DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
158TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 28, 2011

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 158th regular meeting on 28 June 2011, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 28 June 2011, from 9:00 a.m. to 3:15 p.m., and closed to the public on Tuesday, 28 June 2011, from 3:30 p.m. to 5:30 p.m. The NCAB Chair, Dr. Bruce A. Chabner, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, Boston, MA, presided during both the open and closed sessions.

NCAB Members
Dr. Bruce A. Chabner (Chair)
Dr. Anthony Atala
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Marcia R. Cruz-Correa
Dr. Kevin J. Cullen
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong
Mr. Robert A. Ingram (absent)
Dr. Judith S. Kaur
Ms. Mary Vaughan Lester (absent)
Dr. H. Kim Lyerly
Dr. Karen M. Meneses
Dr. Olufunmilayo I. Olopade
Dr. Jennifer A. Pietenpol
Dr. Jonathan M. Samet
Dr. William Sellers (absent)

President's Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson)
Dr. Margaret L. Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC (absent)
Dr. Patricia Bray, OSHA/DOL
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH (absent)
Dr. Sharlene Weatherwax, DOE

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. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Mr. John Czajkowski, Deputy Director for Management and Executive Officer
Dr. James Doroshow, Deputy Director for Clinical and Translational Research
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
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. Barnett 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. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Acting Director, NCI Center for Global Health
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
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carlton Brown, Oncology Nursing Society
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Mr. Adam Clark, Lance Armstrong Foundation
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Mr. Matthew Farber, Association of Community Cancer Centers
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambarresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Steven Klein, National Science Foundation
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials

Dr. Patricia Mullan, American Association for Cancer Education
Ms. Barbara Muth, American Society of Therapeutic Radiology and Oncology
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Ms. Pamela Wilcox, American College of Radiology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

TABLE OF CONTENTS

TUESDAY, 28 JUNE 2011

TUESDAY, JUNE 28, 2011

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 8 FEBRUARY 2011 MINUTES—DR. BRUCE A. CHABNER

Dr. Chabner called to order the 158th NCAB meeting. He welcomed members of the Board, the President's Cancer Panel (PCP, the Panel), *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. Chabner reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 8 February 2011 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. BRUCE A. CHABNER

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

Motion. A motion was made to confirm the February 2012 meeting date and the 2013 meeting dates. The motion was seconded and approved unanimously.

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

Dr. Harold Varmus, Director, NCI, welcomed members and described recent news regarding personnel, budgetary, and programmatic changes occurring in the NCI and activities of interest across the NIH. Dr. Varmus announced that Dr. James H. Doroshow is the Deputy Director for Clinical and Translational Research, and that Drs. Jeffrey Abrams and Joseph Tomaszewski are serving as co-Acting Directors of the Division of Cancer Treatment and Diagnosis (DCTD). In other recruitment news, the search for a Director of the Division of Cancer Prevention (DCP) is near completion.

Budget. Dr. Varmus informed members that the NCI's budget for FY 2011 was finalized in April and reflected a 1 percent decrease compared to the FY 2010 level. This reduction required tough decisions, which Dr. Varmus outlined in a May 6 letter to NCI staff and later described at town meetings. To meet its larger than usual commitment base, cover grants initially supported by American Recovery and Reinvestment Act (ARRA) funds, and continue construction at the NCI facility at Shady Grove, Maryland, the NCI reduced all research project grants (RPGs) and operating costs by 3 percent below FY 2010 levels. These and other reductions, including a small decrease in funding to the Cancer Centers, allowed funding of approximately 1,100 new grants and provided support for the restructuring of the Cooperative Groups and for genomic science. The scientific community overall has been receptive to these changes, which the NCI has tried to enact fairly while protecting young investigators. Dr. Varmus reminded members that the NCI is not adhering to a specific payline rate for grant awards, but he noted that most applications with a priority score of 7 percent or higher have been funded.

Dr. Varmus said that the FY 2012 likely will begin without appropriations set. The political climate is unfavorable for persuading the legislative branch to fund biomedical science at a normal pace.
Dr. Varmus informed members that Dr. Francis Collins, Director, NIH, presented an excellent summary of the NIH's ongoing and future activities at a Senate Appropriations Subcommittee hearing in May, with Dr. Varmus and Directors from three other Institutes and Centers (ICs) present. The audience turnout at the hearing, however, was disappointing. Mr. Denny Rehberg (R-MT), Chair, Labor, Health and Human Services, Education, and Related Agencies Subcommittee, has had discussions about the NIH with the U.S. Department of Health and Human Services (HHS) Secretary Dr. Kathleen Sibelius, but no House hearing is

expected. The Subcommittee markup is scheduled for July 26, with a full Committee markup on August 2. Senator Tom Harkin (D-IA) would like appropriations for the NIH to equal the proposed President's Budget, which is 2 percent higher than the FY 2010 level. Dr. Varmus encouraged the NCAB and other bodies to consider future NCI and NIH budgets beyond FY 2012.

NCI Programmatic Activities. Dr. Varmus informed members that Dr. David Heimbrook is the new chief executive officer of SAIC-Frederick, Inc. A high-level advisory board is planned for NCI-Frederick, with a membership of distinguished people and the inception meeting scheduled for late August. Dr. Varmus also attended a meeting at Cold Spring Harbor with Cancer Center Directors and Cooperative Group Chairs and heard talk about procurement of tissues and more clinically based protocols grounded in molecular science.

In other NCI news, Dr. Varmus reminded members that the Board of Scientific Advisors (BSA) conducted a review of cancer Biomedical Informatics Grid (caBIG®), made notable recommendations in a report, and that Mr. John Czajkowski, Deputy Director for Management, is leading efforts to reshape the activity to its original ambitions. Changes include a marked reduction of caBIG®'s budget and establishment of an internal advisory committee that will meet in late July. In addition, the cancer Human Biobank (caHUB) activity has been restructured with a budget reduction.

Regarding clinical research in the intramural research program (IRP), Dr. Varmus said that recruitment to the NIH Laskers Scholars Program has been disappointing, and advertisement of the Program should be rethought. Two programs on the NIH campus that target medical students to interest them in research—the Clinical Research Training Program, which is co-supported by Pfizer and the NIH, and the Howard Hughes Medical Institute (HHMI)/NIH Scholars Program—are being reshaped together, partly in response to HHMI's decision to reduce its financial commitment to the program. Dr. Varmus also noted that the NCI is working to simplify guidelines for Cancer Center applications and reapplications. A meeting of the NCI Cancer Centers Directors held in February 2011 was productive, with collegial discussions about improving interactions with the Cooperative Groups, and improving the application and evaluation processes.

The Provocative Questions activity has held four workshops led by Dr. Ed Harlow, with four additional workshops planned for the West coast. An RFA proposal using the R01 and R21 mechanisms has been approved by the Scientific Program Leaders and the BSA. Dr. Varmus indicated that potential questions are available on the NCI website and that topics could be presented at a future NCAB meeting.

Dr. Varmus described the establishment of new NCI Centers and related programs. He acknowledged the efforts of Dr. Paul Spellman who ably directed The Cancer Genomic Atlas (TCGA) in the recent past months. Dr. Barbara Wold is taking sabbatical leave from her academic commitments to set up the Center for Cancer Genomics. Efforts are underway to ensure that the activities of the NCI, the Sanger Institute, and other major genomic organizations are coordinated. Dr. Ted Trimble is the Acting Director for the Center for Global Health, and the plan for the Center will be a topic of discussion at the upcoming NCI leadership retreat.

