DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
4TH JOINT MEETING OF THE BOARD OF SCIENTIFIC ADVISORS AND THE NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 2, 2014

Building 31C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
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The Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) convened for the 4th Joint Meeting on 2 December 2014, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 2 December 2014, from 8:30 a.m. to 12:30 p.m. and 1:15 p.m. to 4:55 p.m., and closed to the public from 12:30 p.m. to 1:15 p.m. The BSA Chair, Todd R. Golub, Chief Scientific Officer, The Broad Institute of Harvard University and Massachusetts Institute of Technology, and the NCAB Chair, Tyler Jacks, Director, Koch Institute for Integrative Cancer Research, David H. Koch Professor of Biology, Massachusetts Institute of Technology, presided during the open session. Dr. Jacks presided during the closed session.

BSA Members
Dr. Todd R. Golub (Chair)
Dr. Francis Ali-Osman (absent)
Dr. Kenneth C. Anderson
Dr. Dafna Bar-Sagi
Dr. Ethan M. Basch
Dr. Sangeeta N. Bhatia
Dr. Andrea Califano
Dr. Arul M. Chinnaiyan (absent)
Dr. Curt I. Civin (absent)
Dr. Graham A. Colditz
Dr. Chi V. Dang (absent)
Dr. Joseph M. DeSimone (absent)
Dr. Daniel C. DiMaio
Dr. Brian J. Druker (absent)
Dr. Karen M. Emmons (absent)
Dr. Betty Ferrell (absent)
Dr. Kathleen M. Foley
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Theodore S. Lawrence (absent)
Dr. Maria E. Martinez
Dr. Luis F. Parada
Ms. Diane Zipursky Quale
Dr. Martine F. Roussel (absent)
Dr. Kevin M. Shannon (absent)
Ms. Mary L. Smith
Dr. Lincoln D. Stein
Dr. Bruce W. Stillman
Dr. Gregory L. Verdine (absent)
Dr. Cheryl L. Walker (absent)
Dr. Irving L. Weissman
Dr. Eileen P. White (absent)
Dr. Kevin P. White

NCAB Members
Dr. Tyler E. Jacks (Chair)
Dr. David C. Christiani (absent)
Dr. Marcia R. Cruz-Correa (absent)
Dr. Kevin J. Cullen
Dr. Judy E. Garber
Dr. Elizabeth M. Jaffee
Dr. Beth Y. Karlan (absent)
Dr. Olufunmilayo I. Olopade
Dr. Mack Roach, III
Dr. Jonathan M. Samet
Dr. Charles L. Sawyers (absent)
Dr. William R. Sellers

Alternate *Ex Officio* NCAB Members
Dr. Robert T. Anderson, DOE
Dr. Michael A. Babich, CPSC
Dr. Vince Cogliano, EPA
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA
Dr. Craig D. Shriver, DOD (absent)
Dr. Kerry Souza, NIOSH (absent)
Dr. Michael Stebbins, OSTP
Dr. Richard J. Thomas, OSHA/DOL
Dr. Lawrence Tabak, NIH (absent)

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Harold Varmus, Director, National Cancer Institute
Dr. Jeff Abrams, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Lynn Austin, Executive Officer, Deputy Director for Management
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Deputy Director for Clinical and Translational Research
Dr. Daniela S. Gerhard, Director, Office of Cancer Genomics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Associate Director for Prevention
Dr. Ed Harlow, Special Assistant for Science Planning
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
Dr. Warren Kibbe, Director, NCI Center for Bioinformatics and Information Technology
Dr. Barry Kramer, Director, Division of Cancer Prevention
Dr. Douglas R. Lowy, Deputy Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis Staudt, Director, Center for Cancer Genomics
Dr. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Director, Center for Global Health
Dr. Margaret A. Tucker, Acting Director, Division of Cancer Epidemiology and Genetics
Mr. Michael Weingarten, Director, Small Business Innovation Research
Dr. Linda Weiss, Director, Office of Cancer Centers
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Carolyn Best, American Urological Association
Ms. Paula Bowen, Kidney Cancer Association
Dr. Susan Braun, National Cancer Institute, Director's Consumer Liaison Group
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Mr. Matthew Farber, Association of Community Cancer Centers
Dr. Margaret Foti, American Association for Cancer Research
Dr. Francis Giardiello, American Gastroenterological Association
Dr. Mary Gullatte, Oncology Nursing Society
Ms. Shandi E. Hill, American Society of Therapeutic Radiology and Oncology
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Gerald F. Joseph, Jr. American College of Obstetricians and Gynecologists
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Steven Klein, National Science Foundation
Ms. Laura Levit, American Society of Clinical Oncology
Dr. W. Marston Linehan, Society of Urologic Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Dr. Patricia Mullan, American Association for Cancer Education
Ms. Christy Schmidt, American Cancer Society

Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Johannes Vieweg, American Urological Association
Ms. Pamela Wilcox, American College of Radiology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, DECEMBER 2, 2014

I. CALL TO ORDER AND OPENING REMARKS—DRS. TODD R. GOLUB AND TYLER JACKS

Dr. Jacks called to order the 4th Joint BSA and NCAB meeting and welcomed members of the Board, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Jacks reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to approve the minutes of the 9 September 2014 NCAB meeting was approved unanimously.

II. FUTURE BOARD MEETING DATES—DRS. TODD R. GOLUB AND TYLER JACKS

Dr. Jacks called Board members' attention to future meeting dates.

III. NCI DIRECTOR'S REPORT—DR. HAROLD E. VARMUS

Dr. Harold E. Varmus, Director, NCI, welcomed members of the NCAB and BSA to the fourth joint meeting of the Boards. Dr. Varmus introduced new BSA members: Dr. Joseph M. DeSimone, University of North Carolina at Chapel Hill; Ms. Diane Zipursky Quale, Bladder Cancer Advocacy Network; Dr. Eileen P. White, Rutgers Cancer Institute of New Jersey; and, Dr. Kevin P. White, The University of Chicago. Dr. Varmus reviewed the agenda and remarked on the theme of cancer prevention for the meeting.

Personnel: Members were informed of various personnel actions, i.e., the upcoming departure of Dr. Linda Weiss, Director, Cancer Centers Program, and recent hiring of Dr. Lynn Austin, Executive Officer, and Deputy Director for Management. Dr. Varmus lauded Drs. Douglas R. Lowy, Deputy Director, and John Schiller, Senior Investigator, Center for Cancer Research (CCR), recipients of the National Medal of Technology and Innovation. Members were informed that President Barack Obama bestowed the award to Drs. Lowy and Schiller with praise for their 30-year-long collaborative effort to develop a technology that led to a vaccine to prevent the cancer-causing human papillomavirus (HPV). A video about the technology was also shown.

Dr. Varmus informed members of President Obama's planned visit to campus in the afternoon and showed film segments of President Franklin D. Roosevelt's visit to the NIH campus in 1937, the year that he signed the National Cancer Act and established the NCI. Speech excerpts during President Roosevelt's visit concerning infectious diseases, a topic that President Obama would be addressing, were also shown.

Grants: Dr. Varmus discussed the NCI grant success rates. He noted that the success rates are comparable and members were referred to the NCI website, where score profiles are posted from previous years. He informed members that the overall success rates are approximately 13 to 14 percent, and grants continue to be funded at a 90 percent level while the Continuing Resolution (CR) is in effect through 11 December. Dr. Varmus also noted that 221 applications had been received for the new Outstanding Investigator Award (OIA), and encouraged members to volunteer to serve on the review panel. He stated that NCI expects to fund approximately 50 OIA awards.

Congressional News of Interest: Dr. Varmus reflected on changes in Congress due to elections in November 2014. He stated that: 1) Rep. Hal Rogers (R-KY) will remain as the Chair of the House Appropriations Committee; 2) Sen. Thad Cochran (R-MS) will be the new Chair of the Senate Appropriations Committee; 3) Rep. Tom Cole (R-OK) will chair the Labor-Health Subcommittee in the House; and, 4) Senate leadership is to be determined. Members were told that Rep. Fred Upton (R-MI) will remain as the Chair of the House Energy and Commerce Committee, and Sen. Lamar Alexander (R-TN) likely will be the Chair of the Senate Health, Education, Labor, and Pensions (HELP) Committee, with Sen. Patty Murray (D-WA) serving as the minority ranking member.

