DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
156TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 7, 2010

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
December 7, 2010

The National Cancer Advisory Board (NCAB) convened for its 156th regular meeting on 7 December 2010, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 7 December 2010, from 9:00 a.m. to 4:04 p.m., and closed to the public on Tuesday, 7 December 2010, from 4:15 p.m. to 5:00 p.m. The NCAB Acting Chair, Dr. Bruce A. Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, Boston, MA, presided during both the open and closed sessions.

NCAB Members

Dr. Bruce A. Chabner (Acting Chair)
Dr. Anthony Atala (absent)
Dr. Victoria L. Champion
Dr. Donald S. Coffey
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. Jennifer A. Pietenpol

President's Cancer Panel

Dr. LaSalle D. Leffall, Jr. (Chairperson)
Dr. Margaret L. Kripke

Alternate *Ex Officio* NCAB Members

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

Members, Scientific Program Leaders Committee, National Cancer Institute, NIH

Dr. Harold Varmus, Director, National Cancer Institute
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
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
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
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, DECEMBER 7, 2010

TUESDAY, DECEMBER 7, 2010

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 7-8 SEPTEMBER 2010 MINUTES—DR. BRUCE A. CHABNER

Dr. Chabner called to order the 156th NCAB meeting. He welcomed members of the Board, the President's Cancer Panel (PCP), *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. He also expressed the Board's condolences on the death of the husband of Board member Ms. Mary Vaughn Lester, Board of Directors, University of California, San Francisco Foundation.

Motion. A motion was made to approve the minutes of the 7-8 September 2010 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, which have been confirmed through 2012.

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 said that the slate of new NCAB members is making its way through the Presidential approval process. The second NCI Town Hall Meeting will occur on 10 January 2011.

NCI Personnel. Dr. Varmus announced that Mr. John Czajkowski is the new Deputy Director for Management and will be assisted by Mr. Jason Donaldson. Mr. Rick Borchelt will assist with public relations activities and help prepare the narrative document for the NCI's bypass budget. Dr. Ed Harlow is joining the NCI part time to help with the Provocative Questions Initiative and the reviews of some programs. Dr. Paul Spellman, University of California, Berkeley, is filling in part time for several months as head of The Cancer Genome Atlas (TCGA) Program. Recruitment is underway for a Deputy Director for Translational Medicine and Clinical Research, and for heads of the Center for Cancer Genomics and the Center for Global Health. In addition, to emphasize the importance of cancer prevention, recruitment has begun for an Associate Director for Cancer Prevention in the Office of the Director (OD).

Budget. Dr. Varmus reminded members that the FY 2012 budget planning process is ongoing. The NCI is managing its FY 2011 budget at last year's funding level under a Continuing Resolution (CR) that lasts until 18 December. By that time, it is expected that the CR will be extended or that Congress will pass an Appropriations bill, which could either increase funding by approximately 3 percent above the FY 2010 level or reduce the federal budget to the FY 2008 funding level. Dr. Varmus indicated his goal to support approximately 1,250 new research project grants (RPGs) in FY 2011, which reflects the number of RPGs funded by the NCI in FY 2009 and 2010. In each of those years, one-quarter of the funded grants were competitive renewals (Type 2), of which 80 percent were awarded to individual investigators (R01s). Approximately 920 new grants (Type 1) were awarded, of which 50-60 percent were R01 grants; 220 of the awardees received the R01 grant for the first time, and one-half of the grantees were considered early-stage investigators. To support 1,250 new RPGs in FY 2011 that focus on the best science, the NCI will need to reallocate between $75 M and $150 M of its current commitment base.

NIH News. Dr. Varmus informed members about trans-NIH activities of interest. The Scientific Management Review Board (SMRB) has recommended that a new institute be formed concerning substance abuse and addiction, and that the National Institute for Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) be dissolved. The NCI's tobacco research portfolio would be affected, with research explicitly focused on the neurological aspects of tobacco addiction being handled by the new Institute. Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), will serve on an NIH-wide committee regarding the new institute. In addition, following a discussion at the recent NIH Institutes and Centers (IC) Directors' Forum about the biomedical workforce and the suitability of the NIH current training programs to future research, Dr. Varmus has asked Dr. Jonathan Wiest, Director, NCI's Center for Cancer Training, to begin a review of the NCI's training programs, including efforts in predoctoral and postdoctoral training as well as training in clinical, basic, and multidisciplinary science.

The SMRB is considering a proposal to create a new center to enhance therapeutics research across the NIH, which would amalgamate some screening programs for chemicals; work with the National Center for Research Resources' (NCRR) Clinical and Translational Science Award (CTSA) Program; and have an affiliation with the NIH Mark O. Hatfield Clinical Research Center (CRC) and interactions with all ICs, including the NCI, that currently conduct therapeutics-oriented research. The SMRB has also approved a plan to move the CRC's budget under the NIH OD's budget. This would move school tax items that previously were adjudicated among the IC Directors to a line item under the OD. The NCI plays a major role in the CRC, successfully occupying 37 percent of the beds; some ICs, however, have difficulty financing the research in those beds as the cost is significantly higher than research in the laboratory.

Dr. Varmus informed members that an announcement is expected at the upcoming NIH Advisory Committee to the Director's meeting concerning the creation of a new program called the Lasker Scholars Program for Clinical Research to promote the recruitment of clinical investigators to the NIH; the Lasker Foundation is lending its name to this effort but no financial support. The Program will allow ICs to offer tenure-track faculty positions to new clinical investigators for up to 8 years, with the option of paying their start-up costs if they move into an academic position outside the NIH. The intention is to attract the best trainees into clinical research during early stages of their careers through an honorific that conveys serious intention and distinction.

NCI News. In November 2010, the NCI announced a decision made by the Data Safety and Monitoring Board (DSMB) to cease the National Lung Screening Trial (NLST) because interim findings demonstrated that patients scanned with helical CT scan, as opposed to conventional chest X-ray, experienced a 20-percent lower lung cancer-specific mortality rate over the course of the study (7-8 years). The NLST involved more than 50,000 heavy-smoker enrollees who were scanned with a helical CT scanner three times over several years and followed for the development of lung cancer and certification of fatality from lung cancer. The NCI's announcement stressed the continued need for the cessation of smoking and inhibition of the start of smoking among young people, and also voiced concerns about radiation exposure. Dr. Varmus said that a paper is forthcoming and issues such as whether helical CT scanners should be regulated as a device will continue into the future.

Dr. Varmus informed members that TCGA, which will be housed within the NCI Center for Cancer Genomics, has undergone significant changes in its direction following a recent meeting of its investigators. Policy issues concerning sample numbers and standards have been adjusted to maintain high quality without rigidity. Under the guidance of Dr. Douglas R. Lowy, NCI Deputy Director, TCGA will begin analyses of mouse tumors and important cell lines.

The NCI has initiated numerous changes in response to the Institute of Medicine's (IOM) report on the structure of the Cooperative Groups, their functions, and how they implement clinical trials. Dr. Varmus said that his predecessor, Dr. John E. Niederhuber, had requested the IOM's review. The changes are

described on http://ccct.cancer.gov and include: the realignment of cooperative groups into four adult groups and one pediatric group; the creation of three biorepositories to ensure the adequate use of clinical samples from patients enrolled in trials; the development of information technology infrastructure called the National Trial Management System; strengthening of the centralized Institutional Review Board (IRB); and refocus of trials based on strong science to support research on molecularly informed therapeutics.