NIH News. Dr. Varmus told members that Dr. Collins will address the Board about the National Center for Advancing Translational Sciences (NCATS) and consolidation efforts to form one institute on addiction. The drug shortage affecting oncology agents also affects other ICs, and IC Directors are considering ways to address the shortage by influencing legislative and regulatory processes. Discussions continue among NIH colleagues regarding challenges in funding the NIH Mark O. Hatfield Clinical Research Center (CRC) and extending CRC advantages to collaborating, extramural scientists in bedside research. Dr. Varmus is serving as co-chair in the search for a Director of the National Institute of General Medical Sciences (NIGMS). The National Heart, Lung and Blood Institute (NHLBI) is still without a permanent director. The NIH continues its interagency collaborations with the U.S. Food and Drug

Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) on topics such as tobacco labeling on cigarette packaging, putting genetics into the practice of oncology, and implementing lung cancer screening.

Dr. Varmus noted that Dr. Siddhartha Mukherjee has written *The Emperor of All Maladies: A Biography of Cancer*, a stimulating and insightful history of cancer. He recounted a recent visit to Sen. Richard Durbin (D-IL), who was reading the book; following the visit, Dr. Varmus facilitated a meeting between Sen. Durbin, Sen. Harkin, and Dr. Mukherjee. A retreat of the NCI leadership is scheduled for late July, with the agenda including budgetary issues and the Center for Global Health. Dr. Varmus informed members that Deputy Directors Drs. James Doroshow and Douglas Lowy would next present on specific topics.

Consolidation of the NCI Cooperative Groups. Dr. Doroshow described structural and other changes to the Cooperative Groups, which are being reformed into four adult groups, one pediatric group, and three tissue specimen banks. Voluntary consolidation efforts are well underway, which will abet the NCI in conducting fair peer reviews and evaluations. Several productive meetings have been held and led to significant improvements in communication and in understanding roles and interactions. There is formal agreement for an oversight body to advise the network; the advisory group will include principal investigators (PIs) from the Cooperative Groups, Cancer Centers Directors, and representatives from the advocacy community. The NCI is monitoring timelines carefully to ensure that goals are met. Training has begun regarding the National Clinical Trials Network (NCTN), a remote data capture site that eventually will be available for all NCI clinical trials to ensure that all trials are reported in the same format.

NCI Community Health Programs. Dr. Lowy told members that, in response to the NCAB's 2010 report to the Director, the NCI has initiated a review of its community health initiatives, including current programs, opportunities for synergy, and potential gaps to determine how best to utilize NCI-supported, community-based research. The review, which includes discussion of comparative effectiveness research, will actively engage other government agencies and the nongovernment sector to develop a more efficient and comprehensive program.

Interactions Between Intramural Investigators and Industry. Dr. Lowy reported on recent changes to interactions with industry. He said that the Technology Transfer Center has been instrumental in providing Cancer Therapy Evaluation Program (CTEP) staff with the authority to negotiate Cooperative Research and Development Agreements (CRADAs) directly with the companies who manufacture drugs and associated materials. Pilot efforts have since realized a 50 percent decrease in the time to develop CRADAs, with the average time reduced from 6-9 months to 3 months. In addition, the NCI is working to make more effective use of SAIC by providing it the ability to have its own CRADA authority while the NCI would retain supervisory authority. This effort is supported by the NIH. It would allow the extramural community to use SAIC services on a cost-fee basis; a significant advantage is that multiple extramural groups could be involved but would not have to be named at the time of CRADA establishment, in contrast to NIH's current CRADAs. In closing, Dr. Lowy thanked the many NCAB members who arrived early to attend the Subcommittee meeting on interactions with industry and conflicts of interest.

Questions and Answers

Dr. Chabner asked for further details about the HHMI's reduced commitment to the NIH. Dr. Varmus said that the NIH and HHMI are discussing how to retain their connection to benefit students and continue collegial interactions. Dr. Chabner also requested an update at a future meeting about changes to the NCI Cancer Centers Program, including scientific components of the Centers.

A discussion ensued about international research and training opportunities and careers for Fellows and other young cancer investigators. Dr. Varmus said that there are many ways to obtain international

experience, including the Center for Global Health, pharmaceutical companies, international organizations and professional societies, and he encouraged members to take advantage of training and funding opportunities offered by the NIH Fogarty International Center. Dr. Varmus added that a meeting of leaders from most of the cancer research funding agencies around the world is being planned, and foremost on the agenda is how to position cancer in the global health arena to improve standards of care, better treat cancer, and exploit opportunities to reduce the cancer burden worldwide. 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, noted that interest in global health has risen among young academic researchers, and she expressed support for training grants in the international cancer research arena. She recommended that the NCAB *ad Hoc* Subcommittee on Global Health incorporate career development issues in its agenda, and Dr. Chabner suggested that Dr. Olopade could survey NIH and other opportunities and report to the Board about these possibilities. Dr. Varmus said that he has requested that Dr. Olopade represent Dr. Varmus at the upcoming Africa Cancer Initiative meeting in Cairo, Egypt.

In response to a question by Dr. Marcia R. Cruz-Correa, Associate Professor of Medicine and Biochemistry, University of Puerto Rico Comprehensive Cancer Center, Dr. Varmus confirmed that the Office of Latin American Cancer Developing Program will be incorporated into the Center for Global Health.

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham, School of Nursing, requested clarification about the review of the NCI community health initiatives. Dr. Lowy explained that the activity seeks to improve NCI community-based programs, including the Community Clinical Oncology Program (CCOP), NCI Community Cancer Centers Program (NCCCP), and other initiatives through a broader examination.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, asked about how scoring will be used in the review of Cooperative Group applications. Dr. Doroshow responded that the NCI will be considering the level of expertise, functionality, and capabilities of the individual groups and the applicants as a larger network. Dr. Chabner congratulated Dr. Doroshow and staff on their efforts with the reorganization of the Cooperative Groups.

IV. PRESIDENT'S CANCER PANEL REPORT—DR. LASALLE D. LEFFALL, JR.

Dr. LaSalle D. Leffall, Jr., Chair, President's Cancer Panel (PCP, the Panel) and Charles R. Drew Professor of Surgery, Howard University Hospital, thanked the NCAB and stated that the PCP consisted of himself and Dr. Margaret Kripke, who are serving past their terms; three new members will be appointed by the White House. The mission of the PCP is to monitor the development and execution of the National Cancer Program (NCP) and report directly to the President. The PCP should notify the President immediately of any delays or impediments to the NCP's progress.

The 2009-2010 PCP report entitled, *America's Demographic and Cultural Transformation: Implications for Cancer*, was released on April 27, 2011, and received significant print, online media, radio, and television coverage. Among the report's recommendations: serious data deficiencies that inhibit efforts to understand and address cancer disparities should be addressed; data sharing and compatibility among government agencies must be improved; diversity in cancer research and care must be better supported through training and outreach; cultural competency must become an integral part of all medical training; research on cancer health disparities must be increased; patient navigation models and patient-centered medical home models of care should be examined in terms of decreasing cancer and other health disparities, and current cancer screening guidelines should be evaluated regarding their applicability to diverse populations; policies to enable clinicians to gather socio-cultural and medical information about patients

should be developed; translators should be available to providers and hospitals; and funding for American Indian health care should be increased. Upon presentation of the report to White House Staff, the Panel was asked to consider the impact of the Patient Protection and Affordable Care Act (PPACA) on the recommendations. The PCP released an addendum to the report stating that provisions of the PPACA could improve: data collection, analysis, reporting, and sharing; health services research; diversity and capacity of the health care workforce; and health information technology. However, some provisions of the law are still being debated in Congress and the full impact of the law is as yet unknown.

The 2010-2011 meeting series, *The Future of Cancer Research, Accelerating Scientific Innovation*, has been completed. Meetings were held in Boston, MA; Philadelphia, PA; Bethesda, MD; and Atlanta, GA. The series report is currently being drafted and is expected to be released in spring of 2012. The Panel and staff have been discussing possible topics for a 2011-2012 meeting series, but planning is on hold until the new Panel members have been appointed. Further information can be found on the PCP's website (http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm).

