Ph.D., Director, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration

Daniel Sarewitz, Ph.D., Professor, School of Life Sciences and School of Sustainability, Co-Director, Consortium for Science, Policy and Outcomes, Arizona State University

Ellen V. Sigal, Ph.D., Chairperson and Founder, Friends of Cancer Research

Naz Sykes, Executive Director, Dr. Susan Love Research Foundation

Harold Varmus, M.D., Director, National Cancer Institute

## **OPENING REMARKS—LaSALLE D. LEFFALL, JR., M.D., F.A.C.S.**

On behalf of the Panel, Dr. Leffall welcomed invited participants and the public to the meeting. He introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings.

## **PANEL I**

### **MS. NAZ SYKES:**

## **ARMY OF WOMEN: A PARADIGM-CHANGING RESEARCH RESOURCE AND A NEW MODEL FOR DEMOCRATIZING RESEARCH**

### **Background**

Naz Sykes serves as the Executive Director of the Dr. Susan Love Research Foundation (DSLRF) and in the past five years has made substantial impact on the growth of the organization. She spearheaded the Love/Avon Army of Women initiative, with the goal of recruiting one million women nationwide to take part in breast cancer research studies. Ms. Sykes also spearheaded the Health of Women Study, the first online breast cancer cohort initiative studying potential new risk factors for breast cancer and other diseases, in partnership with the National Cancer Institute and City of Hope. In addition to overseeing and setting the strategic direction for the major initiatives of DSLRF, she is also responsible for the organization's overall strategic planning, oversight, and fundraising. Ms. Sykes received her Bachelor of Science degree in biology and psychology, with a minor in chemistry, from the University of Denver and has over 13 years of experience in management, development, and strategic planning for nonprofits.

### **Key Points**

- The mission of the Dr. Susan Love Research Foundation is to eradicate breast cancer and improve the quality of women's health through innovative research, education, and advocacy. The goal is to identify barriers to research, explore new approaches, and create new solutions. DSLRF differs from many other nonprofit breast cancer organizations in that it is working to move breast cancer beyond a cure—to understand the cause of the disease and how to prevent it.
- DSLRF sought funding for the Army of Women (AOW) program for many years, but was told that the program was not innovative enough and that women would never sign up. DSLRF worked with the Avon Foundation for two years to obtain funding and received a grant in February 2008. The AOW initiative was officially launched in October 2008 on NBC's TODAY show.
- To date, over 347,000 women of all ages and ethnicities, as well as a small number of men, have signed up to take part in the program. Eighty-six percent of AOW members are women with no history of breast cancer. Fourteen percent of enrollees are cancer survivors or are going through active treatment. Seventy-four percent of AOW members have no family history of breast cancer; 50 percent are between the ages of 40 and 59; 85 percent are Caucasian, 3 percent are African American, and 3 percent are Hispanic/Latina. On average, 1,500 new recruits join AOW per month. This success is largely due to the grassroots nature of the initiative—Dr. Susan Love makes many media appearances and AOW is actively promoted via social media and has partnerships with many other women's organizations.
- The goal of AOW is to encourage all women—both healthy women and those diagnosed with cancer—to take the next step in breast cancer advocacy by participating in research studies. AOW wants women to become invested in the concept of research. It is believed that if individuals are educated about the importance of research before they are diagnosed with a disease, it will be easier to get them to participate in clinical trials. Other important goals of the AOW are to increase the

amount of research focused on the cause and prevention of breast cancer and to accelerate research by providing investigators access to a large pool of healthy volunteers.

- Women enroll in AOW online ([www.armyofwomen.org](http://www.armyofwomen.org)), at which time they provide basic contact and demographic information (e.g., date of birth, ethnicity, zip code). “Call to Action” emails with trial information are sent to the entire database of women when a study becomes available. With the help of social networking sites, these emails often cause the studies to “go viral.” Each time a Call to Action is sent out, AOW membership slightly increases. Women respond to the Call to Action if they are interested in the study and go through an online screening process. DSLRF manages the subject list and information is passed on to the researchers.
- AOW does not match women to studies and is not a tissue bank. Rather, it is a “just-in-time” resource for basic scientists and epidemiologists who need biological samples and/or information for breast cancer research. Scientists are able to collect the information they need when they need it.
- Researchers register on the AOW Web site for access to the current membership base. Research studies can fall under one of three categories: those without funding, those with non-peer-reviewed funding, and those with peer-reviewed funding. Studies without funding are reviewed by DSLRF staff; if they are found appropriate, a letter of support is provided for inclusion in the grant submission package. Studies with non-peer-reviewed funding are reviewed for scientific merit and appropriateness by members of the external Scientific Advisory Committee (two scientists and an advocate). Peer-reviewed funded studies are also reviewed by members of the Scientific Advisory Committee (one scientist and one advocate) for appropriateness. Over 90 percent of AOW studies are peer-reviewed funded studies.
- The AOW Scientific Advisory Committee consists of 35 members, at least half of whom are patient advocates, with the remaining members comprising researchers and clinicians. All AOW studies must obtain institutional review board (IRB) approval, as well as special IRB approval for online recruiting, before being launched. AOW also has its own umbrella IRB approval from Western IRB.
- An important aspect of the AOW initiative is the partnership being built between women and researchers. AOW researchers are responsible for explaining studies to participants, as well as communicating results of the study. Researchers must do this in person if they are conducting the study themselves, or through a DSLRF-hosted webinar if they have no personal contact with the women. Through this process, the public is being educated about research and how it is conducted.
- Since initiation of the program in October 2008, 44 studies have launched, 17 have closed after meeting their enrollment goals, and 6 have increased recruitment due to success in obtaining responses from members. On average, two new studies launch per month. AOW has been involved with one global study, 17 national studies, and 20 regional studies. Over 60 percent of AOW studies have reached full recruitment within 30 days of opening. More than 49,000 AOW members have registered to enroll in at least one study.
- An example of a regional research study launched on AOW is the BEAM (Breast Estrogen and Methylation) Study at Northwestern University. The goal of this study was to collect NAF (nipple aspirate fluid) and core biopsy and blood samples from 300 healthy women. Over 13,000 women responded to the Call to Action email, and 624 were qualified to participate following the online screening process. The study recruitment goal was increased due to this success.
- The Milk Study is a national research project at the University of Massachusetts. The study needed 250 lactating, healthy women scheduled for a breast biopsy. Over 62,000 responses to the Call to Action were received, and within 24 hours 31 women were successfully recruited. Recruitment was eventually increased to 2,000 women.
- A national study of Ashkenazi Jewish women at NYU School of Medicine was launched in November 2010. This is a DNA study focused on Ashkenazi Jewish women to identify new genes that might reduce breast and ovarian cancer risk in women who have a *BRCA1* or *BRCA2* mutation

and to identify mutations in genes other than *BRCA1* and *BRCA2* that increase breast and ovarian cancer risk in Ashkenazi Jewish women. The initial recruitment goal of the study was 1,000 women; to date, 5,627 responses have been received and over 3,000 women have been recruited.

- AOW is also helping to support studies looking at health disparities. The Narrowing the Gap study needed to recruit 400 newly diagnosed breast cancer patients and collect their medical records; the study was having difficulty recruiting African-American women. AOW recruited 224 women, 25 percent of whom were African American. Although there are often barriers to collecting medical records for research studies, 90 percent of the women recruited to this study have submitted their medical records to date.
- The Quality of Life in Latina Breast Cancer Survivors study needed to recruit 100 Latina women newly diagnosed with breast cancer. The AOW received 125 responses from its Call to Action. Of the 125 women who responded, 120 were eligible for the study.
- The biggest complaint from AOW members is that there are not enough studies for healthy women. In response, DSLRF has teamed up with Dr. Leslie Bernstein at the City of Hope Beckman Research Institute to create the first completely online cohort research project—the Health of Women (HOW) Study. With technical help from NCI’s Cancer Biomedical Informatics Grid (caBIG), an infrastructure has been developed that enables DSLRF to establish a large online cohort of women and follow them over time.
- The HOW Study empowers women to be part of and feel invested in research. This is accomplished by educating women about the research process and including women in the collection and maintenance of clinical data and biospecimens. One of the primary goals of the Health of Women study is to identify potential new risk factors for breast cancer and other diseases.
- The online format of the HOW Study will reduce participant burden by administering multiple short questionnaires at regular intervals. Skip patterns within the questionnaires will allow for individual customization. Some of the questionnaire topics will focus on breast cancer history and treatment, reproductive health, family history, environmental factors, diet and exercise, and metastatic disease. A comprehensive medical history, including all other diseases and cancers, will also be collected from participants. The HOW Study will provide an open platform so that researchers can access deidentified data to form hypotheses and create sub-cohorts.
- The HOW Study will also engage the public in developing questions. Each questionnaire will solicit questions from participants. Advocacy groups will also help design questions relevant to their experience with certain issues, such as fertility or metastatic disease.
- The HOW Study was beta launched in December 2009. To date, 25,414 women and 116 men have signed up; 82 percent of the participants are healthy and 18 percent are cancer survivors. Some user-interface issues with the initial site have been identified; the site has been redesigned and will officially relaunch in January 2011 ([www.healthofwomenstudy.org](http://www.healthofwomenstudy.org)). DSLRF is working toward utilizing mobile phones to collect clinical data in 2011, which is particularly important for African-American and Latina communities. Many women in these populations do not have home computers, and the mobile phone is their information hub.
- Through the AOW and HOW Study, DSLRF has shown that women are willing and ready to take part in clinical research. Scientific literacy and support will be increased by including the public in the conduct and design of research. Researchers must educate the public about the importance of taking part in research before the onset of disease. With the right funding and support, the AOW model can be expanded into other disease areas.

