DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
151ST NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 15–16, 2009

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

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BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 151st regular meeting on 15 September 2009, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 15 September 2009, from 8:30 a.m. to 3:30 p.m., and Wednesday, 16 September 2009, from 8:30 a.m. until adjournment at 12:10 p.m., and closed to the public on Tuesday, 15 September 2009, from 3:30 p.m. to 5:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala
Dr. Bruce A. Chabner
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Lloyd K. Everson
Ms. Kathryn E. Giusti
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong
Mr. Robert A. Ingram (absent)
Dr. Judith S. Kaur
Mr. David H. Koch
Ms. Mary Vaughan Lester
Dr. Diana M. Lopez (absent)
Dr. H. Kim Lyerly
Dr. Karen M. Meneses
Dr. Jennifer A. Pietenpol (absent)
Dr. Daniel Von Hoff (absent)

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 (absent)
Dr. Allen Dearry, NIEHS
Dr. Michael Kelley, VA
Dr. Peter Kirchner, DOE
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 A. Tabak, NIH (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Mr. Jim Dickens, Acting Director for Management and Executive Officer
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
Ms. Kathy McBrien, Administrative Resource Center Manager
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Craig Reynolds, Associate Director, NCI-Frederick
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Mr. Adam Clarke, Lance Armstrong Foundation
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
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
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, SEPTEMBER 15, 2009

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 11 JUNE 2009 MINUTES DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 151st NCAB meeting. She 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. Runowicz 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 11 June 2009 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2011, with a proposed change to the June 2010 meeting date.

Motion. A motion was made to confirm the 21–23 June 2010 NCAB meeting. The motion was seconded, and the Board unanimously confirmed the meeting date.

III. NCI DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, welcomed members and provided information about the closing out of the FY 2009 budget and the American Recovery and Reinvestment Act (ARRA) funding to support vital science.

FY 2009 Budget. Dr. Niederhuber reminded members that the fiscal year (FY) 2009 appropriated budget was $4.968 B, reflecting a 2.9 percent increase from FY 2008. The final number of grants to be awarded in FY 2009 is estimated at 7,075, similar to FY 2007 (7,103) and FY 2008 (7,010) levels.

American Recovery and Reinvestment Act (ARRA). Dr. Niederhuber said that the NIH Institutes and Centers (ICs) received $7.4 B in funds from the ARRA, of which $1.26 B was allocated to the NCI. In addition, $1 B was allocated for extramural construction; $500 M for NIH construction; $300 M for shared instrumentation; $400 M for comparative effectiveness research (CER); and $800 M to the NIH Office of the Director (OD). The NCI has planned carefully to use ARRA dollars to fund vital science, particularly by employing strategies to minimize the out-year effect and generate Congressional enthusiasm about investments in cancer research. A total of 369 research project grants (RPGs) have been funded, extending the NCI 2009 payline from the 16th to 25th percentile. The NCI has allocated its ARRA funds to grants (59%), research and development contracts for the academic community (39%), support (2%), and intramural equipment (< 1%). There were 140 NIH-funded cancer grants awarded, for a total of $106 M, including: CER (27 awards); summer (77 awards); Grand Opportunity (18 awards matched); and challenge grants (18 awards). The ARRA process has been complex, but most of the grants that the NCI submitted for approval by the NIH, the Office of Management and Budget (OMB), and the Vice President's Office have been approved.

The NCI has a diverse portfolio that it supports through its grant mechanism, including administrative and competitive supplements, to add resources to ongoing activities. Members were told that the current estimate for ARRA funds to supplements is $342 M. Examples of research and development contracts include cohort studies, Phase I/II therapeutic and imaging clinical trials; caBIG;

Division of Cancer Treatment and Diagnosis' (DCTD) Clinical Assay Development and Characterization Center; The Cancer Genome Atlas (TCGA) project and Chemical Biology Consortium (CBC). The CBC is a government-academic collaboration intended to accelerate new therapies; 11 awards were made, including 8 academic and 3 commercial laboratories.

For the challenge grants, the NCI selected 41 high-priority grants (totaling $38 M) in addition to the NIH's 18 cancer-related grants funded, attaining an overall success rate of 20 percent of grants reviewed. The NIH matched NCI's funding of 18 cancer Grand Opportunity grants ($24 M); the NCI funded an additional 33 grants ($64 M) through this contract vehicle, with the overall success rate of 17 percent of grants reviewed. The NCI also funded 37 studies through the Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW) mechanism, which focuses on the movement of novel agents from pilot studies into first-in-man studies or early Phase I trials. Awards were contingent on obtaining Institutional Review Board (IRB) approval, opening to patient enrollment within 90 days, and completing the project within 2 years. ARRA funding for cancer research by organ site included: breast, 76 grants ($14.7 M); prostate, 54 grants ($7.4 M); colorectal, 40 grants ($7.2 M); lung, 35 grants ($6 M); pancreatic, 17 grants ($2.9 M); and ovarian, 8 grants ($1.4 M).

The NCI has devoted significant resources to increasing the base in cancer research via technology to meet the challenges of cancer (understanding the disease, of developing biomarkers, of developing markers of early diagnosis, of using these tools to follow disease and follow through at the end to design novel therapies), such as through gene sequencing or the ability to isolate and identify protein structures.

TCGA illustrates how the study of three cancers (brain, lung, and ovarian) can connect multiple sources, experiments, and data types. Technology is advancing quickly, and TCGA is moving to the "next generation" sequencing technology. It is expected that complete sequencing of an individual's genome will be able to be completed in a timeframe counted by hours rather than weeks, thus revolutionizing medicine and effecting significant cost savings. The glioblastoma pilot revealed associations with mutations in genes, providing the ability to begin stratifying a disease into different prognosis categories. Numerous translocations and a complexity of genetic changes have been identified in ovarian cancer. TCGA is one of seven NIH Signature Projects. It involves more than 24 institutions and more than 100 scientists in the identification of relevant genetic alterations of cancer. ARRA funding has allowed expansion up to 25 tumors, and the long-term goal is to address all major cancer types and subtypes. The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project uses the TCGA approach in childhood cancers.

The cancer Human Biobank (caHUB) is a unique, centralized public resource to ensure the adequate and continuous supply of human biospecimens and associated data. The caHUB includes tissue procurement, pathology reference center and core biospecimen resource, and biospecimen research and development; it is supported by $60 M of ARRA funds.

TCGA, along with the Functional Biology Consortium, CBC, good manufacturing practice production, and preclinical testing and technology, are part of a robust platform that uses technology to inform science and medicine to attain translational research results more quickly. The information being uncovered through technologies should be usable by the administrator, physician, patient, and scientist to help informed decisionmaking, improve outcomes, and reduce costs. The data should be translated to match markers, and hence appropriate patients, to specific trial questions. To facilitate this, the NCI supports the development of a cancer health record.

Dr. Niederhuber informed members that Dr. Francis Collins, Director, NIH, recently identified five themes for the NIH to address: 1) apply high-throughput technologies to understand fundamental biology and uncover causes of specific disease states; 2) translation, including development of diagnostics,

preventive strategies, and therapeutics; 3) put scence to work for health care reform; 4) a greater focus on global health; and 5) reinvigorate and empower the biomedical research community.