Questions and Answers

Dr. Chabner lauded the timeliness of the report. He described how the population he serves in Boston continues to diversify and each group brings new attitudes and issues to cancer screening. The Navigator program has been a great help, but it is difficult to produce data quantifying its effectiveness in engaging diverse populations.

Dr. Olopade complimented the report and asked if the PCP had any recommendations on how Cancer Centers or organ centers could be organized to meet the needs of minority populations. Dr. Leffall responded that the Cancer Centers would be aware of the cultural and demographic changes at hand and would take steps to organize programs that would meet the needs of relevant patient groups.

Dr. Victoria Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research and Scholarship, Indiana University School of Nursing, noted that many utilization navigators in minority communities have not been tested for efficacy. Dr. Olopade asked about the infrastructure needed to produce the necessary science, particularly the incentives that should be included in the scientific enterprise to study policies before they are implemented, such as by Cancer Centers, which historically are inwardly focused on basic and translational research,.

Dr. Chabner commented on the difficulty in determining who was a minority - he asked specifically about Brazilians - and noted that the NIH should take clarifying action. Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities (CRCHD), explained that for the purposes of eligibility for grant awards, diverse populations include racial and ethnic minorities, first generation college students, and individuals from low socioeconomic status in rural areas, but Brazilians are not considered underrepresented in the biomedical sciences yet. Dr. Olopade commented that once scientists become more global in their research and as the genome research advances, the scientific community will have a better understanding of ancestry and genomics across different populations. Dr. Chabner stated that social context in which patients are treated is important. Dr. Donald Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology and Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, Johns Hopkins University School of Medicine, suggested that Dr. Leffall's colleague at Howard University, Dr. Georgia Dunston, could provide more information on genetic markers and identification of minorities.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, asked whether steps could be taken to fulfill the report's recommendations not addressed in the PPACA. Dr. Leffall agreed that there

were, and he said that the White House staff had commented that the PCP report would help them make needed changes to address the cultural and demographic diversity in the population.

V. STATUS REPORT: PHARMACODYNAMICS AND THERAPEUTICS FUNCTIONAL WORKING GROUP—DR. JOSEPH E. TOMASZEWSKI

Dr. Joseph E. Tomaszewski, Acting Co-Director, Division of Cancer Treatment and Diagnosis (DCTD), presented an update on the activities of the Pharmacodynamics and Therapeutics Functional Working Group (PTF-WG). Dr. Tomaszewski reminded members that the PTF-WG was created to advise the NCAB, DCTD, and NCI regarding the molecular pathways that the NCI should target to develop pharmacodynamic assays supporting Phase 0 and Phase I clinical trials. Two primary activities are building a pharmacodynamic assay portfolio and assessing promising drugs in novel combinations; a third initiative is identifying therapeutic or investigational agents that could serve as positive controls in assays and drug combination studies. The program commenced in September 2009, and the PTF-WG met between December 2009 and May 2010 to discuss and suggest potential targets, pathways, and molecules that could be synthesized for positive controls in combination therapy studies.

The PTF-WG identified 10 critical molecular pathways that warranted development of multiplexed, pharmacodynamic assays. Assays currently are in development for five of these pathways. The strategy is to develop methods that allow assessment of agents downstream of the putative point of action as well as in related molecular pathways. Therapies hitting a single target may not produce a durable response because of additional pathways that reactivate tumor growth through autocrine or paracrine loops. The goal is to develop assays that can help researchers understand why only some targeted agents are effective, off target toxicity, and the basis for patient non-responsiveness to new agents. Details for a panel of assays being developed for a global assessment of DNA repair, including specific analytes and methods, were presented as an example of this strategy for assay development. Additional data demonstrated how assays helped determine which indenoisoquinolines (topoisomerase inhibitors developed by the intramural program) would be selected for advancement to Phase I clinical trials.

Dr. Tomaszewski described challenges to developing combination targeted therapeutics, including incomplete understanding of the mechanisms of action of agents available for trials; a lack of assays, imaging tools, and assay standardization; a lack of commercial agents available for *in vitro* use; and intellectual property and regulatory challenges. There has been recent progress on intellectual property and regulatory challenges, and the NCI is funding efforts to address limitations in assay and imaging methods. The Developmental Therapeutics Program (DTP) has a set of "combo" plates available for use by academic investigators containing 89 Federal Drug Administration (FDA) approved anti-cancer agents with diverse mechanisms of action. These plates are intended to enable cancer research, drug discovery, and combination drug studies. To date, 31 pairwise drug combinations have been tested against the NCI's 60 human cancer cell lines. More than one-half of the tested combinations showed equal to or better than additive activity, with only 5 percent of the combinations being antagonistic. A combination study of Dasatinib and 6-mercaptopurine (6-MP) against the NCI 60 cell lines showed that the drug combination may have activity against some cancer types that would not have been predicted by their individual activities. When the Dasatinib/6-MP combination was tested against LOX IMVI melanoma xenografts, the combination therapy showed significantly greater inhibition of tumor growth over either agent alone. This suggests that systematic combination screening will provide novel, hypothesis generating data, which can be used to develop therapeutic combinations.

A comparative pharmacodynamic and efficacy study compared the activities of a variety of Poly (ADP-ribose) polymerase (PARP) inhibitors. Three of the molecules had similar effects on Poly (ADP-ribose) (PAR) levels in melanoma xenografts. The BSI-201 molecule, however, showed no PARP inhibition. PAR levels and DNA damage also were examined in an *in vivo* combination of study of ABT-

888 and Irinotecan. The addition of Irinotecan to ABT-888 increased PARP inhibition and DNA damage over ABT-888 alone.

Questions and Answers

Dr. Olopade asked if any DNA damage was observed for the compound BSI-201, which failed to show PARP inhibition. Dr. Doroshow responded that there were small amounts of DNA damage at very high drug concentrations.

Dr. Chabner commented that tumor profiling is becoming the most important biomarker in Phase I trials and is replacing random selection of patients. Dr. Doroshow responded that next generation sequencing of all 60 NCI cell lines has been completed; in the future, cell line genetic profiles will be correlateable with assay results.

Dr. Jennifer Pietenpol, Director, Vanderbilt-Ingram Cancer Center and B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, commented that available gene expression data, even for the 60 NCI cell lines, should be incorporated into the study design, rather than using an agnostic approach.

Dr. Pietenpol asked if the program was working with industry on the development of pharmacodynamic assays, whether these assays have been clinically validated, and whether the assays are being shared with the research community. Dr. Tomaszewski responded that the NCI is collaborating with industry and that after assays are crossvalidated in a clinical setting, the assay standard operating procedures are posted on the DCTD's web page.

VI. UPDATE: 12TH REPORT ON CARCINOGENS—DR. JOHN BUCHER

Dr. John Bucher, Associate Director, National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), stated that the Report on Carcinogens (RoC) is a congressionally mandated document directed by the Public Health Service Act of 1978 and produced by the NTP. The RoC is cumulative, and the 12th Report lists 54 known human carcinogens and 186 substances reasonably anticipated to be human carcinogens.

The RoC identifies hazards but is not a regulatory document. To be considered a known human carcinogen, there must be sufficient evidence of cancer from human studies; to be considered reasonably anticipated to be a human carcinogen, there may be limited evidence from studies in humans, sufficient evidence from animal studies, or the substance may belong to a class of listed substances or cause effects that are recognized to cause cancer in humans. Each listed substance has a profile containing its listing status, summary of studies supporting the listing, and information on physical properties, use and production, sources of exposure, and current Federal regulations and guidelines to limit exposure. The RoC is prepared by a rigorous process that involves the input of experts from two federal and one non-government review groups, and at least six opportunities for public comment, before consideration by the HHS Secretary. Regulatory and health research agencies, the public, the scientific community and stakeholders all use the RoC. The release of the 12th Report was covered in approximately 500 news articles published in the first 10 days from release.