## **DR. BRADLEY MALIN:**

### **REPURPOSING CLINICAL DATA FOR CANCER RESEARCH WITH FORMAL PRIVACY PROTECTIONS**

#### **Background**

Dr. Malin holds a primary appointment as Assistant Professor of Biomedical Informatics in the School of Medicine and a secondary appointment as Assistant Research Professor of Computer Science in the School of Engineering at Vanderbilt University. He is the founder and current director of the Health Information Privacy Laboratory (HIPLab), an interdisciplinary endeavor that was established to address the growing need for data privacy research and development for the rapidly expanding health information technology sector. The HIPLab is funded through grants from the National Science Foundation and National Institutes of Health to construct technologies that enable privacy in the context of real-world organizational, political, and health information architectures. To build practical solutions, the HIPLab draws upon methodologies in computer science, biomedical science, and public policy, but has also been known to innovate novel computational techniques when the state of the art is insufficient. For the past several years, in addition to its role as a scientific research program, the HIPLab has functioned as a data privacy consultation service for the Electronic Medical Records and Genomics (eMERGE) network, a consortium sponsored by the National Human Genome Research Institute and National Institute of General Medical Sciences. Dr. Malin completed his education at Carnegie Mellon University, where he received a bachelor's degree in biological sciences, a master's degree in data mining and knowledge discovery, a master's degree in public policy and management, and a Ph.D. in computer science.

#### **Key Points**

- Healthcare providers are collecting enormous amounts of information about patients. Many of these providers want to share these data for a variety of worthwhile secondary uses (i.e., applications beyond individual patient care), including cancer research.
- The Electronic Medical Records and Genomics Consortium, also called the eMERGE Network, is a consortium of biorepositories linked to electronic health record (EHR) data for the purpose of conducting genomic studies. Consortium members include Vanderbilt University, Group Health Cooperative of Puget Sound, Marshfield Clinic, Mayo Clinic, and Northwestern University. eMERGE, which is supported by the National Human Genome Research Institute and the National Institute of General Medical Sciences, is in its fourth and final year of funding. If the program is renewed, it will be expanded to include additional centers.
- The eMERGE database includes information from the medical records of over 1.5 million patients (updated weekly) and currently has discarded blood samples from 105,000 patients from whom informed consent has been obtained. Of these samples, approximately 15,000 have been prospectively genotyped; the DNA of the remaining samples will be analyzed as needed for particular studies.
- The NIH Data Sharing Policy, which was put forth in 2003, states that data should be made as widely and freely available as possible and that researchers who receive more than \$500,000 in NIH funding must develop a data-sharing plan or describe why data sharing is not possible at the time that they submit their grant application. NIH went further with its 2007 policy on genome-wide association studies (GWAS), stating that any researcher receiving NIH funds for GWAS must deposit their data into the NIH-managed Database of Genotypes and Phenotypes.
- The 2003 NIH policy on data sharing indicates that data should be shared in a manner that is devoid of identifiable information; however, rather than defining "identifiable information" itself, NIH generally refers to the U.S. Health Insurance Portability and Accountability Act (HIPAA). The HIPAA Privacy Rule regulates a covered entity's ability to use or disclose protected health information, which is information that is explicitly linked to a particular individual or could

reasonably be expected to allow individual identification. HIPAA allows secondary sharing of some data without informed consent if deidentification is performed through one of two approaches: Safe Harbor or Expert Determination.

- Safe Harbor requires that 18 possible identifiers be removed from data before it can be shared. Included among these are names, geographic information (unless a zip code has more than 20,000 inhabitants), dates, information that would indicate an individual is over 89 years of age, contact information, and biometric data. Safe Harbor does not guarantee anonymity. In fact, in every state there are a small percentage of individuals who are unique with respect to certain combinations of common demographic features (e.g., gender, ethnicity, year of birth, and state of residence) that do not need to be removed based on Safe Harbor guidelines, making them vulnerable to identification. Access to additional information (e.g., diagnosis codes, pedigree structures) further increases the likelihood that an individual listed in a deidentified data set could be distinguished from others.
- The HIPAA Expert Determination guidelines state that investigators must use generally accepted statistical and scientific principles and methods to certify that the risk is very small that the shared information could be used (alone or in combination with other reasonably available information) by the anticipated recipient to identify individuals. HIPAA indicates that this is the preferred approach for deidentification, but it is used much less frequently than Safe Harbor, in part because researchers cannot or do not work with statisticians who have the expertise necessary to implement Expert Determination guidelines.
- The potential for reidentification was illustrated using a 2,500-person cohort from a genome-wide association study at Vanderbilt. Based on the associated standard health insurance billing codes, 97 percent of the individuals in this cohort were unique; in fact, most were unique within the entire 1.5-million-person Vanderbilt patient population.
- The potential for reidentification does not necessarily mean that it can be easily done. Various “threat models” developed by the presenter’s research group found that it is generally difficult to identify individuals using deidentified data. These models take into account the people or organizations that have access to various information sources and/or know the names of people who would be listed in a particular data set. For example, while voter registration data is viewed as a potential source for linking individual’s names with their deidentified data, in many cases, the cost of procuring these records may make it unlikely that it will be done. Of note, the information provided as part of voter registration records and the cost of obtaining these records vary by state, influencing the ease with which records can be linked to names and the likelihood that the records will be used for such a purpose.
- It is possible that ethically sound research policies that allow for a certain level of risk will need to be developed in order to avoid stagnancy in biomedical research. However, in order for informed decisions to be made, it is important that the magnitude of risk be understood. Knowledge of actual reidentification risk associated with a given data set would help determine whether it is underprotected and in need of additional safeguards or sufficiently deidentified. The Expert Determination standard should be more extensively used to help achieve this.
- One model that has been tested is the K protection model. This approach involves removing certain information elements so that no single record maps to less than a defined number of people; this number is referred to as  $k$ . Various options for data elements to be removed can be tested and an approach can be selected based on the data deemed most important for future analyses. For example, it may be possible to share detailed information on age if information on ethnicity is withheld. Viable options will depend on the characteristics of the individuals in the data set.
- There are a number of challenges related to privacy and sharing of EHR data. Mechanisms should be put in place to train and certify experts capable of deidentifying data; one option would be to establish national centers of excellence that focus on issues related to deidentification. In addition, mechanisms

are needed to facilitate longitudinal studies capable of following individuals who receive care at multiple institutions; this would require anonymous linking of data sets. It is also necessary to determine acceptable levels of risk with respect to deidentification, recognizing that acceptable levels of risk may depend on the type of data set in question. NIH should provide more guidance with respect to risk rather than simply referring to the privacy clauses of HIPAA.

**DR. RAJ K. PURI:**

## **CHALLENGES AND OPPORTUNITIES IN THE DEVELOPMENT OF CANCER VACCINES AND IMMUNOTHERAPY PRODUCTS**

### **Background**

Raj K. Puri, M.D., Ph.D., is the Director of the Division of Cellular and Gene Therapies (DCGT) in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER). He is also Chief of the CBER Tumor Vaccines and Biotechnology Branch. He has been at CBER for the last 22 years in various positions. Dr. Puri was trained at NCI's Surgery Branch and at the Mayo Clinic prior to joining CBER. He oversees the regulation of tumor vaccines, immunotherapies, cellular and gene therapies, tissue engineering, and xenotransplantation products and the development of policies and guidance documents in these cutting-edge areas of medical research. Dr. Puri and his staff interact with stakeholders to bring FDA, industry, patient advocates, scientists, and the public together in collaboration to promote and develop new therapies for the 21st century, while protecting human subjects and maximizing biological product safety. In addition, Dr. Puri oversees and manages the Critical Path research performed by principal investigators in DCGT to support medical product development. Dr. Puri also directs translational research programs in the field of cancer vaccines, cancer targeting, and immunotherapy. In addition, he is vigorously involved in the application of genomics technology in product development, policy and guidance documents development, outreach efforts, and research focusing on cancer and embryonic stem cells. Dr. Puri is an associate editor of *Immunotherapy*, a member of the editorial boards of three international medical journals, and author of over 250 peer-reviewed articles.

### **Key Points**

- The regulation of biological products for applications in oncology takes place within two FDA Offices. The Office of Cellular, Tissue, and Gene Therapies—which is responsible for the evaluation of cancer vaccines and immunotherapies as well as gene therapy products for cancer—is housed within the Center for Biologics Evaluation and Research. The FDA Office of Oncology Biologics—which oversees small molecules in addition to biologics such as monoclonal antibodies, therapeutic proteins, and cytokines—is housed within the Center for Drug Evaluation and Research.
- Cancer vaccines and immunotherapies are a diverse set of products. They can include cells, such as dendritic cells, activated T lymphocytes, B cells, monocytes, or cancer cells (chemically modified or unmodified); tumor cell lysates; proteins or peptides (often mixed with adjuvants); and idiotypic and anti-idiotypic antibodies. Gene therapy products include plasmid DNA vectors, replication-defective viral vectors, and attenuated bacterial vectors. Gene-modified tumor vaccines may involve *ex vivo* gene-modified cells or nonviral or viral vectors expressing immunogenic molecules. Another area of emerging interest is the generation of gene-modified peripheral blood nuclear cells and T cells capable of recognizing and attacking cancer cells.
- Many cancer vaccines and immunotherapy products are combined with other agents. For example, dendritic cells are often treated with tumor antigen, purified or recombinant proteins, cell lysates, nucleic acids, or transduced with gene-transfer vectors. Growth factors or cytokines used in the culture of cellular immunotherapies are often administered to patients along with the cells. Tumor antigens or cells are often administered with adjuvants. In some cases, different components of a

regimen are subject to oversight by different FDA Centers or Offices, which requires close collaboration between them.