Questions and Answers

Mr. David H. Koch, Executive Vice President, Koch Industries, asked whether ARRA funds were available for extramural equipment and the amount. Dr. Niederhuber confirmed this and noted that disbursements likely would occur through institutional grants; a total of $300 M was assigned to the NIH for this purpose. Dr. Bruce Allan Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, and Chief of Hematology/Oncology, Massachusetts General Hospital, asked about the ARRA materials submitted and the review process by OMB and the Vice President's Office. Dr. Niederhuber said that a summary of each grant was included and recognized that, although the review process is not normal for most funding, it was instituted to ensure that the funds are carefully managed and monitored.

Dr. Chabner asked about the process for choosing the CBC projects. Dr. Niederhuber answered that the NCI has established an elaborate structure for reviewing the science and prioritizing potential projects. Dr. James H. Doroshow, Director, DCTD, further explained that Special Emphasis Panels focus on discovery and development to determine the prioritization. Mr. Koch asked about the life and size of the projects. Dr. Niederhuber indicated that both their size and longevity could vary based on the specific activity, but that most are shorter term, with a span of 6 to 9 months; their size varies with the complexity of the given project. Dr. Chabner recalled previous discussions of an intramural chemistry group. Dr. Niederhuber replied that a nucleus of chemical support has been added to the NCI to ensure some in-house expertise, but it was determined that the amount of work needed a bigger array of chemists and a larger breadth of specialties or expertise that the NCI at any point in time could apply to the project. Dr. Robert Wiltrout, Director, Center for Cancer Research, agreed and said that NCI chemists support a chemical biology program rather than a chemical program.

Mr. Koch asked about the current error rate in DNA sequencing in detecting actual defects in genes. Dr. Niederhuber said the error rate has been reduced with the help of evolving technology and that the lines are changing in relation to the number of tumors and statistics needed.

Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., asked whether centralized resources exist for the three tumor types that TCGA is examining. Dr. Niederhuber replied that no one resource supplies the tissue, and this has been one of the limiting steps in moving this project through the high-throughput pipeline that has been designed so effectively.

Dr. Lloyd K. Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, voiced agreement with the need to reach the patient through the practicing oncologist, and thought that intertwining the electronic medical record and cancer research likely would facilitate the progress of research; the small size of oncology practices around the United States, however, presents challenges. He offered his network's assistance in promotion of this endeavor.

Dr. Chabner championed the idea of profiling patients at the molecular level at the time of diagnosis, particularly for tumors that currently are incurable; research should be considered as a fundamental part of patient care. Dr. Niederhuber agreed, and Dr. Doroshow noted that part of the ARRA funds are being used to support a characterization facility to develop population approaches to mutational analysis and to develop assays for critical drug studies. Dr. Runowicz observed that IRBs require re-consent forms to use stored tissue; the American Society of Clinical Oncology (ASCO) and a number of academic centers are working to address this issue. Ms. Giusti commented that patient advocacy groups have noticed several obstacles to patient profiling, including an increased number of patients being treated in the community rather than in academic centers, a reluctance of patients to agree to profiling as treatments do not exist for them, and lack of consensus among centers regarding categorization of genomic

data.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, supported the NCI's direction but observed that issues of confidentiality pose challenges to this move forward. In addition, electronic medical records should be considered holistically in terms of all of a patient's chronic diseases. Dr. Niederhuber recognized that cancer affects the aging population, which often has other health issues as well.

IV. PRESIDENT'S CANCER PANEL—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, acknowledged his colleague on the Panel, Dr. Margaret Kripke, Vivian L. Smith Chair and Professor Emerita, The University of Texas M.D. Anderson Cancer Center. Dr. Leffall noted that the mission of the PCP is to advise the President on the activities of the National Cancer Program, particularly the obstacles the Program may face in conducting its work.

The report of the 2008–2009 PCP meeting series on "Environmental Factors in Cancer" currently is being prepared and has an expected release date of late 2009. The 2009–2010 meeting series is addressing "America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise." The series will explore implications for U.S. cancer trends as proportions of ethnic subpopulations increase, and the appropriateness and relevance of current cancer screening guidelines for these subpopulations. Other topics include biological and clinical-encounter differences between ethnic groups, and differences in ethnic groups' understanding and discussing cancer as compared to that of mainstream populations. The meetings are planned for 22 September 2009 in Seattle, WA; 27 October 2009 in Los Angeles, CA; 9 December 2009 in Wilmington, DE; and 2 February 2010 in Miami, FL. NCAB members were encouraged to submit suggestions for topics for the upcoming 2010–2011 meeting series.

Dr. Leffall informed members that the Panel prepared a letter addressed to President Obama regarding the challenges to reducing the Nation's deaths from cancer. The letter (which was included in the briefing books) summarized the Panel's findings and recommendations during the past 10 years and provided the Administration with a summary of the challenges that must be addressed to ensure progress in controlling cancer. These challenges include: the magnitude of the problem and impact of the aging population; continued use of tobacco products; unequal access to cancer care; lack of overall coordination of the Nation's cancer program; and limited resources (i.e., dollars, time, and personnel). Other concerns include the growing population of cancer survivors and the mismatch between research priorities and disease impact.

Questions and Answers

Mr. Koch requested specific examples of mismatches between research priorities and disease impact. Dr. Leffall explained that money spent on research of one disease, such as AIDS, should not detract from the money that is necessary for cancer research; likewise, funding for breast cancer research should not decrease the amount of money allocated to pediatric cancer research.

Dr. Runowicz encouraged the Panel to consider the socioeconomic impact factor in upcoming PCP meetings addressing cancer issues affecting ethnic groups. Dr. Leffall confirmed that the topic will be included, and he reaffirmed the PCP's strong commitment to universal access to health care.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on appropriations and Congressional committee assignments. The FY 2010 appropriations bill was passed by the House on July 24 and by the Senate Appropriations Committee on July 30; it is awaiting vote by the full Senate. The House Appropriations Report (111-220) expressed concern in the NIH section about the harmful precedent of setting specific funding levels for particular diseases. In the NCI section, the Report requested that the NCI develop a plan for the CIS Partnership Program and report to Congress by February 2010. The Senate Appropriations Report (111-66) noted in the NIH section that the record-high increase for NIH in ARRA mitigates the need for more funding than the FY 2010 President's Budget (PB) amount, and rejects the administration's proposals for a funding increase for cancer research, noting that funding levels for diseases should be determined without political interference. Both reports highlight specific cancers, including gastro-intestinal, cervical (and HPV vaccine), liver, lung, melanoma, neuroblastoma, pancreatic, and pediatric cancers, as well as international training programs in hematology. Ms. Erickson informed members that assignments to the Senate Health, Education, Labor, and Pensions (HELP) Committee include the new chairman Senator Tom Harkin (D-IA) and new member Sen. Al Franken (D-MN).

VI. ANNUAL REPORT: AMERICAN SOCIETY OF CLINICAL ONCOLOGY— DR. DOUGLAS W. BLAYNEY

Dr. Douglas W. Blayney, President, ASCO, explained that the focus of ASCO's mission this year is advancing quality through innovation. Concerns about growth in health spending coupled with a desire for cost savings threatens the clinical trials infrastructure, particularly given the substantial unfunded costs of clinical research. Costs of clinical research are likely to rise, given the increased need for personalized care for cancer patients, the challenges in identifying the most effective treatment among numerous options, increasing regulatory burdens faced by oncology clinical researchers, and the growing shortage of oncology workers, including nurses, biostatisticians, and administrative staff as well as clinicians. ASCO believes that these challenges also present opportunities for the oncology community to respond and create value by fostering a learning health care system. We can enhance the quality of translational and clinical research by promoting use of innovative trial designs; collection of real-time clinical data on quality and outcomes; recognition and support of quality research sites; and more effective, rational regulations. Federally funded clinical trials are an essential part of improving the quality of cancer care. However, these trials are at risk because of concerns about the pace of trial development and accrual.