New listings in the 12th report include two known human carcinogens (aristolochic acids and formaldehyde) and six substances reasonably anticipated to be human carcinogens (captafol, cobalt-tungsten carbide powders and hard metals, certain inhalable glass wool fibers, *ortho*-nitrotoluene, riddelliine, and styrene). Aristolochic acids are botanicals that can be found in certain herbal remedies, and those who consume them show increased risks of urothelial cancer. Human exposure to captafol could have occurred through contact with the now-banned fungicide; animal studies show it to be a multi-site carcinogen. People are exposed to *ortho*-nitrotoluene during manufacture of dyes and certain agricultural chemicals, and it has

been shown to be a multi-site carcinogen in rodents. Riddelliine exposure occurs through contact with certain plants that can inadvertently be included in teas and supplements. Animal studies show it to be a carcinogen and supporting mechanistic studies show that it is genotoxic. Exposure to cobalt-tungsten carbide occurs during the manufacturing and grinding of tools; limited evidence from studies in humans shows a relationship to lung cancer. People can be exposed to inhalable glass wool fibers during their manufacture, installation, or removal, and based on animal studies, biopersistent fibers are likely to cause cancer in humans. Styrene exposure occurs during the manufacture of reinforced plastics or styrene-butadiene rubber or through smoking, from indoor air, or consumption of certain foods. Limited evidence of cancer in humans is seen in several styrene industries, and studies of laboratory mice provide sufficient evidence of lung tumors.

Exposure to formaldehyde can occur in industrial settings and in occupations such as embalmers and health professionals, in the home from off-gassing of construction products and home furnishings, and from consumer goods such as hair straighteners. Studies of formaldehyde exposed workers show elevated rates of myeloid leukemia and nasopharyngeal and sinonasal cancers, as well as genetic damage. NCI studies of embalmers, industrial workers, and a molecular epidemiology study of Chinese workers were used in the evaluation of formaldehyde. Because myeloid leukemia has been found in three industries using formaldehyde, the relationship is unlikely to be explained by confounding.

Questions and Answers

Dr. Jonathan 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, mentioned that he chaired the National Research Council Committee that reviewed the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) assessment of formaldehyde, and the chemical received significant media coverage because of the Brazilian Blowout, a hair straightening procedure. The Committee found that the EPA had not met its own weight of evidence guidelines sufficient to state that formaldehyde causes leukemia.

Dr. Chabner asked about the anticipated impact of the 12th RoC on U.S. industries and specific consumer products. Dr. Bucher replied that the issue that has received the greatest concern from the public is the use of polystyrene, as in Styrofoam cups, but the amount of material leaching from those products is orders of magnitude less than that in the workplaces that have been studied. He stated that he is not aware of any forthcoming regulatory activity regarding these listings.

Dr. Kevin Cullen, Director, Marlene and Stewart Greenbaum Cancer Center and Professor of Medicine, University of Maryland, queried whether the NTP tried to estimate the cancer burden associated with the agents placed on the list. Dr. Bucher answered that the NTP did not have the resources to examine the cancer burden.

VII. ONGOING AND NEW BUSINESS—DR. BRUCE A. CHABNER

***Ad hoc* Subcommittee on Facilitation of Industry Interactions.** Dr. Chabner said that the Subcommittee discussed concerns that the recruitment and retention of intramural scientists and their ability to collaborate outside the NIH were being hampered by the rigid enforcement of rules regarding conflict of interest and other aspects of collaboration, as well as restrictions regarding personal financial holdings. The Subcommittee heard about how conflict-of-interest issues are handled intramurally, specific cases related to interactions with industry and sponsored travel, and examples of unsuccessful recruitment attempts that failed because of these issues.

Dr. Chabner expressed the Subcommittee's strong belief that the current restrictions are counterproductive and that mechanisms should be in place to manage conflicts of interest. The

Subcommittee prepared a Statement of Concern regarding an atmosphere that inadvertently discourages public-private collaborations at the NIH, which Dr. Chabner read to the Board. Dr. Chabner said that the Subcommittee recommended that an expert panel, composed of both basic and translational scientists, be convened to further investigate these issues and to recommend changes that will facilitate a more equitable and timely process to manage conflicts of interest. He added that the Subcommittee's concerns were centered on intramural research scientists who are not in leadership or management positions, and that the overall sentiment is that collaborations with industry are necessary from both translational and clinical perspectives for the maximum growth of the NCI's intramural science research.

Questions and Answers

Dr. Chabner informed members that he discussed the Subcommittee's Statement of Concern with Dr. Varmus, who has no objection to efforts to decrease barriers in the recruitment and retention of intramural scientists. Dr. Varmus said that the most productive efforts would include other ICs, and he asked for further details about the panel membership. Dr. Chabner replied that the panel should include experts from the scientific and ethics communities. He suggested that, Dr. Kim Lyerly, NCAB representative to the NIH Council of Councils, could bring the Statement of Concern, if adopted by the NCAB, to the NIH Council of Councils for consideration.

Dr. Champion expressed support for the Statement and the need to involve other ICs in the topic and recommended the Board's adoption of the Statement.

Motion. A motion to accept the Statement of Concern prepared by the *Ad hoc* Subcommittee on Facilitation of Industry Interactions was approved unanimously.

Motion. A motion to accept the summary report of the 27 June 2011 *Ad hoc* Subcommittee on Facilitation of Industry Interactions meeting was approved unanimously.

Subcommittee on Clinical Investigations. Dr. Waun Ki Hong, Head, Division of Cancer Medicine, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, informed members that the Subcommittee met but focused on only one of two agenda items because of time constraints. He said that Dr. Margaret Mooney presented on Cooperative Group reorganization and other related initiatives. The primary goal is to improve the speed and efficiency of the design, launch, and conduct of clinical trials. A second goal is to incorporate innovative science and trial design into clinical trials. Dr. Mooney described progress on these goals, especially the implementation of biomarkers, imaging, and the quality-of-life (QOL) study program. A tertiary goal is to improve the prioritization, selection, support, completion of clinical trials.

The Subcommittee asked for the rationale for consolidating into four adult groups. Additionally, there was substantial discussion about the trials, especially about quantity versus quality. The Institute of Medicine (IOM) report states that almost 40 percent of trials initiated are never completed, but the quantity of trials conducted is less important; the NCI should emphasize higher quality, innovative, and provocative trials. The review process and the role of the Clinical Trials Support Unit (CTSU) was discussed as well in terms of measurement of operational efficiency. The importance of involving young investigators into Cooperative Group activities was discussed. Another important item considered was the role of the Steering Committee and especially how more innovative and transitional research, such as developing biomarkers as an innovative therapeutic trial, could be conducted. More physician scientists are needed to serve on the Steering Committee.

Dr. Hong said that the Subcommittee also discussed health disparity research. Dr. Olopade emphasized the importance of genetic mapping and completion of TCGA and development of more personalized targeted therapies through the Cooperative Group mechanism. In addition, the R21 mechanism

was discussed as an important vehicle for bringing young investigators to the cooperative studies. Drs. Doroshow, Abrams, and Mooney have made tremendous progress, and the reorganization of Cooperative Groups should be followed closely as it proceeds. Subcommittee members should review the minutes and return comments to Dr. Gray.

Questions and Answers

Dr. Chabner noted a change to the minutes, and stated that NCAB was grateful to NCI staff for the amount of progress seen in record time. The meeting allowed an excellent exchange of ideas of how to capitalize on the changes. Dr. Kaur also requested a correction to the minutes.