- There are several challenges associated with the development of cell-based cancer vaccines and immunotherapy products. Unlike traditional small-molecule drugs, these products do not have a defined chemical formula; thus, it is a challenge to be able to rapidly and accurately determine their identity and potency. In addition, these products are complex cell mixtures that are not easily purified; thus, it is difficult to ensure consistency between batches. The short shelf life of most of these products makes it difficult to confirm safety (sterility) before use and stability over time.
- Some approaches have been developed to attempt to address the challenges associated with cell-based cancer vaccines and immunotherapies. In some cases, oversight of both the process and the product is conducted. Other options are to conduct quality control on intermediate products and/or consider surrogate measures of potency. Rapid tests for mycoplasma infection and endotoxin contamination are used to ensure that products administered to patients are as safe as possible. FDA also encourages investigators to continue studying their products so that new knowledge can be used to help develop meaningful assays and novel approaches for monitoring product manufacture and administration.
- In 2010, Provenge<sup>®</sup>, which was developed by Dendreon Corporation, became the first cancer immunotherapy to be approved for use in the United States. Provenge<sup>®</sup> is indicated for the treatment of asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer. Provenge<sup>®</sup> contains T cells that have been taken from the patient to be treated. These cells are administered back to the patient after they have modified in the laboratory with a fusion protein called PAP-GM-CSF.
- Although Provenge<sup>®</sup> has shown some success, the success rate of cancer vaccines as a whole is relatively low. To address the challenges related to therapeutic cancer vaccines, FDA has worked with NCI through efforts such as the Interagency Oncology Task Force, joint workshops, and interagency agreements that support scientific collaboration.
- In 2007, FDA and NCI cosponsored a workshop, along with several professional societies, during which several challenges in the field of therapeutic vaccines and immunotherapy were discussed. This workshop informed the development of FDA guidelines on this topic, which were released in 2009. Also in 2007, NCI and FDA cohosted the Immunotherapy Agent Workshop to identify and prioritize resources and agents needed for research. As a result, some of these agents are being made available through the NCI Rapid Access to Intervention Development (RAID) program (now part of the NCI Experimental Therapeutics [NExT] program) and others have been made available to researchers through Cooperative Research and Development Agreements between NCI and various companies.
- A joint FDA-NCI workshop in 2009 focused on considerations for early-phase clinical trials in the areas of cancer vaccines and immunotherapies. The premise of the workshop was that improvements in early-phase study design may improve the success rates of later-phase studies. Lessons learned from past trials were presented and discussed. One of the lessons learned is that randomization of Phase II trials is preferable because it gives a preliminary estimate of treatment effect, confirms proof of concept, refines target populations for Phase III studies, and helps determine and understand the kinetics of patient immune responses to the experimental vaccine. Other insights gained through past trials are that it is important to develop potency assays early in the clinical trials process and that selection of control groups is critical.
- The FDA guidance document on cancer vaccines released in late 2009 provides several recommendations to investigators planning to initiate clinical trials of cancer vaccines. For example, investigators should establish patient enrollment criteria based on scientific information. Also, preclinical evidence of activity of a particular vaccine should be established before it is moved into clinical trials. The presence of the target antigen on normal cells should be well characterized so that this information can be taken into account when monitoring safety. It is also recommended that trials

be conducted in patients with early- rather than late-stage disease because patients with early-stage disease are likely to have more robust immune systems. Unlike traditional drugs for which early-phase trials establish maximum tolerated doses, early-phase trials for immunotherapies and vaccines must establish optimal biologic dose. In clinical trials for immunotherapies and vaccines, it is critical that investigators monitor patient immune responses, which will provide the opportunity to identify relationships between biomarkers and clinical outcomes.

- FDA provides input to investigators and sponsors through a variety of mechanisms. Some of these interactions are informal. FDA sends representatives to scientific meetings to give presentations and talk with investigators; these are sometimes referred to as pre-pre-Investigational New Drug (IND) meetings. FDA also has formal pre-IND meetings during which sponsors and FDA staff get together to discuss product development activities prior to the submission of an IND application.
- CBER employs research-regulators who perform critical path research to facilitate development of safe and effective medical products. This research may include developing assays and methods and learning how to predict product safety and effectiveness.
- Resources regarding regulation of therapeutic cancer vaccines and immunotherapies can be found on the FDA Web site ([www.fda.gov](http://www.fda.gov)).

## **MS. SUSANNAH FOX:**

### **CANCER 2.0**

#### **Background**

Ms. Susannah Fox studies cultural shifts taking place at the intersection of technology and health care. As an associate director of the Pew Research Center's Internet Project, Fox has used national survey research to document the role of the Internet in Americans' lives, including people living with chronic disease. Her research finds that health professionals, friends, and family members remain central to patients seeking information, but search engines and online patient communities are gaining in influence, particularly due to the power of mobile technology and online social networks. Further, patients and the people who love them are not just a target audience, according to Fox's research, but a resource for innovation and knowledge.

#### **Key Points**

- The charge of the Pew Internet & American Life Project is to study the impact of the Internet on education, government, civil life, and health care, among other areas. All reports and data sets from the past 10 years of this research are available free of charge on the Pew Internet Web site ([www.pewinternet.org](http://www.pewinternet.org)).
- In 1995, only about five percent of American adults had Internet access. Currently, about 75 percent of American adults and 95 percent of teenagers use the Internet. Adults 65 and older—a population group with high cancer incidence—are least likely to be online. Sixty-one percent of people living with chronic disease have Internet access, and 80 percent of caregivers have access.
- In 2000, only five percent of American homes with Internet access had a broadband connection. About two-thirds of American homes had broadband in 2010. The percentage of American adults with Internet access has not changed much in the past three years; however, the percentage of adults with broadband has greatly increased in the same time span. Having a broadband connection changes the way people use the Internet. Dial-up Internet users take part in three online activities per day, whereas a broadband user takes part in seven online activities.

- Eighty-five percent of American adults have a cell phone. For about a quarter of the population, a cell phone is their only telephone. Since this cell-only population will continue to grow, the Pew Research Center incorporates cell phone components in all of its telephone surveys conducted for research.
- There is also a growing cohort of the American population that is not only cell-only in terms of telephone use, but mobile-only in terms of Internet usage. Public Wi-Fi and mobile Internet devices are erasing the “digital divide:” when mobile is included in the Pew’s definition of Internet users, the differences in Internet access between African-American and white adults disappear. Mobile access is also changing Internet users, making them more likely to gather and share information online.
- The Pew Internet Project recently conducted a study on social networking use by age group. From 2008 to 2010, there was a great increase in the percentage of older adults using social networking sites. The study also revealed that social networking sites are becoming the default homepage—the first stop on the Internet—for many Americans, especially younger age groups. This finding is relevant to health and cancer research because it suggests that the best way to relay a health message or educate the public online is through social networking.
- Last year, the Pew Internet Project conducted an Internet study aimed at people living with chronic disease. The study found that living with a chronic disease is associated with being social about health. Once online, chronic disease patients are more likely than healthy individuals to participate in online discussions and blog about health issues.
- The Internet is creating a parallel health information system—it allows people to break down geographical barriers and share data. Expert patients are able to gather online and trade knowledge about a specific health issue, just as experts in any type of hobby gather online to share skills and tips.
- A new phrase being touted in the medical community is “participatory medicine.” Participatory medicine is a cooperative model of health care that encourages and promotes active involvement of all connected parties (e.g., patients, caregivers, health care professionals). It is integral to the full continuum of health care. Pew Internet data show that patients are ready, willing, and able to participate in such a system that can be fostered by health information technology (IT). Currently, only about 5 to 7 percent of Americans have access to EHRs; this access needs to be expanded and incorporated into the emerging health IT culture.
- The Life Raft Group is an example of the type of participatory medicine that the Internet can foster. The Life Raft Group began with a group of patients with a rare cancer called gastrointestinal stromal tumor (GIST) who gathered via a listserv to discuss their disease. In 2000, the group discovered a Phase I clinical trial for a drug called Gleevec® that showed efficacy against GIST; however, not many people were discussing this study. The Life Raft Group contacted the principal investigator of the study and lobbied for access to the trial, which started out with only 30 patients. It was this online advocacy that persuaded the drug company sponsoring the trial to move from Phase I to Phase II, which it was not originally planning to do.
- The scientific community needs to take heed of the Life Raft Group example and utilize the many potential opportunities to engage members of the public and educate them about the benefits of participating in clinical research. The information and communications landscapes are shifting and the research community must adapt to them.

## **DR. ARTHUR L. CAPLAN:**

### **THE HIGH COST OF NEW CANCER TREATMENTS: CAN EVIDENCE HELP US RATION?**

#### **Background**

Dr. Arthur Caplan is currently the Emmanuel and Robert Hart Director of the Center for Bioethics and the Sidney D. Caplan Professor of Bioethics at the University of Pennsylvania in Philadelphia. Dr. Caplan is the author or editor of 30 books and over 550 papers in referenced journals. His most recent books are *Smart Mice Not So Smart People* (Rowman Littlefield, 2006) and the *Penn Guide to Bioethics* (Springer, 2009). Dr. Caplan has served on a number of national and international committees; most recently, he was the Co-Director of the Joint Council of Europe/United Nations Study on Trafficking in Organs and Body Parts.