Dr. Varmus told members that he requested a study by the IOM's National Cancer Policy Forum regarding how the validity of molecular signatures used in clinical trials and future clinical practices are regulated, certified, and established. Genomics data, ancillary data, gene expression, methylation patterns, and other molecular-based findings are becoming increasingly important in the design of clinical trials and the choice of therapies, and following recent experiences in the academic research community, there is a need to validate the molecular criteria that are used to assign patients to arms of clinical trials or various therapeutic regimens.

Dr. Varmus said that the "Big Questions" Initiative has been re-named "Provocative Questions" to be semantically more appropriate. The first meeting included individuals from molecular biology communities interested in targeted therapies and oncogene dependence or oncogene addiction. Questions of interest included: Why does chemotherapy actually cure some cancers like testicular cancer? Why does obesity lead to increased rates of certain kinds of cancers? How does the context of a certain tissue type influence the response to therapy? Dr. Varmus is being assisted by Drs. Lowy, Ed Harlow, and Tyler Jacks in planning three additional workshops to cover population sciences, clinical research, and a broader perspective of basic research. A Web site is under development to engage the scientific and advocacy communities in developing, evaluating, and promulgating these questions.

The annual Cancer Centers Directors meeting, scheduled for February 2011, will cover the relationships between NCI-designated centers and those community centers, their role in clinical trials, and concerns about the process for applications and renewal applications.

A number of the NIH changes, including the budgeting of the CRC, the Lasker Scholars Program, and the potential NIH Center on Therapeutics, will affect the Intramural Research Program (IRP). Dr. Varmus met with the Board of Scientific Counselors (BSC) (Basic Sciences and Clinical Sciences and Epidemiology) concerning the application review process and the reconfiguration or closing of laboratories, as well as issues related to intramural investigators working with industry, including intellectual property rights, Cooperative Research and Development Agreements (CRADAs), and technology transfer. Although government officials cannot receive monetary compensation from industry, the private sector still can access the wisdom and experience of intramural investigators working in official government capacity. Dr. Varmus also indicated that changes are underway in the NCI's Frederick Cancer Research Facility (FCRF), including both the intramural program and the contract program mediated through Science Applications International Corporation (SAIC). A new advisory board composed of both NCI employees and extramural members is being established. Recruitment for the new CEO of the SAIC-Frederick program also is under way. Further details about these changes will be provided to the NCAB at a future meeting.

Dr. Varmus concluded his remarks by noting that progress has been made in many areas, especially programmatically. The major impediment facing the NCI is obtaining adequate funds to support all of its programs. Nevertheless, it is a fantastic time to work in cancer research.

Questions and Answers

Dr. Chabner asked about the establishment of the grant funding policy by the NIH or NCI. Dr. Varmus replied that some of the policies, such as cost of living allowances and the percentage of grants for early stage investigators, are applicable across the NIH. Each IC, however, has the responsibility to manage its own portfolio and the flexibility to shift funds.

Dr. Chabner asked whether a cost-benefit analysis would be conducted regarding the results of the NLST, noting the high level of biopsies conducted for each case of cancer discovered. Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, agreed that the cost-benefit analysis will have significant policy implications. Dr. Varmus replied that a risk-benefit analysis currently is underway, but that the insurers' approach to reimbursement is not presently known. He added that a large percentage of those screened will have some finding that usually involves additional radiation and further cost. Dr. Varmus indicated that Dr. Donald M. Berwick, Administrator, Centers for Medicare and Medicaid Services (CMS), has stated publicly that the CMS is considering the cost and other implications. Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, Professor of Oncology, Mayo Clinic, commented that the emphasis on prevention of the initiation of smoking and smoking cessation can increase disparities if the population with the highest smoking percentage, specifically the minority and poor populations, do not have access to this screening. Dr. Varmus agreed and suggested that the NLST results be discussed in further detail following publication.

Dr. Chabner asked whether industry is allowed to compensate the government for the expense of an employee who provides consulting assistance or sits on an advisory board. Dr. Varmus responded that the government will allow such consulting to occur as an official duty. He added that, following queries by Congress about travel by intramural investigators, it was shown that the travel was to legitimate sites.

Dr. Chabner encouraged the NCI to involve the Board more fully in the Provocative Questions activity. Dr. Varmus agreed that the status of the initiative could be presented at a future NCAB meeting.

Dr. Chabner requested further details about the NCI's budget situation. Dr. Varmus explained that currently the NCI is employing the conservative NIH approach of paying noncompetitive renewal awards (Type 5) at 90 percent. He added that a reduction of the NCI's budget to FY 2008 levels would result in a decrease of $300 M, and this level of budget stringency would be particularly devastating to research opportunities for new investigators.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, George Barth Geller Professor of Cancer Research, Duke University Medical Center, asked Dr. Varmus about his interactions with other agency heads, such as the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). Dr. Varmus replied that he maintains close relations with the leaders of those agencies. In addition, an FDA-NIH cooperative agreement is in place that extends to training, and meetings with the FDA have focused on changes to the trial designs that will be needed as targeted drugs become more numerous and innovative treatment strategies become more common; the FDA recently released draft guidance on multidrug trials. The FDA has personnel in the CRC and elsewhere on the NIH campus learning about contemporary cancer research. Dr. Varmus expressed his pleasure in working with trans-Agency colleagues in comparative effectiveness research and other issues but added that good synergy does not substitute for the funding needed to cover the research.

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, reminded members that the Panel currently consists of Dr. Leffall and Dr. Margaret L. Kripke. The White House appointment of a third Panel member is pending. Dr. Leffall stated that the mission of the Panel is to monitor the development and execution of the activities of the National Cancer Program (NCP) and to report any delays or blockages in the rapid execution of the NCP directly to the President.

The 2009–2010 meeting series covered the topic "America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise." Meetings were held in Seattle, Washington; Los Angeles, California; Wilmington, Delaware; and Miami, Florida, and statements and summaries of the meetings are available on the PCP Web Site (http://deainfo.nci.nih.gov/advisory/pcp/). The Panel has begun preparing the 2009–2010 report and anticipates its completion in January 2011.

Dr. Leffall informed members that the 2010–2011 meeting series "The Future of Cancer Research: Accelerating Scientific Innovation" is inspired by the upcoming 40th anniversary of the 1971 National Cancer Act. The meetings will attempt to better define the role of stakeholders in the NCP and will reflect on past progress and consider the best direction for the future of cancer research and the NCP. The series also will consider how the cancer community can utilize a broad array of scientific, computational, and emerging disciplines to accelerate the progress of the NCP. The first two of the meetings were held in Boston, Massachusetts (22 September), and Philadelphia, Pennsylvania (26 October), and the remaining two meetings will occur on 14 December 2010 in Bethesda, Maryland, and 1 February 2011 in Atlanta, Georgia. At the Boston meeting, the Panel heard how different federal agencies, public and private sectors, and non-profit and academic organizations define the NCP and their roles and responsibilities within the NCP. In Philadelphia, the Panel heard about the need to examine the current environment in which cancer research is conducted, and the importance of fostering high-risk, creative projects with the potential to result in innovative breakthroughs. In addition, speakers stressed the importance of investment in infrastructure and the role of electronic health records and other technologies as critical to the future of cancer care and research. Subsequent meetings in this series may explore topics related to technologies applicable to research on cancer prevention, causation, and care; collaborations needed to apply such technologies to cancer research; medical, ethical, and legal issues; and barriers to advancing to a new era of cancer research.