Dr. Olopade queried about the dissemination of the use of biomarkers and entry points for patients entering a study, particularly the screening of patients prior to enrollment in large studies. Dr. Doroshow replied that with respect to early phase drug development, NCI's goal is to pilot the applicability of various target-based assays and educate other institutions regarding their conduct. Given budgetary concerns, the NCI will not support or maintain the same number of trials or accrual rates because of trial reimbursement costs. Dr. Chabner agreed but expressed concern that the capacity for large-scale screening to identify the right patients for a specific agent is needed as trials conducted correctly in limited populations should be more cost effective in the long term than treating thousands of people with inappropriate drugs. Development of the assay and then validation of the assay are very significant steps, and it will be a challenge to screen at the community level through Cooperative Groups.

Motion. A motion to accept the summary report of the 27 June 2011 Subcommittee on Clinical Investigations meeting was approved unanimously with the provision that several changes requested by attendees be incorporated.

Future Agenda Items. Dr. Chabner reviewed several potential agenda items raised during the meeting, including progress in the Provocative Questions initiative, changes to the review of Cancer Centers, global health initiatives and training related to cancer, and management of community health programs. He invited members to send additional items to him and Dr. Gray.

Questions and Answers

Dr. Chabner said that newly appointed Board members asked during their orientation whether opportunities existed for the NCAB to contribute to the development of priorities in the NCI budget process. Dr. Varmus said that one such opportunity is the Scientific Program Leaders' retreat in mid-July, and that some members of the Board would be invited to attend the retreat as NCAB representatives.

Dr. Olopade asked about balancing the sacrifices that will be made in the process of streamlining the NCI cancer research enterprise while maintaining optimism about the future. Dr. Varmus responded that the NCI's budget of $5 B will support new programs, such as the initiatives on global health, genomics, and provocative questions, but that changes needed to make the enterprise efficient may include such areas as the contract between the NCI and the universities and institutions or significant reduction (e.g., 17%) of new research project grants (R01s) at time of award.

VIII. OVERVIEW OF NATIONAL LUNG SCREENING TRIAL (NLST) RESULTS— DRS. CHRISTINE BERG, DENISE R. ABERLE, ILANA F. GAREEN, AND WILLIAM C. BLACK

Dr. Christine Berg, Chief, Early Detection Research Group, DCP, presented information about the NLST design, initial trial results, positive rates, and radiation dose. The study is a prospective, randomized trial comparing low-dose helical computed tomography (CT) screening to chest x-ray (CXR) screening with

the endpoint of lung cancer specific mortality in high-risk participants. Eligible participants were ages 55 to 74, asymptomatic current or former smokers with a 30 pack-year smoking history, former smokers who quit within the preceding 15 years, had no prior lung cancer diagnosis, and no evidence of other cancer within the preceding 5 years.

The annual interim analyses were conducted from 2006 to 2010. Three rounds of screening ended in September 2006, with studies conducted across the United States. Screening exam compliance was excellent, with 95 percent of all participants returning for three rounds of CT screening and almost equally high participation in the chest x-ray arm. The probability of an individual who has a low dose CT of having a positive screen suspicious for lung cancer is 39 percent. Of 7,193 individuals, 270 had lung cancer the first round, 168 the second, and 211 the third. A chest CT was used in 73 percent of those individuals who had positives, transthoractic biopsies in 120, and another 40 had extrathoracic biopsies from other approaches. Bronchoscopies were used in 306 individuals; noninvasive subsequent imaging was used in most cases. A 20 percent mortality reduction and a reduction in all cause mortality of 6.7 percent were seen. A 50 percent 5-year survival exists in the low-dose CT arm compared to 37 percent in the CXR arm. The Lung Screening Study conducted a CT dose index calculation on the 96 CTs used in this trial across the United States. The doses were calculated both in the center and the periphery of the Phantom and averaged over the volume of the chest; they averaged 2.9 miligray (mGy). Estimating three screens for smokers starting at age 55 with the same parameters that are utilized in the NLST, the radiation risk would be approximately one to three lung cancer deaths per 10,000 screened, and cumulative mortality reduction in the NLST is 30 lung cancer deaths per 10,000.

Dr. Berg introduced the other speakers: Drs. Denise R. Aberle, Professor, Vice Chair of Research, Radiology, David Geffen School of Medicine, University of California at Los Angeles (UCLA); Ilana F. Gareen, Assistant Professor, Department of Epidemiology, Center for Statistical Sciences, Brown University; and William C. Black, Professor, Department of Radiology, Dartmouth-Hitchcock Medical Center.

NLST Operational Issues: Image Acquisition, Interpretation, and Communication; Diagnostic Evaluation, Outcomes Collection, and Endpoint Verification. Dr. Aberle noted that the NLST detection task is to be able to identify nodules of at least 4 mms in diameter and to be able to reliably detect change in size over time using low dose. The image interpretation findings are centered on the identification of nodules with 4 mm as a threshold for a positive screen. Each of those identified were characterized by anatomic location and certain morphologic features. Other features were used to render a positive screen suspicious for lung cancer that may have included major atelectasis, masses, or pleural pathology.

Three categories of screen results were found. The first category was a negative screen with either no or minor abnormalities and deemed not pathologically or clinically relevant. The second category of negative screen had findings significant for other pathology unrelated to lung cancer. In those instances, a diagnostic recommendation typically is mandated in the report. Finally, there was the category of positive screen that was a nodule of at least 4 mm or other findings that were suspicious for lung cancer. In that setting, a diagnostic recommendation also was required. The first diagnostic pathway in the trial is for subcentimeter nodules, and the most current followup for these is a CT scan, a low dose CT scan, or a diagnostic CT. In nodules that were highly suspicious or over 10 mm in diameter, patients frequently went to biopsy or to dynamic contrast enhanced CT (DCE-CT) to look at nodule enhancement features as a proxy for angiogenesis or neovascularity. There were similar diagnostic pathways for the CXR, with two tasks: to confirm an abnormality and to characterize that nodule further. Again, in many instances the CXR patients went to some kind of low dose or diagnostic CT scan as their next step. The results were required to be reported within 1 month and sent to both the participant and the primary care provider. Patients with a positive screen were telephoned at 3 months to determine whether the diagnostic evaluation had been initiated.

Lung cancers are categorized by histology and grade as well as their size and anatomic location, and the clinical state was obtained in all patients and pathologic stage in those patients who underwent resection. The American College of Radiology Imaging Network (ACRIN) captured all treatments as part of the cost-effectiveness analysis, and captured time to progression or time to second primary lung cancer. Thirty-nine percent of participants in the NLST had a positive screen at least one time, which is dependent on the threshold for test positivity. If the trial were implemented for public policy, a controlled vocabulary would need to be used. Computer-aided diagnosis, which was not a feature of the NLST but a feature of the Dutch/Belgian trial, is important; the findings from that trial are relevant to NLST analysis in determining whether volumetric assessment should be incorporated.

In the course of characterizing positive screens, nodules were defined by their consistency as either ground glass, solid, or part-solid. The ability to characterize these nodules may have implications with respect to whether patients undergo sublobar resections for these very indolent high-survival, low-grade lesions. The NLST looked at the diameter of a nodule at its widest axial equator as the measurement size. With computer-aided, volumetric analysis, the reader concordance is about 90 percent; in about 10 percent of cases, there are discordances that most typically are found with the smallest nodules, spiculated nodules, or irregularly shaped nodules.

A biorepository includes media specimens collected from approximately 10,000 NLST participants as well as remnant tissues that were used to create tissue microarrays trial-wide. Looking forward, scientists will examine the cost effectiveness of screening. The risk cohorts for CT screening could be optimized, and acquisition, communication, and outcomes collection must be standardized. Finally, it is hoped that the molecular biology community will assist by better stratifying risk and identifying participants who might warrant more aggressive followup.