#### **Key Points**

- Many people in the United States believe that scientific evidence will facilitate health care reform and help contain costs by informing treatment decisions and payment/reimbursement policies. However, there are several examples illustrating that medical practices are not driven by evidence alone. Politicians, who hope that evidence will relinquish them from having to make hard choices, have often chosen to ignore or go against data. Courts generally rule in favor of patient autonomy in decision making over evidence and professional judgment; consequently, physicians are likely to do what patients want versus what the evidence suggests that patients need. In addition, although many argue that evidence should resolve disputes regarding the pursuit of a particular innovation or the approval of an intervention, this often does not occur. This is because evidence does not elucidate societal values or “norms,” which is what people rely on to make decisions. Values help people interpret the evidence.
- Most physicians today believe that it is their responsibility to secure any and all resources that may potentially benefit their patients. Physicians also feel they need to secure informed consent by offering patients an exhaustive list of options and alternatives. However, these approaches may not be in the best interests of patients.
- The Patient Protection and Affordable Health Care Act (PPACA), which was signed into law in March 2010, will significantly alter the practice of medicine by putting a stronger emphasis on physician adherence to government-determined measures of care quality. PPACA mandated creation of the Patient-Centered Outcomes Research Institute, which will establish research priorities and studies that compare the effectiveness of medical and surgical treatments.
- PPACA gives the Secretary of Health and Human Services (HHS) authority to use evidence from findings of comparative effectiveness research to make coverage determinations under certain statutory conditions. Also, beginning in 2013, hospitals that treat Medicare patients will be reimbursed at different rates based on performance.
- Critics of evidence-based medicine (EBM) believe that population-based study results will be applied to patients’ situations despite unique health conditions, personal values, and doctors’ experience. This may occur in part because physicians will be incentivized to adhere to standard protocols to maximize reimbursement rather than act in the best interests of their patients. This practice would hurt medical innovation and weaken the doctor-patient relationship.
- Another problem with EBM is that data have failed to withstand politics, and the concept of autonomy has been upheld even when at odds with the good of the group or the community.
- The U.S. Preventive Services Task Force (USPSTF) is the leading independent panel of private-sector experts in the United States and Canada. Its recommendations are considered the “gold standard” for

clinical preventive services. USPSTF evaluated routine mammograms last year and recommended against routine screening mammography in women aged 40 to 49 years old. These recommendations were based on the conclusion that the resulting radiation exposure, false-positive rates, and numbers of unnecessary procedures were too high to justify the benefits of mammography for women in this age group. The recommendations stated that the decision to start regular, biennial screening mammography before the age of 50 should be an individual one and take patient context into account. The USPSTF recommends every-other-year screening mammography for women aged 50 to 74 years old.

- The reaction to the USPSTF mammography recommendations was swift and not evidence-based. The First Lady, many women's health groups, doctors who conduct mammograms, and others expressed displeasure with the recommendations. HHS Secretary Kathleen Sebelius issued a statement saying that the recommendations would not influence government policy and should not influence private insurers' policies. In an interview with CBS News anchor Katie Couric, Sebelius said she was not refuting the recommendations, but she stated that women should "do what they've always done" and discuss their healthcare decisions with their doctors.
- One reason the USPSTF's work has become so closely scrutinized is that the healthcare reform bill requires that only preventive services given an "A" or "B" recommendation by the Task Force will be fully covered by insurance.
- In 2008, USPSTF concluded that there was insufficient evidence (an "I" rating) to assess the balance of benefits and harms of prostate cancer screening for men younger than 75 years and recommended against screening for men over 75 years of age (a "D" rating). The USPSTF was initially going to downgrade its recommendations for prostate cancer screening for men under 75 years of age to a "D" rating based on two large screening trials published in 2008, which showed no evidence that benefit of screening outweighed the harm. However, the decision was delayed. The cancellation of the early November 2010 meeting at which the final vote was scheduled to occur precipitated the resignation of a key government official, who stated that the decision to cancel was politically motivated (the meeting was scheduled to occur a few days before Election Day).
- Politically, the United States is not accustomed to debating values or norms in a public venue. The evidence obsession associated with healthcare reform is a way to avoid having to make hard moral choices. A discussion must be forced about what values will be considered along with evidence. Public policy must acknowledge the values or norms that guide implementation of evidence. Hard choices about those norms are almost never made easier by accumulation of more and more evidence.
- The current model of physician advocacy—trying to obtain and encourage use of all resources and options for patients—must shift toward a stewardship model. When patients are presented with all treatment options and asked to make a choice, their emotions can override their capability to make a sound decision. The role of the doctor cannot simply be to offer all possible options and let the patient carry the burden of decision making. This is a distortion of informed consent.
- U.S. society and culture are associated with a moral imperative to rescue individuals in desperate situations. However, the value of rescue is not compatible with evidence. It is not efficient in terms of resource expenditure to devote enormous amounts of resources to the rescue of small numbers of people. The value placed on rescue in American society overwhelms economic discussions of cost-effectiveness, especially with respect to emerging cancer treatments.
- For example, Provenge<sup>®</sup> is a recently approved therapeutic vaccine for older men with advanced prostate cancer who have failed standard therapy—about 100,000 men per year. Dendreon, the company that makes Provenge<sup>®</sup>, processes a patient's immune cells with biological additives that are intended to help them kill prostate cancer cells. The therapy costs about \$93,000 per patient. The vaccine typically extends life about four months and does not control pain or other symptoms.

Nevertheless, the Centers for Medicaid and Medicare Services (CMS) gave approval for coverage of the vaccine in November 2010.

- Hard decisions in cancer care require much more evidence than is currently available. However, they also require a willingness to reach consensus about norms and values. Without such a consensus, more and more evidence will be compiled with no ability to put it to use.

## **DR. ELLEN V. SIGAL:**

### **TEARING DOWN THE SILOS: ADDRESSING SYSTEMATIC BARRIERS IN THE RESEARCH PROCESS**

#### **Background**

Ellen V. Sigal, Ph.D., is Chair and Founder of Friends of Cancer Research (“Friends”), a cancer research think tank and advocacy organization based in the Washington, D.C., metropolitan area. Dr. Sigal is Vice Chair of the inaugural board of directors of the Reagan-Udall Foundation, a partnership designed to modernize medical product development, accelerate innovation, and enhance product safety in collaboration with the FDA. She chairs the Public-Private Partnerships Committee of the Foundation for the National Institutes of Health Board, serves as a Trustee of the American Association for Cancer Research Foundation, is a board member of Research!America, and was most recently appointed to the Patient-Centered Outcomes Research Institute (PCORI) Board of Governors. Dr. Sigal is a member of the Stand Up To Cancer (SU2C) Advocate Advisory Council, and she is one of two Council members nominated to the SU2C Scientific Advisory Committee. She holds leadership positions with a broad range of cancer advocacy and public policy organizations, as well as academic health centers, including the MD Anderson Cancer Center External Advisory Board, the Duke University Cancer Center Board of Overseers, and The Sidney Kimmel Comprehensive Cancer Center Advisory Council. She serves on the C-Change Research Committee and the Entertainment Industry Foundation Oversight Committee for the Biomarker Discovery Project. During her more than 20-year commitment to cancer research, Dr. Sigal has served in a number of critical public positions. She served on the National Cancer Institute Board of Scientific Advisors from 2003 to 2009, and the National Institutes of Health Director’s Council of Public Representatives from 2003 to 2006. She was a Presidential Appointee to the National Cancer Advisory Board from 1992 to 1998, where she chaired the Budget and Planning Committee that oversees the federal cancer budget.

#### **Key Points**

- The cancer plan set forth by candidate Barack Obama during the last presidential campaign included the goal of doubling funding for cancer research. Unfortunately, with the nation shouldering \$228 billion in health care expenses for the 1.5 million people diagnosed with cancer, this may not be a realistic immediate goal. However, it is imperative that funding for life-saving research and treatments, both public and private, not become another victim of the recession.
- Although significant progress in cancer research has enabled some reduction of the cancer burden, continued lack of harmonization has created silos within the biomedical research enterprise, creating barriers among those receiving and using funding. These silos are both the cause and the result of systematic barriers present across the biomedical research continuum. It is imperative that all stakeholders within the biomedical research community prioritize and commit to tearing down these silos and breaking down barriers that prohibit the efficient and effective use of limited resources.
- There are four types of barriers that must be addressed to create more efficient research processes: institutional barriers, cultural/educational barriers, barriers to open dialogue, and scientific barriers. Institutional barriers promote isolation among federal agencies and across public and private sectors, slowing rather than streamlining drug development. Cultural and educational barriers result in lack of

exposure and understanding of the activities and strengths of different agencies/organizations, which creates untapped opportunities and prevents agencies from extending beyond their core mission. Barriers to open dialogue illustrate the need for venues and programs to encourage and provide incentives for communication between all sectors of the biomedical research enterprise. Scientific barriers—from challenges in understanding cancer biology to drug development hurdles—require goal-oriented collaboration across sectors to overcome.