The vulnerability of the clinical trials enterprise is clear; a recent ASCO survey found that approximately 40 percent of Cooperative Group sites are considering limiting their participation in NCI-funded trials. The primary reason cited for this is reimbursement—the NCI reimburses $2,000 per case, but an ASCO and C-Change study found that the actual per case cost is closer to $5,000 or $6,000. Of the sites that cited inadequate reimbursement as a factor, 42% are taking steps to increase participation in industry-funded trials. While NCI is engaged in efforts to prioritize trials, improve efficiency, and examine the optimal structure for the Cooperative Groups, there has not been a concerted effort to ensure adequate payments for conducting clinical trials. ASCO believes that this step is a necessary component to improving the overall system.

ASCO has embarked on a series of initiatives to provide increased opportunities for education and training, including developing Web-based training modules, supporting the Quality Oncology Practice Initiative (QOPI) online community, and providing online access to presentations from ASCO meetings. ASCO is working with the FDA and NCI to create a standardized case report form and with caBIG to influence the federal electronic health record (EHR) certification organization to mandate adoption of oncology-specific standards by EHR vendors. ASCO also has worked with FDA's Critical Path Initiative to promote innovative trial designs. Finally, ASCO has conducted a study to analyze Health Insurance Portability and Accountability Act (HIPAA) regulations and their effects on clinical research and is working on promoting effective approaches to HIPAA compliance.

Dr. Blayney asked Board members to consider several proposals to enhance NCI's support for clinical trials. He encouraged them to recommend that the NCI consider increasing its per-case reimbursement rates; explore and enhance innovative training partnerships between the NCI and organizations such as ASCO; work with other federal agencies to harmonize regulatory requirements; and develop ways to leverage existing data collection projects.

Questions and Answers

The Board members agreed that the declining interest in participating in NCI-sponsored trials among Cooperative Group sites was distressing. Mr. Koch requested clarification regarding the most significant impediments to participating in these trials. Dr. Blayney explained that regulatory requirements can be particularly difficult and significantly delay opening a trial for accrual. He recommended that the NCI, FDA, other federal agencies, and representatives from the pharmaceutical industry work to harmonize regulations.

Dr. Everson asked how the difficult economic situation in the United States would impact efforts to improve clinical research. Dr. Blayney explained that resolving some of the inefficiencies and duplications inherent to clinical research would improve clinical research and be cost effective. For example, many regulatory and data collection requirements are onerous and of questionable value. Dr. Blayney noted that ASCO is working with FDA, NCI, CALGB, and industry to make recommendations to optimize data collection for supplemental applications. The NCI has established a group that is working to optimize Cooperative Group clinical trials. The Southwest Oncology Group has successfully reduced its time to trial opening by half.

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Johns Hopkins University School of Medicine, asked how ASCO could differentiate its activities from those of the American Association for Cancer Research (AACR) and the NCI. All three organizations have foundations to raise funds and also communicate with Congress. Dr. Blayney noted that ASCO focuses on practice and practitioners, including developing tools practitioners can use to deliver high-quality cancer care and to place patients on clinical trials. ASCO also has worked effectively with AACR and other oncology organizations to present the concerns of the community to Congress.

Dr. Waun Ki Hong, Professor and Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, suggested that funds allocated to comparative effectiveness research could be used to increase reimbursement rates for Cooperative Group clinical trials, which will become necessary even in the face of improved clinical trial design.

Dr. H. Kim Lyerly, Director, Duke Comprehensive Cancer Center, George Barth Geller Professor of Cancer Research, Duke University Medical Center, asked how, specifically, the quality of cancer care and clinical trials needed to be improved. Dr. Blayney answered that safety is an important component of quality, given the use of highly toxic chemotherapeutic drugs. In addition, treatment of quality-of-life issues vary more than is appropriate across different sites. Dr. Blayney provided examples of how improvements in care can save money. In one case, comparison of treatment of stage IV lung cancer using an evidence-based pathway that is guideline-compliant and was assessed for cost effectiveness found that survival was the same for on-pathway versus off-pathway treatment and on-pathway treatment saved approximately $10,000 per patient. In the other case, a QOPI project found that 40 percent of patients treated at the University of Michigan received chemotherapy during the last 2 weeks of life, versus 15 percent of community-treated patients.

VII. UPDATE: THE CANCER GENOME ATLAS—DRS. ANNA BARKER AND MARK GUYER

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership, and Dr. Mark Guyer, Director, Division of Extramural Research, National Human Genome Research Institute (NHGRI), described the progress made by TCGA and plans for future activities. The goal of TCGA is to identify all significant genomic changes in the genome of each tumor type, as a basis for defining cancer subtypes, facilitating drug discovery, and targeting patients to appropriate trials and treatments. Analyses undertaken through TCGA will increase understanding of the biological significance of genomic changes in cancer, including those affecting gene copy number, transcription, translation, and the epigenome.

TCGA was initiated as a pilot program to evaluate and test the processes needed to perform high throughput, large scale, disease-focused genomic characterization, as well as data integration and analysis. The pilot focused on three tumors: glioblastoma, ovarian cancer, and lung cancer. The goal was to collect five hundred cases and matched controls; this number was statistically determined as needed to detect those genes in which changes occurred at a frequency of 3% in a tumor type. One of TCGA's initial activities was to set strict parameters for sample collection, based on advice from Dr. Carolyn Compton. TCGA collaborated with caBIG to create a database, and clinical data elements required to accompany specimens were defined. DNA is prepared by the International Genome Consortium, and aliquots are distributed to sequencing centers and to centers that perform analyses of expression, copy number abnormalities (CNAs), loss of heterozygosity, and epigenetic changes. The results of these analyses are integrated by an Analysis Working Group. TCGA network consists of seven cancer genome characterization centers, three genome sequencing centers, and a data coordinating center.

Preliminary analyses have created a large, integrated dataset for glioblastoma and identified a number of genes and three core biological pathways altered in this cancer. Pathway analysis reveals potential drug targets, and epigenetic analysis found that promoter methylation and inactivation of *MGMT* may be responsible for temozolomide resistance in previously treated glioblastomas. Initial analysis of ovarian tumors has found the ovarian cancer genome to be "noisy", with many large rearrangements and amplifications. *P53* appears to be altered in 100 percent of ovarian cancers. A high frequency of *BRCA1* and *BRCA2* mutations also were observed, particularly in tumors with poor response to therapy. These data have permitted definition of subtypes for glioblastoma (4 subtypes) and serous ovarian cancer (3 subtypes) based on expression data; methylation analysis likely will refine subtypes further. The information exchange and integration analysis facilitated by TCGA has been integral in defining these tumor subtypes.