Studies To Evaluate the Impact of NLST Screening on Smoking Behaviors and Participant Quality of Life. Dr. Gareen provided an overview of smoking studies that included sub-studies of the relationship between smoking, QOL, and the perception of risk for lung cancer. She informed members that her presentation described the design and methodology of these studies and that a forthcoming article would provide results from the QOL sub-studies. The trial, which was co-administered by the ACRIN and the NCI's Lung Screening Study, screened more than 18,500 patients across 23 ACRIN sites through questionnaires disseminated at study entry and every 6 months.

Dr. Gareen informed members that the majority of former smokers (approximately 6,200 out of 9,000) had quit smoking 4-15 years earlier. The average lifetime number of cigarettes smoked per day ranged between 25.7 and 32.6. At the time of entry into the study, the greatest amount of participants (more than 7,100) indicated they had ceased smoking and expressed full confidence in not smoking again, followed by participants (approximately 4,200) who considered smoking cessation but had made no specific plans. The majority of former and current smokers both indicated less than 30 minutes from waking as the time to their first morning cigarette. Dr. Gareen next described the methodology used to conduct three QOL sub-studies that considered the impact of screening itself on QOL, the impact of a positive test on QOL and anxiety, and lung cancer risk perception and its association with smoking cessation behaviors in a sample of participants. This included standardized questionnaires from which eight profiles of functional health and well-being were derived, which in turn yielded physical and mental component scores.

Cost-Effectiveness of Screening in the NLST. Dr. Black presented a preliminary cost effectiveness analysis (CEA) of the NLST. The CEA is still in progress; however, much of the important data is already in the public domain. The CEA will compare Low Dose Spiral Computerized Tomography (LDCT) screening against chest x-ray (CXR) screening and no screening. The effectiveness will be measured in life years (LY) as well as quality adjusted life years (QALY). Life years will be observed from entry into the study until 2009; after 2009, survival will be projected taking into account the current age,

sex, smoking status, and cancer status of the study participants. QALYs will be based on surveys that were given to subsets of the study participants and estimated for the whole group based on age, sex, screening method, and cancer status. These methods are well established for cost effectiveness analyses.

The costs will be measured in 2009 U.S. dollars with time horizons of within trial and lifetime. Costs that will be considered include: direct medical costs, associated non-medical costs (i.e., travel and lodging), and lost wages. Costs will be observed until 2009 and projected beyond 2009 based on age, sex, and lung cancer stage at the end of the trial. Missing cost information will be imputed.

When evaluating cost effectiveness data, there are generally four broad outcomes: the cost of the tested intervention can be greater than or less than the current standard and the effectiveness of the tested intervention can be greater than or less than the current standard. When costs are decreased and effectiveness is increased, the new intervention should clearly be used; conversely, when costs are increased and effectiveness is decreased, the new intervention should clearly not be used. When effectiveness and costs either both increase or both decrease, however, a judgment needs to be made about how much society is willing to pay for the benefit of an intervention. In the United States, a commonly considered threshold is $100,000 per QALY gained.

Preliminary CEA data comparing LDCT versus no screening were presented making the following assumptions: three annual LDCT screens, 40 percent of patients will screen positive over the life of the study, each positive LDCT would generate two follow-up CT scans, and the costs of lung cancer treatment will be equal in both arms. The annual cost of screening was estimated to be $1,520 per patient and the number of LYs gained through screening was estimated to be 40 per 1,000 patients. This equates to a cost of approximately $38,000 per LY gained. Most experts in the field of cost effectiveness research consider any intervention less than $50,000 per LY gained to be clearly cost effective. This preliminary CEA indicates that it is plausible that LDCT could be implemented in a cost-effective way; Dr. Black cautioned, however, that many assumptions were made and this preliminary finding could change in the final analysis. The population in the NLST is high risk compared to the general population, and cost effectiveness is expected to decrease when a screening strategy is applied to a lower risk population. Total costs will depend on screening guidelines and the populations recommended for screening.

Questions and Answers

Dr. Chabner stated that if the presented study were generalized to all 40 pack-year smokers, many of whom have diseases or comorbidities, the reduction in mortality would be less. Dr. Berg agreed and noted that the LSS operative mortality was 1 percent compared to Dr. Peter Bach's estimate of the Medicare population, which is 4 percent. Dr. Chabner commented that, in some of the other screening studies, many of the patients chose not to proceed with all of the diagnostic and therapeutic procedures. Dr. Berg said that the LSS also had initiated collaborative investigations with others who are doing other CT studies.

Dr. Chabner expressed the Board's interest in hearing study results, which were not presented because of their imminent publication. Dr. Atala echoed this sentiment.

Dr. Atala commented that estimations often understate costs, noting that many studies involve ancillary activities that should be incorporated in cost estimations. Dr. Black supported the inclusion of all costs in estimations and pointed out that the NLST analysis will incorporate the utilization; in addition, two studies are planned to examine the trial's unexpected findings and to review all medical costs, including Medicare costs, of a subset of age 65 or older patients from the two arms, irrespective of their screening results.

Dr. Chabner asked about the cost of biopsies in the trial for the 7,000 positive findings. Dr. Black answered that each positive screening test led to two additional CTs or the equivalent (including biopsies);

his analysis did account for biopsies, but that only 4 percent of positive CTs led to biopsies, with the vast majority of positive CTs handled through a follow-up CT.

Dr. Samet recommended that the investigators should consider the healthy volunteer effect, particularly in relation to the pattern of cardiovascular disease and other comorbidities to ensure that risk prediction is accurate. He also asked about modeling risk and benefit for smoking in younger individuals and whether the optimal screening criterion for youth should be the age of the patient. Dr. Berg replied that the healthy volunteer effect will need to be examined, and that modeling is needed for younger smokers; although age of onset and smoking duration are important, age remains the best risk predictor for population-based screening.

Dr. Hong observed that current lung cancer models mark sensitivities at 60-70 percent. He suggested that incorporating data from the three top risk prediction models for lung cancer to increase sensitivity to 90 percent could better target smokers at highest risk for cancer for screening and prevention trials. Dr. Aberle said that the biorepository will be publishing a number of characteristics, including the number of patients and the number of specimens from participants who were positive or negative for lung cancer. She noted that chronic obstructive pulmonary disease (COPD) was not considered in the risk predictions due to cost factors, but that other definite risk prediction models that incorporate the very high proportion of COPD patients who get lung cancer will inform the NLST's categories of risk.

Dr. Champion cautioned that unanticipated consequences may result if people who screened negative believe that they could continue smoking. In response to Dr. Champion's comment that the number of years out from when the no-longer smokers entered should be taken into consideration, Dr. Berg explained that this was factored in aggregate into the results presented but will be examined separately as well.

IX. NIH DIRECTOR'S REPORT—DR. FRANCIS COLLINS

Dr. Francis Collins, Director, NIH, expressed his pleasure in speaking to the NCAB and discussed issues related to the new center on translation and efforts to consolidate NIH research on addiction. When beginning his tenure as NIH Director, Dr. Collins solicited ideas from colleagues about areas that would provide exceptional cross-cutting opportunities for biomedical research, which resulted in five themes: output of high-throughput technologies; translation of basic science discoveries into new and better treatments; putting science to work for the benefit of health care reform; a greater focus on global health; and reinvigorating and empowering the biomedical research community.