- Over the past two decades, new models have emerged that are beginning to address these barriers. For example, the Joint NIH-FDA Leadership Council oversees activities across the two agencies to find areas for cooperation on issues of safety, quality, and effectiveness. Similarly, the NCI-FDA Interagency Oncology Task Force capitalizes on the great expertise at both agencies. The Multiple Myeloma Research Foundation has been successful in bringing four new treatments to market, while The Michael J. Fox Foundation for Parkinson's Research and SU2C each have been equally effective at providing funding to research organizations focused on developing new treatments. International models that approach the cancer enterprise from an economic growth standpoint, such as Israel's Office of the Chief Scientist or Singapore's Biomedical Science Initiative, can be an influential guiding tool for government agencies to promote cancer research and drug development as an economic driver.
- In addition to developing collaborative research efforts across sectors, it is critical to evaluate gaps in coordination between federal health agencies and industry and address areas that are wasteful and unnecessarily duplicative. In doing so, it is important to heed three recommendations.
- The first recommendation is to reevaluate the activities of health-related federal agencies. The President should create a task force led by the Secretary of Health and Human Services, in collaboration with agency officials, academic researchers, and patient advocates, to comprehensively examine the various cancer-related efforts of federal agencies and the silos that exist among and between them.
- The second recommendation is to develop multidisciplinary mechanisms to support translational research. Rather than rely solely on traditional study sections for the review of translational research projects, new review paradigms that draw upon individuals with expertise in drug development and commercialization are needed to gain an interdisciplinary perspective and help identify opportunities with the greatest potential for success. Programs such as the Interagency Council on Biomedical Imaging in Oncology, the Joint NIH-FDA Leadership Council, and the Interagency Oncology Task Force—which, in addition to utilizing academic scientists as reviewers, seek input from FDA and industry—are examples of initiatives that have already embraced this recommendation.
- The third recommendation is to develop approaches to healthcare delivery that enhance research. New and better processes and systems are needed to collect and aggregate patient data produced as part of the routine care process, as well as data from clinical trials. The recent investment in health IT and incentives for adoption of EHRs in the Affordable Care Act will lay the foundation for new research opportunities. In order to capitalize on this investment, the federal government should develop policies that enhance data collected within EHRs to optimally contribute to research activities. As a starting point, collaborative efforts should be encouraged between agencies developing large-scale, interoperable health data networks to facilitate improved outcomes research and comparative effectiveness research on diverse patients treated at various points of service.

## DISCUSSION AND CONCLUDING COMMENTS:

### PANEL I

#### Key Points

- The considerations discussed regarding risk of identification pertain primarily to retrospective use of data, not use in prospective clinical trials. Rather than creating additional barriers to research, developing ways to reduce risk to acceptable levels will help lower barriers to using retrospective data by minimizing or eliminating the need to work with institutional review boards (IRBs) and removing the need to obtain informed consent from each individual from whom information was collected.
- AOW collects only contact information from its members. The HOW Study collects health information and includes an IRB-approved consent form. For both of these groups, survey data indicate that privacy is not a significant concern. It was stated that, in general, people who are extremely healthy or extremely ill tend to have little concern about privacy issues; however, people who have moderate health issues and/or treatable disorders tend to be more concerned about privacy. It was also pointed out that private foundations are not subject to the same privacy-related regulations as academic health centers; the latter cannot circumvent privacy rules to share data even if patients indicate that they are willing to give up their privacy.
- AOW is committed to having its participants be representative of the population, which means that more needs to be done to recruit minority women, including African Americans and Latinas. Recognizing that minority communities are more likely to access the Internet through mobile technologies, AOW is hoping to develop a way for women to sign up using their mobile phones. It would be helpful if a woman could notify AOW immediately using her mobile device when she is diagnosed with breast cancer. The mobile phone could then be used as a medium for AOW to deliver educational information and information about clinical trials. In addition, the organization is thinking about ways to use mobile phones to collect information for the Health of Women Study.
- AOW has found that many researchers are not prepared to interact with people who do not speak English. Often, consent forms are only available in English. In addition to expanding minority participation, AOW is also encouraging researchers to better accommodate minority women and conduct research that is relevant to them.
- AOW is interested in discovering the causes of breast cancer and ways to prevent the disease—areas that have been understudied.
- The majority of women in AOW have not had breast cancer. AOW does not collect information about other cancer diagnoses, but this type of health information is collected as part of the Health of Women Study. One of the future goals of AOW is to allow its participants to indicate whether they are interested in learning more about diseases other than breast cancer. AOW would then partner with other organizations to help participants access the desired information.
- Two notable trends are occurring worldwide: the increase in technology adoption and the increase in chronic disease. These two factors intersect and are driving society toward online engagement related to health issues.
- Differences in Internet access among racial groups (i.e., the digital divide) have greatly diminished over the past 5 to 10 years. Households of all types are stretching their budgets to gain Internet access, particularly if they have children. Even if families do not have computers and Internet access within their homes, the widespread use of mobile devices and availability of wireless Internet has provided most people in the United States access to the Internet.
- Researchers and clinicians need to be cognizant of the ways that people access information on the Internet. They need to make sure that important information will be found easily using Internet search engines such as Google. Information should be posted to the Internet in formats that are easily

accessible via mobile devices since this is the primary mode of Internet access for many users; this means that information should not be published only as a PDF file.

- Although the Internet provides unprecedented access to information, it also creates an opportunity for accelerating the spread of misinformation. More study is needed on the influence of information accessed through the Internet on people's decision making. Many researchers have looked for evidence of clinical harm caused by patients looking for information online, but very few instances have been identified.
- People often use the Internet as a "just-in-time" resource to identify people who are in similar situations to themselves. For example, a 40-year old who has young children and has been diagnosed with cancer will likely want to interact with someone who is in a similar situation rather than a 90-year old cancer patient.
- Many organizations involved in grassroots cancer issues do not seem to be taking full advantage of opportunities created by the Internet for education and communication. Because the Internet has created a network for information dissemination, large organizations such as NCI, NIH, and the Centers for Disease Control and Prevention (CDC) do not need to recreate this network but should make sure they are aware of the conversations ongoing in this medium and ensure that the best information is represented.
- The Life Raft Group interacted via an email listserv, which can be a powerful tool for connecting people. Virtually all Americans with Internet access use email, although usage rates are lower among teenagers.
- Therapeutic cancer vaccines and other immunotherapies hold great promise because they are based on a strong scientific foundation. There have been many promising leads in this area but, overall, the therapies tested in Phase III clinical trials evaluated by the FDA have not been effective. Many of these therapies may have performed better in Phase III trials if additional work had been done at earlier stages (e.g., if researchers had gained information to help with patient selection).
- A number of logistical challenges are associated with the manufacture, storage, and delivery of treatments such as Provenge<sup>®</sup> that are patient specific (i.e., customized using cells from individual patients). However, there is significant interest in the area of cancer vaccines, including treatment vaccines for early-stage disease and preventive vaccines such as the cervical cancer vaccine Gardasil<sup>®</sup>.
- FDA has been working with other regulatory agencies around the world (e.g., Japan, Europe) in an attempt to harmonize approaches to regulation. FDA also works with patient advocates and appreciates the input of advocates who serve on advisory committees.
- There is a lack of coordination within the National Cancer Program, but this is a difficult problem to address. Even within the federal government there are several agencies that have different missions and that do not have coordinated leadership with regard to cancer. However, people are starting to recognize that there needs to be coordination among and within all sectors. There are some examples of this beginning to happen, but more needs to be done. High-level leadership and/or a mandate will be required to achieve coordination of cancer-related activities within the federal government.
- The scarcity of resources for cancer research may encourage the various sectors to work together more effectively.
- Identification of the impact of environmental factors on health was one component of the Obama Cancer Plan. If funded, the recent health reform bill will facilitate collection of data in this area, but this has not yet been implemented.
- The fact that society invests heavily in end/late-stage disease is consistent with the cultural value of rescue. The fact that sicker people have priority on organ transplant lists is an example of this. Society

can commit to this value of rescue, but it should do so only after open discussion about what the allocation of resources to this area means for other areas.

- In addition to presenting patients with options for treatment, physicians should also be trained and encouraged to provide insights based on their professional experiences. Many clinicians are unlikely to do this based on the idea that patients should make decisions autonomously, but this may not be the best approach. Autonomy can be very lonely for people who are sick with cancer. In addition to presenting facts, physicians should be encouraged to recognize the emotional component of patient decision making and discuss with patients their reasons behind making certain decisions. Physicians, patients, and families need to understand that it is acceptable to choose not to undergo or pursue treatment in certain cases. The cultural value of rescue often makes it difficult to make or accept these types of decisions.
- Researchers need to get better at generating evidence but also at communicating evidence to the general public. The USPSTF recommendations about breast cancer screening released last year were not well received, in part because of the way in which they were presented. Women viewed getting their annual mammograms as “virtuous” and were uncomfortable with having this practice called into question.
- The NCI Cooperative Group program will be undergoing changes in the near future in response to recommendations made in the recent Institute of Medicine report. This will likely include consolidation of the Cooperative Groups and more careful consideration of the types of trials supported.

## **PUBLIC COMMENT**

### **Key Points**

- With respect to the need for physicians to offer guidance to patients, the concern that physicians may not be well informed about current evidence was discussed. In order to ensure a minimal quality of care, it is important that practice be tied to established standards. Linking malpractice protection and evidence-based standards may encourage physicians to be knowledgeable of and adhere to standards.
- There should be investment in communication and education in the area of end-of-life care. In general, the quality of communication between patients and providers declines near the end of life. This should be changed so that physicians can become stewards of and partners with their patients.
- The view of physicians as stewards will require redefining what a physician is. In the past, physicians were often viewed as infallible experts; the recent shift toward a more technocratic approach to patient care and patient autonomy was a reaction to this. Encouraging physicians to provide advice is not the same as encouraging the paternalistic approach that was practiced in the past. Patients need to understand that they have the freedom to make their own decisions but they should have the benefit of the expert opinions of their providers.

## **PANEL II**

### **DR. JULIA I. LANE:**

## **SCIENTIFIC INVESTMENTS AND INNOVATION**

### **Background**

Dr. Lane is Program Director of the Science of Science and Innovation Policy program at the National Science Foundation (NSF). She has been the recipient of over \$20 million in grants from numerous sources, including the NSF, Sloan Foundation, MacArthur Foundation, Russell Sage Foundation, Spencer Foundation, U.S. Department of Health and Human Services, U.S. Department of Commerce, U.S.