This pilot program has shown that changes relevant to carcinogenesis can be detected even in the "noisy" genomes of tumors. It also has shown that it is possible to build teams and develop a comprehensive, integrated approach to cancer genome analysis. Phase II of TCGA will feature deep characterization of 15 to 20 more tumors (a mix of rare and common cancers, with an emphasis on highly lethal tumors), and integration of next generation genome characterization/sequencing technologies. Other goals include complete genome characterization of each cancer case, as well as development of standards for biospecimen acquisition and clinical information, advanced approaches and tools for data visualization and management, and a quality management system.

Phase II of TCGA will rely on second generation sequencing techniques, which permit analysis of individual DNA molecules, rather than populations, and facilitates detection of rare variants and analysis of heterogeneous DNA populations. Sequencing throughput rates have increased using new technologies from approximately 1 gigabase per week to 25 gigabases per week per instrument. As of the end of August 2009, the three NHGRI-supported sequencing centers had generated 18 terabases of sequence, with one-half of that generated in the past 9 months.

Data for glioblastoma was generated using first generation, PCR-based sequencing methods. Second generation sequencing data are available for 10 completed glioblastoma genomes; 2 more are in progress. All data for ovarian cancer were generated using second generation techniques. Twelve whole genomes have been sequenced for ovarian cancer; in addition, 238 tumor-normal pairs have been assayed for 6,000 genes using a targeted capture approach. TCGA plans to increase the number of genes or regions to assay using the targeted capture approach, with the goal of sequencing the entire exome, defined as the collection of all coding sequences in the genome. Data per case (tumor-normal pair) will include information on coverage, sample purity, ploidy, a summary of point mutations, and general information on the tumor genome. For Phase II, the first discovery set of genes for each tumor should be completed within 4 months of analyte availability; the data will be subsequently analyzed and then sent for integrated analysis.

Lessons learned from the first phase of TCGA include: that the project has been difficult and complex, but has generated useful data as anticipated. Specimen quality has been found to be key for generating sound data, and 500 cases per tumor is the minimum number needed to detect changes at the 3 to 5 percent level. Retrospective cancer cases have been important because they provide clinical data, but prospectively collected samples will also be needed. The data must be useable by clinicians and other investigators and to this end, a model for drug/diagnostic development should be developed. The data also must remain public, which may raise intellectual property issues. Analysis of single genes is likely to become less informative, and a translational infrastructure (translational genomic centers) will be needed to make effective use of the data.

Questions and Answers

Dr. Chabner recommended continued consideration of single gene analyses, because these provide targets for drug development; TCGA data in its current form does not easily translate into treatment or clinical experiments. Successful therapies that target single genes have been developed, and these are effective when targeted to the correct patients.

Mr. Koch recommended that TCGA develop a clear, succinct description of the methodology and overall objective of TCGA to help garner support from the lay community. Drs. Barker and Guyer explained that genomic analyses facilitate the early stages of discovery and provide a catalog, or atlas of the tumor genome, particularly alterations that may be relevant to therapeutic development.

Ms. Giusti recommended broadening the scope of TCGA to other tumor types because this will help draw more interest and support from both the research community and private industry.

Dr. Hong suggested developing a partnership with an institution that has in place a translational infrastructure to facilitate clinical use of TCGA data.

Dr. Coffey supported intense characterization of fewer tumor types because factors other than sequence, such as methylation, micro RNAs, and transposable elements, may have roles in tumorigenesis. He recommended focusing on subtyping cancers that have a broad range of lethality, for example, prostate cancer. Identifying lethal phenotypes will help leverage early detection information. He also recommended investigating field effects to determine whether normal tissue adjacent to the tumor can provide information on lethality, and techniques to visualize nuclei in living cells to understand long-range chromosomal interactions.

Dr. Kaur recommended that the NCI consider developing specialty fellowships in bioinformatics and mathematical computational biology. Investigators trained in these fields will be needed to fully understand and make use of TCGA data.

VIII. CLINICAL INVESTIGATIONS SUBCOMMITTEE REPORT AND ONGOING AND NEW BUSINESS—DR. CAROLYN D. RUNOWICZ

Clinical Investigations Subcommittee Report. Dr. Hong, Chair, Clinical Investigations Subcommittee, informed members that the Subcommittee discussed the Cancer Therapy Evaluation Program (CTEP), NCI's Clinical Grants and Contracts Branch (CGCB), and CTEP's Early Clinical Trials Program. The Subcommittee complimented CTEP staff on their tremendous work.

CTEP sponsors more than 110 INDs, involves 11,000 registered investigators at 3,300 institutions, and includes more than 1,000 active protocols with 500 new protocols annually. The program accrues approximately 30,000 patients each year, with accrual rates remaining steady, and it maintains collaborative agreements with more than 80 pharmaceutical companies. New data suggest the importance of biomarkers, particularly regarding mutation-positive patients.

CGCB manages grant programs on clinical oncology, surgical oncology, and cancer nutrition. It also provides administrative and fiscal management of CTEP's extramural research and support contracts. Trials are ended prematurely if accrual rates are low and target numbers are not met though obtaining data from investigators can be difficult. Subcommittee members agreed that it is difficult to end trials ahead of schedule, even when stringent criteria is in place and goals are not being met. To date, R21 grants have been notably successful. In addition, the P01 portfolio has yielded the most significant research results, and the Subcommittee encouraged increasing the number of P01 grants.

CTEP's Early Clinical Trials Program includes 25 NCI cancer centers and includes 9 Phase 2 N01s, which are distributed in the United States, Canada, and the Pacific Rim. Currently the Phase 2 N01 program includes: 4,560 patients enrolled and 44 agents studied in 215 trials; 236 LOIs submitted, with 56 approved; 104 protocols activated; 81 protocols closed; 38 investigational combination trials with CTEP-held INDs for both agents; and 18 cancer indications, including rare diseases not likely to be evaluated in company-sponsored trials. A tissue acquisition and analysis program coordinates and integrates the Phase 2 program with caHUB and other NCI programs. The Pharmacodynamic Assay Development and Implementation Section (PADIS) develops and validates biomarker assays; the assays will be available to the public in the future. The NCI Experimental Therapeutics Program (NExT) is working to shorten the drug development cycle by 1-2 years; approximately 12 companies and institutions participate in the program.

Dr. Hong said that the Subcommittee recommended that the NExT program be discussed in detail at a future NCAB meeting.

Motion. A motion was made to approve the minutes of the 14 September 2009 NCAB Clinical Investigations Subcommittee meeting. The Board unanimously approved the minutes.

Ongoing and New Business. Dr. Runowicz asked members to indicate their interest in serving on the Global Cancer Research Subcommittee. In addition, members were told that the December NCAB meeting might include a Board visit to the White House.

IX. COMPARATIVE EFFECTIVENESS RESEARCH: OVERVIEW AND AN INDICATION OF NCAB'S ROLE—DR. ROBERT CROYLE

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), provided an overview of the NCI's approach to CER. The Federal Coordinating Council (FCC) defines CER as: "The conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating

evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances." Types of CER include clinical trials, observational studies and modeling, and secondary data analyses using registries and linked databases. CER and evidence-based medicine is included in most health care reform initiatives, and in total dollars, the NIH funds the largest amount of CER in the Department of Health and Human Services (HHS). The NCI brings relevant experience, expertise, and infrastructure to CER.