NCI Bypass Budget Proposal: Members were informed that this year's Bypass Budget and Narrative Report emphasize broad themes and changes in the NCI during the past several years despite budgetary shortages. Dr. Varmus stated that the Report focuses on elements of the NCI's scientific infrastructure, including new grant mechanisms such as the OIA and Provocative Questions (PQ) initiative, the NCI-designated Cancer Centers, clinical trial systems, training mechanisms, the Intramural Research Program (IRP), informatics, and the Frederick National Laboratory for Cancer Research (FNLCR). The Bypass budget also describes advances and new scientific programs in basic science, genomics, clinical trial design, immunotherapies, pediatric cancer, the RAS oncogene, cancer prevention, and cancer health disparities. Dr. Varmus noted even though the Report proposes a 15 percent increase for FY 2016. Such an increase would only partially compensate for the money lost over the past decade because of inflation. He thanked Dr. Lowy and other NCI staff for preparing the Report.

NCI and NIH News of Interest: Dr. Varmus remarked on the NCI's role regarding Ebola, particularly the FNLCR's role in developing reagents for testing and vaccine production for the National Institute of Allergy and Infectious Diseases (NIAID). The Ebola vaccine which will be tested soon was initiated by Dr. Gary Nabel when he was the Director of the Vaccine Research Center (VRC). He noted that President Obama's visit to the NIH campus will include stops at the VRC and Clinical Research Center (CRC).

Dr. Varmus provided updates of several policies. Specifically, 1) a new NIH-wide policy that all NIH grant holders are expected to serve on peer review panels, if asked to do so, 2) that the results of all NCI-supported clinical trials must be communicated to the public either through clinicaltrials.gov or another mechanism; the NIH is working to implement this policy across its Institutes and Centers (ICs). The upcoming Advisory Committee to the NIH Director meeting will address reports on the future direction of the Children's Health Study (CHS), allocation of the Office of AIDS Research's (OAR) monies and topics appropriate for use of AIDS funds, and progress in the evaluation of the NIH IRP.

Precision Medicine: Dr. Varmus stated that precision medicine remains a dominant factor in the NCI, and reviewed relevant NCI trials focused on applying genomic data to facilitate focused therapeutic interventions. Those trials were: 1) Molecular Profiling-based Assignment of Cancer Therapeutics (M-PACT), 2) Lung Cancer Master Protocol (Lung MAP), 3) Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST), and 4) NCI Molecular Analysis for Therapy Choice Program (NCI-MATCH) trials, which are conducted under the National Clinical Trials Network (NCTN).

He stated that he had spoken at a White House event on the topic of pediatric cancer and precision medicine, and that Dr. Francis Collins, NIH Director, had attended a Congressional caucus on pediatric cancer. Additional meetings have been held with activists from the pediatric advocacy community to discuss activities underway to make better use of the genomic data ensuing from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Program; these include a workshop involving pediatric cancer genomicists and clinical trialists, and a pediatric MATCH trial that is scheduled for launch in early 2015.

Members were told the informatics has a role in precision medicine, and the NCI awarded three genomic cloud pilot contracts and launched the Genome Data Commons. Investigators are discussing how biocomputing and the new proposed informatics infrastructure could be used to explore cancer genomes and to integrate cancer genomic information into a large database. Dr. Varmus also noted the role of cancer immunotherapy in precision medicine as researchers have begun to look at the genomic profile of cancers that have responded to immunotherapy, including melanomas, kidney, bladder, and lung cancers.

FNLCR: Members were told that the NCI continues to consider new projects to conduct at the FNLCR and plans to evaluate a proposal to create a Center for cryo-electron microscopy (EM), a form of imaging that has experienced dramatic successes recently in achieving close to 3-Angstrom resolution. A workshop is planned to discuss the Center and its role in training and collaboration with extramural scientists.

NCI's Commitment to Clinical Trials: Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, referred members to a Letter to the Editor published in the Journal of Clinical Oncology from Drs. Varmus, Doroshow, and other NCI leaders clarifying that the reorganization of the NCI clinical trials system would better facilitate patient screening and the conduct of precision medicine trials, and in no way should be construed to be a lack of strong support and appreciation for the activities of the National Clinical Trials Network (NCTN).

Questions and Answers

In response to a query by Dr. Golub about the scope of NCI's approach to precision medicine and the relevance of a more focused approach to study a few cancers in more detail, Dr. Varmus noted the challenges of funding as the cost of research has gone up at a rate that exceeds the biomedical research price index, and as science increases in complexity, there is similarly dependence on expensive technologies. He reflected on the NCI's ability in recent years to reallocate funds to create important programs focused on genomics, global health, provocative questions, and the RAS initiative.

Dr. Olufunmilayo F. Olopade, Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, and Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine, commented on the opportunities for investment and intervention in areas of the country, such as the South, where populations are dense and cancer prevalence is high but fewer NCI-designated Cancer Centers are located. Dr. Varmus responded that the importance and productivity of the Cancer Centers Program represents one of the best partnerships between the NCI and extramural community and agreed that the Centers greatly benefit patients. He added that Centers must have the research capacity to become an NCI-designated Cancer Center, and acknowledged that cancer patients in the Midwest and Rocky Mountain states may not be close to an NCI designated cancer center and thus must travel a long distance to reach a Cancer Center. He reminded members that even though several Cancer Centers have attained NCI designation during the past decade, the overall Cancer Center budget has not increased.

IV. CANCER GENOMICS—DR. LOUIS M. STAUDT

Dr. Staudt provided an overview of a systematic, genome-wide approach to defining the molecular basis of malignancy to identify curative strategies for cancer by interrogating the functionally important pathways in the cell that maintain the malignant phenotype. The field of cancer genomics traditionally was divisible into three broad areas: structural genomics; functional genomics; and computational genomics, integrating knowledge from structural and functional genomics. The goal of the integrative analysis of the cancer genomic program has been to determine the essential cancer pathways, and improving patient outcomes is at the center of the need to better understand which aspects of the

tumor genome and cancer cell function make a difference in treatment response. Instead of thinking of cancer as a genetic disease, Dr. Staudt suggested that cancer could be considered a cell biological disease that is driven by abnormal pathways. Cancer also now is known to be an organismal disease in which cellular interactions and the stromal microenvironment are key, and can be thought of as a societal disease.

There are three main initiatives currently at the NCI Center for Cancer Genomics (CCG): The Cancer Genome Atlas (TCGA); the TARGET Program, focusing on pediatric cancers; and the Cancer Target Discovery and Development (CTD2), a functional genomics effort using small molecules, RNAi and other manipulations of cancer cells. The pipeline of the Center has grown significantly from TCGA to include the Biospecimen Core Resource, Genome Characterization Centers, the Genomics Data Commons (GDC), and the Genome Analysis Network. Dr. Staudt indicated that a request for proposals (RfP) on molecular platforms is forthcoming in January 2015, and in mid-2015, another request for applications (RFA) will be released related to re-funding and improving the Genome Analysis Network. Dr. Staudt noted that two "game-changers" in structural genomics have been the ability to do both DNA and RNA sequencing from fixed tissue samples, which increases the number of samples available for genomic discovery, and the dramatically decreased cost of whole genome sequencing.

Future initiatives for the CCG include defining the molecular basis for clinical phenotypes, focusing on completed cooperative group trials in the colon and lung, the ALCHEMIST prospective trial in lung adenocarcinoma, and the Exceptional Responders Initiative; defining the "full" set of genetic drivers in cancer, including pilot projects in colorectal, lung adenocarcinoma, and ovarian cancer; developing next generation cancer models for genomics beyond existing cell lines; and continuing to develop the NCI GDC.

The TCGA Program has been highly successful. As of December 2014, more than 10,000 cases were accrued, resulting in the publication of many papers, including exciting findings on gastric cancer. Dr. Staudt then shared several successful studies funded through the TARGET initiative. For example, researchers were able to identify novel recurrent translocations involving tyrosine kinase genes in B Cell Acute Lymphoblastic Leukemia (B-ALL) patients that could potentially be treated with existing therapeutics. These exciting findings in cancer genomics resulted in a precision medicine clinical trial that will treat patients on the basis of translocation screening results.

Among the open questions in structural genomics is an opportunity to address the molecular basis of cure versus relapse following adjuvant chemotherapy in colorectal and other cancers. Even when adjuvant therapies do not perform statistically better in the overall trial, whole genome or exome sequencing plus transcriptome sequencing can be used to identify molecular predictors of response to treatment, thus informing health care decisions for individual patients. Another opportunity in structural genomics is to identify the complete set of driver mutations in cancer; the idea being to discover all genetic abnormalities that occur at a 2 percent frequency or higher in human cancer. This information, along with an analysis of which mutations co-occur, can help elucidate genetic pathways of oncogenesis. Whole genome sequencing of additional tumors—which can be performed in conjunction with existing clinical trials—also allows for the identification of noncoding driver mutations and cryptic chromosomal translocations.