National Center for Advancing Translational Sciences (NCATS). Dr. Collins reminded members that science has provided remarkable discoveries and opportunities, with more than 4,000 disorders having a known molecular basis, but only 200 of these having therapies currently available. Many are rare disorders that may provide insight into common diseases. Investigators have developed an extensive list of associated risks by employing the genome-wide application (GWA) approach to identify common variants associated with some cancers, cardiovascular disease, diabetes, asthma, hypertension, and other common diseases; many appear to be regulatory variants rather than coding region changes. The application of DNA sequencing, particularly through TCGA and its efforts in ovarian and other cancers has been particularly exciting in understanding the cancer of the genome; TCGA's goal is to identify recurrent genomic and epigenomic drivers for at least 20 cancers during the next 3 years.

Dr. Collins said that the Scientific Management Review Board (SMRB) recommended that the NIH create a translational medicine and therapeutics center to facilitate the efficient movement of fundamental scientific knowledge into application. A 2010 trans-NIH inventory of activities relevant to therapeutics development found 550 activities, spanning preclinical (65%) and clinical (35%) research. The proposed center, NCATS, would be tasked with catalyzing the generation of innovative methods and technologies to

enhance the therapeutic and device development pipeline. Dr. Collins said that the NCATS will facilitate, not duplicate, the ICs' translational research activities. It also will complement, not compete with, the private sector, as well as reinforce NIH's commitment to basic science research.

NCATS is envisioned to handle a variety of topics. One example is discerning the value of exploring new uses for abandoned and approved therapeutics, such as occurred with AZT, which was developed to treat cancer, was found ineffective, but was successful as the first AIDS drug. A roundtable held on this topic in April 2011 has enjoyed strong support and commitment from the biomedical research community, including the possibility that pharmaceutical companies might make available compounds that have not yet been approved, provided intellectual property principles are addressed. Another topic for NCATS might be a more systematic approach to target validation for GWAS findings; Dr. Collins shared an example of the proprotein convertase subtilisin/kexin type 9 (PCKS9) antibody, effective against coronary heart disease, which illustrates successful targeting of variants. He pointed out that the Chemical Genomics Center has developed a comprehensive database. The NCATS would oversee the Cures Acceleration Network (CAN), which was authorized in the Affordable Care ACT but awaits appropriation.

Substance Use, Abuse, and Addiction. Dr. Collins informed members that the SMRB recommended the creation of a new Institute to focus on substance use, abuse, and addiction research and related public health initiatives. The Institute would integrate relevant research portfolios from the National Institute on Drug Addition (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and other ICs, including parts of NCI's tobacco portfolio. An SMRB Task Force led by Dr. Lawrence Tabak, NIH Deputy Director, conducted internal discussions and developed guiding principles that led to the recommendation for the Institute; the principles included the nature of the science as the primary driver of the recommendation; concern for populations with co-morbid addictive behaviors (e.g., schizophrenics addicted to morphine); and that the special expertise of staff needed to manage and foster a research area influenced the placement of programs. The NIH is completing a portfolio analysis of all relevant grants, projects, and activities to develop an integration plan, as well as a scientific strategic plan.

Dr. Collins said that the NCI's tobacco research portfolio also is being analyzed, and the Task Force has determined that portions of the portfolio related to addiction and control could be candidates for inclusion in the proposed Institute. He next reviewed the current timeline, including release of the integration and strategic plans for public comment by the fall of 2012, with final recommendations to Dr. Collins in December 2012. The Institute would be included in the President's FY 2014 budget, and hopefully be operational in October 2013 as the National Institute of Substance Use and Addiction Disorders.

Dr. Collins acknowledged the trying economic times and described challenges to biomedical research in terms of the NIH's appropriation history and actual purchasing power. He reflected on the difficult funding decisions facing all the ICs and investigators. He expressed appreciation for being able to call upon Dr. Varmus for his long experience and wise advice on many topics.

Questions and Answers

Dr. Chabner informed Dr. Collins that an NCAB Subcommittee recently discussed issues concerning the recruitment and retention of NCI intramural investigators, including the difficulties in establishing interactions with industry and the stringent enforcement of policies regarding conflict of interest without waivers, which inhibits recruitment of people from the outside. He said that the Board prepared a Statement of Concern about these issues, which Dr. Lyerly, NCAB member, will bring to the NIH Council of Councils for possible discussion.

Dr. Atala commented on the length of time and high cost of developing potential technologies from concept and trial phases, and he asked about NIH support for internal development (i.e., bench to bedside)

of technologies to a point at which industry might take interest. Dr. Collins replied that the NIH and NCI have worked to de-risk projects to make them commercially attractive to industry as a means to deal with the "Valley of Death", including through: the NCI's RAID program, which now exists in the NIH Common Fund; the Therapeutics for Rare and Neglected Diseases (TRND) program; and NCATS, which will help accelerate the ability to improve the technologies to make the process quicker, cheaper, and more successful. Dr. Collins added that the NIH works in concert with the FDA as a sister agency to take advantage of the FDA's ability to accept a technology as an alternative way to validate a compound for human use. He referred members to an article on NCATS forthcoming in a peer reviewed journal.

Dr. Coffey expressed support for using a multiplex of approaches to drug toxicity, including studies of multiple drugs versus indepth query of a single agent, and encouraged the pharmaceutical industry to examine targets for toxicity. Dr. Collins agreed and noted that examination of many matrices reflecting the exposure of perturbagens to various cell types will yield patterns of results that could suggest new uses for existing agents.

Dr. Kaur expressed concern regarding the amount of data generated, translation of the data into useable patterns of information, and interconnections with other disciplines, such as nanotechnology and bioinformatics. Dr. Collins acknowledged the challenges presented by massive amounts of data generated from genomic, transcriptomic, metabolomic, and proteomics projects, and he added that the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is addressing storage and access issues. In addition, he affirmed that NIH's most important resource is its people and told members that NCATS will address training needs for translation, such as in the discipline of clinical pharmacology, better alignment of chemistry with clinical aspects, and components of the developmental pipeline. Dr. Chabner encouraged career development support for M.D./Ph.D. researchers, who are important for the future of translational research.

X. WORKFORCE AND TRAINING—DRS. SANYA SPRINGFIELD AND JONATHAN WIEST

Workforce and Diversity Training. Dr. Springfield stated that the NCI's Continuing Umbrella of Research Experiences (CURE) program is based on the successes and failures of the diversity supplement program in which additional R01 grants are attached to existing grants to support individuals from high school through their first academic appointment. Dr. Springfield said that a series of mechanisms to increase the talent pool (high school and undergraduate program) were created along with individual fellowships (F31s). To extend the period of training, the NCI created a series of career development awards for mentored and nonmentored investigators with the aim of increasing the diversity and competiveness of diversity trainees. One of the unique aspects of the CURE program is program navigation, which provides coaching, mentoring, and mock review. The CURE pipeline created mechanisms for transition, retention, and competitiveness. This snapshot of the program examines a cohort of trainees from 2001 to 2010 that represents about 1,400 individuals, primarily graduate students and early-stage investigators. CURE primarily supports women and mostly African American and Hispanic trainees, and it operates under the Office of Management and Budget (OMB) Directive 15, which defines the term "minority." CURE cancer researchers study all cancer areas, particularly breast and prostate, and conduct basic, clinical, translational, population-based and cancer health disparities research. There has been a 17 percent increase in the number of trainees focused on cancer health disparities research in just 1 year.