The ARRA CER bill states that the FCC cannot mandate coverage, reimbursement, or other policies of public or private payers. CER will not include national clinical guidelines or coverage determinations. The HHS Secretary is required to: publish information on awards; disseminate research findings to clinicians, patients, and the general public; ensure that the recipients of the funds offer an opportunity for public comment on the research; and annually report on the research conducted or supported. In addition, the Institute of Medicine's (IOM) CER report, released in June 2009, lists 100 national priorities for CER. It was informed by testimonials given by advocacy, industry, and other groups. Recommendations for long-term investment include ensuring meaningful participation by consumers, patients, and caregivers; building robust information systems and research methods; development and support of a highly skilled CER workforce; and support efforts to translate CER knowledge into everyday clinical practice. The FCC for CER released a report on June 2009, as required by the ARRA, and lists priorities for spending the HHS $400 M. Its definition of CER is now used HHS-wide. Dr. Croyle reminded members that the CER ARRA allocation totaled $1.1 B, including $400 M to the NIH, $300 M to the Agency for Healthcare Research and Quality (AHRQ), and $400 M to the HHS.

The NIH CER process is guided by a Committee, which is co-Chaired by Drs. Betsey Nabel, Director, National Heart, Lung and Blood Institute (NHLBI), and Richard Hodes, Director, National Institute on Aging (NIA). The Committee solicited ICs for ideas and lists of potential applications and then reviewed and recommended grants for funding to the NIH Director. In its review, the Committee carefully weighed whether projects met the definition of CER and considered the IC priority ranking of submitted projects. The NIH Director approved the final grants to be paid in FY 2009.

The NIH's primary spending areas include CER-related grants with scores beyond institute paylines, Grand Opportunity grants, challenge grants, competitive revisions, administrative supplements, contracts, and other projects, such as NIH signature initiatives. The NCI's approach was focused on: 1) Grand Opportunity grants, particularly in genomic and personalized medicine, and cancer prevention, screening, and treatment; and 2) challenge grants, for which the NCI received more than 4,000 applications. Other examples of NCI involvement in CER activities are the NIH Fingerprinting Subcommittee, the trans-NIH CER Portfolio Workgroup, and the trans-NIH CER Workgroup.

The NIH allocations for the CER funds include: Grand Opportunity grants, $153 M (38%); challenge grants, $85 M (21%); competitive revisions, $7 M (2%); administrative supplements, $19 M (5%); other, $60 M (15%); remaining dollars, $33 M (8%); and payline expansion, $43 M (11%). Approximately 23 percent ($84.5 M) of these funds are supporting cancer-related research, such as for surgical treatment options for prostate cancer, surveillance capabilities, colon cancer screening methods, and genomic medicine in cancer. Other NCI CER topic areas include smoking cessation trials, risk behavior interventions in health care settings, lymphadenectomy trials, and remote genetic counseling in underserved populations. Dr. Croyle informed members that the HHS and AHRQ spending plans of $400 M and $300 M, respectively, for CER continues to be defined, and final plans have not yet been released.

Questions and Answers

Dr. Everson asked how outcome and cost issues for the patient are considered in terms of CER. Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham

School of Nursing, also expressed a similar concern. Dr. Croyle answered that cost and other values are considered in the policy context of CER. In the broader discussion, which is not just about cancer, the NCI is committed to ensuring that good science is funded; and that existing NIH infrastructure, networks, and capacity are used to inform how research is conducted. He added that, in the oncology personalized medicine domain, the NCI's charge is to make sure that CER makes available more practice informed evidence and practice informing evidence.

Dr. Lyerly encouraged the NCI to assume a greater role in the gathering and generating information process as more attention likely will be devoted to developing these forms of data following real health care reform; the cancer community could provide a leading example of CER in the role of biomarkers.

Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, commented that the grant reviewers will need to be educated about CER and research is needed on translating findings quickly into policy and practice. Dr. Croyle agreed and noted that both the IOM and FCC were clear that health care system interventions need to meet the definition of CER; moreover, the AHRQ currently is studying a new series, called technical briefs, whereby their evidence-based practice centers are funded that prepare reports more rapidly, with the first report on particle beam radiation therapies for cancer just released.

Dr. Meneses expressed her appreciation for the presentation and commented on the importance of involving experts from other disciplines, such as health economics, particularly in cancer centers. Dr. Croyle replied that in the shorter term most of the cancer centers' involvement in CER will be through collaborative work. Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, suggested that the NCI Community Cancer Centers Program (NCCCP) might serve as an appropriate vehicle for CER. Dr. Kaur supported prioritizing the CER building process to enable use of data to assist with cancer health disparities.

Dr. Chabner recommended that the NCI should consider how a project under CER might affect the practice of medicine, including health care coverage and reimbursement decisions, before committing to supporting the project.

X. THE CANCER INITIATING CELL AND STEM CELL BIOLOGY—DRS. ROBERT WILTROUT, RONALD MCKAY, KATHLEEN KELLY, AND JONATHAN VOGEL

Dr. Wiltrout introduced the speakers: Drs. Ron McKay, Chief, Laboratory of Molecular Biology, National Institute of Neurological Disorders and Stroke (NINDS); Kathy Kelly, Chief, Cell and Cancer Biology Branch, Center for Cancer Research (CCR); and John Vogel, Senior Investigator, Dermatology Branch, CCR.

Using Human Stem Cells To Understand and Treat Disease. Dr. McKay provided introductory information on stem cells. Mouse embryonic stem (ES) cells are derived from the inner cell mass of the early embryo, can be grown in culture, and are pluripotent. Human ES cells appear to derive from a later developmental stage compared to mouse ES cells. However, mouse ES cells isolated from the epiblast behave similarly to human ES cells. Understanding similarities and differences between human and mouse ES cells is important, because working with mouse ES cells may be more straightforward, given federal limits on human ES cell work.

Stem cells show promise for studying functional human genetics. Techniques have been developed to allow the cells to be grown reproducibly over many passages. Analysis of ES cell gene expression after

the cells are induced to differentiate by using the classic reprogramming genes KLF4, OCT4, SOX2, and MYC shows that the transcriptomes of the differentiated ES cells closely resemble those of adult human cells. The ability to accurately reprogram ES cells implies that cancer cells, which may arise as a result of disruption in developmental processes, also could be reprogrammed to terminally differentiate. Analysis of GST expression levels across a number of ES cell lines showed that levels vary in ES cells, as is observed in the human population. Expression of MGMT, which is controlled by promoter methylation, is similarly variable. Undifferentiated cells also can be reprogrammed to become hepatocytes; human hepatocytes grafted onto the spleen of a mouse liver injury model colonize the injured liver and also appear to improve function of the host hepatocytes.

Modeling PTEN and P53 Function in Mouse Prostate Cancer Stem Cells. Dr. Kelly described work to analyze the role of stem cells in prostate cancer development. The prostate is composed of CK5+ and P63+ basal cells, CK8+ luminal secretory cells, and neuroendocrine cells. These three cell types share a common stem cell, which grows independently of androgen, in contrast to differentiated luminal cells that undergo apoptosis in the absence of androgen. Human prostate cancer cells resemble a transformed luminal cell; initially prostate cancer cells are sensitive to androgen deprivation therapy, but eventually this therapy fails and the cancer recurs and metastasizes. Although they can be heterogeneous, prostate cancer metastases often resemble poorly differentiated CK8+ carcinomas that also express mutated androgen receptors, which suggests that they evolved from formerly androgen-responsive cells.