The putative cancer driver genes identified through structural genomics can be studied further through the development of relevant cancer models using functional genomic strategies. Application of technologies, such as RNAi and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), that inactivate individual genes in a broad fashion can provide knowledge about essential cancer pathways. An emerging opportunity is to develop next generation cancer models that fully mimic the generic diversity of human cancer and avoid limitations of current cell line models (e.g., lack of models

for rare lesions and insufficient information about the relationship between the tumor cell lines and the patients' clinical outcomes). New technologies may allow scientists to readily generate new cancer cell lines or more complicated structures from epithelial cancer biopsies, such as organoid cultures and conditionally reprogrammed cell techniques. Recent results have demonstrated that prostate organoids accurately reflect the histological and genetic characteristics of primary tumors.

Dr. Staudt informed the Board members about the possibility of initiating a next generation cancer model network to develop the models, perform uniform genomic analysis, and deposit the data and cells in publically accessible repositories for broad distribution to cancer researchers. Dr. Staudt referred to the Institute of Medicine's vision of applying computational genomics to create a knowledge network of disease that would integrate data from clinicians and research laboratories to develop a taxonomy of disease that could be propagated through the health care system and support precision medicine. A new generation of the GDC—which already houses TCGA and TARGET data—to foster the molecular diagnosis and treatment of cancer would comprise the following functionality: (1) import and standardize genomic and clinical data from legacy programs; (2) harmonize mapping of sequence data to the genome/transcriptome; (3) implement state-of-the-art methods for derived data of mutation calls, copy number and structural variants, and digital gene expression; (4) maintain data security and manage authorized access; (5) provide data for download or computation; and (6) open GDC for upload of new genomic data for comparison with existing data and shared access. Dr. Staudt emphasized that the sharing of data fosters scientific discoveries that would not otherwise be possible with the resources in individual laboratories.

Questions and Answers

Dr. Luis F. Parada, Chairman, Department of Developmental Biology, University of Texas Southwestern Medical Center, expressed concerns about the complexity and hierarchy of cancer biology and wondered whether genomic advancements were outpacing biologic discoveries. Dr. Staudt described promising organoid technology to recapitulate the hierarchy of human cancer. For example, in genomic studies of colorectal cancer, the stem cell has been found to give rise to its own stroma, differentiating into one supporting cell and the divided cell whereas the differentiation in the normal gut is recapitulated in the organoid cultures.

Dr. Andrea Califano, Director, Columbia Initiative in Systems Biology, Director, Sulzberger Columbia Genome Center, Associate Director, Herbert Irving Comprehensive Cancer Research Center, and Professor of Systems Biology, Department of Biochemistry and Molecular Biophysics, Biomedical Informatics, and Institute of Cancer Genetics, Columbia University Medical Center encouraged the NCI to support an integrated effort by the cancer genomics community to comprehensively chart a full set of mechanistic underpinnings for one particular tumor type. Dr. Staudt acknowledged that better examination of raw data from other projects could be a useful approach. Dr. Olopade suggested that an emphasis on germline genomics could improve cancer prevention research and discoveries. Dr. Staudt noted that data are available but not mined appropriately in TCGA and added that functional analysis could be applied to the germline.

Dr. Irving L. Weissman, Director, Institute of Stem Cell Biology and Regenerative Medicine, Stanford University, recommended that the NCI develop a prospective method for viable frozen cell suspensions to elucidate biology, particularly considering the order of mutations and importance of events. Dr. Staudt responded that such a method could be built into a cancer model network. Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, OHSU Center for Spatial Systems Biomedicine, and Associate Director for Translational Research, Knight Cancer Institute, Oregon Health and Science University, noted that microenvironment opportunities could be

explored through attention to anatomic regions from which tissue is extracted and stored as a formalin-fixed, paraffin-embedded (FFPE) sample.

In response to a query by Dr. Golub regarding why the NCI was the best place to conduct the science, Dr. Staudt said that the NCI provides scientific uniformity, ensures data sharing among investigators, and makes use of the resources in the CRC. Dr. Jacks agreed that the NCI provides coordination, funding, and leadership, and he encouraged the NCI to further engage in dialogue with patients about the need and use of the data in the scientific and medical community.

Dr. Bruce W. Stillman, President and Chief Executive Officer, Cold Spring Harbor Laboratory, described challenges faced by patients with a single disease when they are asked to participate in trials and must complete multiple consent forms. He recommended that the NCI assume a leadership role in developing a uniform patient consent form that covers genomic research and is accepted by Institutional Review Boards (IRBs) across the Nation. He also observed that the clinical application of genomic data lags behind research.

Dr. Lincoln D. Stein, Director, Informatics and BioComputing Platform, Ontario Institute for Cancer Research, asked about efforts to align GDC with international efforts. Dr. Staudt indicated interest and noted that a common consent form could overcome challenges posed by the different models for data sharing used by the GDC and the International Cancer Genome Consortium (ICGC).

V. UPDATE: ELECTRONIC CIGARETTES—DRS. ROBERT T. CROYLE AND MICHELE BLOCH

Dr. Robert T. Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), introduced the update report on electronic cigarettes (e-cigarettes). Dr. Croyle reminded members that the February 2014 NCAB meeting had a special session on tobacco control and covered thematic issues including smoking cessation, clinical implementation, and global health. He stated that research on e-cigarettes represents an example of the NCI's work with many other agencies and institutions supporting public health. Members were informed that the NCI, National Institute on Drug Abuse (NIDA), and National Institute on Alcohol Abuse and Alcoholism (NIAAA) are launching an adolescent cohort study that incorporates neuroimaging to examine the impact of early exposure of drug use, including tobacco use, on adolescent brain development. In addition, recent data released from the National Health Interview Survey (NHIS) on current adult tobacco use in the United States show a slight reduction in prevalence of smoking among adults; the report also identifies significant disparities in prevalence based on education levels and other factors. Dr. Croyle also mentioned collaborative tobacco control-related efforts with officials in China, a country that produces one-third of all cigarettes in the world. He next introduced Dr. Michele Bloch, Chief, Tobacco Control Research Branch, DCCPS.

Dr. Bloch reminded members that an electronic cigarette contains a cartridge, atomizer, battery, and LED light; is available in numerous forms; and includes disposable, rechargeable, pen- and tank-style. E-cigarettes aerosol includes chemicals such as formaldehyde, lead, nickel, and nicotine, and have measurable emissions. Aerosol composition varies based on the device characteristics, composition of the e-liquid, and user topography. Potential hazards from e-cigarette aerosol include exposure to propylene glycol, nicotine, metal, nanoparticles, and flavorings. Dr. Bloch noted that more than 7,000 flavorings are available for e-cigarettes.

Members were told that surveys of e-cigarette use by U.S. adults indicate the highest prevalence among people 18–24 years of age, and lower levels of use among groups ages 25–44, 45–64, and over 65. In 2013, e-cigarettes use among U.S. high school students was estimated at 4.5 percent. Dr. Bloch described use by non-smoking youth; use of e-cigarettes by U.S. youth who had never smoked

conventional cigarettes increased from 79,000 in 2011 to 263,000 in 2013. In addition, an intention to smoke conventional cigarettes was expressed by 44 percent of ever e-cigarette users but only 22 percent of never e-cigarette users. Public health stakeholders are concerned that e-cigarettes could lead to nicotine addiction and the use of conventional cigarettes among youth who would not otherwise become tobacco users.

Dr. Bloch stated that e-cigarettes have sparked an intense debate in the public health community, in part because of different interpretations of limited scientific data. Their potential benefit is a reduction in harm if smokers use e-cigarettes as a substitute for cigarettes. Potential harms include nicotine addiction among youth, the potential to lead to use of other tobacco products or other drugs, former smokers could return to smoking, dual use or deterrence of quitting among smokers, and renormalization of smoking behavior. The World Health Organization (WHO) has stated that the effect of electronic nicotine delivery systems on tobacco control depends on the interplay between industries marketing the products, consumers, regulators, policymakers, practitioners, scientists, and advocates. Dr. Bloch described e-cigarette marketing efforts in the United States, including various products (e.g., NutriCig), marketing themes (e.g., lack of negatives such as smoke, ash, or second-hand smoke), and a wide array of flavorings. Preliminary data from studies that have examined nicotine delivery, the effect on withdrawal from nicotine, and the effect on smoking cessation suggest that e-cigarettes may facilitate quitting and reduced cigarette consumption. Testimonials found on the Web appear to reveal strong enthusiasm from past smokers.