Department of Labor, Economic and Social Research Council (ESRC) in the UK, New Zealand Department of Labour, and World Bank. Dr. Lane has published over 60 articles in leading economics journals, authored or edited six books, organized over 30 national and international conferences, received several national awards, and served on a number of national and international advisory boards. She is one of the founders of the Longitudinal Employment and Household Dynamics (LEHD) program at the U.S. Census Bureau, which is the first large-scale linked employer-employee data set in the United States. Dr. Lane's undergraduate degree in economics is from Massey University in New Zealand; her M.A. in statistics and Ph.D. in economics are from the University of Missouri. She became an American Statistical Association Fellow in 2009.

## Key Points

- There is a tenuous link between science investments and innovation. It is assumed that science funding generates economic growth, but there is little evidence to support this claim. A more scientific basis for science policy is needed. Federal agencies involved in science have been asked in recent years to collect data to document the impact of investments in science and technology and develop outcome-oriented goals and timelines for evaluating performance and making resource allocations.
- The scientific challenge in this regard is to develop a hypothesis about how science investments relate to innovation. Identification of causal parameters and mathematical analysis of real data can be used to examine the impacts of specific types of investments. After the impacts of variables such as capital, energy, and materials have been evaluated, additional increases in productivity may be attributable to innovations resulting from research and development (R&D). The next problem is understanding the process by which the impact of R&D operates within the economy. Without this understanding, it is difficult to determine where to focus new investments.
- It is difficult to develop a hypothesis about the role of R&D within the economy because the relationship between scientific inputs and production-related outputs is nonlinear. Outputs are not linked to inputs or infrastructure investments in a systematic way. The unit of analysis is unclear (e.g., individual scientists, group of scientists, scientific fields or subfields). Measures of input are also unclear and highly dependent on organizational systems (e.g., social science versus basic science). A very complex set of scientific, economic, and social outcome measures is required. In addition, bias in the selection of inputs is an issue, and randomization is usually not an option.
- There is no consistent empirical data infrastructure among science-funding agencies. Agencies keep track of research grant awards, whereas individuals and clusters of individuals are the more appropriate unit for measuring impact of innovation. Agencies collect information only for the duration of a grant, whereas the impact of the scientific inquiry initiated through a grant extends well beyond that period. Data are not captured on people who do not receive funding, so it is difficult to establish counterfactual comparisons needed for causal effect evaluation.
- The types of outcomes of interest are heterogeneous and often lag behind investments. There are also technical issues in attribution of scientific activities due to a lack of unique research identifiers across agencies or publications, which impedes efforts to identify scientific outputs associated with individuals.
- In 2008, the Science of Science Policy (SoSP) Federal Research Roadmap initiative was developed in response to calls for a new “science of science policy” to address the need for better tools, methods, and data for evaluating the efficacy and impact of policy decisions guiding science and technology. An interagency group developed two key findings: (1) although many federal agencies have their own communities of practice, the collection of data about the science and scientific communities they support is heterogeneous and unsystematic; and (2) the existing data infrastructure is inadequate for decision making.

- One step being taken to address the theoretical and empirical basis for science and innovation policy is the interdisciplinary Science of Science and Innovation Policy (SciSIP) program supported by the NSF. Its goals are to develop useful theories, improve measurement, and cultivate a community of practice focusing on these issues. SciSIP is actively collaborating with SoSP.
- SciSIP supports: (1) qualitative research to identify processes and develop hypotheses that describe the theoretical and empirical basis of science and innovation policy; and (2) quantitative research to build new linked data sets (e.g., on researchers, grants, patents, publications, research firms, and other variables), develop new tools for describing complex outcomes, and develop new models to discover marginal impacts of funding. The program is also exploring new computational approaches to help manage the vast amount of data being generated through research.
- The Science and Technology in America's Reinvestment (STAR) project, a joint effort supported by NIH and NSF, is building a data infrastructure to measure the effects of American Recovery and Reinvestment Act (ARRA) science-related spending on innovation and competitiveness. Phase I focuses on the impact of ARRA science funding on job development, while Phase II is designed to address measures of impact of that funding on economic growth, workforce outcomes, scientific knowledge, and social outcomes.
- Phase I of STAR is based on the approach used by the Census Bureau's LEHD program. Administrative data from universities and other research organizations are used to track the numbers and proportions of individuals whose work is supported by ARRA science funding. Data are also associated with specific vendors and subcontractors. The program works with 14 existing administrative data elements and produces minimal burdens on research organizations.
- Phase II of STAR will work on developing systems for linking inputs and outputs using automated approaches and leveraging existing data. It involves collaborative development of data infrastructure on broad impact categories such as knowledge, economics, the workforce, and social factors. This infrastructure will enable examination of how knowledge spreads over time from initial funding through subsequent research network collaborations and commercial activities.

## **DR. DONALD A. BERRY:**

### **ADAPTIVE CLINICAL TRIALS: FOCUS ON I-SPY 2**

#### **Background**

Dr. Donald Berry holds the Frank T. McGraw Memorial Chair for Cancer Research at The University of Texas MD Anderson Cancer Center, where he is Head of the Division of Quantitative Sciences and Chairman of the Department of Biostatistics. He serves as a faculty statistician on the Breast Cancer Committee of the Cancer and Leukemia Group B (CALGB), a national oncology group. In this role he has designed and supervised the conduct of many large U.S. intergroup trials. Through Berry Consultants, LLC, he has consulted with many pharmaceutical and medical device companies on clinical trial design and analysis issues. He is well known as a developer of Bayesian adaptive designs that minimize sample size while increasing the likelihood of detecting drug activity, efficiently using information that accrues over the course of the trial.

#### **Key Points**

- Seventy percent of Phase III clinical trials fail, resulting in a tremendous waste of resources and an unwise use of patient populations. Improved utilization of adaptive and Bayesian methods could help resolve the issues of low success rates and high expenses of Phase III clinical trials.
- Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research, has been instrumental in the last several years in developing the Critical Path Institute, which provides

guidance for the biotechnology, pharmaceutical, and medical product industry in developing adaptive clinical trial designs.

- There are many examples of current use of Bayesian adaptive trial designs. Over an 11-year period at MD Anderson, more than 300 trials have adopted this innovative approach. Device companies have actively been promoting adaptive Bayesian approaches and over 25 premarket approvals have been approved on the basis of the approach. Drug companies, including most of the top 40, and many biotechnology firms are adopting Bayesian adaptive trial design at varying levels. Bayesian adaptive drug trials are being conducted in disease areas such as oncology, migraine, diabetes, HIV, overactive bladder, and Parkinson's disease, among many others.
- The Bayesian model of clinical trials builds in performance metrics to measure how patients are doing over time and trials can be adapted based on observed responses. Common trial adaptations are stopping early or continuing beyond the original plan when no answer has been uncovered. Bayesian trial adaptations also include dose adjustment, seamless phases (Phase I/II or Phase II/III trials), population finding, adaptive randomization, and ramping up accrual. MD Anderson often conducts Phase I/II trials in which maximum tolerated dose and efficacy as a function of the dose are identified in the same study.
- Usually, adaptive clinical trials are smaller than standard clinical trials, often by as much as 30 percent. However, in some cases, when trial accrual needs to be extended, adaptive trials are larger. Adaptive trials always result in more accurate conclusions. Researchers conducting adaptive trials can focus on better treatment of patients in trials—patients may receive treatments more quickly with a higher probability of success.
- An example of an adaptive Phase II/III trial was developed for the 2010 Institute of Medicine report *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*. Two agents, possibly from different pharmaceutical companies, are used as single agents and also as a combination in comparison with a control arm. Interim analyses of each of the four arms are conducted early and often to drop arms as needed and potentially stop the trial. Adaptive randomization occurs for the appropriate arms, and eventually the trial goes into a confirmatory stage with the best performer.
- Another example is an adaptive biomarker study that tests a single experimental therapy in comparison with a control among patients with different biomarker profiles. Interim analyses are conducted early and often so that patients with biomarker profiles that are associated with lack of response to the therapy can be removed from the trial. Characterizing patients most likely to respond in early-phase trials facilitates the conduct of smaller Phase III trials because the effects of the treatment will not be diluted by lack of response in a large proportion of patients. Additionally, patients are saved from being exposed to a treatment that will not benefit them.
- In building Bayesian adaptive design trials, simulations are usually required to determine operating characteristics, such as error rate, power, and sample size distribution. The design is prospective and is modified automatically based on what is happening in the patient population.
- It is possible to limit sample size when using biomarkers to inform adaptive trials. This is exemplified by the nonadaptive, CALGB-sponsored trial of taxol for adjuvant treatment of breast cancer. Taxol was given to patients based on HER2 and ER status. Most early breast cancer is HER2-negative and ER-positive, but over half of the patients on the trial with this status did not respond to Taxol. However, the three other patient subsets (HER2-/ER-, HER2+/ER-, HER2+/ER+) showed a statistically significant benefit from Taxol with small sample size. Had the non-responsive subset of patients been removed, as they could have been under an adaptive trial design, three trials could have been conducted, each showing statistical significance with as few as 200 patients.
- The I-SPY 2 trial is a clinical trial for women with newly diagnosed, locally advanced breast cancer to test whether the addition of investigational drugs to standard chemotherapy prior to surgery

influences outcomes. This trial uses genetic profiles to highlight biomarker differences among patients and to match drugs to patients with biomarkers that predict a benefit. The trial started with five experimental arms along with a standard therapy arm as a control. Randomization is adaptive within biomarker subsets of the disease. Arms are replaced as they graduate from the trial to Phase III, or are dropped for futility.