Questions and Answers

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, asked about the audiences targeted and attendance levels at the Panel meetings. Dr. Leffall explained that the meetings are open to the public and that time is allotted for public comments. Dr. Kripke added that the Panel members themselves are the audience. Invited experts present testimony to the PCP at these public meetings, and this testimony informs the recommendations made by the PCP to the White House. The PCP reaches its largest audience through the dissemination of its annual reports.

Dr. Chabner asked about the Panel's current focus on the progress of cancer research and wondered whether it duplicates strategic planning efforts by the NCAB *Ad hoc* Working Group To Create a Strategic Scientific Vision for the National Cancer Program and Review Progress of the National Cancer Institute. Dr. Kripke indicated that the Panel is taking a much broader look at the NCP but not providing advice to the NCI Director about specific actions needed.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on appropriations, legislation of interest, and NCI's Congressional outreach activities. The NCI continues to operate through mid-December under a continuing resolution (CR) at the FY 2010 funding level. The NCI's FY 2011 budget could be established through the passage of an Omnibus Appropriation Bill, or the Institute could operate under a short- or long-term CR.

Ms. Erickson informed members that Rep. Lois Capps (D-CA) introduced a House companion bill (H.R. 6224) to former Senator Edward Kennedy's (D-MA) Senate health bill on 21st Century Access to Life Saving Early Detection, Research and Treatment (ALERT) Act. In addition, Rep. Mary Jo Kilroy (D-OH)

introduced the Cancer Centers Assistance for Renovations and Expansion Act (H.R. 5861), which would establish a loan program for qualifying cancer centers.

The NCI and the Association of American Cancer Institutes (AACI) co-sponsored a pilot education event in July 2010 to provide a firsthand view of translational research to several Congressional staff and members of advocacy organizations. Dr. Varmus conducted a briefing for House members on 29 September at an event sponsored by the American Association for Cancer Research (AACR). Ms. Erickson informed members that the ratio of Committee seats in the House and Senate for the 112th Congress will be adjusted to reflect the results of the recent elections, and that all House Committees will have new chairpersons. Committee and Subcommittee rosters will be finalized in January 2011.

Questions and Answers

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, asked about the status of Department of Defense (DoD)-supported cancer research. Ms. Erickson replied that the NCI is aware of the funding level for the DoD Congressionally mandated programs but does not monitor DoD's appropriations. Dr. John F. Potter, Director, United States Military Cancer Institute, Walter Reed Army Medical Center, noted that the DoD's cancer research activities are managed at the Fort Detrick Army Base in Frederick, Maryland.

Dr. Coffey asked whether interactions at the global level were monitored, given that the United States represents 5 percent of the world's population, but approximately 80 percent of cancer research funds. Ms. Erickson indicated that Congress is not specifically involved with international activities, which are managed at the Agency level.

VI. NCAB AD HOC WORKING GROUP REPORT—DRS. BRUCE A. CHABNER AND PHILLIP A. SHARP AND MR. WILLIAM H. GOODWIN, JR.

Dr. Chabner, Mr. William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc., and Dr. Phillip A. Sharp, Institute Professor, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, presented the report of the NCAB *Ad hoc* Working Group To Create a Strategic Scientific Vision for the National Cancer Program and To Review Progress of the National Cancer Institute. The Working Group was established in February 2010, and involved members from the NCAB, industry, academia, and the lay community. The Working Group met in May, July, and August 2010, to review the NCI's current operating structure and strategic vision, assess the effectiveness of its scientific programs and management structure, and determine opportunities to advance cancer research. The Working Group developed 19 recommendations to assist the NCI as it faces a period of fiscal restraint, expanding opportunities for scientific advances, and increased incidence of cancer worldwide.

Industry is now the major source of new cancer drugs, but relationships between industry and the NCI are hampered by conflict of interest (COI) rules and overlapping activities in drug evaluation and clinical development. The NCI should avoid competition and overlap with industry in areas of drug discovery and evaluation, where industry has a clear responsibility and financial interest. In addition, the NCI/NIH should revise COI regulations that unnecessarily hamper interaction of their intramural scientists with industry.

The Cooperative Groups continue to be vital to defining treatment strategies. The Working Group endorsed the 2010 IOM Report, which called for efforts to address delays in protocol development and review, unnecessary duplication in group functions, underfunding of trials, and failure to complete trials. The NCI should rapidly implement IOM recommendations for streamlining review, improving funding, and consolidating functions, and should provide interim reports to the NCAB on the progress made.

The Medical Oncology Branch (MOB) has been the focal point of translational research in the intramural program but has had difficulty recently in attracting top researchers and fellows and has lost its leadership role nationally. The Working Group recommended that the medical oncology faculty be consolidated within the MOB, new mechanisms be developed to recruit and retain talented investigators, collaborations with industry be encouraged to promote new drug evaluation and development, and the growing financial predicament of the CRC be resolved.

The Working Group reviewed the cancer prevention programs managed by the Division of Cancer Prevention (DCP) and DCCPS. The DCP supports clinical trials in cancer prevention and a screening program for chemoprevention that do not connect effectively with either basic science, cancer drug development, or clinical trials activities in other divisions of the NCI. It was noted that the DCCPS has forged important collaborative relationships within and outside the NCI that are essential to an effective cancer control program and should continue. Alternative organizational structures should be evaluated for the DCP to encourage closer ties between prevention research and related programs in other NCI divisions and with basic science; likewise, the DCCPS should pursue further synergies and efficiencies in resource utilization with the DCP and Division of Cancer Treatment and Diagnosis (DCTD).

The FCRF provides a critical rapid response mechanism for the NCI and NIH for drug development, AIDS support, and research resources. However, numerous research initiatives in the past decade have been established or expanded without fully transparent external review. Major initiatives, such as the cancer Biomedical Information Grid (caBIG™) and cancer Human Biobank (caHUB) may require periodic review. In addition, the NCI should consider establishing a chartered committee to advise and evaluate ongoing activities at the FCRF, as well as consolidate the review of its community oncology programs into one competitive process.

In the NCI training programs, the NCI T32 program eligibility policy has been skewed strongly toward mentors holding RPG (R01) funding and toward postdoctoral trainees pursuing projects that are explicitly cancer related. Predoctoral training has been de-emphasized, and team research during training has not been pursued effectively. Because cancer can arise from defects in cellular processes that often are poorly understood, the NCI should consider rebalancing its training mechanisms to support a more equal blend of cancer-directed and basic, clinical, and population-based science. It also should increase expenditures for training programs, especially for early training, such as through medical student research programs or support of predoctoral trainees. An Integrative Cancer Research Training Award would bring together trainees with different disciplinary foci to establish a collaborative research and training plan that presents basic research in a direct cancer context and fosters a culture of teamwork.