Members were informed that the FDA has proposed to deem products meeting the statutory definition of tobacco products, including e-cigarettes, are subject to FDA's authorities, including misbranding, registration, minimum purchase age, and health warnings. In addition, the American Heart Association (AHA) has provided clinical guidance, including that there is not yet enough evidence for clinicians to counsel patients to use e-cigarettes as a cessation aid, and that patients who choose to use these products should be informed that they are unregulated, have not been proven effective or safe as cessation devices, and that patients should quit smoking cigarettes entirely as soon as possible.

The NIH supports research on e-cigarettes through the Tobacco Regulatory Science Program (TRSP) and through other mechanisms. Activities include: the NCI's State and Community Tobacco Control Research Initiative has produced a supplement in *Tobacco Control* on e-cigarettes; funding support by the NIDA for research, including a proposed contract to develop a standardized e-cigarette for research; and a recent workshop on e-cigarette research needs, with proceedings published in *Nicotine and Tobacco Research*. Dr. Bloch reminded members that vulnerable populations also should be considered, including youth, pregnant women and women of reproductive age, and patients with mental health disorders and chronic diseases conditions.

Questions and Answers

Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, and Professor of Medicine, University of Maryland, remarked on legislative efforts to overturn Clean Air laws to allow e-cigarettes in restaurants and bars. Dr. Bloch agreed that public health stakeholders are continuing to oppose these efforts and support clean air as the standard. Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, and Director, Institute for Global Health, University of Southern California, referred to recent hearings in California regarding the definition of what is covered under the Clean Air legislation, and he noted the incorporation of e-cigarettes under smoke-free air laws. Dr. Sellers asked about the measurement of nicotine levels in second-hand exposure and suggested that non-smokers would react negatively to unintentional nicotine exposure. Dr. Bloch indicated research is ongoing.

In response to a query by Dr. Judy E. Garber, Director, Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, and Professor of Medicine, Harvard Medical School, Dr. Bloch stated that data regarding weight loss and e-cigarettes are not currently available.

Dr. Samet said that the FDA is considering regulation and noted recent applications have been made for Swedish snus as a modified risk product. He also observed that flavorings found in e-cigarettes generally are recognized as safe for ingestion, but not for inhalation, and at least one compound found in e-cigarettes (diacetyl) has been linked to a small airways disease.

Dr. Chanita Hughes-Halbert, Professor and Endowed Chair, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Hollings Cancer Center, asked about the cost variance between traditional and e-cigarettes. She also noted the positive effect of taxation in terms of nicotine cessation for traditional smoking products and wondered if a similar result has been found for e-cigarettes. Dr. Bloch responded that e-cigarettes are approximately one-third to one-half the cost of traditional cigarettes, and that the devices generally are not taxed.

Dr. Califano asked about data that demonstrate e-cigarettes are a path for youth to move to traditional cigarettes. Dr. Bloch stated that the question greatly concerns public health researchers.

VI. REDUCING THE NUMBER OF K AWARD MECHANISMS—DR. JONATHAN S. WIEST

Dr. Jonathan S. Wiest, Director, Center for Cancer Training (CCT), described a proposal to condense NCI's K award mechanisms. Dr. Wiest informed members about the complexity of the training program, which includes 15 training and career development mechanisms in the NCI, and 23 training mechanisms NIH-wide. The NCI offers nine K awards, four F awards, and one R and T mechanism. The current structure includes training awards that cover the areas of basic science; patient-oriented research; prevention, control, behavior, and population sciences; and quantitative sciences in cancer. The awards also are based on the investigator's career stage: mentored (e.g., postdoctoral); mentored/independent (e.g., late fellowship, non-tenure track faculty); or newly independent. Members were told that the use of numerous mechanisms causes confusion, discourages applicants, impedes review and program recommendations, and discourages interdisciplinary training and research.

The proposed recommendations would reduce the NCI training mechanisms from 15 to 7 by merging or retiring several mechanisms. Members were told that the K23 and K08 mechanisms both support physician-scientists and that the current separation of basic/translational and clinical research discourages interdisciplinary training; the merge of K23 into K08 would eliminate the arbitrary separation in review and program management. Dr. Wiest explained that a merge of the K07 into the K99/R00 would encourage the transition to independence; the K07 mechanism generally supports independent researchers, does not carry the benefits of the K99/R00, and is not available to foreign nationals. Retirement of the K05 and K24 mechanisms is proposed as they have provided mentoring awards to only a limited number of researchers and have experienced a low number of applicants. Similarly, the K25 mechanism is proposed for retirement as emerging scientific areas could be supported by RFAs, training should be an essential component of an RFA, and the recently expanded K22 and K99/R00 will support quantitative training for competitive applicants. A final recommendation to expand scientific disciplines supported by K99/R00 to all cancer research fields would better promote the transition to independence for applicants with no more than 4 years of postdoctoral experience. The recommendations streamline the K award mechanism structure into all cancer-relevant science awards for (1) all applicants and (2) physician scientists. Dr. Wiest reviewed the next steps and timeline, including work with the NIH on policy and procedure issues, and approval of final recommendations by the NCAB.

Questions and Answers

Dr. Califano recommended that the NCI revise the 4-year term for interdisciplinary applicants, noting the length of time needed to train scientists in multiple disciplines. Dr. Wiest said that the 4-year term limit is an NIH rule; however, the K22 mechanism provides support for postdoctoral researchers for up to 8 years.

Dr. Ethan M. Basch, Associate Professor of Medicine, Division of Hematology/Oncology, and Director, Cancer Outcomes Research Program, University of North Carolina at Chapel Hill, expressed concern about the consolidation of the K07 with the K99/R01 mechanism and asked how the review process will ensure that applications from researchers in fields such as population science do not become diffused with more general applications. Dr. Wiest acknowledged this challenge and indicated the NCI's intent to continue to support similar numbers as in the past.

Dr. Stanton L. Gerson, Shiverick Professor of Hematological Oncology, Director, Case Comprehensive Cancer Center, Director, National Center for Regenerative Medicine, Case Western Reserve University, and Director, Siedman Cancer Center, University Hospitals Case Medical Center, requested further clarification about training support for applicants who had K12 awards. Dr. Wiest explained that such individuals would be eligible, and some have successfully competed, for other NCI training mechanisms. In response to a question by Dr. Sellers, Dr. Wiest clarified that the proposal is to merge the K23 into the K08 award.

Dr. Olopade asked about the allocation of funds garnered from the consolidation of awards and suggested that clinicians would benefit from more training at the beginning of their careers. Dr. Wiest described the NCI's support of Fellows through various mechanisms, including the F30, F31, and F32.

Motion: A motion to accept the proposal to condense the NCI K award mechanisms was approved unanimously.

BSA Career Paths Working Group. Dr. Wiest stated that the Working Group met on December 1, 2014. The Working Group considered aspects of a predoctoral to postdoctoral transition award, including timing of applications, review criteria, and stipend levels. Dr. Dafna Bar-Sagi presented a laboratory staff support analysis that showed that increases in postdoctoral stipends have a greater effect in laboratories that are smaller in size, as the level of support is relative to the total size. In addition, Dr. Ed Harlow presented provocative ideas to stimulate discussion about relevant issues such as market forces and the size of the postdoctoral population. Dr. Wiest indicated that the Working Group will discuss a Research Specialist Staff Scientist Award at a future meeting.

VII. MODULAR GRANTS—DR. DOUGLAS R. LOWY

Dr. Lowy presented several options being weighted by the NCI regarding the funding of modular grants and asked the Boards to reflect on the current reductions of modular grants and the possible increase of the maximum amount funded. He told members that the NIH Extramural Activities Working Group (EAWG) recommended that the maximum amount of modular grants be raised from $250,000 to $275,000. No consensus was reached by the IC Directors in August 2014, and opinions included support for a larger increase, no increase, and the elimination of modular grants.