In the high school program, individuals are being trained at NCI designated Cancer Centers. CRCHD receives 8 to 10 applications and supports 6 to 8 applications per year for 2-year training programs. CURE's high school students have progressed to an undergraduate school at a 33 percent rate, which is better than the 10 percent national average for underrepresented groups; 54 percent of them went on to graduate school, and another 23 percent advanced to professional schools. Diversity research supplements are the mechanism through which CRCHD applies additional funds to existing grants, each year supporting

between 80 and 90 new supplement awardees, who are primarily African American and Hispanic women. The graduation rate of individuals trained with diversity supplements is 91 percent. One of the goals of the diversity supplements is to ensure that students and trainees advance to competitive careers as quickly as possible. Of predoctoral students who are trained on diversity supplements for less than 2 years, 73 percent receive individual fellowships, and 80 percent of postdoctoral fellows on diversity supplements then move into career development awards (K awards). Early-stage investigators are 33 percent successful in achieving R01s, and 30 percent are successful at receiving other RPGs. The success rate is higher than that of the NCI, the NIH, and national averages. The number of awards is small compared to the number of applicants, which is not based on scientific merit but on the available dollars. The predoctoral (F31) graduation rate is 95 percent, most of whom remained in biomedical positions: of these, 67 percent moved into postdoctoral training; 11 percent entered industry; and 9 percent went into medical residency. In the career and career transition awards (K series), the success rate is higher than that of both NCI and NIH. The nonmentored awards are close in success to the NCI and NIH levels, but those with mentored awards do much better. Those who have been in the CURE pipeline for the nonmentored awards, however, do better than the non-CURE K22s.

NCI Training and the Cancer Research Workforce. Dr. Jonathan S. Wiest, Director, Center for Cancer Training (CCT), said that the CCT was established to create a cohesive program for the NCI's extramural and intramural training activities. Dr. Wiest informed members that the funding for and number of NCI's training awards have remained mostly stationary for the past 5 years. In FY 2009, the NCI ranked third among the ICs in the amount in its budget (more than $175 M) for training, fellowships, and career development; the training budget accounted for 3.6 percent of the NCI's total budget. Dr. Wiest told members that the NCI's extramural training portfolio in FY 2009 included: fellowships (114 awards, $5.7 M); K awards (432 awards, $68 M); R25 awards (85 awards, $28 M); T32 awards (179 awards, $59 M); and other awards (9 awards, $1 M). The NCI supports training in a diverse array of scientific fields, including biology, etiology, prevention, early detection, treatment, cancer control, scientific model systems, and interdisciplinary fields.

The major goals of training are to produce scholarly work, master technical skills, develop critical questions and hypotheses, develop critical thinking skills, grow and expand scientifically in many disciplines, develop other skills (e.g., writing, presenting, management); and build towards independence and the next career step. The biomedical workforce faces numerous challenges, including: an increasing number of postdoctoral and predoctoral researchers; more predoctoral students are receiving postdoctoral training; most trainees are supported on research grants; tenure track positions are not growing; trainees have difficulty transitioning to independence; and the time to the first R01 award continues to increase. In addition, there is need for a more scientifically diverse workforce, it is difficult to track trainee outcomes, and the increased time in training may have a negative effect on students choosing science as a career track. Forces driving the workforce include that colleges and universities are mostly graduate student driven because there is a need for a "low cost" but highly trained workforce. Also, a tournament or competitive model of employment, rather than supply and demand, is prevalent, and there is increasing competition for tenure track positions and grant funding.

Dr. Wiest said that the CCT has added the F30 and F31 awards to the portfolio to better support researchers pursuing the dual M.D./Ph.D. degree and the Ph.D. degree. An analysis of future grant funding suggests trainees receiving F30, F31, and F32 awards may be more likely to have academic-focused careers than trainees supported via institutional grants. Obtaining individual F grants will help demonstrate fundability and assist in future funding. The CCT has modified the K awards, which includes expanding the science of all cancer research for the K22 and K99/R00 awards. Other modifications to the K22 awards include eligibility limitations to 8 years of postdoctoral experience, only investigators in mentored positions, and to not include previous K support. Additional activities that the CCT has initiated include: maintenance of a three-to-one training grant ratio of postdoctoral to predoctoral researcher; building a scientifically diverse workforce by maintaining a diverse scientific portfolio; developing career options and training on

institutional training grants; publicizing the R25 mechanism for broader use; and conducting an outcomes evaluation of the K portfolio.

Questions and Answers

Dr. Chabner commented on the workforce and diversity training information, noting the small number of K awards; he expressed disappointment at not supporting students who have entered the research pipeline. Dr. Varmus asked whether there would be advantages in funding an increased number of later stage awards and fewer early stage awards. Dr. Springfield replied that there is a need to maintain the stream of individuals entering the K award pool, but in fact, the center has offered to eliminate the high school and undergraduate program for the past several years but with the support of the NCI leadership and exception funding, the program remains supported and the funds do not come from the CURE budget. Dr. Chabner noted that only a small number of K awards were funded considering that faculties are underrepresented in terms of diversity. Dr. Springfield answered that, because CURE's budget is $25-30 M per year, with approximately $10 M for career development awards, the program does not have the funds to support all meritorious applications. In response to a question by Dr. Chabner, Dr. Springfield indicated that she will approach the NIH Foundation for additional funding.

Dr. Olopade suggested that the NCAB could weigh in regarding a balance between workforce needs and the larger need to train a diverse population to care for cancer patients; she asked about CURE's training ability to meet this latter need. Dr. Springfield responded that the budget has not kept up with the training and the changing demographics, but produces competitive researchers from diverse populations with success rates above that of the NCI, NIH, and the national norm.

Dr. Cruz-Correa congratulated Dr. Springfield, her staff, and the forthcoming scientists in the program, and noted that some of the minorities trained through the CURE program are the scientists who take care of the diseases that most commonly affect minority populations and take care of the minority patients. Studies have shown that patients have better adherence when they are taken care of by their own gender or minority group. Dr. Springfield agreed, and stated that the CURE program strategy has more plans in place for additional programs to better address the workforce gaps but currently lacks resources to implement them at this time.

Dr. Coffey commented that the old C-Change program worked with the workforce inside and outside the academic sector, with dismal results outside the academic sector.

Dr. Olopade observed that supplements have allowed more students to gain experience in different laboratories, and she expressed concern that a limited number of mentors may prevent many investigators from taking advantage of the supplements. Dr. Varmus replied that the program had a 60 percent success rate, and this rate is much higher than the current R01 success rate. Dr. Chabner said that Dr. Springfield's table on K awards showed many applicants and very few awards; he expressed the Board's support for the program.

Dr. Varmus cautioned that he heard an increasing number of complaints about the size of the workforce. The NCI has encouraged more training, and now the success rate for the NCI this year will be below 15 percent; costs of research versus training grants must be balanced.

Dr. Champion congratulated the program but advocated for better advertising to increase applications and perhaps drive up the funding. Dr. Springfield answered that the program has not done much marketing in the past 5 years because word-of-mouth has been effective.

Dr. Champion advocated increasing the number of training awards for predoctoral students, which would encourage the M.D./Ph.D. students and possibly increase interest in interdisciplinary and translational research. Dr. Wiest noted that the F30 awards also are attractive to M.D./Ph.D. students.

Dr. Olopade commented that most training awards help investigators obtain R01 grants, but the workplace needs clinical oncologists who understand science, can develop hypothesis-driven research, deliver the results to patients, and work in teams. Dr. Chabner said that his institution has used the K12 mechanism successfully to attract physicians, and that the K12 award could be more broadly used.

XI. CLOSED SESSION—DR. BRUCE A. CHABNER

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 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).

Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Board would be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

The *en bloc* vote for concurrence with the IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 4,691 applications were reviewed requesting support of $1,305,183,239 and 9 FDA applications were reviewed.

XII. ADJOURNMENTcDR. BRUCE A. CHABNER

Dr. Chabner thanked all of the Board members, as well as all of the visitors and observers, for attending.

There being no further business, the 158th regular meeting of the NCAB was adjourned at 3:15 p.m. on Tuesday, 28 June 2011.

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Date Bruce A. Chabner, M.D., Chair

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Date Paulette S. Gray, Ph.D., Executive Secretary