The Cancer Centers and their investigator-initiated grants have led the revolution in cancer biology and the application of this knowledge to treatment and diagnosis. The NCI should streamline the process of applications and review of Cancer Centers with a focus on scientific accomplishments and translational applications, and also encourage and reward partnerships among Cancer Centers.

Specialized Programs of Research Excellence (SPORE) grants have become a major instrument for supporting disease-specific research, encouraging team science, and supporting early translational research that is not easily funded through RPGs (R01). The NCI should consider establishing SPOREs directed at specific pathways or molecular mechanisms common to multiple cancers. Alternatives for integrating SPORE and Cancer Center reviews also should be considered.

The NCI has invested substantially in comparative effectiveness research (CER) to date, and involvement in the following efforts should continue: developing data infrastructure for CER; facilitating the development and refinement of methods for CER; ensuring that priority populations are included in cancer CER; and training future generations of researchers to carry out cancer-related CER.

Questions and Answers

Members complimented the Working Group leadership for providing an atmosphere of open debate and preparing an outstanding report. Dr. Varmus expressed appreciation to the Working Group and speakers for their efforts in preparing the report. He will report back to the NCAB as recommendations are implemented.

Dr. Waun Ki Hong, Professor, Head, Division of Cancer Medicine, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, asked about the prioritization and implementation of the recommendations. Dr. Chabner said that it was not the Working Group's job to propose implementation solutions; the NCI leadership was involved in the discussions, and changes are under way to take advantage of new science and new opportunities. Mr. Goodwin said that Dr. Collins, Director, NIH, recommended the Working Group's approach, with progress reports provided to the NCAB during the next few years. Dr. Sharp reminded members that the NCAB provides advice and oversight, and that the NCI has the responsibility to execute the strategy.

Dr. Champion expressed support for greater collaboration between population science and clinical trials, and she encouraged the use of training mechanisms as a means to foster collaboration. Dr. Sharp agreed and commented that clinicians must rethink their concept of clinical trials related to pathologic diseases and population scientists must rethink the boundaries between their specialties and the basic sciences and clinical medicine.

Dr. Lyerly asked how the MOB consolidation is envisioned to promote quality interactions with basic science laboratories while avoiding the creation of an isolated scientific unit. Dr. Chabner replied that the intent was to empower the MOB leadership to achieve the clinical research mission; the MOB should be unified, but connections with basic science laboratories should be continued.

Dr. Kaur expressed support for the redirection of the NCI budget to make the most critical changes. Dr. Sharp said that the Working Group meetings revealed the deep appreciation for the NCI and its contributions during the last 40 years in establishing the groundwork to advance the treatment and control of cancer.

Dr. Michael A. Babich, Directorate for Epidemiology and Health Sciences, Consumer Product Safety Commission, asked whether the Working Group considered cancer etiology, including environmental causes of cancer, noting that this was the subject of the PCP's 2009 report. Dr. Coffey said that the environmental component (i.e., pathobiology), should be stressed a bit more to help reinforce the differences between solid and liquid tumors. Dr. Chabner said that the Working Group considered cancer etiology and the environment as part of the NCI's strong RPG (R01) program, which was not reviewed. The recommendation to strengthen prevention programs by improving ties to basic science, the clinical drug development program, and translational research could be amended to include environmental sciences and environmental research. Dr. Leffall said that the PCP's environmental report generated more comments from the public, private sector, institutions, and organizations than any other PCP report. Dr. Varmus pointed out that the National Institute on Environmental Health Sciences (NIEHS) also has a keen interest in cancer. Dr. Kripke observed that one-third of NIEHS' research funding supports cancer-related activities. Drs. Sharp and Chabner commented on the NCI's extensive interactions with other Institutes and federal Agencies, such as the FDA, to share information and standards.

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, asked whether the Working Group discussed global health issues. Dr. Sharp responded that issues of the worldwide incidence of cancer, as well as collaboration between countries and scientific communities in different countries, are discussed in the report's introduction.

Dr. Pietenpol commented that this activity has initiated a national discussion concerning the Cancer Centers, streamlining of clinical trials, training, the Cooperative Groups, and other topics discussed by the Working Group, and notable progress already is under way.

Motion. A motion was made to accept the report of the NCAB *Ad hoc* Working Group To Create a Strategic Scientific Vision for the National Cancer Program and Review Progress of the National Cancer Institute. The motion was seconded and approved unanimously with the caveat that the report be amended to include "environmental science" in the list of interactions for the cancer prevention program.

VII. OPERATIONAL EFFICIENCY WORKING GROUP (OEWG) DEMONSTRATION—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Director, DCTD, provided an update on the NCI's activities to streamline the process of activating clinical trials based on the recommendations of the OEWG. Dr. Doroshow described significant improvements in the timeline from concept submission to protocol approval for trial stages and mechanisms. The target timeline offers an ideal schedule to traverse from concept review to trial activation, and it excludes contracting, drug supply, and FDA review. A pause in the timeline ("time-out") occurs following the concept review cycle and other specific milestones if industry negotiations cause delay.

Of the 13 Phase III concepts received since 1 April 2010, 4 have been approved, 4 have been disapproved or withdrawn, 3 are in review or time-out, and 2 are awaiting review by the Cancer Therapy Evaluation Program (CTEP) Steering Committee. The target timeline for Phase III trials is 300 days from concept review to trial activation, and the protocol will be terminated if it is not activated within 2 years. The average number of days for concept approval by the Steering Committee totaled 89.5 days, meeting the 90-day target timeline for approval. In addition, one of the concepts included a protocol submission that was approved at the same time.

Phase I and II letters of intent (LOIs) have a target timeline of 210 days and termination of a protocol if it is not activated within 18 months of concept submission. Dr. Doroshow said that 45 Cooperative Group LOIs have been received, with 10 approved; 11 in review or time-out; and 24 disapproved, withdrawn, or declined by the pharmaceutical company. The average concept approval process took 47 days, compared to a 60-day target. Six protocols have been submitted in an average time of 55 days from Group LOI approval, compared to a 60-day target, and the average time-out length was 16 days.

Dr. Doroshow described similar positive results for U01/N01 and intramural LOIs. Fifty U01/N01 LOIs have been received, with 16 approved, 16 in review or time-out, and 18 disapproved or withdrawn. The average number of days for LOI concept approval was 37 days, and the average for protocol approval was 55 days, compared to a 60-day target for each process. Ten protocols are in the activation stage. For intramural LOIs, 12 have been received, 8 of which are approved, 3 have been disapproved, and 1 is in review or time-out. In addition, seven protocols were submitted and are in the activation stage. Approvals occurred on an average of 30 days for concepts and 47 days for protocols.

To achieve OEWG goals, the NCI has streamlined processes and improved communication, identified at-risk trials, established teleconference calls to resolve outstanding issues, and held regular coordination and working group meetings. In addition, a secure, role-based Web portal shares tracking reports with intramural and extramural investigators and support staff. Between 1 April and 1 December 2010, 158 teleconference calls occurred to clarify and discuss comments in the Consensus Review and prevent review iterations that otherwise might slow the approval process. The timeline targets are aggressive but necessary to reduce Cooperative Group Phase III trials from 830 to 300 days; Cancer Center investigator-initiated trials from 200 to 90 days; and CTEP early drug development Phase II trials from 550

to 210 days. Dr. Doroshow next introduced Mr. Steve Friedman and Ms. Shanda Finnigan, CTEP, who provided a demonstration of the online Web tool to follow timelines of the concept and protocol process.