Members were informed that modular applications and awards were developed to reduce the workload for applicants and reviewers, and to enable reviewers to focus on evaluating science rather than on budgets. However, they function largely to contain costs. The NCI's reduction is higher than that of the 13 percent for the average reduction of the NIH Institutes and Centers (ICs). The vast majority of the

NCI's successful applications are at the 17 percent reduction level because they are at $175,000 to $250,000. The proportion of modular applications (R01) decreased from approximately 72 to 57 percent from FY 2007 to FY 2013, with the majority (90%) in FY 2013 supported at the maximum level of $250,000 in direct costs. Dr. Lowy reflected on the purchasing power of $250,000 in FY 2003, which equates to $181,000 (28% decrease) in FY 2013. To keep pace with inflation, the modular budget would need to increase 38 percent to approximately $345,000.

During the past 3 years (FY 2012–2014), modular R01 competing awards have decreased (61% to 54%), while non-modular have increased (39% to 46%). Although the overall number of awards shifted (661 in FY 2012; 611 in FY 2013; and 629 in FY 2014), the average size of awards increased: $389,000 in FY 2012; $394,000 in FY 2013, and $420,000 in FY 2014. In FY 2014, there were 342 modular awards with an average award of $330,000 compared to 287 non-modular awards with an average award of $527,000. A removal of the 17 percent reduction would result in $23 M in increased costs for modular awards and $31 M for non-modular awards. Members were told that the increased costs would continue for the duration of each award.

Dr. Lowy described possible solutions for modular and non-modular awards. One is to phase out the 13 percent reduction immediately, which affects only a small number of the grants and would have a small impact. A second option is to phase out the 17 percent reduction for modular awards over 2 years, which would cost $23 M or 8 percent of the total competing R01 spending when the phase-out is complete. Another concern is how to handle non-modular awards. Members were told that increasing the maximum modular amount from $250,000 would require NIH approval. A greater increase than the EAWG's recommended increase to $275,000 may be needed to maximize the proportion of awards that are modular. Each $25,000 increase would cost approximately $9 M for 350 fully funded modular grants or $7 M for 350 grants with the 17 percent reduction.

Questions and Answers

Dr. Stillman expressed support for eliminating the 17 percent reduction for modular awards, particularly for early career investigators, and also support for increasing the modular cap. He suggested a graded reduction, such as lowering the reduction to 10 percent for the first year and then eliminating it. Dr. Joe Gray agreed and commented that raising the levels of modular grants, which currently are inadequate to sustain an individual's research program, would benefit the cancer research community. Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., concurred with the elimination of the reduction and the benefit to the community, and he suggested that the cap for modular grants be raised to $350,000. Drs. Gerson and Garber voiced their support for the change.

Dr. Parada encouraged the NCI to incorporate algorithms in the funding of non-modular grants to reduce accounting burdens.

Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President, and Chief Scientific Officer, and Professor, Department of Biochemistry and Molecular Pharmacology, NYU Langone Medical Center, New York University School of Medicine, expressed support for reducing the 17 percent reduction. She recalled anecdotal information that study section reviewers favor modular grants relative to non-modular grants and also that young investigators are not the primary customers for these applications. Dr. Lowy clarified that the success rates of modular and non-modular grants are similar. He added that applications from investigators who have more than $1 M in direct costs undergo additional scrutiny. Dr. Varmus said that the number of investigators who receive 4 to 5 grants is small and does not affect the overall situation.

Dr. Kenneth C. Anderson, Kraft Family Professor of Medicine, Harvard Medical School, and Director, Lebow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute, strongly endorsed the elimination of both the 13 and 17 percent reductions. He noted that the impact of the elimination would reduce the total number of awards possible and present challenges for new investigators in establishing themselves. Dr. Cullen noted the difficulties for young investigators in obtaining their first R01 grant.

VIII. NCAB CLOSED SESSION—DR. TYLER JACKS

"This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c) (6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2)."

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There also was a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

IX. RFA/COOP AGR. CONCEPTS—REISSUES—NCI STAFF

Office of the Director
Innovative Molecular Analysis Technologies (IMAT) Concept (RFA)—Dr. Tony Dickherber

Dr. Dickherber informed members that the IMAT Program provides the majority of NCI's support for investigator-initiated technology development that is not met by other funding opportunities. The trans-NCI initiative emphasizes high-risk, high-impact multidisciplinary, cancer-relevant technologies for the molecular and cellular analysis of cancer. The Program supports investigator-initiated research utilizing the R21 and R33 exploratory/developmental research award mechanisms for Phase I and Phase II levels of support. Applications have been solicited annually since 1998 and a total of 3,914 applications were received with 478 new competitive awards provided. Approximately 70–100 projects are active at a given time.

Outcomes from 30 R21 awards made from applications submitted in FY 2010 have included 74 publications, 19 patent applications submitted and 7 awarded for supported platforms, and 9 licensure agreements completed or in progress. In addition, 75 publications, 15 patent applications submitted and 2 patents awarded, a product driving clinical profiling, and four commercially available products have resulted from 11 R33 awards made from applications submitted in FY 2010. Additional new applications have been submitted that indicated use of the technologies developed under these grants. Successful IMAT technologies cover genomics, proteomics, epigenomics, clinical diagnostics, sample preparation, and drug screening or delivery. Examples include single molecule Molecular Inversion Probes (smMIP); flag-tagged multiple-labeled tetravalent RNA imaging probes detected by proximity ligation assay; kinase activity biosensors; biomarker and histology preservative; and a platform for exclusion-based sample preparation.

The concept reissuance supports four RFAs addressing innovative emerging and early-stage technologies for cancer. These include 18–20 R21 and 10–12 R33 awards per year to address innovative and emerging molecular and cellular analysis technologies for cancer; and 4–5 R21 and 2 R33 awards per year to support innovative and emerging biospecimen science technologies for cancer. The concept provides assurance of NCI's interest in technology development and is designed to address a specific need that other initiatives are not currently meeting.

Subcommittee Review. Dr. Joe Gray expressed the Subcommittee's support for the concept reissuance and remarked on the impressive, innovative technologies developed under the IMAT Program. The Subcommittee appreciated the examples of IMAT successes and noted that the reissuance includes technologies for tissue sample analysis. The Subcommittee felt that the distribution of funds across the molecular and cellular analysis RFAs and the biospecimen technologies RFAs should be determined by the quality of the submissions.

The first year cost is estimated at $11 M for 34–39 R21 and R33 awards, with a total cost of $25–32 M for 3 years.

Questions and Answers

Dr. Califano asked about IMAT's exclusion of software development. Dr. Dickherber stated that support for software development was originally provided by the IMAT Program, and is now supported through the Informatics Technologies for Cancer Research (ITCR) Program.

Dr. Sangeeta N. Bhatia, John J. and Dorothy Wilson Professor, Division of Health Sciences and Technology and Electrical Engineering and Computer Science, Institute for Medical Engineering and Science, Koch Institute for Integrative Cancer Research, Broad Institute, Brigham and Women's Hospital, Massachusetts Institute of Technology, queried whether support for interventional and therapeutic cancer devices were covered through other nanotechnology programs. Dr. Dickherber explained that, to avoid overlap with other programs, competition in the IMAT Program is limited to those technologies that offer delivery capabilities or targeting capabilities.

Dr. Gerson asked about the dissemination and use of successful technologies within the research community. Dr. Dickherber provided an example of novel imaging tools developed by Dr. Patricia Keely, University of Wisconsin, which have become a significant element in a P01 core facility.

Motion. A motion to concur on the Office of the Director's (OD) three re-issuances request of request for application (RFA) entitled "Innovative Molecular Analysis Technologies (IMAT)," with increased flexibility in how funds are allocated across molecular and cellular analysis and biospecimen science technologies, was approved with 20 ayes, no nays, and 1 abstention.

Small Business Innovation Research (SBIR) Award Concept (RFA)

Subcommittee Review. Dr. Bhatia expressed the Subcommittee's enthusiasm for the concept reissuance. Dr. Bhatia reminded members that the SBIR Phase IIB Bridge Award Program funds projects that will allow groups to achieve critical milestones, such as the initiation of clinical trials, and requires one-to-one matching of non-federal funds. Since 2009, the Program has funded 18 bridge awards for $43 M, and private investors have committed $86 M. The Program which initially focused on cancer therapies and imaging was subsequently expanded to include interventional devices, diagnostics, and prognostics. The Subcommittee recognized the Program's importance in providing funding for diagnostics and therapeutics and bridging the gap between technology development and commercialization as pharmaceutical companies shift away from in-house research and development. Challenges include the need for marketing to improve the number and quality of applications. The Subcommittee noted the evaluation team's support for the reissuance and appreciated responses provided by NCI Program staff.

The first year cost for the NCI is estimated at $10 M for 5–10 R44 awards, with a total of $30 M for 3 years.

Motion. A motion to concur on the Office of the Director's (OD) three re-issuances request of request for application (RFA) entitled "Small Business Innovation Research (SBIR)" was approved with 20 ayes, no nays, and 1 abstention.

Division of Cancer Treatment and Diagnosis
Phase II of the Experimental Therapeutics Clinical Trials Network (ETCTN)
(RFA/COOP. AGR)—Dr. Jeff Moscow

Dr. Jeff Moscow, Division of Cancer Therapeutics and Diagnosis (DCTD), informed members that the concept reissuance is to integrate the current Phase II clinical trial contract program with the new phase I clinical trial UM1 cooperative agreement program to create a unified Experimental Therapeutics Clinical Trials Network (ETCTN) program for early clinical development of investigational new drugs (INDs). Dr. Moscow stated that the NCI has collaborated with industry and academic medical centers to develop more than 60 anticancer agents and combinations of agents to target a wide range of cancer-related pathways and antigens. The NCI's role is to expand clinical indications for novel agents and better understand their biology. He stated that the ETCTN focuses on the conduct of the earliest clinical studies of the INDs, addressing dosage, schedules, target engagement, and biomarkers of response, with investigators conducting mechanism-based early phase studies. The reissuance provides an opportunity to consolidate the Phase I and Phase II programs as early phase and clinical science have evolved and the current programmatic separation of the two clinical components has become undesirable.

Members were told that the goals for the Phase II program reflect new realities, including shorter duration from Phase I initiation, greater incorporation of biomarkers into Phase II study design, expanded pool of eligible patients for rare tumor subtypes, and leveraged resources for ETCTN centralized clinical trials. The proposed ETCTN structure would meld the current Phase II contract program with the UM1 grant program into one unified core grant program, in which Phase I grantees would compete for supplements to expand Phase II expertise, thereby providing an opportunity to redistribute the 31 NCI-designated Cancer Centers currently affiliated with the phase I and phase II program into more streamlined alignments. He noted that a funding opportunity announcement (FOA) would be required for the competitive supplements, with the focus on scientific leadership and expertise for conducting Phase II studies. The proposed annual allocation of funds for UM1 competitive supplements is $9M per year to support accrual of 900 patients.

Dr. Moscow described a proposed pilot Early Therapeutics Opportunity Program for the NCI Cancer Centers Program that would expand participation in early drug development studies through study leadership proposals and Phase II study participation proposals. It would allow 31 Cancer Centers in the ETCTN and 26 Cancer Centers not affiliated with the ETCTN to participate in studies of rare tumors, such as a Phase II trial for a rare molecular subtype for an NCI agent. For a study leadership proposal, an investigator from any clinical NCI-designated Cancer Center could submit a Letter of Intent (LOI) to the NCI, which, following approval, would be administered as a P30 administrative supplement. In the Phase II study participation proposal, NCI Cancer Centers not affiliated with the ETCTN would be able to open selected ETCTN Phase II studies that require screening for rare tumor subsets. Overall additional accrual to the ETCTN trials with both proposals is approximately 91 patients per year with a budget of $1M in administrative supplements.

Subcommittee Review. Dr. Anderson expressed the Subcommittee's support for the reissuance and noted that significant progress has been made in the later phase trials, and the concept reissuance addresses early Phase I and II trials and the need for biomarker-driven trials. The Subcommittee appreciated the visionary approach in having competitive supplements come from the Phase I UM1 cooperative agreements recently recompeted, ensuring greater flexibility, rapidity, and accrual efficiency. The Early Therapeutics Opportunity Program will allow participation from NCI-designated Cancer

Centers that currently are not involved, as well as include rare tumors. The Program should facilitate the interest of Cancer Centers, the pharmaceutical industry, and the NCI Experimental Therapeutics (NExT) Program.

The first year cost is estimated at $9 M for 10 UM1 competitive supplement awards, with a total cost of $27 M for 3 years.

Questions and Answers

Dr. Sellers encouraged the NCI to continue pharmacokinetic/pharmacodynamic (PK/PD) assessment into Phase II and consider exploring more than one dose level at Phase II trials. NCI needs to be watchful that the majority of resources do not drift into Phase II at the expense of Phase I efforts.

Dr. Golub asked about the effect of industry's shift toward smaller, biomarker-driven, early clinical development activities on the vision for ETCTN early phase studies. Dr. Moscow indicated that the Program is involving researchers who have experience in conducting these studies as part of the ETCTN early phase studies.

Dr. Garber observed that an advantage of the ETCTN Program is that it allows for drug combinations from different companies and provides more flexibility.

Dr. Sellers wondered how the rate of accrual for new genetic markers could be increased given the challenges in screening and screen failures. Dr. Moscow acknowledged the issues related to screening and said that collaboration with the Cancer Centers should facilitate the screening process.

Dr. Stillman asked whether industry would have conducted any of these trials. Dr. Moscow replied that the NCI works closely with industry to avoid duplicative trials. He added that the NCI's goal is to answer questions that a pharmaceutical company does not feel is commercially important for them but is scientifically important to the NCI and in the public health interest.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' (DCTD) reissuance of request for application/cooperative agreement (RFA/Coop. Agr.) entitled "Phase II of the Experimental Therapeutics Clinical Trials Network (ETCTN)" was approved with 20 ayes, no nays, and 1 abstention.

X. PERSPECTIVE ON CANCER PREVENTION RESEARCH AND IMPLEMENTATION—DRS. GRAHAM A. COLDITZ, STEPHEN J. CHANOCK, BARNETT KRAMER, AND ROBERT T. CROYLE

Dr. Graham A. Colditz provided an overview on cancer prevention research and implementation. He was joined by NCI leaders who presented the NCI's approach to cancer prevention and described the research portfolio supported by their divisions: Drs. Stephen Chanock, Director, DCEG; Barnett Kramer, Director, DCP; and Robert T. Croyle, Director, DCCPS.

Accelerating Cancer Prevention. Dr. Colditz presented considerations on how to accelerate cancer prevention. Medical interventions such as aspirin, selective estrogen receptor modulators (SERMs), and vaccinations have been proven to prevent some cancers. Both population-wide and high-risk strategies can be employed, but experts suggest that greater benefit would be gained by implementing population-wide strategies, which require good population data to stratify at-risk and consider the risk benefit of the screening intervention. An example of a population-wide strategy is the HPV vaccine discussed by Dr. Barbara Rimer, President's Cancer Panel (PCP). Members also were told of behavioral, social, and policy interventions derived from NCI-supported research that affect cancer prevention, such

as tobacco control, with lung cancer mortality decreased by one third, and colorectal cancer screening, which has increased steadily with a reduction in mortality rates over time.

Members were reminded that NCI-funded science is synthesized to a rage of strategies to act on scientific evidence to generate population interventions to reduce cancer risk. The 1964 Surgeon General's report on smoking linked smoking and lung cancer. A successful example of reduced cancer risk is the effect of tobacco control activities in Massachusetts between 1990 and 2005. A comprehensive effort was implemented at the state level and in partnership with local government, cancer institutions, and public health stakeholders, with the result of changed regulations, cessation aids available to the Medicaid population, decreased cardiovascular events and health care costs, and a 30 percent reduction in lung cancer mortality in men.

Dr. Colditz described lifestyle factors in the United States and the proportion of cancer that they cause, including smoking (33%); obesity (20%); viruses (5–7%); diet, lack of exercise, occupation, and family history (5% each); alcohol (3%); and others. A comparison of the burden of cigarette smoking between the lowest and highest cancer incidence showed a 75 percent lower incidence of cancer in Utah than Kentucky. Time estimates for how quickly benefits could be realized range from a long time for vaccination programs to more quickly for lifestyle changes; Dr. Colditz showed this in terms of risk for lung cancer mortality and total mortality for current smokers, and he noted that a population-wide strategy of smoking cessation could be contrasted against a high-risk strategy of screening the high-risk smokers for early detection of lung cancer.