Dr. Kelly presented a prostate epithelial cell model, in which PTEN and P53 are specifically deleted that was used to determine the mechanistic effect of specific common gene mutations on prostate progenitor populations. The PTEN pathway is the most frequently altered pathway in human prostate cancer; mice carrying PTEN deletions develop invasive adenocarcinoma that is heterogeneous, but with a luminal phenotype. To analyze progenitor cell populations, cells from the tumors were isolated and plated on either plastic or in a dilute solution of matrigel, which permitted the cells to form protospheres. Cells plated on plastic lose their self-renewal ability, but the protospheres can be passaged for multiple generations. The protospheres formed by the PTEN deleted cells have uneven surfaces, are significantly larger than protospheres formed by wild-type progenitors, have larger cells, and weaker cell-cell contacts. However, the PTEN deleted protospheres have a similar architecture to that of the wild-type protospheres, with basal cells in the outer most layer and cells with intermediate differentiated phenotypes located centrally. Analysis of single cells showed that the PTEN-deleted progenitors produced more luminal cells than basal cells, gave rise to more daughter cells, and continued to divide after the wild-type cells have lost self-renewal activity. The PTEN deleted cells also are sensitive to AKT pathway inhibitors and to androgen antagonists. This work may help identify therapies that lead to terminal differentiation of prostate cancer progenitor cells.

Tumor Initiating Cells in Human Squamous Cell Carcinoma. Dr. Vogel said that squamous cell carcinomas (SCCs) are heterogeneous and retain a developmental hierarchy that includes both proliferating and differentiating cells. Such tumors are hypothesized to be maintained by a distinct population of cancer stem cells, or tumor initiating cells (TIC), that have stem cell properties such as self-renewal and the ability to reconstitute the original tumor over several generations.

SCCs have cell populations that express markers of differentiation found in normal skin, such as involucrin. These cells are surrounded by an outer layer of proliferating cells that express Ki67, which is a marker of dividing cells. Dr. Vogel and colleagues analyzed single cell suspensions derived from SCCs and isolated a CD133+ populations. When grown *in vitro*, pure populations of CD133+ cells form spheroid colonies, in contrast to the flat monolayer formed by normal keratinocytes in culture. CD133+ cells are rare, accounting for only 0.8 to 1 percent of the cells in a typical human SCC.

Previous work found that human SCCs cannot be successfully xenografted onto immune-compromised mice unless the stroma at the xenograft site has been extensively humanized. Dr. Vogel has

developed an *in vivo* mouse model in which the graft site is first prepared with human fibroblasts. Using this approach, relatively large numbers of human SCC cells are required to recapitulate the human SCC tumor in the immune-compromised mice. However, use of a pure population of CD133 cells from SCC tumors results in tumor formation when far fewer cells are engrafted representing greater than a 100 fold enrichment in tumor initiating capacity. Additionally, the size of the tumor correlates with the number of CD133+ cells transplanted. To demonstrate the stem cell ability of self renewal, the grafted cells can be isolated and serially implanted in a second recipient and form a tumor that recreates the original tumor morphology. This work suggests that CD133+ cells represent the cancer stem cell population in human SCC. These cells may be useful for understanding normal tissue development and how it is altered in cancer. They also can be used to understand how the stromal environment influences TIC behavior and provide a way to identify therapeutic targets.

Questions and Answers

Dr. Vogel asked the Board to consider: 1) criteria to determine whether a cancer stem cell line would be useful for therapeutic screening purposes; 2) the best approach for analyzing cancer stem cell makers diagnostic and prognostic value; 3) minimum requirements to validate xenograft *in vivo* models for assessing cancer stem cells; and 4) whether the biology of cancer stem cells must be fully understood before they can be used to develop therapeutic agents.

Dr. Hong suggested that markers to distinguish between aggressive and benign SCC be developed; 5 to 10 percent of SCCs are aggressive and can metastasize to colon, even in people with normal immune systems.

Dr. Coffey commented that after successful treatment by bone marrow transplant, the patient's normal blood cells appear to derive from the same stem cell as the original tumor. This implies that the disease is caused not by the cancer stem cell itself, but by an aberration in development/differentiation. Dr. McKay agreed that understanding how differentiation can go awry is important and it is the goal of his research. His work with hepatocytes implies that stem cells can be used to "heal" damaged tissue. Dr. Chabner countered that the blood cells of leukemia patients treated with differentiating agents do not appear to be derived from the tumor; in this case, the malignant lineage has been destroyed.

Dr. Chabner noted that some drugs appear to selectively kill human tumor stem cells; for example, metformin appears to have this property, because diabetic patients who use metformin have a lower incidence of cancer than those using insulin. He asked whether this evidence was sufficient proof of an effect or if an assay or other data would be needed. Dr. Kelly answered that a sound preclinical model should be used to follow up on results from initial screening, particularly to determine if the drug has an effect on normal cells; a useful drug would not affect normal stem cells, hematopoietic cells, or other types of healthy cells.

XI. CLOSED SESSION DR. CAROLYN D. RUNOWICZ

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 IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,050 applications were reviewed requesting support of $611,050,262.

***En bloc* ARRA only**: The *en bloc* vote for concurrence with IRG recommendations was affirmed by all serving Board members present. During the closed session of the meeting, a total of 5,113 applications were reviewed requesting support of $2,007,148,549.

XII. NCI GLOBAL CANCER HEALTH/RESEARCH PROGRAM—DRS. ANNA BARKER, JORGE GOMEZ, JOE B. HARFORD, AND RICHARD R. LOVE

Overview. Dr. Barker provided an overview of NCI's investment in cancer research around the world. Cancer has become an international human and economic burden of enormous magnitude. Progress in the molecular and clinical sciences depends on global partnerships, with advances in technologies and community driving changes in oncology. The Institute needs to be at a level to deliver or help deliver 21st century cancer medicine to the world; 7.6 million people died of cancer in 2005, and estimates project 16 million new cases of cancer and 10.3 million deaths per year worldwide by 2020.

The NCI's portfolio includes partnerships that facilitate advances in cancer research and aid countries to address their cancer burdens. Collaborative funding and development of in-country independence are key elements of the Institute's approach. The NCI's efforts are overseen by the NCI's Office of International Affairs (OIA), and also involve research programs in all NCI Divisions and Centers, particularly in epidemiology, molecular sciences, cancer control, and clinical studies, as well as collaboration with the NIH Fogarty International Center and other NIH ICs. Other components involve an emphasis on international training programs and strategic pilot programs in Latin America, Russia, and China, along with ongoing trials in Bangladesh.

The strategies to support global development in cancer research include: build on strengths in epidemiology; draw on an existing strong base of intramural alumni and intramural relationships; leverage strengths in cancer databases, cancer control, and advanced technologies, such as nanotechnology; refine coordination across the NCI and NIH; and introduce new funding models into international programs. Steps include assessment, development of pilot projects, integration of successes to improve patient management, advancement of in-country cancer research, and development of trust-based partnerships and collaborations. Challenges in global health care policy mirror many domestic concerns, such as informed consent, reduction of redundancy, bioethics, advanced technologies, and intellectual property issues. Dr. Barker introduced the other speakers: Drs. Jorge Gomez, Director, Office of Latin American Cancer Program Development; Joe B. Harford, Director, OIA; and Richard R. Love, Senior Advisor, NCI Office of the Director, and Professor of Internal Medicine and Public Health, Ohio State University.