Questions and Answers

Dr. Chabner asked about the current status of the portal. Mr. Friedman replied that the tool was deployed in late July 2010, and eight training sessions have been held with intramural and extramural staff and investigators. Some Cooperating Groups are actively using the system. Web usability measurements will help staff better understand and respond to users' needs.

Dr. Hong applauded the tremendous progress made in activating trials more quickly and asked about the number of protocols under development. Dr. Doroshow answered that there are nearly 300 early phase (Phases I and II) and approximately 100 Phase III active protocols.

Dr. Chabner asked whether other areas of the process could be expedited. Dr. Doroshow explained that each component involves shortened timelines, with reviews handled by the Steering Committee and extramural reviewers; timeliness is recognized as a priority, and once the process has been established at meeting the 300-day target, the timeline can be shortened. Dr. Jeff Abrams, Associate Director, CTEP, added that protocols are reviewed weekly and that teleconferences ensure that issues related to regulations and drug distribution are addressed quickly. Dr. Doroshow said that the changes likely will improve accrual rates to clinical trials.

Dr. Lyerly asked how priorities will be achieved without additional resources available. Dr. Doroshow acknowledged the issue and said that improvements to the process included external oversight to help the NCI prioritize and make difficult decisions. He added that ARRA funds supported a small staff dedicated to ensuring that the timelines were met.

VIII. CENTER FOR CANCER RESEARCH: UPDATE ON PROSTATE CANCER IMAGING—DRS. W. MARSTON LINEHAN, PETER L. CHOYKE, AND PETER A. PINTO

Introduction. Drs. Lee J. Helman, Scientific Director for Clinical Research, and W. Marston Linehan, Chief, Urologic Oncology Branch, introduced the update report on the Center for Cancer Research's (CCR) activities in prostate cancer imaging. The CCR is an internal arm of the NCI that integrates basic, translational, and clinical research, translating advances rapidly to the clinic; developing innovative technologies for detection, diagnosis, and treatment; and pioneering novel interventions for underserved patient populations and rare cancers. The CCR collaborates with the NIH Center for Interventional Oncology to investigate cancer therapies that use imaging technology to diagnose and treat localized cancers in precisely targeted ways that are minimally or noninvasive.

Dr. Linehan reminded members that prostate cancer affects more than 200,000 men in the United States each year, with more than 32,000 deaths attributed to the disease and 1 million prostate biopsies conducted each year. Men undergo prostate biopsy because they have elevated prostate-specific antigen (PSA) levels, or they have prostate cancer and either require active surveillance for tumor grade evaluation or undergo focal therapy, such as cryotherapy. Prostate cancer is the only solid tumor currently diagnosed by random sampling of the organ; in addition, organ-sparing treatments that have been developed for other cancers are not available for prostate cancer. Magnetic resonance imaging (MRI), ultrasound, and other imaging technologies provide a means to significantly improve the diagnostic accuracy of the biopsy and turn focal therapy into image-guided, systemic therapy that targets localized prostate cancer and advances pharmacodynamics and tumor response evaluation. Dr. Linehan next introduced the speakers: Drs. Peter L. Choyke, Program Director, Molecular Imaging Program; and Peter A. Pinto, Clinician, Urologic Oncology Branch.

Molecular Imaging of Prostate Cancer. Dr. Choyke presented findings from studies of MRI for molecular imaging of prostate cancer. It could provide the best anatomic and functional information of all imaging techniques currently being used. MRI has been integrated into practically every step of the prostate cancer workup for localized prostate cancer. Multiparametric MRI, using a 3 Tesla MRI system in combination with an endorectal coil generates the best overall image quality for tumor detection. This involves taking data from each technique—T2 weighted scans, Diffusion weighted scans, and Dynamic contrast enhanced (DCE MRI) scans—and segmenting out the prostate cancer, then training a software algorithm to reliably detect prostate cancers. Each time a new case is entered, the algorithm is refined to improve the reliability of the probability map. It is thus possible to train the algorithm and decision support system to recognize cancer with a high rate of accuracy.

Quantitative T2 mapping generates a reproducible result that is useful for longitudinal studies, and it provides information to support the multiparametic analysis that will be a component of the decision support system for prostate cancer. Improvement in the quantitation of T2 imaging is being studied at the NIH. Similarly, diffusion weighted imaging is used to quantitate Brownian motion of water within the prostate using the Apparent Diffusion Coefficient (ADC) that has proven generally reliable in predicting the Gleason score.

Quantitative pharmacokinetic mapping from DCE MRI is being significantly improved. For instance, improvement in the measurement of the arterial input function to identify the center of the feeding vessel has been developed to reduce variability. These techniques have improved the quality and reproducibility of DCE MRI so that a quantitative permeability map of the prostate can be generated.

The software algorithm combines each type of MR image and compares it to histology. Training is a critical component of refining the probability map. After correlation with histology, a clustering analysis of pixels is conducted to find image clusters that correlate with cancer. While each individual technique in the multiparametric MRI system is not sufficient to distinguish cancer from noncancer, when these techniques are combined together, the technique has a sensitivity of 90 percent and specificity of 90 percent after optimization. Although this will not replace the biopsy, it can confidently lead clinicians to better identify sites that should be biopsied and those that can be safely left alone.

Other techniques also are being investigated for localized prostate cancer, including molecular imaging by PET and SPECT scans. Because prostate cancer is one of the few tumors that does not involve the glycolysis pathway (Warburg effect), other pathways are being investigated, including fatty acid synthesis using radiolabeled acetate and amino acid metabolism using radiolabeled amino acids. In a recent Phase II study of 40 patients using C11 acetate, the uptake of C11 acetate was greater in more advanced tumors, than in lower grade and smaller tumors. In a small study in 30 patients with a synthetic L-leucine analog, preliminary results in 7 of the patients showed that the analog is taken up by fairly low grade tumors within 5 to 7 minutes after injection. Both of these newer techniques show promise for earlier identification of localized prostate cancer and with higher specificity and sensitivity than current tests. Another technique in early development is radio-labeled prostate-specific membrane antigen (PSMA) combined with an endorectal probe that was designed at Brookhaven National Laboratories.

The use of sodium fluoride, an agent that was developed many years ago but has not been used, provides a promising future avenue of research. Labeled sodium fluoride is far more sensitive than conventional bone scans for metastatic disease to the bone; a Phase II trial in 50 patients is being conducted. This includes 30 patients in a reproducibility study to determine the intra-scan variability. Early results show that more lesions are seen with the labeled sodium fluoride than with conventional bone scan, which raises the possibility that what had been called localized prostate cancer in the past may be early metastatic prostate cancer.

Questions and Answers

Dr. Chabner applauded the presentation because of the prevalence of prostate cancer and because better quantitative techniques will simplify complex decision-making processes in the clinical setting. He encouraged efforts to use imaging to screen patients who do need treatment; this would help with one of the overriding issues in prostate cancer diagnosis and treatment and help reduce costs significantly. Dr. Choyke responded that imaging techniques do a better job of identifying cancers, but the goal is to identify those that are biologically aggressive cancers. Dr. Linehan added that clinicians often see men with small prostate cancers that were thought not to be significant and 5 to 10 years later they have a positive bone scan. The ability to quantitate bone imaging of prostate cancer would radically change how clinical trials are conducted. Dr. Coffey agreed with Dr. Linehan and added that the information on sodium fluoride may lead to a better understanding of how to correlate bone mass with grade of prostate cancer.