Prevention strategies are available for a number of infections, such as HPV, hepatitis B and C, and *Helicobacter pylori*. IARC estimates that 23 percent of cancer in low- and middle-income countries is caused by infections, compared with approximately 7 percent of cancer in high-income countries, and prevention strategies exist only for some. Challenges in moving from a population-wide strategy to successful implementation can be seen in hepatitis B coverage, for which China has achieved close to 100 percent whereas India is struggling to reach 50 percent despite having the same science base. A similar scenario exists in the United States regarding the HPV vaccine, which remains at the 30 percent coverage with three doses of vaccine for girls. The high-risk context provides research opportunities to stratify risk, identify high-risk women, communicate risks and benefits, implement tools and strategies in the clinical setting and reduce HPV incidence through uptake and sustained use by women.

Members were informed that the steps from discovery to delivery involve identifying what is effective, developing guidance from evidence, using benefits to determine the timeframe for risk reduction, and assessing changes to disparities. Cancer disparities can occur in social conditions and policies, institutions, neighborhoods, social relationships, individual factors, and biologic/genetic pathways. Dr. Colditz stated that an opportunity exists to bring basic science and population science together to understand these issues. An example is a study that brought together population data and laboratory studies to examine potential mechanisms for endocrine burnout and receptor-negative breast cancer in the African-American women living in inner cities.

Barriers to preventing cancer include skepticism, the short-term focus of cancer research, and deployment of interventions too late in life. Members were reminded that the time required for cancer prevention does not match funding periods, and that long-term benefits such as from smoking cessation take decades to show at the population level. The challenge in maximizing the potential to prevent cancer is to address multiple factors (genetic, individual, demographic, and macro-level) that influence cancer.

Dr. Colditz informed members that the NCI has released a Program Announcements with Special Report (PAR) to fund research to better understand how evidence-based interventions can be moved into practice and policy. Research opportunities exist in discovery; sharpening the distinction between

individual focus of prevention versus population-wide strategies; increasing translation from discovery to delivery; and understanding the roles of the NCI and funding partners. Dr. Colditz reiterated the importance of considering these issues to achieve and sustain the potential for cancer prevention.

Questions and Answers

Dr. Olopade asked about the science needed to drive implementation in the context of the NCI portfolio. Dr. Colditz responded that the NCI's broad set of population science skills, including surveillance, evaluation, and Cancer Intervention and Surveillance Modeling Network (CISNET)-type modeling, need to be applied in the community to identify gaps and scientific questions. Dr. Hughes-Halbert referred to the Centers of Population Health and Health Disparities (CPHHD) as an example of NCI's successful role in implementation science.

Dr. Stillman requested clarification about data related to obesity and cancer and other elements affecting the cancer burden. Dr. Colditz indicated that the data come from strong cohorts and reflected on the increased number of prospective studies and DCCPS portfolio during the past decade; he noted that prospective studies continue to show that long-term excess weight and obesity increase the incidence of non-Hodgkins lymphoma and multiple myeloma.

Role of Prevention Research in DCEG. Dr. Chanock said that the DCEG addresses the prevention research continuum through studies of cancer etiology, prevention, and implementation, including such topics as HPV, tobacco, obesity, and radiation. The DCEG has focused on foundational, etiologic research, with randomized prevention trials as an outgrowth of etiologic work, and observational studies performed when trials were not feasible.

Members were informed that natural history studies of HPV established the virus as the necessary cause of cervical cancer and as a risk for cancers of the oral cavity, anus, and other sites. These etiologic observations led to HPV prevention research, including a vaccine trial in Costa Rica that considered levels of dosage and found the vaccine to provide protection against anal and oral infections; long-term followup is planned. The DCEG is conducting HPV implementation research through Pap testing, along with partners such as Kaiser Permanente, with the aim to develop screening and clinical management guidelines. Dr. Chanock next described the DCEG's portfolio of tobacco and radiation research. The NIH-AARP cohort provides a valuable resource to help understand the relationships between the differences in men and women in terms of cancer incidence and mortality with respect to smoking. The DCEG conducts observational studies based on cohort data, including such topics as smoking and second-hand cancer risk, smokeless tobacco, and new and emerging tobacco products. The goal is to refine screening guidelines and develop new biostatistic approaches to improve screening for tobacco-related cancers. Members also were informed about the DCEG's strong portfolio in radiation exposure. The Division studies medical radiation exposures, including diagnostic and screening procedures (low-dose exposure), radiotherapy treatments (high-dose exposure), and occupational exposures (repeated low-dose exposure). Studies also address environmental exposure, such as caused by nuclear testing or nuclear power plant accidents, and the etiology of radiosensitive malignancies.

Dr. Chanock stated that the DCEG is participating in a pilot project that emanated from the Global Alliance for Genomics and Health. The project is a Challenge to synchronize existing and new *BRCA* data in a federated public database. The goals are to review existing variants, create an API for display of annotated variants, and create a template for other genes. Members were informed that at least 115 other genes have been implicated in cancer susceptibility syndromes. The Challenge involves coordinated activities to bring together an evidence group for a variant classification, interpreting the variants, and engaging the community to ensure consent and interoperability. Databases around the world have a different number of *BRCA1/BRCA2* variants, including the NIH National Center for Biotechnology

Information (NCBI; 6,431 variants), European Leiden Open Variation Database (LOVD; 3,262 variants), and French Universal Mutation database (3,913 variants). The goal is to expand and include datasets from around the world, particularly to make interoperable the scientific and clinical classifications of the data. A data submission process is being developed to allow data to be entered in multiple countries, aggregated and curated, and then made available through other sites. Outcomes for the Challenge include population-based allele frequencies displayed using available sequencing resources, federated collection of pathogenic variants for *BRCA1/BRCA2*, and improved penetrance estimates.

Questions and Answers

In response to a query by Dr. Golub, Dr. Chanock confirmed that the BRCA Challenge could include laboratory experimental assessment of alleles. Dr. Kevin P. White, James and Karen Frank Family Professor, Department of Human Genetics, Professor, Department of Ecology and Evolution, and Director, Institute for Genomics and Systems Biology, Knapp Center for Biomedical Discovery, The University of Chicago, asked whether the application programming interfaces (APIs) being developed under the BRCA Challenge are open source and how they would relate to software used in clinical testing laboratories. Dr. Chanock noted the importance of using open source software to ensure interoperability and added that the databases will be built and curated by one variant and gene at a time.

Dr. Garber asked about the NCI's level of investment in the data curation process. Dr. Chanock expressed the NCI's interest in working with The Ontario Institute of Cancer Research, the Wellcome Trust, and others in the work.

Dr. Olopade asked about the inclusion of ethnically diverse populations in the United States in the BRCA Challenge. Dr. Chanock stated that one of the key elements in the Global Alliance's first deliverable is the population genetic assessment of the allele frequencies across the world for BRCA. In addition, having an API will allow clinicians to be able to interpret variants in individuals of different continental ancestry more effectively.

Dr. Joe Gray observed the value of the data organization and curation exercises over time and wondered about the incentives needed for the generation of a successful resource. Dr. Chanock answered that the scientific and clinical implications of building a large database are persuasive. He remarked on the cultural shift in the community and reminded members that effective January 25, 2015, all new sequencing data under NIH grants must have data sharing plans and deposition of that data for the public. Dr. Varmus stated that the Global Alliance no longer intends to run its own database but has the goal of gathering base representation at a single position in one chromosome to determine the level of willingness to share data. Drs. Sellers and Joe Gray reflected on the challenges of data sharing, and Dr. Chanock agreed and noted that the focus is the creation of a database that is driven by scientific opportunities.

Division of Cancer Prevention: Impact of Prevention and Screening Research. Dr. Kramer reminded members of prior presentations to the Boards from 2011 to 2014 on DCP research. The cancer prevention research continuum includes hypothesis and methods development, controlled intervention trials, defined population studies, and implementation projects, with research training occurring throughout all phases. Core issues in screening and prevention are: (1) it is difficult to make healthy people better off than they already are; and (2) strong evidence of benefit is therefore important when putting large numbers of healthy people in harm's way.

Large randomized screening and primary prevention studies funded by NCI have had major clinical and public health impact: for example, the ASCUS-LSIL Triage (ALTS) trial established the role of HPV testing in triaging low-grade cervical lesions. This finding set the stage for change in policy and the ultimate establishment of HPV testing as a primary screening test for cervical cancer. The National

Lung Screening Trial (NLST), the Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) provided evidence leading to changes in the U.S. Preventive Services Task Force (USPSTF) recommendations for lung cancer screening and breast cancer prevention, respectively to Grade "B" recommendations in favor of offering the interventions. The PLCO (Prostate, Lung, Colorectal, Ovarian) screening trial led to USPSTF Grade "D" recommendations not to offer screening tests for prostate or ovarian cancers. Results from randomized trials of beta-carotene and selenium led to Task Force recommendations not to offer dietary supplementation with these two micronutrients.