- The goal of Bayesian adaptive Phase II trials is to conduct much smaller Phase III trials and to focus in Phase III on patients who respond to the therapy. Adaptive randomization enables more rapid learning about which drugs benefit which patients, thus shortening the timeline of drug development and avoiding wasting resources on drugs that perform poorly.

## **DR. HAROLD VARMUS:**

### **NCI UPDATE**

#### **Background**

Harold Varmus, co-recipient of the Nobel Prize for studies of the genetic basis of cancer, became Director of the National Cancer Institute on July 12, 2010, after 10 years as President of Memorial Sloan-Kettering Cancer Center, which followed six years as Director of the National Institutes of Health. He is a member of the U.S. National Academy of Sciences and the Institute of Medicine and has received the National Medal of Science. The author of over 350 scientific papers and five books, including a recent memoir, he served as a co-chair of President Obama's Council of Advisors on Science and Technology, was a co-founder and Chairman of the Board of the Public Library of Science, chaired the Scientific Board of the Gates Foundation Grand Challenges in Global Health, and is involved in initiatives to promote science in developing countries, including the Global Science Corps.

#### **Key Points**

- Because cancer is a heterogeneous disease, NCI works across a broad range of disciplines (from engineering and computational sciences to clinical and behavioral sciences) to improve the ability to prevent, diagnose, classify, and treat a wide range of cancers.
- NCI is also working in a variety of arenas, including discoveries in basic science, efforts to understand and translate those discoveries, and development of a broad range of applications to address ongoing goals of improving cancer diagnosis, treatment, and prevention.
- To accomplish these goals, NCI must build, maintain, and expand an infrastructure of buildings, resources, and processes that support both intramural and extramural research. The Institute must also sustain training programs for young investigators and collaborative enterprises such as cancer centers. NCI is addressing these responsibilities in a time of diminishing resources. There is a real possibility that the government will be required to operate under a continuing resolution for the whole current fiscal year.
- While the Institute can prescribe a number of initiatives, intellectual growth is sustained by unanticipated ideas brought forth by investigators who have been trained to be inquisitive scientists. Increasing the research productivity of NCI-trained scientists is becoming more difficult. The number of grants funded this year is likely to be significantly less than in the previous year.
- One way to measure NCI's success is to examine cancer statistics. NCI research has contributed to falling incidence and mortality rates through therapeutic advances and prevention strategies. New screening methods (e.g., the helical CT scan) provide a means of reducing mortality in targeted patient groups. New interventions using new information about the genetics of cancer are being built on the foundation of conventional platforms. However, the increasing incidence of some diseases, such as non-Hodgkin lymphoma and melanoma, is of great concern.

- Other contributions that are not reflected in incidence and mortality statistics involve the experiences of individual cancer patients. Advances in symptom control are reducing the burden of cancer and its treatment and are improving quality of life for cancer survivors.
- Another way to measure success is to compare what is known about cancer now with the knowledge base 40 years ago. The transformation has been revolutionary. A vast amount of information has been generated about causative elements in cancer and mechanisms that drive the behavior of cancer cells; in addition, knowledge is growing about interactions between cancer cells and the environment and about immune responses to cancer.
- One theme that dominates modern cancer research is the previously mentioned heterogeneous nature of cancer. Years ago, scientists could only acknowledge that cancer originates in different organs and that different cancers can be distinguished histologically. Newer methods for classifying cancers inform development of targeted preventive, therapeutic, and monitoring strategies.
- Three NCI areas of activity are informed by this change in the way cancer is categorized. The first is the genomics approach to cancer studies. The Cancer Genome Atlas (TCGA) project is cataloging genetic and epigenetic changes that occur in a wide variety of cancers. Recent reductions in the cost of platform technologies for sequencing are expanding the ability to make unanticipated advances in this area. Increased availability of biospecimens is also driving the speed of discovery. Advances in cancer genomics not only elucidate processes by which cancer arises, but also help us understand the vulnerabilities of cancer cells and new ways to intervene in the process. TCGA and similar projects provide excellent examples of NCI-supported collaboration across the country.
- The second area of activity is in the application domain. All advances in therapeutics or prevention must be subjected to evaluation in high-quality clinical trials. NCI is aware that the current system for managing trials, especially therapeutic trials, is not optimal. A recent Institute of Medicine report has amplified those concerns. NCI has been focusing on ways to speed up the clinical trials process to swiftly approve trials, accrue patients in a timely manner, and terminate underperforming trials as early as possible. Clinical trial Cooperative Groups are being realigned to make them more efficient and make better use of multi-drug trials. NCI is working with the Food and Drug Administration on new guidelines for trials using combinations of drugs. Stratification for some new drug trials will be based on genetic analyses being conducted by TCGA and other initiatives. Genetic information will not be used simply to test targeted therapies; it will also be employed to help understand why patient response to therapy varies among individuals.
- The third area of activity is encouraging investigators and other stakeholders (e.g., patient advocates) to explore key unanswered questions. Through the new “Provocative Questions” exercise, NCI is empanelling groups of experts to identify novel ways to achieve traditional goals of preventing, diagnosing, and treating cancer. One workshop has been held and three more are planned. These panels will discuss inadequately explored observations from the past that could be investigated with new tools and recent discoveries. Examples of such questions include why testicular cancer can be cured with conventional chemotherapy and why obese people are more prone to certain cancers such as colon and breast cancer.

## **DR. JONATHON N. CUMMINGS:**

### **LESSONS LEARNED FROM NSF’S INFORMATION TECHNOLOGY RESEARCH PROGRAM**

#### **Background**

Dr. Jonathon Cummings is an Associate Professor of Management at the Fuqua School of Business, Duke University. During graduate school he interned at Intel (studying collaborative software) and at Motorola (studying knowledge management). After completing his dissertation and postdoctoral fellowship at

Carnegie Mellon University, he spent three years at the MIT Sloan School of Management as an Assistant Professor, where he received a National Science Foundation (NSF) Early Career Award for his research on innovation in geographically dispersed teams and networks. His subsequent research focused on virtual teams in corporations as well as collaboration in science, and his publications have appeared in journals ranging from *Management Science* to *Research Policy* to *MIS Quarterly*. He is also faculty director for the Center for Technology, Entertainment, and Media at Fuqua, where he is initiating new research on technological disruption in knowledge-based firms.

## Key Points

- The NSF Information Technology Research (ITR) program was created to advance interdisciplinary technology research. The program was funded at \$90 million in 2000 and grew to almost \$300 million in funding in 2004. A typical project was funded for three to five years (at \$500,000 to \$1 million per year), had five principal investigators (PIs), and represented two or more disciplines and two or more universities.
- ITR projects focus on interdisciplinary research at the intersection of computer and information sciences and other disciplines. Three examples illustrate the broad scope of ITR projects. “Project ZebraNet” studied the use of IT for remote tracking of wildlife over large distances by biologists. This project involved computer scientists, electrical engineers, and biologists. The “Simulation-Based Medical Planning for Cardiovascular Disease” project carried out by Stanford University, constructed computational models for physicians to predict differential changes in blood flow. This study involved medical researchers, but also required IT, computer science, engineering, and data collection expertise. The final example, “Integrating Smart Sensing, Data Mining, Pervasive Networking, and Community Computing,” developed tools for security personnel to monitor and respond to disasters or disease outbreaks. Tracking such events requires the intersection of a broad number of disciplines.
- A study of scientific collaboration within the ITR program was conducted. The study evaluated 491 out of 549 funded projects in the ITR program. Interviews were conducted and observational data were collected from 2-day ITR PI meetings. The interviews were followed up with a large-scale survey; 885 surveys were completed by PIs across the ITR program, for a response rate of about 70 percent.
- One of the striking findings from the surveys was the impact that working across disciplines and universities has on the ability of PIs to coordinate with one another. Having a larger number of universities involved with a project, on average, predicted fewer outcomes, such as fewer knowledge outcomes (e.g., publications, patents), fewer tools (e.g., software, hardware), fewer students trained and placed in new jobs, and less leverage for future research (e.g., new grants). Additionally, having multiple disciplines involved at multiple universities produced even fewer outcomes. Teams that spanned multiple institutions were also less likely to engage in coordination activities, such as utilizing project managers and holding conferences to facilitate interaction.
- Though projects with a greater number of disciplines were also likely to involve a greater number of universities, there was no direct relationship between number of disciplines represented and outcomes; rather, problems arose from working across universities. Interdisciplinary research often became multiuniversity research when specialized expertise needed for a project was not available locally.
- A network analysis was conducted on pairs of ITR PIs. Roughly one-third of the pairs of researchers on the same project never worked directly with each other. About 40 percent of ITR pairs worked together, but did not publish together. The remaining pairs worked together and published together. The analysis also revealed that if the PIs did not interact with each other prior to initiation of the ITR project, the chances were small that they would work and publish together within the context of the ITR project. Funding agencies and research managers often fail to appreciate that funding everybody together does not mean that all of the PIs actually publish and work together on a daily basis.

- The dominant factor that predicted ITR PIs' working together was whether the researchers had worked together before. Lack of prior collaboration should be a red flag for funding agencies if they receive a large multiuniversity, interdisciplinary proposal.
- Interdisciplinary and multiuniversity research significantly influenced the coordination costs for investigators, especially around research management. Reviewing ITR project budgets revealed that when PIs were given 70 to 80 percent of their requested budgets, the first items eliminated were those in support of coordination and knowledge transfer activities, such as support of postdoctoral fellows, project managers, seminars, and workshops.
- These data analyses suggest that if resources are constrained, review bodies should pay particular attention to the number of universities and disciplines included on a proposal; however, in reality, reviewers usually only consider the quality of the study idea.
- Funding agencies should encourage more collaboration across disciplines within universities, exploiting in-house expertise. They should also make the PIs' track records with interdisciplinary collaborators an explicit standard, especially for collaborations across universities. Another suggestion for funding agencies to consider is giving multidisciplinary projects small grants to explore collaborations and overcome institutional barriers. Additionally, agencies could grant enough individual awards to interdisciplinary investigators so that PIs do not collaborate just to receive funding.