China. Dr. Barker described NCI's plans for research collaborations in China. The cancer burden in China is significant and expected to increase due to an aging population, increasing levels of obesity, high rates of hepatitis B infection, large numbers of smokers, and exposures to environmental and occupational hazards. The types of cancer prevalent in China differ from those in the United States; lung cancer rates are similar, but liver and stomach cancers occur at higher rates. Establishing research collaborations in China will provide an opportunity to examine genetic differences that may influence cancer etiology and outcomes, as well as the effects of unique Chinese dietary habits (e.g., consumption of soy) and the effects of exposure to chemicals and infectious agents that are uncommon in the United States on cancer risk.

Chinese investment in research is increasing, creating opportunities for collaborations. U.S.-trained Chinese scientists—approximately 500 Chinese scientists participate in NIH's intramural program each year—also are returning to China in increasing numbers. The United States has a history of

collaboration with China, beginning with the establishment of the Health Protocol in 1979, under which the NCI sponsored studies with Chinese collaborators on topics such as benzene exposure, esophageal and gastric cancer, liver cancer, lung cancer screening, cancer in textile workers, and tobacco control.

Successful collaboration depends on understanding the Chinese research funding system. The Ministry of Science and Technology funds research in China. The major organizations involved in cancer research are the Chinese Academy of Medical Sciences (CAMS), the Chinese Academy of Sciences (CAS), the Chinese equivalent of the Centers for Disease Control and Prevention (CDC), and leading cancer research universities in China. As part of its effort to develop a broader global cancer research strategy, the NCI posted Dr. Julie Schneider to Beijing to better understand research opportunities and needs in China. Analysis of effective models of international research collaboration found that joint research opportunities are preferred by the Chinese scientific community. Significant challenges to NCI collaborations with China include strict rules that limit biospecimen export; differences in human subjects protection and research integrity guidelines; intellectual property issues; and lack of a strong informatics infrastructure.

Several areas that are promising for NCI-China research partnerships have been identified. Projects to analyze cancer genomics can take advantage of large populations of patients with cancers that are common in China (e.g., gastric and liver) but rare in the United States. The Chinese Cancer Genome Project was recently launched and will facilitate this work. China has significant expertise in nanotechnology, making this an area ripe for collaboration. China also suffers from levels and types of environmental pollution exposures that are not observed in the United States, providing a setting for analyzing the effects of these exposures on cancer risk. Efforts are underway to plan an environmental pollutants and cancer meeting, co-organized with CAS, the Fogarty International Center, and National Institute of Environmental Health Sciences (NIEHS). Finally, collaborative cancer treatment clinical trials offer the potential for faster patient enrollment and study of cancers that are less common in the United States. A number of Cooperative Groups and Specialized Programs of Research Excellence (SPORES) have international activities in place, and the NCI plans to expand these efforts and build on Chinese central and local government support for globalizing clinical research in China.

Questions and Answers

Dr. Runowicz commented that combating cigarette smoking in China will be difficult because the government sponsors cigarette production. Dr. Croyle explained that the World Health Organization (WHO) Framework Convention on Tobacco Control likely will influence the Chinese government to recognize the impact that smoking will have on health care costs. In addition, a number of large tobacco control initiatives are underway in China. Dr. Hong said that the success of collaborative clinical trials in China will depend on having cooperation from Chinese scientists and medical oncologists. American Association for Cancer Research (AACR) and ASCO have international affairs committees, which may provide an opportunity for the NCI to connect with Chinese clinicians.

Dr. Coffey mentioned the history of medical collaboration between China and the United States and suggested that these previous collaborations be used as models and that the NCI speak with people involved in these activities. Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), noted that food science research collaborations with China exist; these may become increasingly important given that a significant amount of the U.S. food supply comes from China.

Office of Latin America Cancer Program Development: Partnering for Cancer Research in Latin America. Dr. Jorge Gomez presented information on NCI's efforts to advance cancer research in Latin America. The Hispanic population in the United States accounted for nearly 15 percent of the U.S. population in 2006 and accounted for one-half the Nation's growth between 2000 and 2006. The median age of Hispanic Americans is younger than that of the U.S. population and this group also represents a mix

of European and Amerindian or Native American Ancestry. Cancer is now one of the top two causes of death for U.S. Hispanics, although the prevalence of types differs from that of U.S. Whites. The types of cancer that impact U.S. Hispanics are similar to those observed in the countries of origin. Cancers associated with infectious agents (*Helicobacter pylori*, human papilloma virus, and hepatitis B and C virus) are more common among Hispanics. Breast cancer in Hispanic women is more likely to occur before menopause and is usually more lethal than breast cancer in U.S. Whites. Analysis of cancer in Latin American populations will be beneficial to Hispanics residing in the United States, who will soon represent the largest minority population in this country. To this end, the Office of Latin American Cancer Program Development (OLACPD) plans to develop local and global initiatives to prevent, diagnose, and treat cancer by facilitating development of a comprehensive cancer research infrastructure in Latin America. These projects will take into account cultural and regulatory differences among the countries, will advance the science, promote high bioethical standards and quality cancer research, and build Latin American research capacity to create an independent, sustainable research infrastructure in this part of the world.

The U.S.-Latin American Cancer Research Network (US-LA CRN) is a collaboration among the United States, Mexico, Argentina, Brazil, Chile, and Uruguay. The Network supports basic and clinical research, training programs, and technology and capacity building. Informatics will play a major role in this endeavor, and the countries are eager to adopt tools developed by caBIG. The first pilot projects address the high breast cancer incidence in Latin America and will provide data useful for managing this condition among U.S. Hispanics. Activities include molecular profiling of breast cancer in each country to determine how this disease is stratified across populations; efforts to understand and improve early detection; and clinical trials to determine best treatment options based on molecular profiling. The biobanking process in Latin America will be improved and sustainable infrastructures and cancer research networks established. The study is scheduled for launch in January 2010.

Questions and Answers

Dr. Everson asked if the US-LA CRN would sponsor opportunities for Latin American scientists to receive training in the United States. Dr. Gomez answered that the Network will offer training in methodology standardization for experienced researchers, and also opportunities for students; the Network plans to work with the Fogarty International Center to enhance their existing programs.

Dr. Kaur noted that the Hispanic population is heterogeneous and thus members will have different knowledge, attitudes, and beliefs about cancer. In addition, cancers caused by infectious diseases are declining among younger Hispanics while cancers linked to diabetes and obesity are increasing. Dr. Gomez agreed that the Network must take care to acknowledge cultural differences and use culturally appropriate approaches in its work. Dr. Brenda Edwards, Associate Director, Surveillance Research Program, DCCPS, commented on the surveillance information collected for the Hispanic populations; although the Surveillance, Epidemiology and End Results (SEER) Program has not extensively characterized cancer in Hispanic subpopulations, work is underway to gather better data.

Dr. Meneses asked if the increased prevalence in Latin American countries of cancers that are rare in the United States offered opportunities for research. Dr. Gomez confirmed this, and explained that gallbladder cancer has high incidence and mortality among Chilean women and collaboration between the NCI and Chilean researchers is being developed to study this problem.

Dr. Coffey recommended that the US-LA CRN develop metrics to assess improvement in the research infrastructure of the participating Latin American countries. Such metrics could include publication rates, increases in government support for research, and numbers of clinical trials implemented.