Dr. Kramer next outlined the DCP's research directions and programs. The NCI Community Oncology Research Program (NCORP), a national network that studies the effects of health care organizations on cancer prevention and care, and the Aspirin in Reducing Events in the Elderly (ASPREE) trial are examples. In addition, the PLCO Trial biorepository serves as a national resource for future studies of cancer etiology and early detection; an RFA for the molecular characterization of screen-detected lesions and overdiagnosis closed in September; applications for the Early Detection Research Network (EDRN) RFA are due in January 2015; and the Interactive Diet and Activity Tracking in AARP (iDATA) Measurement Error in Diet and Physical Activity study is in preparation.

The NCI Cancer Prevention Fellowship Program provides a postdoctoral fellowship for early-career scientists that is multidisciplinary and emphasizes independent, mentored research in cancer prevention and control. The fellowship provides up to 4 years of funding support for 10–15 fellows selected annually through a competitive application process. Fellows' scientific disciplines include basic science (32%), clinical (20%), behavioral or social science (20%), and epidemiology (17%). Dr. Kramer also noted areas of potential expansion in prevention and screening research, including microbiomics, immunoprevention, HPV gaps, and genomics of pre-malignant lesions.

Questions and Answers

Dr. Jacks requested further details on work being conducted in areas identified for expansion, such as immunoprevention and the genomics of premalignant lesions. Dr. Kramer explained that several areas identified already are being funding by the NCI, whereas others such as the genomics of premalignant lesions are not yet supported through an organized program. He added that earliest phases of the DCP's prevention agent development include an agent development program and a clinical consortium. An RFA focused on overdiagnosis is aimed at screen-detected lesions and will encompass the genomics of premalignant lesions, and example areas of emphasis include studies of the microenvironment and single-cell studies. Dr. Sellers reflected on screening challenges, observing that higher resolution imaging cannot differentiate between premalignancies and malignancies. Dr. Kramer agreed and said that is an area of emphasis in the programs he mentioned. Dr. Elizabeth M. Jaffee, The Dana and Albert "Cubby" Broccoli Professor of Oncology, Co-Director of the Gastrointestingal Cancers Program, and Associate Director for Translational Research, The Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University, stated that an opportunity exists to better understand early inflammation and early premalignancy.

Dr. Golub wondered if a particular approach to prevention provides special opportunities. Dr. Kramer described aspirin and metformin studies as two examples of effective prevention approaches initiated elsewhere and now supported by the DCP. Dr. Chanock said that a key issue is having data that leads to good hypotheses for study; microbiomics and proteomics offer promising opportunities for the DCEG.

Dr. Olopade encouraged the DCP to use genomic technologic advances for risk assessment and risk stratification. Dr. Kramer fully agreed, noting that better tools to conduct risk stratification will provide more opportunities for innovation in cancer prevention.

Division of Cancer Control and Population Sciences: NCI's Bridge to Public Health, Research, Practice, and Policy. Dr. Croyle provided an overview of the NCI's activities in research, science, and implementation within the context of prevention generally within the Nation. He informed members that the DCCPS' budget in FY 2014 equaled approximately 9.6 percent of the total NCI budget. The Division has a large epidemiology portfolio that encompasses molecular analytic epidemiology cohort studies, case control studies, surveillance infrastructure, Surveillance Epidemiology and End Results (SEER) contracts, and other surveillance activities. Tobacco control, obesity-related, cancer screening, and health services grants also comprise the portfolio. The DCCPS has led numerous research efforts starting in 1998, addressing such topics as long-term cancer survivorship, breast cancer surveillance, health communications, basic biobehavioral research, state and community tobacco control interventions, exposure assessment methods, cancer care outcomes, physical activity, and smoking cessation. Initiatives include Post Genome-Wide Association (GWAS) and Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR). Centers of Excellence initiatives have supported research on tobacco use, cancer communication, health disparities, and energetics and cancer. In addition, the Tobacco Centers of Regulator Sciences are funded by the FDA and cover research areas ranging from tobacco products, addiction, toxicity, health consequences, communications, tobacco product marketing, and economics and policies. Dr. Croyle described recent DCCPS-led RFAs that address social media, tobacco regulatory science, cervical cancer screening, and cancer modeling.

Dr. Croyle stated that the NCI's role in cancer prevention and implementation science can be seen in the context of public health and health care policies. He referred members to the *National Prevention, Health Prevention, and Public Health Council Report*, a National Prevention Strategy that concerns disease prevention in the United States and provides a "health in all policies" approach; 22 Departments and Agencies across the Executive Branch of the government participate in the process. HHS work occurs in a framework of healthy people, including goals and formal goal-setting and measurement and metrics development processes, and DCCPS is active regarding the methods and measurement of progress in cancer control. In addition, health IT has become a significant issue in cancer control, particularly in terms of implementation of evidence in health care systems and provides opportunities to leverage policies, such as meaningful use and electronic health records as a resource and tool for cancer research. Cancer control efforts in the prevention context often involve other Agencies, including the CDC, CMS, HRSA, NLST, FDA, AHRQ, and PCORI, as well as other NIH Institutes. Collaborative activities include Common Fund initiatives (e.g., the science of behavior change); Tobacco Regulatory Science; a neuroimaging cohort study looking at uptake of drug use and addiction with NIAAA, NIDA, and others; and the NIH Obesity Task Force and Office of Disease Prevention. Dr. Croyle noted the efforts of the American Cancer Society (ACS), Robert Wood Johnson Foundation (RWJF), and other extramural partners that fund work on social determinants of health, disparate populations, access to health care, metric development and quality of cancer care, and health care quality.

Dr. Croyle stated that the DCCPS has participated in the Provocative Questions RFA, including the influence of decisionmaking processes on habitual behaviors, physical activity and cancer risk and prognosis, and obesity and cancer risk. Funding gaps include disease site, underrepresented subpopulations, insufficient intervention evidence, and low utilization despite evidence, as seen in HPV vaccination uptake rates in pediatric settings.

Members were told that implementation science is the study of methods to promote the integration of research findings and evidence into health care policy and practice. Dr. Croyle introduced Dr. David Chambers, DCCPS' new Deputy Director of Implementation Science. The DCCPS' portfolio of implementation science includes the *Cancer Trends Progress Report*, a research-tested intervention program tool; Cancer Control Planet (P.L.A.N.E.T.), a comprehensive Web portal that combines data, surveillance data, intervention data, cancer control evidence for public health application; and the State

Cancer Profiles, in which the NCI works closely with the CDC to provide usable, relevant evidence and data to state and local cancer control programs and planners. Another example is the provision of small supplements to Cancer Centers to pay for a person to work from the cancer center with state and local cancer control coalitions and vaccine programs to accelerate uptake of HPV vaccination.

Dr. Croyle described challenges to cancer prevention research and implementation science, including the increasing diversity of the population, how best to inform policy, understanding the changing health care context, and the NCI's role in obesity. Other issues include the new information environment, the role of social determinants of health, and prevention among cancer survivors.

Questions and Answers

Dr. Golub asked about the use of social media wearable devices in cancer prevention. Dr. Croyle described several NIH mechanisms supporting mobile health research, including ambulatory exposure and behavior assessment through the trans-NIH Genes and the Environment Initiative (GEI), ambulatory monitoring by the iDATA Project, and an NCI RFA on mobile health technology in the global health context.

Dr. Olopade asked about interdisciplinary training opportunities in mobile technologies for new cancer control investigators. Dr. Croyle replied that the NCI supports a week-long training course on dissemination and implementation science and methods titled a Training Institutes in Dissemination and Health, and an upcoming trans-NIH dissemination implementation conference will include training activities.

Dr. Gerson asked about the prioritization of cancer research within related domains such as poverty, obesity, and nutrition. Dr. Croyle noted the challenges of determining the most cancer-relevant issues mechanistically and the importance of collaboration to promote cancer prevention at the population level.

XI. ADJOURNMENT—DRS. TODD R. GOLUB AND TYLER JACKS

There being no further business, the 4th joint meeting of the BSA/NCAB was adjourned at 4:55 p.m. on Tuesday, 2 December 2014.

Date	Todd R. Golub, M.D., Chair, BSA
Date	Tyler Jacks, M.D., Chair, NCAB
Date	Paulette S. Gray, Ph.D., Executive Secretary