Dr. Coffey asked whether the acetate and sodium fluoride are being correlated to circulating tumor cells. Dr. Helman responded that he has asked Drs. Pinto and Marston to build a research protocol for imaging of circulating tumor cells, and what study questions to pursue in that context. Dr. Linehan illustrated how this is done in kidney cancer using PET scans to identify those individuals with the disease. Because kidney cancer is characterized by Kreb cycle enzyme mutation, a PET scan for glucose uptake is positive; if an agent blocks glucose uptake, the PET scan becomes negative and the tumor completely resolves. Something similar is needed in prostate cancer diagnosis.

A short discussion of the meaning of the recent drop (40 percent) in the tumor specific death rate in prostate cancer ensued. In discussions with the administrators of the Surveillance, Epidemiology and End Results (SEER) program, it was determined that the drop was not associated with a coding change in death certificates or other data artifacts. The conclusion of the group that met to discuss this issue 13 years ago was that early detection and treatment of prostate cancer saves lives.

Image Guided Biopsy of Prostate Cancer: Implications for Diagnosis and Therapy. Dr. Pinto said that imaging provides a link to answer the primary questions in prostate cancer research regarding random sampling to attempt to detect a tumor and the lack of organ-sparing treatment for the prostate. Surgical techniques have not advanced much since the late 1930s, although transrectal ultrasound (TRUS) offers more accurate image guidance. This limited progress means that success in finding tumors generally is not more than 50 percent, even with 12-core biopsies. Patients with a negative biopsy are told that perhaps they do not have cancer or the needle may have missed the tumor.

Since 2000, spectroscopy and MRI have improved from the pre-PSA to the post-PSA era, although much progress is needed to accurately diagnose prostate cancers that are of concern. A technology is needed that can detect cancer within the gland and provide a location, size, and grade, similar to the mammography field, where those identified at high risk have higher levels of screening based on other factors; for prostate cancer, this would be factors other than PSA.

Correlating the placement of the tumor as seen by imaging and the tumor excised during surgery has been a challenge, but one that has been met by making a mold individual to each prostate specimen excised and allowing the pathologist to slice the prostate in the exact location that the MRI indicates. It required many years of work to make this model useful. The model is made before surgery and accounts for the sagital, axial, and coronal coordinates; once the prostate is removed, it is snap-frozen, with fresh tissue taken for genomics, DNA, RNA, and virology (e.g., XMRV). This method has been used on 45 patients to determine whether the axial whole mount slice can be specifically characterized in the exact location as the MRI has predicted based on this molding method. Based on these patients, the positive predictive value of finding the tumor at the location noted by combining methods is approaching 100 percent.

Merging technological platforms is another strategy in prostate cancer diagnosis. Working collaboratively with Phillips under the CRADA mechanism, a urologic oncology group at the NIH is developing a research platform to fuse MRI images with a standard ultrasound machine to conduct an ultrasound office-based biopsy. The platform is based on a GPS-type system that has sensors in the probe that navigate in the prostate in real time. During the biopsy, the sensors fuse the technologies, communicate with each other, and allow the magnetic field to act like a GPS targeting device. The first cohort of patients for this protocol was established in the past few weeks.

Patients in the community setting who may benefit from this new technology have low PSAs (approximately 5.8); some have previous positive or negative biopsies; and some are those under active surveillance. These patients are likely to have localized disease, low volume, and well-differentiated cancer, and likely would benefit from a different approach than those treated for aggressive tumors pre-PSA. Even in the best of hands, there is a risk for impotence, incontinence, and other morbidities from the therapy. Patients and physicians are asking and seeking better treatment options. Localized prostate cancer is the new challenge in the PSA era. There must be improvement in the area of tumor sampling and therapy that addresses the disease as it exists. MRI research is promising and may provide an opportunity to partner with other imaging modalities (e.g., PET, SPECT, and ultrasound), but more work is needed in the field to ensure that patients benefit.

Questions and Answers

Dr. Chabner commented that the challenge will be to apply what has been learned to either provide less treatment or to select the right patients for treatment. Dr. Helman added that this technology would be ideal for testing in multiple centers and in large enough numbers to prove that focal therapy for prostate cancer is possible in the next decade.

IX. STATUS REPORT: DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS—DRS. JOSEPH FRAUMENI, JR., AMY BERRINGTON DE GONZALEZ, ERIC ENGELS, SHARON SAVAGE, AND STEPHEN CHANOCK

Introduction. Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), noted that last year's program review emphasized the Division's work on environmental cancer and its impact on public policy. This year's report reflects the broader mission of the Division and illustrates the spectrum of research activities conducted. The studies to be presented include an evaluation of the cancer-causing potential of medical radiation exposures; the cancer risks associated with immunosuppressive disorders; studies of dyskeratosis congenita, a cancer-predisposition syndrome, that have clarified the role of telomere biology in cancer; and a status report on the Division's program of genome-wide association studies (GWAS). For these four topics, Dr. Fraumeni introduced the speakers: Drs. Amy Berrington de González, Radiation Epidemiology Branch; Eric Engels, Infections and Immunoepidemiology Branch; Sharon Savage, Clinical Genetics Branch; and Stephen Chanock, Chief, Laboratory of Translational Genomics and Director, Core Genotyping Facility.

Cancer Risks from Medical Radiation Exposure. Dr. Berrington de González presented findings from her studies of cancer risks from both diagnostic and therapeutic radiation exposures. Exposure risks from diagnostic radiation are a concern because of the 6-fold increase in its use from average radiation exposure from medical sources in 1980 of 0.5 millisievert (mSv) per year to an estimated 3 mSv per year in 2006. Based on data on the levels of use from the early 1990s, approximately 1 percent of cancers in the United States might be related to diagnostic radiation and exposures. It is difficult to study the cancer risks of radiation directly, as it typically takes 5 to 10 years after an exposure for a radiation-related cancer to develop. Information from long-term studies such as the Japanese atomic bomb survivors can be used in risk projection models which provide more timely estimates of these potential risks. Dr. Berrington de

González described the NCI radiation risk calculator, an interactive tool that allows estimation of risks based on the organ exposed, age, and sex of the exposed person.

Of the 29,000 cancers projected from CT scans conducted in the United States in 2007, abdominal and pelvic scans could cause 14,000 projected cases. Cardiac stress tests have received less attention to date but also make a major contribution to overall radiation from medical sources: specifically, 20 percent of the collective dose to the U.S. population. The average dose from a cardiac stress test is higher than that from many CT scans depending on the type of radioisotope used. Dual isotope tests deliver a dose five times higher than a standard chest CT scan. Using the risk calculator, this source of radiation exposure could result in an additional 7,400 projected cancers based on the frequency of use in 2008, with the Technetium-99m, the most common test, accounting for approximately 5,000. In combining the effects of these tests, if they are used at the same level into the future, approximately 3 percent of cancers will relate to these diagnostic radiation exposures, which represents a 3-fold increase from the estimates from the early 1990s. These and similar studies have resulted in a number of campaigns to mitigate the potential risks: the NIH Clinical Center has instituted a radiation dose tracking program; the U.S. Food and Drug Administration (FDA) has published a white paper on reduction of radiation exposure; and the American College of Radiology has launched the Image Wisely campaign. Recommendations include reduction of CT use and reduction of dosage.

Dr. Berrington de González also has examined the risks of therapeutic radiation exposure for the estimated 12 million cancer survivors in the United States. This population has a 14 percent higher risk of subsequent malignancy than the general population. Currently, it is not known what proportion of second cancers might be related to the radiotherapy treatment for the first. The SEER cancer registries database was used to analyze the second cancer risks in 15 first cancers routinely treated with radiotherapy. Data on 1.3 million survivors indicate that approximately 9 percent of the patients developed a second cancer during the followup period; using regression models, it is estimated that approximately 3,300 excess cancers were diagnosed in those who received radiotherapy treatment, 8 percent of the cancers diagnosed, or one excess cancer for every 150 patients treated. Risks were higher for younger patients and those who received pelvic radiation. These estimates can be used to communicate the risks to physicians and patients; in general, the benefits should outweigh the risks. The last decade has seen rapid changes in radiotherapy modalities; intensity modulated radiotherapy and proton therapy are more widely used to reduce high-dose exposures, and these therapies may increase the amount of medium- and low-dose exposures to the rest of the body.

Questions and Answers

Dr. Chabner asked why proton therapy, which produces less scatter than other forms of treatment and has been shown by a study to have a reduced risk of second cancers, would constitute a greater risk. Dr. Berrington de González responded that the therapy potentially results in a whole body neutron dose and neutrons have higher relative biological effectiveness; the study that Dr. Chabner mentioned still has relatively short-term followup. Dr. Chabner added that it followup is important as children often are treated with proton therapy.

Dr. Meneses asked about the risk related to radiation therapy, given that many cancer survivors had received combination therapy, and wondered if those of “younger age” mentioned as at higher risk in the study were adolescents or young adults. Dr. Berrington de González replied that in general it is not thought that there are significant second cancer risks from chemotherapy, but it is a limitation of the study that potential interaction with radiation could not be taken into account because of the lack of data on chemotherapy. She confirmed that the study was conducted on adult cancer survivors. Dr. Chabner added that the biggest problem currently seen is in Hodgkin lymphoma patients, who are radiated during adolescence and have a high incidence of breast cancer.

Dr. Kaur asked if the correlations among age of exposure, amount of exposure, and tissue sensitivity, as well as ATM-mutations' impact on sensitivity to radiation were examined. Dr. Berrington de González said that examination of the sensitivity of different tissues is part of the ongoing mission of the branch, and a study is being completed on second gastrointestinal cancers focusing on esophageal, pancreatic, and stomach cancers and clarifying whether they could be radiation-induced.

Dr. Chabner asked about the use of helical scans in diagnosing lung cancer and the risk of second cancers for patients who undergo three helical CTs. Dr. Berrington de González responded that another area of her research examines screening radiation and evaluating the potential radiation risk compared to the benefit; a study on lung CT screening before age 55 suggested that in younger participants, it is not clear that the benefits outweigh the risks because the cancer rates are low.

The Burden of Cancer in Immunosuppressed People in the United States. Dr. Engels reported on two studies of HIV-infected people and transplant recipients that allow the comparison of patterns of cancer risk among immunosuppressed populations. The two record-linkage studies described are complementary; represent successful collaborations between NCI, other federal agencies, and state public health authorities; and address questions of public health and scientific importance. The largest immunosuppressed population is people living with HIV infection, and recipients of solid organ transplants on immunosuppressive medication to prevent graft rejection are another significant immunosuppressed population. Cancer in these populations occurs because of immunosuppression and also because of cofactors such as infectious agents, tobacco and alcohol, potential medication toxicity, and (for transplant recipients) possibly the transplanted organ itself. The standardized incidence ratio (SIR)—a relative risk measure comparing the immunosuppressed to the general population—is highest for Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer, all caused by viruses and considered AIDS-defining cancers. The risks for lung, Hodgkin lymphoma, anus, and liver cancer also are increased in the immunosuppressed population, but the risks for breast, prostate, colon, and ovary cancer are not.

NCI's HIV/AIDS Cancer Match Study links HIV and cancer registries in 14 U.S. areas and provides data on 780,000 HIV infected people from 1980-2009, including 630,000 AIDS cases. The study allows examination of the epidemiology of specific cancers, comparison with the risk in the general population, and study of risk factors for cancer. Dr. Engels conducted a study of Merkel cell carcinoma, a rare skin cancer for which people with HIV have a 13-fold elevated risk compared to the general population. These results pointed to a viral etiology, and encouraged by those findings, other laboratory researchers discovered Merkel cell polyomavirus. Another study focused on lung cancer, the most common non-AIDS-defining cancer in HIV-infected people. Dr. Engels and colleagues showed a 3.8-fold risk of lung cancer in people with AIDS compared to the general population. This increased risk is caused in part by the high prevalence of smoking in the HIV population, However, this risk is higher than can be explained by smoking alone, and these findings suggest that HIV infection amplifies the effects of tobacco use.

The pattern of cancer in people with HIV is evolving. With the availability of highly active antiretroviral therapy (HAART), the HIV-infected population is living longer. Dr. Engels and colleagues recently evaluated the cancer burden of the U.S. AIDS population. CDC data on the number of people living with AIDS by year and age group show that the AIDS population has grown steeply, driven by the increase in individuals older than 40. The incidence of AIDS-defining cancers, however, has declined steeply over time, and the burden of these cancers decreased after 1996. Non-AIDS defining cancers' incidence has remained steady, but the cancer burden has increased steeply, driven by cases in those older than 40. Data on types of cancer in these cases show that approximately half of the burden is caused by lung, Hodgkin lymphoma, anus, and liver cancer, underscoring the need to better understand the role of HIV in the pathogenesis of non-AIDS-defining cancers. Results from Dr. Engels' studies also have implications for cancer prevention, such as encouragement of smoking cessation in HIV-infected people, prevention and treatment of hepatitis B and C virus infections, and use of anal Pap smear screening.

NCI's Transplant Cancer Match Study has linked the U.S. transplant registry with 13 different cancer registries, and provides data on cancer incidence in 38 percent of all U.S. transplant recipients since 1987. The project is a partnership between the NCI and the Health Resources and Services Administration (HRSA). Preliminary results show data for more than 175,000 transplant recipients with 10,603 cancers, which represent a 2-fold increased cancer risk. The goals of the study are to describe the spectrum of cancer risk in transplant recipients, and examine risk factors for individual cancers as well as the risk of transmission of cancer from donors to recipients.

Questions and Answers

Dr. Hong asked if the histology of adenocarcinoma versus squamous carcinoma in lung cancer had been examined in HIV patients. Dr. Engels responded affirmatively, and that both lung cancer subtypes occur at increased frequency compared to the general population. The development of lung cancer in people with HIV infection seems to be largely restricted to smokers. A strong association does not exist with the CD4 count, nor is a virus suspected of causing the cancers. Chronic inflammation or lung infections may be interacting with the effects of tobacco smoke to promote the carcinogenic process.

Dr. Meneses asked if any specific type of transplant was associated with a higher risk of cancer. Dr. Engels replied that the pattern may differ depending on the type of cancer. He added that the most common cancer in people with transplants is non-Hodgkin lymphoma, and the risk is highest in patients who have a heart, lung, or liver transplant.

Understanding Telomere Biology Through Studies of Dyskeratosis Congenita. Dr. Savage said that dyskeratosis congenita (DC) offers an example of how studies of rare diseases can be used to inform cancer biology and be applied to the general population. Her work examines telomere biology in populations, and telomere length as biomarkers. Telomeres are long DNA repeats and a protein complex at chromosome ends which are critical in maintaining chromosomal integrity. Telomeres shorten with each cell division and when they reach a critical length, cellular death can result. = Cancer cells, however, are able to survive with short telomeres because they upregulate telomerase, the enzyme that extends telomeres, and continue to divide despite genetic instability. A previous study showed that telomere biology genes are highly conserved between ethnic groups and species.

DC is a disorder of telomere biology characterized by abnormally short telomeres, usually diagnosed by the presence of nail dystrophy, oral leukoplakia, and skin pigmentation abnormalities. Patients with DC have a high risk of numerous other diseases, including head and neck cancer, anogenital cancer, and leukemia. In 2006, three genes were known to cause DC: *DKC1*, *TERT*, and *TERC*. However, only 40 percent of patients with DC had a mutation in one of these genes. Dr. Savage's work on the Inherited Bone Marrow Failure Syndromes study developed a diagnostic test for DC that examines telomere lengths in white blood cells using flow cytometry. This knowledge was used to show that germline mutations in *TINF2*, an important component of the shelterin telomere protection complex, cause DC. Dr. Savage's group sequenced the other five components of the shelterin telomere protection complex (*TERF1*, *TERF2*, *POT1*, *TERF2IP* and *ACD*) in 9 patients with DC and 7 "DC-like" patients; mutations in these genes do not appear to be a common cause of DC.

The candidate gene *TCAB1* recently was identified as critical in telomerase assembly in the nucleus. Dr. Savage showed that mutations in TCAB1 can cause DC. These *TCAB1* mutations result in reduced levels of *TCAB1* and thus in defective telomerase trafficking. Cumulative cancer incidence also has been studied in the DC cohort, and one-half of the patients with DC had cancer by approximately age 50. Patients with DC have an 11-fold increased risk of any type cancer and a 1000-fold increased risk of tongue squamous cell cancer. Dr. Savage's group is working with the CRC to refine the phenotype of DC. Major contributions of the DC study include: development of the diagnostic test; discovery of two of the seven

causative genes; quantification of the cancer risk; refinement of the extent of medical complications; creation of a support group, DC Outreach; and creation of a basis for population-based studies of the contribution of aberrations in telomere biology to cancer risk.

The spectrum of telomere biology disorders is heterogeneous, and contains DC, aplastic anemia, pulmonary fibrosis, leukemia, and liver fibrosis. Germline *TERT* or *TERC* mutations exist in 5 to 10 percent of patients who have these disorders, but the cancer risk in patients with isolated aplastic anemia due to telomere biology defects, for example, is unknown, and will be examined in the future. Additionally, individuals in the general population who have shorter telomeres may have increased cancer risk because of telomere dysregulation. A meta-analysis of telomere length and cancer risk showed a nearly 2-fold increased risk of cancer in those who have telomeres in the shortest quartile compared to the rest of the population.

Questions and Answers

Dr. Pietenpol asked if the seven causative genes in sporadic cancers for mutations have been examined and encouraged a survey of current databases that have known genomic sequences for telomere dysfunction related to sporadic cancers. Dr. Savage noted that studies of *TERT* in tumor cells have been conducted and show the presence of aberrant telomerase expression in the cells. Dr. Pietenpol suggested that Dr. Savage mine the databases on genomic sequencing that already has been conducted.

Genome-Wide Association Studies and the Road Ahead. Dr. Chanock presented an update on current and future developments in GWAS, which are carried out in large population samples. GWAS ask whether there are sets of genetic variants associated with greater or lesser risk for particular outcomes, such as cancer risk. This is a very new type of investigation, with results published starting only in 2007, but it builds upon the draft sequence of the human genome project, as well as decades of work at DCEG, including collection of biospecimens from high-risk families and completion of high-quality population studies. Cancer GWAS have linked 145 genetic loci to one or more types of cancer. Nearly all of the identified loci map to non-coding regions of the genome, a finding that emphasizes the importance of the regulatory effects of non-coding regions. The estimated effect sizes are small in almost all instances, but because multiple alleles are involved and many of them are common in the population, their combined effects may be important, particularly at the population level. GWAS findings have been more informative for some cancers than for others. For prostate cancer, 38 relevant regions of the genome have been pinpointed and a long-suspected inverse relationship between prostate cancer risk and Type 2 diabetes risk has been confirmed. In contrast, in lung cancer, although the same number of individuals has been scanned, only three relevant regions have been found. Several regions have been linked to susceptibility to multiple cancers, including combinations of cancers that would not have been predicted on the basis of known patterns of risk (e.g., the *TERT-CLPTM1L* region on chromosome 5p15.33 is associated with brain tumors, melanoma, basal cell carcinoma, and cancers of the bladder, testicles, pancreas, and lung). Only a few examples of gene/environment interactions have been identified through GWAS; for example, an allele for slow acetylation predicts bladder cancer risk in smokers but not in nonsmokers.

Within DCEG, data have been compiled on more than 50,000 individuals who have been scanned for 12 different diseases. These data will facilitate asking questions about population genetics, sex verification, and large genetic abnormalities such as structural aneuploidy. Efforts to improve cancer risk prediction by incorporating GWAS findings into models of cancer risk are in progress. In summary, GWAS findings are pointing to new regions in the genome associated with specific diseases or traits; are providing clues for mechanistic insights, including gene-environment-lifestyle interactions and pharmacogenomics, using common variants; and may contribute to improvement of risk prediction for individual and public health decision-making.

Questions and Answers

Dr. Coffey asked whether GWAS would show the folding back of the chromosome that is seen 10 years before the diagnosis of pancreatic cancer. Dr. Chanock said that this has not been investigated but may be possible by examining previously collected germline material from individuals who have been diagnosed with pancreatic cancer.

Dr. Pietenpol asked whether metformin, glitazones, and body mass index (BMI) had been taken into account in the analyses showing an inverse relationship between prostate cancer and Type 2 diabetes. Dr. Chanock replied that BMI is being actively investigated, as the case-control and cohort studies from which samples are obtained for GWAS include data on height and weight; the other variables are available in metabolic profiles in some studies.

Dr. Chabner asked whether Dr. Chanock foresees a time when whole genome sequencing will replace GWAS studies. Dr. Chanock said that research already is moving in that direction. Dr. Chabner commented that GWAS is an example of the kind of work that can be accomplished only with the involvement of NCI.

X. 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) (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.

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.

XI. 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 156th regular meeting of the NCAB was adjourned at 4:04 p.m. on Tuesday, 7 December 2010.

_____ _____

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

_____ _____

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