**DR. DANIEL SAREWITZ:**

## **INNOVATION, INSTITUTIONS, AND THE ADVANCE OF KNOW-HOW: IMPLICATIONS FOR RESEARCH POLICY**

### **Background**

Dr. Daniel Sarewitz is Professor of Science and Society, as well as co-director and co-founder of the Consortium for Science, Policy, and Outcomes (CSPO), at Arizona State University. His work focuses on revealing and improving the connections between science policy decisions, research and innovation, and beneficial social outcomes. He lives and works in Washington, D.C., where he focuses his efforts on a range of activities to increase CSPO's impact on science and technology policy at the national level. He is a columnist for *Nature*, and his new book, *The Techno-Human Condition* (co-authored with Braden Allenby), will be published by MIT Press in March 2011.

### **Key Points**

- The presenter defined "innovation" as technological advances that improve the capacity to solve problems. His comments were drawn from several decades of scholarship in numerous disciplines (including economics, history, sociology, and anthropology) concerning technological change and its application to problem solving.
- Early-stage technologies and emerging capabilities often precede deep scientific understanding of how they work. Innovation raises new questions and opens new fields of inquiry. The invention of steam engines, for example, stimulated the growth of studies of thermodynamics. Similarly, the first demonstration of human flight stimulated interest in aerodynamics. These and other examples of the backward connection between technology development and science reverses the more commonly understood progression from basic research to practical applications of knowledge.
- Scientific knowledge makes its greatest contribution to innovation when inquiry is disciplined by problem-solving capabilities embodied in existing technologies. These capabilities focus inquiry on scientific questions that are potentially relevant to further advancing technology and improving problem-solving performance.

- This approach to understanding innovation is not a question of basic versus applied research. It is an investigation of where scientific questions come from and how inquiry in areas suggested by experience can rapidly improve the capability to solve problems.
- Improving the capability to achieve desired outcomes depends on the prior existence of an effective core of practice. Without this type of groundwork, decisions about research priorities and pathways are difficult to make. Cores of practice, which often develop without much scientific evidence for why they work, provide a performance baseline against which improvements based on scientific inquiry can be measured. They provide a focal point for effort and investment. Thus, innovation is usually an incremental process. Often, what appears to be a dramatic breakthrough has a long history of incremental development.
- Another reason that incremental progress is the norm is that paths of innovation are strongly tied to particular technological, social, organizational, and cultural processes that make it difficult to stray from the path once it has been initiated. An example is the difficulty of finding a way to reduce dependence on fossil fuels as an energy source. Nevertheless, significant “breakthroughs” can result from the gradual convergence of incremental changes in various arenas. The eradication of smallpox was accomplished in a seemingly short time span, but it depended on gradual improvements in vaccine production, needle design, expanded surveillance, and technological advances, many of which came from outside the medical research field.
- The capability for innovation is strongly tied to institutional arrangements. In the case of health care, a complex system encompasses the scientific community, the technology market, service providers, and patients. Advances made in one area produce feedback and “feed forward” among all the components in the system. Persistent and rapid innovation depends on the quality of the links and pathways among system components. Formal knowledge gained through research is a crucial element of this system but its contribution to innovation depends on its links with other elements. The term “translational research” fails to accurately characterize this process because it suggests that progress is made in only one direction, whereas feedback loops are the key to maintaining innovation. The strengths of linkages with innovation systems may be more important than funding levels.
- Collaboration between the public and private sectors is an important element in any innovation system. The value of long-term relationships between public and private institutions is exemplified by NIH and Department of Defense collaborations with their grantees and contractors.
- In terms of policy, when gains in addressing particular problems are needed, a focus on leveraging existing know-how through appropriate research activities is the most likely path to short- and medium-term progress. This approach helps identify areas of inadequate understanding where research advances are likely to have a very productive impact and encourages the development of synergies between innovation and practice.
- When there is no existing core practice to address a problem, the only alternative is to support relatively undirected fundamental research. Policy makers need to understand that this type of research has a high risk of failing to deliver the public benefit that motivated the investment. They should also understand that scientific innovation is measured by standards that evaluate productivity and impact, but these standards are not the type of measures that can be associated with contributions to improved health outcomes.

## DISCUSSION AND CONCLUDING COMMENTS:

### PANEL II

#### Key Points

- There will be a Web site devoted to the Provocative Questions exercise described by Dr. Varmus. Among other things, the site will allow viewers to comment on existing Provocative Questions and suggest new ones. Dr. Varmus has also discussed the Provocative Questions with a number of advocacy groups and has received input from them on this topic.
- “Innovation” is one of the most overused terms in biomedical research. In the eye of the researcher proposing the project, every idea is innovative. It is relatively easy for experienced researchers to point to findings that have changed a field; however, it is more difficult to do this prospectively. The academic research community should focus on evaluating the novelty of researchers’ ideas rather than evaluating the number of papers they have published.
- There is great interest in research that would improve prevention or early detection of pancreatic cancer or lead to increased understanding of the causes of this disease. It has been known for 25 years that there are mutations in the *KRAS* gene in most cases of exocrine cancer of the pancreas, but this knowledge has not led to any measureable clinical progress. Research on pancreatic cancer is challenging in part because it is difficult to get primary pancreatic tissue sufficiently free of surrounding tissue for analysis; however, NCI and others, including private foundations, have been investing in this area. Two papers on this topic were recently published in *Nature*.
- Innovative research would be encouraged if academic promotion and tenure committees modified their review and decision processes. Rather than look at full-length curriculum vitae, these committees should ask investigators to write short biosketches that outline their contributions to their fields and list their five most important publications. NCI and NIH should also make changes in how they ask investigators to describe their careers, but it is often more difficult for federal agencies to promote change than to have it spearheaded by leadership within academic institutions.
- In response to the statement that NCI receives many interesting grant applications that cannot be funded because of limited resources, it was suggested that NCI conduct an experiment of sorts and randomly select grants for funding. Dr. Varmus responded that NCI has a responsibility to evaluate all applications and use defined criteria to determine which should be funded.
- The proportion of cancer clinical trials using adaptive designs is very small; most are being conducted at MD Anderson. There are some additional trials that conduct interim analyses, but this is not particularly innovative. One of the reasons that adaptive designs are used so infrequently is that most universities do not have the expertise in Bayesian statistics necessary to design these trials. In addition, IRBs at most institutions are not accustomed to reviewing these types of trials.
- Research into the efficiency of adaptive trial designs is being done. Some of these efforts are assessing how past clinical trials would have been different if adaptive designs had been used. NCI and many patient advocate organizations are interested in this type of research.
- The problems associated with interinstitutional collaborations are somewhat surprising and particularly interesting in light of recent trends toward large, multi-institutional scientific initiatives. These shortcomings do not mean that interinstitutional teams should not be funded, but it is important that resources also be devoted to projects with a higher likelihood of success. Multi-institutional studies should have budgets devoted to travel, workshops, and communication efforts and priority should be given to teams that have successfully worked together in the past. It was also noted that multi-institutional collaborations built on interactions between two or three investigators are more likely to succeed than those consisting of large numbers of investigators who plan to work together as a single group.

- Funding agencies should be encouraged to collect and make available data regarding their investments. Agencies can use these data to determine which types of incentive structures and collaborative arrangements are most effective. Organizations should also analyze their programs so that they do not devote too many of their resources to large, collaborative projects when a larger number of small projects could potentially have a greater impact. The analysis of the NSF ITR program did identify some shortcomings but it has allowed the agency to alter proposal requirements so that investigators are required to more carefully articulate how they will work together, which may facilitate long-term improvements.
- The most successful collaborations are usually those that investigators initiate themselves, not those mandated by funding agencies. Funding agencies should offer incentives but should also try to make sure that researchers are coming together because they want to work together, not because they simply want to gain access to funding.
- Advances in know-how are often, but not always, predicated on facilitating technologies. These may be new technologies based on formal scientific inquiry, although it is also possible to improve know-how by applying existing technology in a new context. Existing technologies can come to be applied in new fields through a variety of routes. In some cases, this occurs because people from different fields are communicating with each other. At other times, a person serendipitously learns of a technology and imports it into a new domain. Private firms are sometimes responsible for identifying new applications of existing technologies because they want to expand their markets.
- It is known that a significant number of cancer patients are overtreated; however, it is difficult to identify these patients with enough certainty to withhold treatment. More research is needed in this area.
- The current funding structure does not promote innovation because researchers tailor their proposals to fit the mold of what they know has a higher likelihood of getting funded, which is incremental science. It is important to experiment with the ways that research is done.
- NIH should require communication and interaction within teams of investigators. Oversight mechanisms should also be in place to ensure these connections are maintained over time, as these projects often take several years to produce tangible results.

## **PUBLIC COMMENT**

- There were no comments from the public.

## **CLOSING REMARKS—DR. LASALLE D. LEFFALL**

- Dr. Leffall thanked everyone in the audience for attending the meeting and thanked the speakers for their insightful presentations.

## **CERTIFICATION OF MEETING SUMMARY**

I certify that this summary of the President's Cancer Panel meeting, *The Future of Cancer Research: Accelerating Scientific Innovation*, held December 14, 2010, is accurate and complete.

Certified by: \_\_\_\_\_ Date: March 18, 2011

LaSalle D. Leffall, Jr., M.D.  
Chair  
President's Cancer Panel