NCI's Office of International Affairs: Health Diplomacy and Capacity Building for Global

Cancer Control. Dr. Harford reminded members that the National Cancer Act of 1971 and subsequent legislation emphasized an international presence in supporting cancer research, collaborations with foreign researchers, and training activities. Cancer cases are rising globally, particularly in less-developed countries, and 12.9 million new incidences of cancer worldwide are estimated to cost $305 B. Risk factors for cancer include tobacco, infections, diet or nutrition, and other risks. In developing countries, infections represent 26 percent of risk factors compared to 8 percent in developed countries. In general, infectious agents cause approximately 20 percent of cancers, but this percentage is disproportionate in terms of location; Asia has very high numbers of liver cancer deaths that are related to infection with hepatitis viruses in contrast to the remainder of the world. As illustrated by research of Burkitt's lymphoma and the Epstein Barr virus in Africa, studies conducted in one part of the world can benefit populations elsewhere. Late presentation is the most significant feature of cancer in developing countries and results in lower cure rates, greater suffering, and higher mortality rates. A more pronounced emphasis on palliative care is needed as well as education of health care workers and the public.

The NCI and NIH contributed to the IOM reports on *America's Vital Interest in Global Health* (1997) and *U.S. Commitment to Global Health* (2009), both of which emphasize the interconnected world and the U.S. responsibility for global health. Additional statements of commitment to reduce global health disease burdens, including cancer, have been made by President Barack Obama and Secretary of State Hillary Clinton as well as Dr. Francis Collins, NIH Director, and Dr. Niederhuber.

The OIA serves to coordinate the planning and management of U.S. activities in international cancer research, including bilateral agreements, international exchange of scientists, and liaison with other international agencies. Ninety percent of NCI's international spending, however, occurs within its intramural and extramural divisions; the OIA assists with monitoring but not managing the budget, and it helps maintain a balance between NCI's support of research collaborations and capacity building. The Office oversees some international activities, including topical workshops, the U.S.-Japan Cooperative Cancer Research Program, and the American Russia Cancer Alliance (ARCA). Collaborations exist between the NCI and the WHO, International Agency for Research on Cancer (IARC), International Union Against Cancer (UICC), and the International Atomic Energy Agency (IAEA). Regional or topic-specific activities include interactions with the Breast Health Global Initiative (BHGI), African Organization for Research and Training in Cancer (AORTIC), International Network for Cancer Treatment and Research (INCTR), and Middle East Cancer Consortium (MECC), as well as the Ireland-Northern Ireland NCI Cancer Consortium. The NCI also interacts with national organizations that have international reach, including ASCO, AACR, and Oncology Nursing Society (ONS).

Dr. Harford concluded with the OIA's perspective of knowledge: knowledge by itself is inadequate; the application of knowledge is important. More research is needed, particularly implementation research to help achieve interventions and improve outcomes everywhere. If breast cancer survival rates were uniformly as high as the best in the world, 100,000 fewer women would die from breast cancer each year in the developing world.

Questions and Answers

Dr. Runowicz suggested that, in regards to creating set-aside funding for capacity building in low- and middle-income countries, the NCI could consider collaboration with a multinational organization, such as the Gates Foundation that has interest in international infectious diseases.

Dr. Atala commended the presentation and noted the pertinence of global healthcare access for cancer as a meeting theme. He encouraged the NCI to consider its existing research and information materials as a resource that could be translated and disseminated for use in other countries. Dr. Harford recognized this resource but noted that cultural context likely would make the process more complex than just a language-translation activity.

Dr. Champion expressed support for research on how to implement prevention strategies; one means might be to apply the NCI's research methods in other countries via mechanisms overseen by the DCCPS. Dr. Allen Dearry, NIEHS, commented that many developing countries lack the proper infrastructure and the capability for writing grant proposals; in addition, much of the infrastructure that does exist was not built to support investigator-initiated research.

Mr. William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc., supported the concentration of funds with some outstanding individuals rather than a larger dilution, and noted that statistics show that the greatest impact in developing countries would be in early detection. Dr. Harford agreed but noted that cost effectiveness can change depending on the location.

Improving Outcomes From Breast Cancer in Bangladesh: Research and Global Citizenry and Diplomacy. Dr. Richard Love described efforts to improve breast cancer outcomes in Bangladesh. Bangladesh is a low-income country undergoing a transition from infectious diseases to increases in chronic diseases such as cancer. Bangladesh's aging population, increased age at first pregnancy, and decreased parity means that breast cancer rates will steadily increase. Improving population health in this setting can be viewed as a research exercise; studies to improve breast cancer outcomes in Bangladesh will generate important information on the tumors themselves, how patients react to medicines and treatments, how cultural traditions impact breast cancer outcomes, and the effects of the health system on outcomes. Choosing an appropriate partner was crucial to effectively implementing a breast cancer program in Bangladesh; Dr. Love partnered with Amader Gram, a non-governmental rural IT development organization. The goals of the Amader Gram Program were to observe, describe, and understand breast cancer problems in Bangladesh and develop a comprehensive "search and research approach" that would be sensitive to cultural issues.

The Program evaluated 1,565 women seeking care for breast problems in rural Bangladesh. Of these, 179 were confirmed to have breast cancer. Most of the women (87%) had Stage III+, regionally advanced cancer; cure was unlikely. To reduce morbidity and mortality from breast cancer and other breast diseases, the Amader Gram Breast Care Program was developed. This program places high importance on community activation and empowerment, as well as cultural education to help sustain clinics and care programs. The Program created local committees and educational materials for use in village meetings. One form of cultural education is the "pot song," a traditional type of performance art that is designed to change perceptions about serious breast problems and the acceptability of seeking help and to increase the numbers of women who seek help for breast problems. The efficacy of the breast problem pot song will be evaluated in a village-randomized trial. The Program also has developed a family welfare visitor training program in which health care workers are trained in breast exams and provided with a cell phone and software that allows them to send data about breast problems to the Amader Gram server. The Program has developed a multidisciplinary breast care center in Khulna, Bangladesh that will make arrangements for serious breast problems including initial and long-term treatment. The Program has created the first breast cancer clinical practice guidelines that are applicable to low- and middle-income countries. The high prevalence of Stage III breast cancer in Bangladesh also offers an opportunity to study the theory of self-seeding tumors and other aspects of metastasis and recurrence.

Questions and Answers

Dr. Coffey mentioned that scientific collaborations offer an opportunity for diplomacy; in a number of cases, countries with significant differences have managed to put these aside to work toward a common goal of ameliorating a medical issue. Dr. Love agreed that activities such as those sponsored by the Amader Gram Program can help achieve cross-cultural understanding and stability. Dr. Harford added that the MECC has successfully brought together people from across the Middle East to work on cancer.

In response to Dr. Coffey's question about significant health problems facing developing countries, Dr. Harford answered that decreasing smoking by women, implementing HPV testing for cervical cancer, and downstaging breast cancer are issues that should be addressed.

Dr. Gomez asked about projects that could have an immediate impact on public health in Latin America or other developing countries. Dr. Love answered that a small grants program to fund investigators from low- or middle-income countries could be effective. In addition, the governments of those countries would be required to match funds received through such a program.

XIII. ADJOURNMENTCDR. CAROLYN D. RUNOWICZ

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

There being no further business, the 151st regular meeting of the NCAB was adjourned at 12:10 p.m. on Wednesday, 16 September 2009.

Date	Carolyn D. Runowicz, M.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary