DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
3RD JOINT MEETING OF THE BOARD OF SCIENTIFIC ADVISORS AND THE NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 23–24, 2014

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
June 23–24, 2014

The Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) convened for the 3rd Joint Meeting on 23–24 June 2014, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, 23 June 2014, from 8:30 a.m. to 6:00 p.m., and Tuesday, 24 June 2014, from 8:30 a.m. to 10:45 a.m. and closed to the public on Tuesday, 24 June 2014, from 10:45 a.m. to 11:10 a.m. The BSA Chair, Todd R. Golub, Chief Scientific Officer, The Broad Institute of Harvard University and Massachusetts Institute of Technology, and the NCAB Chair, Tyler Jacks, Director, Koch Institute for Integrative Cancer Research, David H. Koch Professor of Biology, Massachusetts Institute of Technology, presided during the open session. Dr. Jacks presided during the closed session.

BSA Members
Dr. Todd R. Golub (Chair)
Dr. Kenneth C. Anderson (absent)
Dr. Francis Ali-Osman
Dr. Dafna Bar-Sagi
Dr. Ethan M. Basch
Dr. Sangeeta N. Bhatia
Dr. Andrea Califano
Dr. Arul M. Chinnaiyan (absent)
Dr. Curt I. Civin
Dr. Graham A. Colditz
Dr. Chi V. Dang (absent)
Dr. Robert B. Diasio (absent)
Dr. Daniel C. DiMaio
Dr. Jeffrey A. Drebin
Dr. Brian J. Druker
Dr. Karen M. Emmons (absent)
Dr. Betty R. Ferrell
Dr. Kathleen M. Foley
Dr. Stanton L. Gerson (absent)
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Joshua LaBaer
Dr. Theodore S. Lawrence
Mr. Don Listwin (absent)
Dr. Maria E. Martinez
Dr. Luis F. Parada
Dr. Martine F. Roussel
Dr. Kevin M. Shannon
Ms. Mary L. Smith (absent)
Dr. Lincoln Stein
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Gregory L. Verdine (absent)
Dr. Cheryl L. Walker
Dr. Irving L. Weissman

NCAB Members
Dr. Tyler E. Jacks (Chair)
Dr. Victoria L. Champion
Dr. David C. Christiani
Dr. Marcia R. Cruz-Correa
Dr. Kevin J. Cullen
Dr. Judy E. Garber (absent)
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong (absent)
Dr. Elizabeth M. Jaffee (absent)
Dr. Beth Y. Karlan
Ms. Mary Vaughan Lester (absent)
Dr. H. Kim Lyerly
Dr. Olufunmilayo I. Olopade (absent)
Dr. Jennifer A. Pietenpol
Dr. Mack Roach, III
Dr. Jonathan M. Samet (absent)
Dr. Charles L. Sawyers
Dr. William R. Sellers

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC (absent)
Dr. Patricia Bray, OSHA/DOL
Dr. Vince Cogliano, EPA (absent)
Dr. Michael Kelley, VA (absent)
Dr. John Balbus, NIEHS (absent)
Dr. Richard Pazdur, FDA (absent)
Dr. Michael Stebbins, OSTP (absent)
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH (absent)
Dr. Sharlene Weatherwax, DOE (absent)

Members, Scientific Program Leaders, National Cancer Institute, NIH

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

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Jeff Allen, National Cancer Institute, Director's Consumer Liaison Group
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. George Dahlman, Leukemia and Lymphoma Society
Mr. Matthew Farber, Association of Community Cancer Centers
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambarresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Gerald F. Joseph, Jr. American College of Obstetricians and Gynecologists
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Steven Klein, National Science Foundation
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. 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
Lance Armstrong Foundation—no representative

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MONDAY, 23 JUNE 2014

TUESDAY, 24 JUNE 2014

MONDAY, JUNE 23, 2013

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

Dr. Golub called to order the 3rd Joint BSA and NCAB meeting and welcomed members of the Board, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Golub reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to approve the minutes of the 27 February 2014, NCAB meeting was seconded and approved unanimously.

Motion. A motion to approve the minutes of the 6 March 2014, BSA meeting was seconded and approved unanimously.

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

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

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

Dr. Harold E. Varmus, Director, NCI, welcomed members of the NCAB and BSA to the third joint meeting of the Boards. Dr. Varmus reviewed the agenda, noted topics for future meetings, and encouraged members to suggest additional topics. Members were told that recruitment is underway for a new Executive Officer following the departure of Mr. John Czajkowski and that Dr. Joseph Fraumeni, previous Director of the Division of Cancer Epidemiology and Genetics (DCEG), was honored by a population sciences symposium and dedication of a conference room at the NCI Shady Grove facility in his name. Dr. Varmus noted the enthusiasm of Sylvia Burwell, the new Secretary of the Department of Health and Human Services (HHS), to address cancer and other national health priorities.

Budget and Congressional Hearings. Members were informed that the FY 2015 appropriations remain in committee, but that the President's Budget includes a 1 percent increase and Senate appropriations an additional 1 percent increase for the NCI. Dr. Varmus stated that Dr. Francis Collins provided testimony at recent Senate and House appropriations hearings, and that final congressional action on appropriations may be delayed until after the November 2014 elections. He informed members of his testimony at a Senate Special Committee on Aging hearing concerning the demographics of cancer in the United States and the effects of aging on how cancer prevention, screening, therapeutics, accrual to clinical trials, and comorbidities are approached. Other speakers included actress Valerie Harper; Dr. Thomas Sellers, Director, H. Lee Moffitt Cancer Center; Mary Dempsey; and former Senate staffer Chip Kennett. Members were told that Congressional interest remains in recalcitrant cancers and that the NCI's report on pancreatic ductal adenocarcinoma has been well received. Dr. Varmus also said that Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, recently spoke at the inaugural briefings of the Congressional Caucus on the Deadliest Cancers. He added that the definition of cancer is rapidly expanding beyond the site of origin and into cell lineages and type.

Clinical Trials Activities. Dr. Varmus informed members about the Lung Cancer Master Protocol (Lung-MAP), a multi-armed, genetically informed clinical trial on squamous lung cell cancer that represents one of the first "precision medicine" clinical trials, along with Molecular Profiling Based

Assignment of Cancer Therapeutics (M-PACT), Adjuvant Lung Cancer Enrichment Marker (ALCHEMIST), and Molecular Analysis for Therapy Choice (NCI-MATCH) trials. Lung-MAP is managed by the Foundation for the NIH (FNIH), with approximately one-quarter support from the NCI and three-quarters support from industry. Members were referred to ClinicalTrials.gov for additional information about these groups and the National Clinical Trials Network (NCTN), NCI Community Oncology Research Program (NCORP), and early therapeutics clinical trials network that support the precision medicine efforts. Other activities related to genomics and data include the initiation of the Genomic Data Commons, continued analysis of data from The Cancer Genome Atlas (TCGA), joint projects with the International Consortium on Cancer Genomics, Center for Biomedical Informatics and Information Technology (CBIIT) cloud pilot awards, and work on the NIH Big Data to Knowledge (BD2K) project. Dr. Varmus said that the NCI continues to be active in the Global Alliance for Global Health, which has begun to initiate pilot projects, including the compilation of all known information about BRCA1 and BRCA2 mutations, co-led by Drs. Stephen Chanock, Division of Cancer Epidemiology and Genetics (DCEG), and John Burn, UK.

Funding and Related Activities. The NCI expects its FY 2014 grant awards to be similar to the FY 2013 level. Dr. Varmus stated that the NIH biosketch in grant applications has been adjusted in that the principal investigator (PI) must list up to five of his/her greatest contributions to science. In addition, the NCI's Outstanding Investigator Award (OIA), a 7-year grants program, will be announced soon, and other Institutes and Centers (ICs) will be issuing similar awards. Dr. Varmus said that a working group recently met to discuss new career awards to help trainees move from the graduate through postdoctoral periods, encourage staff scientists, and help transition researchers who are in the late stages of their research career. He also said that a RFA for the Mouse Models Consortium has ended - providing an example of the NCI's decision to sunset programs.

Dr. Varmus informed members that the NCI's focus during the NIH's intramural research program review is to determine which new or significant scientific research deserves support, such as existing networks of investigators, the best use of the population sciences capabilities that exist in DCEG, and ways to enhance progress made in diversity in the NCI's intramural program, as well as the Clinical Research Center (CRC), in which the NCI constitutes 40 percent of the activity. The NCI is preparing a summary to be incorporated into a report for the NIH Director.

Other NCI Activities. Members were informed that the Frederick National Laboratory for Cancer Research (FNLCR) is seeking new projects with the same importance and impetus as the RAS Project. Dr. Varmus said that Dr. Frank McCormick is developing the RAS Project's Hub team, engaging extramural investigators and industry representatives to participate in workshops on RAS signaling and to share preclinical and clinical data on RAS inhibitors, as well as to create postdoctoral fellowships for researchers to work on RAS projects and act as emissaries as they collaborate with other laboratories on RAS work. In addition, the NCI is providing input to a review of the Office of AIDS Research (OAR) portfolio, with an emphasis on comorbidities (cancer) and HIV therapeutics and vaccines. Members were told that approximately 5.5 percent of the NCI's budget comes from the OAR, which manages approximately 10 percent of the NIH budget. Dr. Varmus stated that the NCI Small Business Innovation Research (SBIR) Program received press attention with the launch of the NIH Innovation Corps (I-Corps) pilot program, which is an effort to help Phase 1 awardees explore markets for their inventions.

Liver Cancer Workshop and Common Fund Fibrosis Proposal. Dr. Douglas R. Lowy, Deputy Director, reported on an NCI-supported workshop on liver cancer in March 2014. Members were informed that mortality from liver cancer has risen 20 percent in the United States between 2000 and 2010, and is attributed to hepatitis C virus (HCV) infections. In addition, there is an epidemic of obesity that is associated with non-alcoholic hepatitis, and when this is associated with fibrosis, there is more than a 10 percent likelihood of progression to cancer over a 3-year period. Globally, liver cancer is the

number 2 killing cancer, attributable to approximately 750,000 deaths. Although etiologic factors in the development of liver cancer are known, opportunities exist for animal model, epidemiologic, and intervention research to better understand liver cancer pathogenesis. Dr. Lowy reminded members that many chronic hepatitis B virus carriers remain in parts of Africa despite an efficacious vaccine because that vaccination is not implemented early enough. Screening estimates in the United States indicate that at least 50 percent of carriers of chronic HCV infection are unaware that they are carriers, and additional research to identify these individuals could be considered. Dr. Lowy stated that a proposal for the NIH Common Fund for FY 2016 has been developed following the workshop to focus on pulmonary and liver fibrosis, including causes, prevention, and treatment. He noted that nearly all cases of liver cirrhosis, failure, and cancer are derived from fibrosis. Members also were informed that the NCI and other ICs, such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Allergies and Infectious Diseases (NIAID), will continue to discuss possible areas of collaborative research.

Small Cell Lung Cancer Workshop. Dr. Doroshow provided a report on the small cell lung cancer workshop held in July 2013, which was the second recalcitrant workshop. Members were informed that the Clinical Trials and Translational Research Advisory Committee (CTAC) recently approved the workshop report, in time to meet the congressional deadline of July 1 concerning the NCI overall approach to small cell lung cancer. Recommendations from the workshop are to optimize and develop a way to collect small cell lung cancer tissues and models, and to expand comprehensive genetic characterization of material from small cell patients who are in remission and at time of relapse. Dr. Doroshow stated that because the National Lung Screening Trial (NLST) results showed that early detection did not improve survival and suggested that small cell lung cancer spreads early, the NCI is considering a Program Announcement (PA) to advance genetic early diagnosis and consent to obtain preneoplasia tissues as well as a funding opportunity to understand early resistance and develop potential molecular vulnerabilities for targeted therapies.

Questions and Answers

Dr. Golub asked whether the NCI could accelerate the pace at which small cell lung cancer biopsies are collected at the time of relapse. In 2013, additional resources were provided to 15 NCI-designated Cancer Centers to obtain tissues, including small cell lung cancer, to build a repository of samples for distribution to the extramural community. Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., wondered if the collection is in coordination with the NCI's patient derived xenograft (PDX) models and cell line efforts, and Dr. Doroshow confirmed this.

Dr. Joshua LaBaer, Chair, The Directorate, Biodesign Institute, Director, Virginia G. Piper Center for Personalized Diagnostics, Virginia G. Piper Chair of Personal Medicine, and Professor of Chemistry and Biochemistry, Arizona State University, suggested that the issue of involving more senior investigators on study sections be considered as a topic for a future meeting. Dr. Varmus agreed that NCI-sponsored peer review organized by the Center for Scientific Review (CSR) could be discussed.

Dr. Patricia Bray, Occupational Safety and Health Administration (OSHA), Department of Labor, suggested that the liver fibrosis studies include occupational exposures, noting that thousands of workers are exposed to solvents and also have infection exposures.

IV. FINAL REPORT: CANCER CENTERS WORKING GROUP—DR. KEVIN J. CULLEN

Dr. Cullen presented the final report of the Cancer Centers *Ad Hoc* Working Group that reflected a new approach to NCI-designated Cancer Centers (Centers) support grant (CCSG) funding. Dr. Cullen

said that the Working Group was led by Dr. William Hait, Janssen Research & Development, and included 10 members from diverse Centers and the private sector. Members were reminded that the NCAB's charge to the Working Group was to assess whether current funding guidelines to the Centers were appropriate and sufficient and to provide guidance on policies and metrics relevant to the allocation of funds to Centers in a time of fiscal stringency. Dr. Cullen reviewed the 2013 guideline amendments that capped CCSG awards that totaled $6 M or greater at current direct costs, allowed CCSG awards of less than $6 M to request an increase of 10 percent or $1 M, and allowed new Centers to request awards of $1 M or less.

Members were told that the Working Group considered questions posed by Dr. Varmus regarding the appropriateness of the 2012 interim funding guidelines, alternative methods for funding decisions, and ways to make budgeting more flexible, such as through supplements or cooperative agreements. The Working Group met six times over 1 year, heard presentations from NCI leadership, and reviewed historical and current funding policies and approaches. Multiple possible approaches were discussed, including various funding models, and the Working Group drew several major conclusions and aligned on recommendations. The conclusions were that significant disparities exist in the size of CCSG awards, often due to factors other than merit, such as longevity, the size of the NCI budget and competitors in the year of application, and prior performance. Additional conclusions included that Centers differ in type, organizational structure, and environmental factors that affect the importance of specific CCSG components; Centers should be evaluated on what they do and how well they do it; components of the CCSG could be streamlined to decrease the administrative burden; and underperforming Centers should be reviewed carefully.

Dr. Cullen said that the Working Group reviewed several example models and reached consensus on three recommendations: (1) CCSG funding should be comprised of a base award, multipliers of the base predicated on merit and size, and possible supplement; (2) Center Administrators should be involved in planning for implementation of the new approach; and (3) the proposed changes should be framed in the context of the NCI and Centers' mission. He referred members to the Working Group's full report in the Board books.

Questions and Answers

Dr. Stillman asked for clarification about Cancer Center competition under the new mechanism and suggested that reviews be distributed to ensure that multiple large Centers do not vie at the same time. Dr. Weiss responded that the approach will be more transparent, more consistent, and fairer, and the Cancer Centers will be able to better calculate award amounts in advance. Dr. Varmus stated that competition is not with other Centers who prepared submissions that year. Dr. Sellers observed that the merit scores can affect awards and said that it cannot be called a merit-independent calculation. Dr. Cullen agreed that the award cannot be based on only merit because of the size difference of Centers.

Dr. Varmus added that the CCSGs are small and underfunded given the work they are tasked with and productivity as engines of new developments. He noted that 80 percent of the NCI-supported cancer research occurs at the Centers. The NCI diligently works to ensure that its efforts are felt throughout the country and that there is a geographic distribution of the Centers. The high success rate of more than 95 percent, however, decreases the dynamics of funding and limits the NCI's ability to make the types of adjustments recommended by the Working Group. Members were told that the NCI has started to use supplements more actively and is examining models to produce an equitable set of changes; discussions continue about how to implement the changes over time in coordination with each Center's review and to determine the optimal ratios.

Dr. Kevin M. Shannon, Roma and Marvin Auerback Distinguished Professor in Molecular Oncology, American Cancer Society Research Professor Department of Pediatrics, University of California, San Francisco, asked about the advantages of a contract versus grant mechanism. Dr. Cullen said that the Working Group did not discuss this but pointed out that although preparing the renewal grant is challenging, it provides a valuable organizational review activity that improves collaboration. Dr. Jacks reflected on the need for a proper review to appreciate the quality of the science, and Dr. Varmus indicated that the NCI is continuing to streamline the application process.

Dr. Maria E. Martinez, Professor, Department of Family & Preventive Medicine, Program Leader, Reducing Cancer Disparities, Moores Cancer Center, University of California, San Diego, asked whether the impact of the site visit, which consumes a significant amount of preparatory administrative time and resources, would be studied. Dr. Varmus reflected on the utility of the site visit as an opportunity for a Center to examine its portfolio, structure, and other elements. Dr. Champion agreed on the importance of the site visit and suggested that the site visit report be given more prominence in the application review. Dr. Jacks commented that the new system likely will ensure greater attention to many aspects of the application.

Dr. Sellers recommended that the NCI identify ways to increase funding to the Cancer Centers and suggested that it be discussed at a future Board meeting.

Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President, and Chief Scientific Officer, Professor, Department of Biochemistry and Molecular Pharmacology, NYU Langone Medical Center, New York University School of Medicine, asked whether the use of consortia might be advantageous. Dr. Varmus referred to Harvard as a consortium and said that the NCI has encouraged new applicants to consider consortia possibilities. Dr. Jacks wondered if the new system might disincentivize a consortium because of the unit size, but Dr. Varmus countered that a consortium increases the complexity of its members. Dr. Weiss listed several consortia that exist in the portfolio (Dana-Farber/Harvard, Stanford, New Mexico, Cleveland Clinic) and said that the Funding Opportunity Announcement (FOA) includes guidelines for a consortium center.

Dr. Charles L. Sawyers, Chairman, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, Investigator, Howard Hughes Medical Institute, Professor of Medicine, Weill-Cornell Medical College, sought clarity about what the Boards will approve in the motion. Dr. Jacks replied that the Boards will accept the final summary of the Working Group report, and that funding and implementation are other topics that will be presented to both Boards at a later date.

Dr. Califano pointed out that the CCSG provides the only mechanism to support institution-based shared resources that can benefit the community, and it allows supplements for innovative technology and shared resources that are in addition to the Cancer Center, which is challenging for institutions to support on their own. Dr. Varmus said that a follow-on discussion at future Board meetings will consider how implementation of the Working Group's report would fare with additional funds. Dr. Sellers suggested an examination of the comparable expenditures in the NCI budget.

Motion. A motion to accept the final report of the Cancer Centers *Ad Hoc* Working Group was seconded and approved unanimously.

V. RECOGNITION OF DEPARTING BSA AND NCAB MEMBERS—DRS. HAROLD E. VARMUS, TODD R. GOLUB, AND TYLER JACKS

On behalf of the NCI, Dr. Varmus recognized the contributions made by members of the BSA whose terms of office expired. He expressed appreciation for their service and dedication over the course

of their terms. Retiring BSA members are: Drs. Jeffrey A. Drebin, John Rhea Barton Professor, University of Pennsylvania School of Medicine, Chairman, Department of Surgery, Hospital of the University of Pennsylvania; Joshua LaBaer, Chair, The Directorate, Biodesign Institute, Director, Virginia G. Piper Center for Personalized Diagnostics, Virginia G. Piper Chair of Personal Medicine, Professor of Chemistry and Biochemistry, Arizona State University; Mr. Don Listwin, Founder and Chairman, Canary Foundation; and Frank M. Torti, Executive Vice President for Health Affairs, University of Connecticut Health Center, and Dean, School of Medicine, University of Connecticut. Retiring NCAB members are: Drs. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing; William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc.; Waun Ki Hong, Professor, Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center; H. Kim Lyerly, Vice President/Global Head of Oncology, George Barth Geller Professor of Cancer Research, and Professor of Surgery, Duke University School of Medicine; and Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center.

VI. CLINICAL TRIALS REPORTING POLICY—DR. JEFF ABRAMS

Dr. Abrams presented a new reporting policy for NCI clinical trials that addresses long lag times in publication of results, the dearth of published negative or incomplete studies, and limits in the FDA Amendment Act (FDAAA). Dr. Abrams explained that the premise for the policy is that the results of all NIH-funded research must be shared to contribute to the general body of science and public health. Grantee and contract institutions are expected to make results of their activities available. Members were told that FDAAA requires registration for Phase 2-4 trials; drug, device, or biologic product; investigational new drug or device exemption (IND/IDE) or one site in the United States; and IND-exempt studies. Results reporting is required within 12 months of the earlier of estimated or actual primary completion date for studies of approved products. Dr. Abrams described gaps in results reporting (Phase 0-1 studies, some surgical trials) and stated that the proposed policy applies to diagnostic, preventive, behavioral, and supportive care studies, some of which may not use agents or devices under FDA jurisdiction. He said that only two-thirds of NIH-supported clinical trials have been published 100 months after trial completion. Less than one-half of NIH-funded trials registered after September 2005 within ClinicalTrials.gov and completed by December 2008 were published in a peer-reviewed biomedical journal indexed by Medline within 30 months of trials completion. After a median of 51 months after study completion, one-third of NIH-funded trials remained unpublished. Studies stopped for toxicity, poor accrual or other reasons should be published because they may prove valuable to other researchers and patients by improving knowledge of side effects or avoiding duplication.

The policy proposes that rapid, public access to final trial results for investigators, clinicians, and patients is particularly important for cancer research trials because the results of such research have the potential to directly affect patient care. It encompasses all NCI-supported interventional clinical trials whether extra-mural or intramural, across all disciplines and trial phases, whether completed or not. Observational studies and any interventional clinical trial in which no subjects are enrolled are excluded. NCI-supported trials include all trials financially supported even in part by the NCI. For NCI-designated Cancer Centers, the policy does not apply to the subset of trials which, although they may benefit from core support from a Center grant, are funded privately and in which the data from the trial belong to the private funder. However, the NCI support includes those Cancer Center trials, funded at least in part by NCI, where the data resides with the academic investigator.

Trials results, including incomplete trials, are expected to be published within 12 months of a trial's primary completion date, which is defined as the date that final data from the subject was obtained. Results that must be reported include: participant flow, baseline characteristics, outcome measures and

adverse events. Final trial results must be reported in a publicly accessible manner, such as a peer-reviewed scientific journal or a publicly accessible registry dedicated to the dissemination of clinical trial information (ClinicalTrials.gov).

In terms of compliance and public input, the NCI will make the policy a term of award for grants or deliverables for contracts. The NCI Program/Project Officers will enforce this policy at the time of preparing the final progress report or at an alternative date for larger grants to trial networks, and non-compliance may result in funds recovery or withholding future support. The proposed policy was published in NIH Guide: NOT-CA-14-005 and received uniformly supportive comments. In addition, the NIH Guide Notice was shared with the Cancer Therapy Evaluation Program (CTEP) clinical investigator distribution list, from which most comments were positive although one respondent was concerned about the added workload. The policy was presented to the CTAC. Provisional to the support of the NCAB and BSA, the NCI will implement the policy in the fall of 2014.

Questions and Answers

Dr. Mack Roach III, Professor of Radiation Oncology and Urology, Chair, Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, expressed support in general but suggested that PIs be required to indicate in their trial designs when data will be made available rather than be mandated in a universal policy. Dr. Abrams replied that NIH grant contracts currently dictate submission to ClinicalTrials.gov within 1 year of the last data gathered for those drugs that are under FDA jurisdiction. He clarified that the reporting requirement commences when the last event to conduct analysis is obtained to conduct the endpoint, not the last day of a patient's treatment, and acknowledged that some trials have long endpoints.

Dr. Frank M. Torti, Executive Vice President for Health Affairs, University of Connecticut Health Center, Dean, School of Medicine, University of Connecticut, encouraged the NCI to expand the policy further to enhance the ability of investigators to access and interpret clinical trial data, commenting that access to data should help build in the newer technologies. Dr. Andrea Califano, Director, Columbia Initiative in Systems Biology, Directory, Sulzberger Columbia Genome Center, Associate Director, Herbert Irving Comprehensive Cancer Research Center, Professor of Systems Biology, Department of Biochemistry and Molecular Biophysics, Biomedical Informatics, and Institute of Cancer Genetics, Columbia University Medical Center, added that correlative data also should be released. Dr. Abrams agreed and stated that the new NCTN mandates that the data-sharing policy be followed.

Dr. Brian J. Druker, Director, OHSU Knight Cancer Institute, Associate Dean for Oncology, OHSU School of Medicine, JELD-WEN Chair of Leukemia Research, Oregon Health and Science University, requested clarification about ways to comply with the policy beyond peer review publications. Dr. Abrams replied that results can be reported in ClinicalTrials.gov or other publicly available registries, and he added that abstracts published in journals do not satisfy the policy unless the journal accepts articles in abbreviated format.

Dr. Sellers expressed support for the policy and requested further details about the exemption of negative observational trials, which might refute positive published results. Dr. Abrams said that information from an observational trial was deemed not to be of immediate, actionable value to clinicians and patients such that it would be mandated by the policy.

Dr. LaBaer remarked on the finding that results from one-third of clinical trials are never published. Dr. Abrams said that investigators may lose interest after several attempts at publication fail, whereas others may not find adequate time to prepare a report.

Dr. Califano asked about the allocation of additional resources, and Dr. Varmus indicated that the NCI will handle resources and is seeking the Boards' support for the overall policy.

Motion. A motion to support the overall NCI Clinical Trials Reporting policy was seconded and approved unanimously.

VII. SPORE PROGRAM WORKING GROUP REPORT—DR. TOBY HECHT

Dr. Toby Hecht, Translational Research Program, Division of Cancer Treatment and Diagnosis (DCTD), informed members that the Specialized Programs of Research Excellence (SPOREs) Program is in its 23rd year of supporting multi-project, interdisciplinary and at times multi-institution translational research with a focus on 17 organ sites to develop new approaches to the prevention, early detection, diagnosis, and treatment of human cancer. Dr. Hecht stated that there are 56 SPOREs in 27 institutions, particularly NCI-designated Cancer Centers, across 19 states. She described unique features of the SPOREs Program, which include ~~that~~ projects that have a human endpoint within 5 years, are flexible, include career development (CDP) and developmental research programs (DRP) as well as a biospecimens core, and must collaborate and receive input from patient advocates. Changes in the Program since 2008 involve the addition of a scientific collaboration component, the elimination of administrative supplements, mandate of a required project for only the four major malignancies, inclusion of IND-directed technology as a 5-year human endpoint, and that related groups of cancers may include those that are related by an activation pathway or other oncogenic mutations across organ sites. Members were told that a Program Announcement (PA) is required for receipt of applications for January 2015.

Dr. Hecht said that the SPORE Program was evaluated by the Science and Technology Policy Institute and a report prepared in 2014 was based on data collected and analyzed from SPOREs that were active in 2004 and after, and that completed at least one 5-year award cycle by mid 2011. The draft report was provided to the CTAC Working Group in January 2014 and received Clinical and Translational Research Operations Committee (CTROC) and CTAC approval in March, with approval from NCI Scientific Program Leaders in April. The evaluation report identified 67 major advances of the SPORE Program, including those accepted into clinical practice, landmark population studies, and advances in late-phase testing and with broad clinical potential. These include enzalutamide for late-stage prostate cancer, heat-shock protein peptide complex, sensitivity and resistance to EGFR tyrosine kinase inhibitors in lung cancer, and identification in African American men with 8q24 as a prostate cancer risk locus, among others. Members were informed that a CTAC Working Group evaluated the program and its March 2014 report advocated funding for a program focused exclusively on translational research and recommended that the NCI continue its support of the SPORE Program, which fills this translational need. Additional suggestions included that SPORE applications include at least one project addressing early detection, prevention, or population sciences, and that the development research and career development programs are valuable features and should be continued.

Dr. Hecht highlighted significant recent accomplishments by SPORE investigators, including the identification using whole genome mRNA profiling of specimens of three molecular subtypes of muscle-invasive bladder cancer that share features with basal and luminal breast cancer. In addition, comprehensive molecular analyses performed on the residual disease of 74 triple negative breast cancers after neoadjuvant chemotherapy and comparison with matched pretreatment biopsies revealed molecular lesions and pathway activation; 90 percent contained an alteration potentially treatable with currently available targeting agents. Another accomplishment was discovered in pancreatic cancer development, specifically that mutant KRAS requires the expression and activation of ligand-dependent EGFR. Without EGFR activity, mutant KRAS activity is insufficient to induce MEK/ERK activity, which is required for epithelial transformation.

Questions and Answers

Dr. Sawyers questioned whether some of the examples highlighted by Dr. Hecht could have been funded through other existing mechanisms. Dr. Hecht explained that the question was addressed in the report. The unique features of the SPORE Program, such as the requirement for translational research, have aided the ability to achieve these transformational results.

As a population scientist familiar with a SPORE center, Dr. Martinez emphasized the importance of incorporating the population sciences as a requirement. Dr. Hecht said that some SPORE programs have been doing population science without a formal requirement; if the expertise is there, they will do it.

Dr. Luis F. Parada, Chairman, Department of Developmental Biology, University of Texas Southwestern Medical Center, noted that the endpoint for a SPORE project is translation, and he questioned why the decision was made to make the projects open-ended rather than impose defined time limits that are a common feature of many large projects. Dr. Hecht said that 93 percent of the grants reach their human endpoint in 5 years, which is a strong indication of success. Furthermore, 50 percent of all competing renewals are new projects, which are peer reviewed to ensure that it is a good direction.

Dr. Francis Ali-Osman, Margaret Harris & David Silverman Distinguished Professor of Neuro-Oncology Research, Professor (Tenured) of Surgery and Pathology, Department of Surgery and Pathology, and Associate Director for Translational Research, Duke University School of Medicine, Duke University Medical Center, asked about the rationale behind combining the CDP and the DRP, which are distinct projects and attract different sets of investigators. The DRP, for example, tends to bring in established investigators in the field. Dr. Hecht affirmed that the CDP and DRP submissions will be reviewed separately and the identity of the programs will remain independent. The reason behind combining the funding was to provide flexibility. At the end of 5 years, the investigator must have made a commitment to each of those programs, which are peer reviewed separately.

Dr. Roach asked Dr. Hecht a question of clarification related to SPORE collaborations with cooperative groups. A new recommendation is to consider collaborations with cooperative groups a favorable feature as an evaluation criteria for SPORE programs. Dr. Hecht said that supplements were eliminated to encourage the SPORE groups to use cooperative group resources and other mechanisms to advance the science on the translational continuum.

In response to a query by Dr. Stillman, Dr. Hecht informed the Board members that the total budget for the SPORE Program is approximately $100 M per year. Dr. Stillman asked why 10 percent of the SPORE programs is on interim funding. Dr. Hecht explained that last year was a unique situation because there were several excellent proposals that could not be fully funded because of budgetary constraints. Those teams were given provisional funding for 1 year to continue their program prior to resubmission; all teams did exceptionally well during the year.

Dr. Champion expressed disappointment that the requirement for a CPC project was eliminated, commenting that a great strength of the Cancer Centers is that they have required translation.

Dr. Califano said that there is value in a mechanism that brings together a dedicated team to solve a problem tactfully. As opposed to the Cancer Centers, the SPORE programs require a different type of review to allow projects that are not going well (i.e., not leveraging the team aspect of the effort) to be downsized or eliminated quickly. Dr. Califano asked how many projects have been cancelled, and how frequently the SPORE programs are evaluated. Dr. Hecht clarified that most of the SPORE programs have careful annual or twice-annual reviews with their advisory boards to evaluate which projects should be continued or replaced.

Dr. Sellers stated that historically, the SPORE programs have provided a seed to encourage clinicians and research investigators to work together. From a translational output perspective, Dr. Sellers expressed disappointment with the results, noting that the highlighted examples are not necessarily causally associated with the SPOREs. Moving forward, Dr. Sellers recommended funding the Cancer Centers rather than the SPORE programs.

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, noted that since most of the SPOREs are within an NCI Center, one could examine the clinical program productivity within the Cancer Centers, and determine if those clinical programs with SPOREs have a higher rate of investigator-initiated trials, bidirectional impact (bench to/from clinic), and trainee career path success. Dr. Hecht said that the comparison study has not been done, but she noted that many graduates of the SPORE career development program are now Center Directors.

Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, OHSU Center for Spatial Systems Biomedicine, Oregon Health and Science University, commented that in his experience, Cancer Centers and SPOREs do very different things. Cancer Centers catalyze a broad view of core development and general thinking about cancer. SPOREs tend to be the intellectual focus for a particular disease group. In many cases, cancer treatment is delivered by organ site, and the SPOREs develop an intellectual community around a particular organ site, whose impact transcends the projects funded by the SPORE. This mechanism is very important; however, it is accomplished. Dr. Cheryl L. Walker, Professor and Director, Institute of Biosciences and Technology, Center for Translational Cancer Research, Welch Chair in Chemistry, Texas A&M Health Science Center, agreed, noting that the SPORE programs often cross institutional boundaries, which is particularly important for rare cancers.

Dr. Jacks stated that programs have their time and place, such as the successful Mouse Models of Human Cancer Consortium, which will be ending to allow the NCI to move on to a different phase that reflects the Institutes' interests in other ways. He noted that a goal can be furthered without the expectation of a large outlay of funding. Dr. Cullen said that in many years, the majority of funding is awarded to existing SPOREs. Although the accomplishments have been very valuable, history tends to ossify programs where they exist, and it is difficult to create a SPORE in a Center that does not already have one. Dr. Torti agreed that the NCI should consider more "sunsetting" of programs.

VIII. NEW RFP CONCEPT—NCI STAFF

Division of Cancer Treatment and Diagnosis
A Prospective Randomized Trial of Carbon Ion Versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer —
Dr. Bhadrasain Vikram

Dr. Vikram described a new concept for a national center for particle beam radiation therapy research based on a recommendation from the NCI Scientific Program Leaders to fund randomized clinical trials of carbon ion radiation therapy (CIRT) at facilities in Europe and Asia. Dr. Vikram explained that CIRT has been administered to several thousand cancer patients, primarily in Japan where no randomized control trials have been performed. Single-arm trials report that CIRT is substantially more effective than photons or protons against some radio-resistant cancers (pancreatic, rare sarcomas, rare head and neck, recurrent rectal cancers). Based on similar uncontrolled trials, protons were claimed superior to photons. The first hospital-based proton facility opened in the United States 20 years ago, and randomized control trials are now being conducted. Because CIRT facilities cost $300 M compared with

$150 M for proton facilities, it seems prudent to sponsor some randomized control trials abroad to determine their value before supporting the construction of CIRT facilities.

Dr. Vikram said the concept is to conduct a randomized control trial in locally advanced, unresectable pancreatic cancer comparing CIRT versus a standard randomized radiation trial. The 2-year survival rate after a standard randomized trial is approximately 10 percent, but recent Japanese data suggest a survival rate of 54 percent. Members were told that NRG Oncology currently is comparing a standard randomized trial with intensity modulated radiation therapy (IMRT), aiming to increase the 2-year survival rate from 10 to 22.5 percent. Identical eligibility criteria, control arm and system therapy are planned. Dr. Vikram indicated that analysis will be conducted in coordination with Radiation Therapy Oncology Group (RTOG) trial 1201.

Subcommittee Review. Dr. Theodore S. Lawrence, Isadore Lampe Professor and Chair, Department of Radiation Oncology, University of Michigan Medical School, University of Michigan, expressed the Subcommittee's enthusiasm for the concept, noting its potential to increase cancer survival rates and that it can address recalcitrant cancer types. The Subcommittee encouraged NCI to also evaluate the technology's benefits, harms, and cost effectiveness in glioblastoma and more common cancers, as well as consider outcomes compared to those of proton facilities and other technologies.

The first year cost is estimated at $200,000 for 1 award, with a total cost of $2 M for 5 years.

Questions and Answers

Dr. Betty Ferrell, Professor, Nursing Research and Education, Full Member, Cancer Control and Population Sciences Program, Comprehensive Cancer Center, City of Hope National Medical Center, asked whether the plan protocol for pancreatic cancer would extend beyond survival, and she encouraged the inclusion of symptom burdens and other quality-of-life parameters during evaluation. Dr. Vikram replied affirmatively provided that the appropriate tools are available in foreign countries.

Dr. Roach recommended that the contract include dosage specifications, including the carbon delivery mechanism, and dose and margins of carbon. Dr. Vikram confirmed that the contractor will provide and justify the regimen for the use of carbon.

Dr. Sellers voiced concerns about the pace of the trial and suggested that increased funding might accelerate accrual. He also wondered about the incentives to randomize patients in a single site that reports a 54 percent survival rate (Japan) and encouraged support for multiple sites (e.g., Japan and Germany). Dr. Vikram said that consortia are encouraged.

Dr. Cullen wondered how carbon ion efficacy can be inferred from one specific population to other ethnic groups and whether conducting this trial with photons, protons, and carbon ion would yield more conclusive results. Dr. Vikram stated that discussions have been underway with proton facilities in the United States but that current data about protons and pancreatic cancer have not stimulated the proton community. Dr. Roach said that one reason for less focus on protons is that the RBE of protons is equal to that of x-rays and there is minimal difference between the dose distribution of IMRT and protons.

Dr. Joe Gray expressed support for the concept and appreciation for the technical sophistication of the delivery of the dose that is required for high efficacy. He encouraged expanding the concept to encompass the proton, photon, and carbon ion modalities to garner useful data as well as to support multiple sites. Dr. Irving L. Weissman, Director, Institute of Stem Cell and Biology and Regenerative Medicine, Stanford University, added that an immune-monitoring core using the most sophisticated tools available should be included.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' (DCTD's) request for proposal (RFP) entitled "A Prospective Randomized Trial of Carbon Ion Versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer" was approved with 25 ayes, no nays, and one abstention.

IX. THE USE OF ASPIRIN FOR PREVENTION AND TREATMENT OF CANCERS— DRS. BARRY KRAMER AND ANDREW T. CHAN

Dr. Barry Kramer provided an overview of clinical studies of aspirin and cancer prevention signals. Members were informed that the U.S. Preventive Services Task Force (USPSTF) is performing a systematic review of benefits and harms for cancer prevention. Dr. Kramer introduced Dr. Andrew T. Chan, Division of Gastroenterology, Massachusetts General Hospital, who described mechanistic studies of aspirin and prevention of colorectal cancer.

Dr. Kramer described results of several clinical studies that demonstrate the benefits of aspirin use for cancer prevention, noting that most benefits were presented as relative rates. One review that synthesized daily aspirin use over 5 years and colorectal cancer risk found similar results across randomized trials, case-control, standard cohort, and nested case-control studies. Results of cohort studies plotted against case-control studies showed similar estimates of benefit across all tumor types. Members were informed about another study that suggested a differential effect on COX enzymes (COX-1 vs. COX-2) between lower and higher (300 mg) dose aspirin. The results indicated a duration effect for people who took aspirin beyond 2.5 years, with trends in differences in incidence and mortality for colorectal cancer. Dr. Kramer said that aspirin use also appears to have an effect late in the spectrum of cancer progression up to and including cancer metastasis, and he shared examples of lung and liver metastases in people who have cancers and are taking aspirin. He added that the effect on metastasis appears to be concentrated on adenocarcinomas. The beneficial effect of aspirin on overall mortality also has been seen across a broad range of tumors as evidenced in three randomized control trials. Dr. Kramer summarized that regular aspirin use is associated with a reduction in the long-term risk of developing a variety of cancers, particularly for gastrointestinal cancers, and metastasis in patients taking aspirin prior to diagnosis of cancer may be reduced. However, mechanistic studies of aspirin effects across the spectrum of pathogenesis, progression, and metastasis are needed.

Dr. Chan presented mechanistic studies of aspirin related to clinical preventable effects for colorectal cancer. Understanding the mechanisms by which aspirin prevents cancer provides additional evidence of causality and can help to develop biomarkers to better target individuals for prevention. Members were told that the anti-cancer effect of aspirin has been indicated by observational data from several adenoma prevention trials in which patients treated with aspirin for 1-3 years saw a reduced risk of developing a recurrent polyp or tumor. Dr. Chan focused his presentation on studies of two NCI-supported population trials: the Nurses' Health Study and the Health Professionals Follow-up Study, which enrolled more than 120,000 female and 50,000 male subjects, respectively. These trial cohorts have been useful because their size, bi-annual surveys that have queried aspirin use, and available biospecimens have allowed mechanistic study of associations. Initial analyses showed that regular aspirin use over 10 or more years reduced the risk of colorectal cancer by 20-35 percent. These observational data have been supported by the Women's Health Study, which revealed no difference in colorectal cancer incidence among trial participants for the initial 10 years of aspirin use but showed lower rates of colorectal cancer in long-term follow-up for those randomized to aspirin. Dr. Chan also described studies of aspirin use related to colorectal cancer patient survival and the risk of gastrointestinal bleeding. Studies showed increased risk of gastrointestinal bleeding for patients who took 1-2 aspirin daily over their lifetime. Members were reminded that in 2007 the USPSTF recommended against the routine use of

aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer in average-risk individuals.

Dr. Chan described two mechanisms to personalize chemoprevention: prostaglandin balance and *Wnt* signaling. Members were told that aspirin inhibits COX-2 enzymes that convert arachideonic acid into prostaglandin, which affects receptors and pathways relevant to cancer progression. Aspirin also may affect COX-2 directly through its effect on platelets and other cells such as tumor stromal cells. Prospective studies have shown that aspirin has greater specificity for COX-2 positive cancers, with long-term aspirin use appearing to reduce COX-2 positive tumors by up to 35 percent and providing a 30 percent improvement in colorectal cancer-specific mortality post-diagnosis. Dr. Chan described studies that indicated that aspirin preferentially reduces the risk of colorectal cancer and the spread of tumors for which growth depends, at least in part, on COX-2 function. In a study of aspirin and mortality, the strongest benefits of aspirin use were seen in patients with both COX-2 positive and PI3 kinase activating mutations. The pilot Adenoma Prevention with Celecoxib (APC) trial showed that individuals with low levels of 15-PGDH in the colon had increased resistance to anti-tumor effects of celecoxib and suggested that aspirin may preferentially reduce the risk of colorectal cancer among individuals with sufficient colonic 15-PGDH. In addition, a case-control study of the Nurses' Health Study that analyzed urine PGE-M showed a 25 percent reduced risk of advanced adenoma for aspirin users. Members also were informed that *Wnt* signaling studies found that aspirin inhibited prostaglandin synthesis. GWAS found that an allele on 8q24 was associated with colorectal cancer, and further studies suggested that aspirin may be most effective in individuals with a specific genotype at that locus that reduces *MYC* expression.

Questions and Answers

Dr. Jacks welcomed USPSTF staff who were in attendance.

Dr. Lincoln D. Stein, Director, Informatics and BioComputing Platform, Ontario Institute for Cancer Research, remarked on the upward curve for risk of colorectal cancer by the placebo group at year 10 of the Women's Health Trial. Dr. Chan said that some differential association by age is expected.

Dr. Martinez asked Dr. Chan if his work included other COX-independent mechanisms, such as the polyamine pathway and ornithine decarboxylase (ODC). Dr. Chan agreed that evidence suggests that aspirin may influence levels of polyamines in addition to prostaglandins in the colon and acknowledged the value in exploring the mechanism as a combination of aspirin and polyamine agents that may have a synergistic effect on tumors.

In response to a query by Dr. LaBaer about the timeline of events, Dr. Chan indicated that research has helped reveal mechanistic processes and the next step is to conduct prospective mechanistic studies to understand, for example, aspirin's effect on the normal epithelium or platelets. Dr. Kramer commented that Rothrow excluded the Women's Health Study in his meta-analyses because the dose was different (every other day vs. daily).

Dr. David C. Christiani, Elkan Blout Professor of Environmental Genetics, Department of Environmental Health, Department of Epidemiology, Harvard School of Public Health, and Professor of Medicine, Harvard Medical School, referred to an alert letter to the cardiovascular community concerning enteric-coated aspirin and observed that variables to administration (e.g., optimizing the low-dose rate) will need to be addressed. Dr. Chan agreed and said that such unanswered questions such as the frequency of dosing could be answered in the context of a biomarker-driven trial.

Dr. Califano noted that the statistics indicate aspirin lowers prostaglandin levels significantly. In response to a question from Dr. Califano, Dr. Chan noted that 15-PGDH was measured on a relatively

small proportion of the cohort, and the study needs to be expanded. The threshold level of 15-PGDH necessary to see a benefit of aspirin is not yet known.

Dr. Califano commented that the patients in the cohorts were taking aspirin, but he noted that it is difficult to differentiate how prostaglandin or COX-2 levels are indicative of a response to aspirin or a lack of response. Dr. Chan acknowledged that it was a good insight. An ideal study would collect tissue at multiple time periods to understand what is going on at baseline and during follow-up. Ultimately, it will be important to address the question prospectively in the normal and diseased epithelium.

Dr. Kramer stated that it is difficult to perform a definitive study of aspirin in the United States because so many people take it for other reasons (e.g., cardiovascular or stroke prevention). The NCI is jointly funding an Australian study with the National Institute on Aging (NIA) to evaluate the balance of benefits and harms in elderly people, specifically looking at disability and cancer endpoints in people ages 70 and older.

Dr. Marcia R. Cruz-Correa, Associate Professor of Medicine and Biochemistry, University of Puerto Rico, Basic and Translational Science Director, University of Puerto Rico Comprehensive Cancer Center, noted that the USPSTF recommendation refers to primary chemoprevention and asked what data the USPSTF would need to provide a recommendation about aspirin use to those who had colorectal cancer. A USPSTF staff member responded that that the USPSTF recommendations address primary and secondary cancers, not tertiary, and would require studies that show mortality benefit and harms in humans. Dr. Chan stated that the impact of screening is clearly evident, and that aspirin and colonoscopy can be complementary strategies.

Dr. Ali-Osman commented on other mechanistic pathways to study prostaglandin and asked about correlations of colorectal cancer with other cancers and diseases in the Nurses' Health Study and the Health Professionals Follow-up Study. Dr. Chan noted the challenges presented by aspirin, which does not have a sole target, and said that the cohorts have been followed closely for other diseases.

Dr. Varmus said that he brought this topic to the Boards because of their interest in hearing more about prevention research, not enough public attention is given to aspirin use as a public health measure, and it links to the Provocative Questions Initiative, which asks a question to understand mechanisms by which aspirin and other commonly used drugs might help to prevent or treat cancers. Dr. Chan expressed appreciation for the Initiative and supports the NCI's movement to understand effects.

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

Division of Cancer Prevention
The Early Detection Network (EDRN)—Drs. Barry Kramer and Larry Norton

Dr. Kramer provided an overview of the EDRN objectives and past accomplishments and introduced Dr. Larry Norton, Deputy Physician-in-Chief for Breast Cancer Programs & Medical Director, Evelyn H. Lauder Breast Cancer & Norna S. Sarofim Chair in Clinical Oncology, Memorial Sloan-Kettering Cancer Center, who provided a report of the EDRN consulting team. Dr. Kramer reminded members that the EDRN's objectives were to establish an investigator-initiated infrastructure to foster interaction among stakeholders, standardize biomarker validation criteria, and bring biomarkers to clinical use. He reviewed the Network's infrastructure, which includes biomarker development laboratories, reference laboratories for analytic validation, and centers for subsequent clinical validation, as well as oversight from a steering committee of the investigators and an external consulting team that provides independent scientific guidance and review. Members were told that biomarker validation involves three phases of marker development: reproducibility, analytic validity, and finally clinical validation. EDRN

has established criteria to ensure high-quality discovery and validation of biomarkers, which evolved into the Prospective Specimen Collection, Retrospective Blinded Evaluation (PRoBE) methodology used as a standard in the field. Dr. Kramer stated that the Network has four collaborative groups addressing prostate, lung, colon, and breast cancers, and he described the breadth of EDRN strategic partnerships with federal agencies and private organizations. EDRN efforts have resulted in five FDA-approved and 11 Clinical Laboratory Improvement Amendments (CLIA)-approved biomarker tests, and the Network is cited as a model for integrated biomarker development and validation. It also has established resources available to the extramural community, including standard biospecimen reference set; 100,000 clinically annotated biospecimens; and bioinformatics resources and annual statistics courses. Scientific accomplishments include decision criteria for biomarker triaging, 800 verified biomarkers in the pipeline, approximately 2,000 publications with more than 20 percent in high profile journals, and five FDA-biomarkers related to early disease detection to determine whether biopsy or surgery is indicated. Dr. Kramer stated that the Network has 12 ongoing and 15 pending studies of markers that have advanced through the early phases of development and are ready for later phase validation. Members were provided with the EDRN consulting team's report and recommendations included expanded comparative effectiveness research that can inform cost-effectiveness studies as well as studies to identify the molecular fingerprints of indolent screen-detected tumors that trigger overtreatment.

Dr. Norton provided the report of the EDRN consulting team, which is charged with providing recommendations to the EDRN process and providing oversight. The consulting team includes members from FDA, industry, and academia staff, representing various constituencies. Members were told that the EDRN strengths include collegiality and inclusivity. One of the most important results of the EDRN process is the development of rules for standards and validation. Dr. Norton noted that the EDRN has evolved as the biomarker field has changed. Activities previously started with early detection and therapy now have shifted to detecting the disease before it occurs, which is important for prevention strategies; developing biomarkers for targeted therapeutics; and sophisticated screening.

Members were informed about recent recommendations from the EDRN consulting team. One recommendation was that the integration of governmental agencies along with academia could be improved, particularly as cost issues become paramount. Another recommendation is that efforts in imaging biomarkers should be supported. Emphasis should continue on standards and validation steps, including the establishment of rules or procedures by which standards, validation, and even clinical application can be measured and monitored.

Members were told that the reissuance concept is to maintain the collaborative and comprehensive EDRN infrastructure, accelerate the development of biomarkers that will change practice, and ensure data reproducibility and integrity. A funding request for an additional $5 M over the current 5-year cycle was requested to cover increased complexity and cost of mid-late phase marker validation, a focus on recalcitrant cancers, and expansion to additional high-priority tumors.

Subcommittee Review. Dr. Sangeeta Bhatia, John J. and Dorothy Wilson Professor, Division of Health Sciences and Technology and Electrical Engineering and Computer Science, Institute of Medical Engineering and Science, Koch Institute for Integrative Cancer Research, Broad Institute, Brigham and Women's Hospital, Massachusetts Institute of Technology, expressed the Subcommittee's support for the valuable infrastructure for biomarker development that the EDRN provides, including its filtration of 1,000 biomarkers out of the pipeline. Dr. Bhatia said the Subcommittee appreciated the Network's ability to validate a pathway for reproducing biomarkers. The program is perceived as highly productive, but the biomarkers that have been found and validated do not appear to have had a high impact and integration of the biomarker pipeline with the new cancer sciences (-omics, imaging) is unclear. Dr. Bhatia said that the Subcommittee felt that the EDRN is uniquely positioned to conduct validation and discussed whether validation efforts could be expanded beyond early biomarkers.

The first year cost is estimated at $30 M for up to 16 Biomarker Developmental Laboratories, up to 4 Biomarker Reference Laboratories, up to 9 Clinical Validation Centers, and 1 Data Management and Coordinating Center, with a total cost of $150 M for 5 years.

Questions and Answers

Dr. Califano referenced the previous review discussion about the spectrum of validation and discovery aspects addressed by the EDRN and the potential conflict of interest in validating their own discoveries. For the level of investment in the program over 15 years, Dr. Califano felt that the number of biomarkers in the research pipeline is quite low. In response to a question, Dr. Kramer reiterated that more than 1,000 markers have been screened, many of which have been generated externally. He noted that there is a distinct advantage to having a discovery process within the EDRN structure to enable EDRN investigators and associate members to learn how to develop markers and what will occur during validation.

Dr. Califano also asked about the process by which biomarkers are prioritized for validation and questioned the percentage of validated biomarkers that originated from outside the EDRN. He noted that biomarkers validated with defined mechanisms have been the most successful, and perhapsan independent review board for prioritization may increase validation submissions to the EDRN. Dr. Kramer explained that the EDRN cutpoints for sensitivity and specificity are publically available and provide an objective measure that all biomarkers must meet. He informed members that when a biomarker is proposed, it is evaluated blindly. NCI staff clarified that two of the FDA-approved biomarkers were externally submitted and three came from the EDRN.

Dr. Basch asked about assessing clinical benefits, as the assessment of clinical validity is not the same as the assessment of clinical benefits. He questioned whether the NCI had considered formalizing the pipeline of markers to assess clinical benefits. Dr. Kramer remarked that the establishment of trials assessing clinical benefit of markers cost upwards of $200 M, which is beyond the reach of the EDRN mechanism. Other mechanisms to handle the transition to evaluate clinical utility are accessible within DCP, such as prospective cohorts. He indicated that the markers are not solely intended to use for screening; they are used to refine screening tests in common clinical use to retain the benefits but diminish the harms of the screening procedure.

Dr. Sawyers asked about the molecular diagnostics industry, as increased investment might indicate success of the EDRN. NCI staff explained that five FDA biomarkers were supported by industry partners, who provided an in-kind contribution of reagents and analysis. In the future, industry partners will be able to contribute monetary funds to the EDRN through the NIH Foundation.

Dr. Torti commented that the validation function of the EDRN is unequivocally valuable and not reproducible elsewhere. The discovery group, however, receives a large proportion of the funds and does not have a clear return on investment. NCI staff explained that out of the $69 M allocated for biomarkers and early detection, EDRN has $9M for discovery to efficiently triage biomarkers.

Dr. Golub remarked on the value of ruling out candidate biomarkers. He noted, however, that ruling out 1,000 biomarkers indicates a failure of discovery. Dr. Norton commented that irreproducibility in methods explains some of the failures.

Dr. Sellers asked about the program's objectives for the highest level of patient impact, as well as the availability of early-stage cancer samples for analysis. The Prostate, Lung, Colorectal and Ovarian

(PLCO) Cancer Screening Trial has available specimens and is one of the best characterized cohorts with associated biosamples.

Dr. Roach said that the program is very impressive, but he expressed doubt that the proposed work of the EDRN would justify increasing the budget by 20 percent. Dr. Roach added that most assays, such as the PCA3 and proPSA assays, have not transformed the practice of medicine or translated into meaningful improvements in survival. Dr. Kramer responded that the EDRN has made an impact in how clinicians practice for at least one of the five biomarkers and it is too early to comment on others.

Dr. Golub reiterated the members' question of whether the biomarkers generated through the EDRN pipeline have been transformative and relayed the members' enthusiasm for the program that approaches standardization and validation with vigor.

Members debated the merits of the discovery and validation components of the EDRN. Dr. Cullen confirmed that the annual budget for the Biomarkers Development Laboratory was $9 M, and he suggested that removing the discovery component would reduce the program's budget. NCI staff explained that it was critical to include discovery in the EDRN since the validation studies inform and tailor discovery. Dr. Norton added that including discovery in the process increases engagement in validation by the research investigators.

Dr. Varmus commented that from the perspective of NCI management, the questions are whether the Board approves the EDRN and whether it should continue at a current, lower, or higher level of funding.

Motion. A motion to concur on the Division of Cancer Prevention's (DCP) reissuance of request of application/cooperative agreement (RFA/Coop. Agr.) entitled "The Early Detection Network (EDRN)" was approved unanimously.

Motion. A motion to support the DCP's reissuance of request of application/cooperative agreement (RFA/Coop. Agr.) entitled "The Early Detection Network (EDRN)" at its current level of funding of $25 M was approved with 16 ayes, 7 nays, and 3 abstentions.

Division of Cancer Control and Population Sciences
Breast Cancer and the Environment Research Program

Subcommittee Review. Dr. Graham A. Colditz, Niess-Gain Professor of Surgery, Professor of Medicine and Associate Director, Prevention and Control, Alvin J. Siteman Cancer Center, Deputy Director, Institute for Public Health, and Chief, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, expressed the Subcommittee's support for reissuance of the concept. Dr. Colditz stated that the Breast Cancer and the Environment Research Program (BCERP) was established pursuant to Congressional interest in environmental exposure and breast cancer and is jointly funded by the NCI and National Institute of Environmental Health Sciences (NIEHS). The reissuance concept emphasizes the environment and early life stages, the importance of which has been highlighted in recent breast cancer reports prepared by the Institute of Medicine (IOM) in 2012 and jointly by the NIEHS and the NCI in 2013. He noted BCERP's productivity and the intent to engage academic community partnerships to facilitate the movement of science from human to animal for confirmation of associations. The initiative incorporates a priority of the NCI Provocative Questions (PQ), and relevant PQ researchers will be invited into the broader BCERP network.

The first year cost for the NCI is estimated at $2.88 M for 9–10 U01 awards, with a total of $14.4 M for 5 years.

Motion. A motion to concur on the Division of Cancer Control and Population Sciences' (DCCPS) reissuance of request for application/cooperative agreement (RFA/Coop. Agr.) entitled "Breast Cancer and the Environment Research Program" was approved unanimously.

Office of the Director
Research Answers to NCI's Provocative Questions (PQs) —Dr. Edward E. Harlow

Dr. Edward E. Harlow, Special Assistant for Science Planning, presented the reissue concept for NCI's Provocative Questions initiative. Dr. Harlow described the Initiative's impact during the past 2 years, with 24 questions asked, more than 750 applications received per year, and success rates of 7.4 and 12 percent in 2011 and 2012, respectively. Members were reminded that the PQs pose research questions in unexplored areas rather than identify projects. The interest in PQs has been considerable, with a committed research community, good press in research journals, and international engagement. Challenges have existed in marketing the PQs initiative to the targeted audience, handling the logistics of 750 applications, ensuring that applications answer the question, and involving the community and NCI program staff in question development. Dr. Harlow highlighted the 2011 obesity question as a success story, with 6 funded applications and 26 publications in less than 2 years, and told members that the question is now retired because of the current scientific momentum in the topic, and the NCI's role has shifted to staging interactions to stimulate progress. Dr. Harlow said that questions that failed to receive adequate responses likely did so because of an immature field, missing key reagents or resources, poorly written questions, or the right people are not applying. Program evaluation found a statistically significant increase in publications associated with question areas following RFA issuance. Additionally, approximately one-half of applications submitted were deemed novel, and the RFAs do as well or better than other high-profile NIH FOAs. Members were informed that many investigators still do not know about the initiative, and most investigators who apply already work in the selected PQ research discipline.

Dr. Harlow said that the reissue concept is for three RFA issuances, with a 2-year active period for each RFA issuance. The RFA will be modified to allow withdrawal of applications that are not scientifically responsive to PQs prior to review, and will allow R01s for 5 years as well as A1 resubmissions. The funding mechanisms allowed include the R01, U01, and R21 and will be determined by the content of a specific PQ. In addition, three sets of metrics will measure success, namely enthusiastic support in the community and the NCI for developing PQ in the short term, a good rate of retiring questions in the mid term, and top-level contributions in PQ research areas in the long term. Members were told of next steps in the PQ process, i.e., modifications to allow Division review of potential questions, fewer questions each year, and better advertisement.

Subcommittee Review. Dr. Joe Gray expressed the Subcommittee's enthusiasm for the reissue concept, commending the Project for its success in galvanizing the extramural community on topics needing study. The Subcommittee appreciated Dr. Harlow's explanation of what is meant by PQs, clear metrics for success, and a mechanism that is less constrained. The NCI was encouraged to increase marketing efforts to raise awareness about the project and consider ways to address early stages of science.

The first year cost is estimated at $20 M for 33-55 awards, with a total cost of $176 M for 5 years.

Questions and Answers

Dr. LaBaer asked how review committees are handling the broad array of scientific applications. Dr. Harlow acknowledged the challenges and said that the program has improved the review process by separating by subject matter and continues to seek the optimal balance of questions.

Dr. Lawrence commented that a program that received 750 applications is well known and added that he has discussed the PQs initiative with investigators who were excited about the RFA but less enthused with the success rate. Dr. Harlow responded that the reissue concept will provide fewer and more specific questions and applications will be withdrawn that are not responsive. In the past, up to 50% of the applications were in the general area but not specifically addressing the PQs. Dr. Basch suggested that the Letter of Interest (LOI) process could help to focus applications, and that perhaps career development awards should be considered to encourage young investigators to focus on the questions.

Motion. A motion to concur on the Office of the Director's reissuance of request for application/cooperative agreement (RFA/Coop. Agr.) entitled "Research Answers to NCI'S Provocative Questions" was approved unanimously.

XI. ONGOING AND NEW BUSINESS—DRS. TODD R. GOLUB AND TYLER JACKS

***Ad Hoc* Subcommittee on Global Cancer Research.** Dr. Marcia Cruz-Correa stated that the *Ad Hoc* Subcommittee on Global Cancer Research met on 22 June 2014 and heard about an RFA on cancer detection, diagnostic, and treatment technologies for global health, which aims to provide health technologies for low- and middle-income countries that are portable, affordable, and could be used for early detection and diagnosis. Dr. Cruz-Correa said that the program's first solicitation was successful, with 97 applications and 5-6 grants prioritized for cervical, breast, liver, and lung cancers, particularly in China, India, and South Africa. Approximately two-thirds of applications came from academic centers but required validation to be conducted abroad.

The Subcommittee also heard a proposal for a Burkitt Lymphoma Trials Network. There is a low rate of response throughout Africa. The Network goals are to develop more cost-effective strategies, develop prevention strategies such as vaccines, and discover new insights into the pathogenesis of the disease. Potential sites with existing infrastructure and sufficient patient population are under consideration, including Guatemala, El Salvador, Malawi, Kenya, and Uganda.

Members were told that the Subcommittee received an update about a proposal in which NCI-designated Cancer Centers could propose a collaborative idea to promote cancer research and increase research capacity in low- and middle-income countries. A total of 43 of the 65 Cancer Centers submitted pilot proposals, with 15 awards made with collaborations in numerous countries. Members were informed that a second pilot is under consideration.

Dr. Cruz-Correa said that Dr. Ted Trimble, Director, Center for Global Health (CGH), provided a summary of the meetings, workshops, and program travel by the CGH during FY 2014 Quarters 1 and 2. She expressed the Subcommittee's appreciation for the NCI's efforts in leveraging the numerous federal agencies and other organizations (Centers for Disease Control and Prevention [CDC], World Health Organization [WHO], Pan American Health Organization [PAHO]) with a presence in the international health arena to develop synergistic activities. Dr. Trimble told the Subcommittee that various countries have requested the NCI's assistance in developing cancer control plans.

Motion. A motion to accept the summary reports of the 22 June 2014 NCAB *Ad Hoc* Subcommittee on Global Cancer Research meeting was seconded and approved unanimously.

IX. NCI AND THE COMMON FUND—DRS. JAMES M. ANDERSON AND DINAH S. SINGER

Drs. James M. Anderson, Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), and Dinah S. Singer, Director, Division of Cancer Biology (DCB), provided a report on the NIH Common Fund and the NCI's participation in the effort. Dr. Anderson said that the NIH Roadmap (the Common Fund) was launched in 2004 and came under the purview of the DPCPSI in 2006. For programs to be considered for the Common Fund, they must be transformatic, catalytic, synergistic, cross-cutting, and unique. Members were told that the FY 2014 Common Fund budget is $533 M disseminated across 28 programs, 4 award programs, and Library of Integrated Network-based Cellular Signature (LINCS).

Dr. Anderson focused his presentation on the Epigenomics Program, LINCS, and the awards programs. The Epigenomics Program supports grants that explore how the epigenome influences risk and disease progression, including through the development of tools, technologies, and datasets. The Program involves mapping centers, computational analyses, a data coordinating center, functional epigenomics, new technology development, *in vivo* imaging, and novel epigenomic markets in mammalian cells to promote health and understand disease. Members were reminded that epigenomics research leads to the link between early environmental exposures and risk of adult-onset diseases, including cancer. Dr. Anderson referred to the Patient-Reported Outcomes Measurement Information System (PROMIS) as an example of a clinical tool used to measure health and described the Person Centered Outcomes Research Resource (PCORR) RFA, an opportunity to standardize patient-centered outcome measures by using PROMIS and other measurement systems already developed.

Members were informed that the NIH Molecular Libraries Program (2004-2014) was developed through assays in high-throughput screening centers that developed 365 probes, with 26 in preclinical development and 7 in clinical development, as well as 132 patented discoveries. In addition, the Small Molecule Repository included nearly 400,000 compounds. Dr. Anderson described the synergies between LINC and the NCI, including the use of LINCS data in cancer studies, the generation of large datasets by cancer investigators, and integration with TCGA. He also shared examples of investigators who have received high-risk, high-reward awards, including a Pioneer awardee who is developing high-resolution strategies to visualize the behavior of cells during growth, regeneration, and cancer formation; a New Innovator awardee building an experimental platform to optimize the personalized treatment of cancer patients and improve their survival; and an Early Independence awardee improving the safety and efficacy of adoptive T-cell therapy.

Dr. Anderson said that a Council of Councils Common Fund Planning and Management Working Group evaluated the Program and presented its report on June 20, 2014. The Working Group was charged with assessing and advising on the processes used to manage the Common Fund, including those used to plan and implement or oversee programs. The report provided approximately 50 recommendations regarding strategic planning and program management, including continued engagement of a broad range of stakeholders, enhanced communication about the strategic planning process and transparency in the decisionmaking process, stronger communication between Common Fund staff and IC Working Group members, enhanced evaluation of programs, and increased dissemination of information about Common Fund programs.

Dr. Singer said that the NCI participates in the Common Fund through development of proposals and the implementation and management of projects. She described the process, which starts with the NIH Office of the Director (OD) soliciting new Common Fund proposals from ICs. NCI staff members, in conjunction with other ICs, develop proposals based on novel scientific opportunities. Proposals are discussed and evaluated by NCI Scientific Program Leaders based on scientific merit, cancer relevance,

relevance to the mission of other ICs, and feasibility. Selected proposals are forwarded to the NIH OD for further consideration. Members were told that NCI proposals forwarded for consideration in FY 2014 addressed mouse population genetic resources, chronic diseases in clinical trials, and imaging for genetic variation in disease. NCI proposals in FY 2015 concerned the 4D nucleome, which was selected, and cachexia; the Institute's proposals for FY 2016 include RNA therapy, fibrotic diseases, mobile health technologies, and next-generation cell engineering. Dr. Singer stated that proposals not selected have become topics in the PQ Initiative. She noted that the NCI participates in many Common Fund programs and serves in a leadership role in several other programs, including Big Data to Knowledge, Extracellular RNA Communication, Metabolomics, and 4D Nucleome.

Members were informed that the NCI benefits from the Common Fund through the development of new resources, including molecular libraries and screening centers, LINCS datasets, metabolomics resource cores, and microbiome. Another advantage is the growth of cancer research in new areas such as high-throughput screening for novel therapeutics, cancers systems biology, cancer metabolomics, and cancer microbiome. Dr. Singer remarked on the growth of the NCI's metabolomics and microbiome portfolios. She also informed members about the 4D nucleome project, which aims for higher resolution and throughput technologies to study nuclear organization at different scales, computational analysis and visualization tools, reference maps of human 4D nucleomes, and an improved understanding of the physical principles and regulatory mechanisms of nuclear organization, the relationship between organization and cell function, and the role of poorly described nuclear structures. Dr. Singer indicated that the recruitment and training of cancer researchers in new areas provides another benefit, and described the NCI's funding of high-risk, high-reward programs for FY 2012-2013, including 6 Early Independence Awards, 14 New Innovator Awards, 12 Pioneer Awards, and 5 Transformative Research Awards.

Questions and Answers

Dr. Lyerly asked about the balance of NCI's investment in the Common Fund compared to other ICs. Dr. Anderson responded that the Common Fund is apportioned to the NIH and that the process starts with the most compelling question rather than featuring a specific IC, and he reflected on the Council of Councils' review process. Dr. Varmus added that because the funds are distributed at the NIH level, a smaller Institute could gain more than their proportion of the budget.

In response to a question from Dr. Jacks, Dr. Singer said that a formal process to solicit ideas for the Common Fund does not exist. Dr. Varmus encouraged members to share ways to solicit ideas from the extramural community. Dr. Weissman suggested the idea of single cell biochemistry.

Dr. Shannon commended the Common Fund as an effective way to handle concepts that cut across ICs. Dr. Singer responded that the process has encouraged IC staff to work together. Members were told that Dr. Judy E. Garber, Director, Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, and Professor of Medicine, Harvard Medical School, serves as the NCI Board representative on the Council of Councils.

TUESDAY, 24 JUNE 2014

X. PEDIATRIC ONCOLOGY—DRS. MALCOLM A. SMITH AND DANIELA S. GERHARD

Drs. Smith and Gerhard presented an update on the NCI's pediatric oncology program, including recent statistics related to childhood cancer incidence, survival, and mortality; NCI research programs for children with cancer, an update on the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) genomics program for childhood cancers, and a discussion on how to move

forward and identify more effective treatments. Dr. Smith informed members that the latest data from the NCI's Surveillance, Epidemiology, and End Results (SEER) Program depict a decline in the mortality resulting from malignant cancers in children ages 20 years and younger. The decreased mortality has been much more rapid for leukemia and lymphoma compared to other cancers, such as solid tumors and brain cancer. The decline in mortality is not due to a decrease in incidence; rather, it results from more effective treatments as evidenced with improvements in 5-year survival rates. For example, the 5-year survival rates for acute lymphocytic leukemia (ALL) now exceed 90 percent and the survival rates for acute myeloid leukemia (AML) have tripled since the mid-1970s. Members were told that the research advances that produced the declines in mortality have averted more than 45,000 deaths since 1975.

Dr. Smith noted that most children with cancer are treated at the more than 200 NCI-supported Children's Oncology Group (COG) centers across the world. The dedication and effort of thousands of health care providers at those institutions, as well as the patients and families that participated in the clinical trials, contributed to the significant improvements in outcome and deaths averted. Despite the many accomplishments of the NCI's pediatric oncology program, challenges remain. The improvements in overall survival mask the cancers for which outcomes remain poor, such as high-grade gliomas for which no curative therapy exists. Approximately 2,000 children will die of cancer each year, and the quality of survivorship is not ideal for many survivors, who are plagued by subsequent cancers and cardiac or psychological difficulties. The NCI's Childhood Cancer Survivor Study (CCSS) is a critical research effort monitoring outcomes of survivors of childhood cancer to ascertain the impact of treatments and identify changes to consider in current treatment paradigms that will improve the quality of survivorship.

Dr. Gerhard described specific NCI programs committed to childhood cancer research and provided an update on the TARGET program, which was initiated in 2009. The goal was to collect tissues from selected pediatric cancers for expression, copy number, and methylation analyses, as well as high-throughput sequencing efforts—including whole exome sequencing (WES), whole genome sequencing (WGS), and transcriptome sequencing. Dr. Smith selected several vignettes to illustrate the results from TARGET studies. For example, osteosarcoma is the most common tumor of the bone in children, and outcomes are poor when the cancer has metastasized at the time of diagnosis. Data from TARGET demonstrated that the genomes within osteosarcomas are highly rearranged. Another research project identified major differences in the gene mutations between children and adults with AML, demonstrating the key point that "children are not little adults." Members were told that the ALL team has been quite productive; one important finding was the discovery of novel gene fusions in BCR-ABL (Ph)-like ALL, some of which could be treatment targets.

Dr. Smith described several case studies to illustrate to the Board how the treatment of pediatric cancer can be improved further by following the adult paradigm. Similar to adults, adding imatinib to standard chemotherapy for BCR-ABL-positive ALL resulted in a 50 percent improvement in event-free survival. Building on the discovery of novel gene fusions in Ph-like ALL, a current clinical trial will investigate the outcomes resulting from treatment selection on the basis of gene testing results. Dr. Smith commended the research team for translating important observations to the clinic. To extend declining mortality from childhood cancer into next decade, a pediatric-specific approach to precision medicine is needed to identify susceptibilities created by oncogenic drivers or the cells of origin of childhood cancer, and the NCI has a critical role to play in these efforts.

Questions and Answers

Dr. Golub suggested that the NCI identify strategies to target directly the oncogenic mechanisms known to be causal in tumor types that are not attractive to industry because of the small numbers of patients. Dr. Smith agreed that it was a great suggestion. Historically, the NCI has supported clinical trials

for therapeutics that industry was unwilling to pursue. When the trial results are positive, industry can step in and proceed with commercialization steps. This process was successful for the anti-GD2 antibody for neuroblastoma. The NCI manufactured the drug and supported the phase III clinical trial, which generated positive results. A pharmaceutical collaborator then was chosen to commercialize the therapeutic.

In response to a question from Dr. Cullin, Dr. Gerhard explained that all of the children with osteosarcoma selected for the study had relapsed; thus, genotypes could not be associated retrospectively because of the lack of control cases.

Dr. Torti suggested using the RFA mechanism to research new drugs or interesting targets that would generate data to attract pharmaceutical companies for further development. Dr. Doroshow noted that the high rate of success of obtaining early-stage compounds for preclinical testing is a major feature of the NCI's pediatric preclinical testing program and added that other NCI programs are actively obtaining and producing new compounds to make them available to research investigators.

Dr. Pietenpol asked to what degree the NCI interacts with the Pediatric Cancer Genome Project at St. Jude Children's Hospital, which could complement the NCI's efforts. Drs. Smith and Gerhard explained that several St. Jude researchers are members of the ALL team.

Dr. Champion applauded the success stories depicting translation of research results in the clinic but cautioned that children who are cured of cancer often experience symptoms that affect their quality of life. The CCSS has provided much information and the challenge is to utilize the descriptive data to move forward with interventions. Dr. Ethan Basch commented that assessing patient-reported outcomes in the clinical trials is very important. A nascent effort in the COG will provide centralized resources to collect information about the experiences of children with regard to symptoms and quality of life.

Dr. Shannon remarked that many elements of the pediatric experience are generalizable to adults. For example, many patients have genetic predispositions, and how that information—including health care implications—is transmitted successfully to family members has been developed within the pediatric centers. A tribute to the NCI's COG is the high, 80 percent accrual rate of pediatric clinical trials. Dr. Shannon suggested that the NCI uses existing data to inform interventions that improve the quality of life of pediatric survivors and continue to support pediatric epigenetic studies that can inform research on adult cancers initiated by epigenetic modifier mutations. He encouraged the NCI to consider ways to educate and engage the cancer technology community about pediatric research and data.

Dr. Bhatia suggested educating the Centers of Cancer Nanotechnology Excellence (CCNEs) about pediatric issues to complement the NCI's efforts. In particular, RNAi and targeted delivery might be useful within the CCNEs. Dr. Gerhard explained that the NCI is collaborating with the CCNEs. Furthermore, targets identified through NCI's Cancer Target Discovery and Development (CTDD) Network will be pursued for translational applications.

XIV. AD HOC CAREER PATHS WORKING GROUP – DR. KEVIN M. SHANNON

Dr. Shannon reported on three proposals discussed at the first meeting of the Career Paths Working Group held June 22, 2014. He noted that at a time when the Ph.D. workforce is expanding and funding continues to be limited, the opportunities for young scientists to have academic careers in cancer research are increasingly constrained. Doctoral trainees should be encouraged to move from T32 funding to independent fellowships (F30/F31) to allow them to feel a sense of independence earlier in their career. A new training mechanism that allows graduate students to apply while in graduate school to fund their last year plus a four year postdoc is envisioned, and would provide more independence in selecting a lab

for training and guiding their own career path. Dr. Shannon described a second funding mechanism for staff scientists or laboratory (lab) managers that would allow them to apply for their own funding under the auspices of their Principal Investigator (PI),and the award could move with them to another lab or institution if their current PI lost funding or moved. Finally, an award similar to the Howard Hughes Medical Institute Capstone award is being considered and would support senior investigators who are near the end of their research careers or considering closing their laboratories. This award would provide salary support for an investigator for five to seven years, and require a plan on how they would make contributions in other areas. Dr. Shannon also noted that the working group discussed increasing stipends to support the most talented committed investigators while further limiting the number of fellowships available. Members were told that since a substantial number of postdoctoral students are supported on R01 awards; limits may be considered in the future on who can be supported on traditional R01 grants.

Questions and Answers

Drs. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, raised concerns that the R25 mechanism would no longer be available, and stated that the T32 mechanism does not provide the infrastructure for training interdisciplinary people. Dr. Champion was encouraged to join the working group to provide input.

Dr. Pietenpol remarked that institutions will welcome these new ideas since they have already started downsizing their doctoral programs.

Dr. Varmus stated that these proposals are in early discussions. Additionally, NIH does not want to limit the ability to attract great talent from around the world and getting approval for certain changes will be difficult.

XV. RFA/COOP AGR. CONCEPTS—NEW—NCI STAFF

Division of Cancer Prevention
Chronic Pancreatitis and Pancreatic Cancer Clinical Research or Consortium of the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CSCPPC)— Dr. Jo Ann Rinaudo

Dr. Jo Ann Rinaudo, Program Director, Cancer Biomarkers Research Group, DCP, introduced a new concept for a consortium to study chronic pancreatitis, diabetes and pancreatic cancer (CSCPPC) to be jointly funded by the NCI, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Institute on Alcohol Abuse and Alcoholism (NIAAA) and led by the NIDDK. Dr. Rinaudo said that the factors involved in the initiation of chronic pancreatitis, progression to severe fibrosis and ultimately diabetes, and transformation into pancreatic cancer are not clear. Members were told that chronic and hereditary pancreatitis increase the risk of pancreatic ductal adenocarcinoma (PDAC), the most common pancreatic cancer. Diabetes also is a risk factor for pancreatic cancer with additional risk from the combination of Type 2 diabetes and chronic pancreatitis. The association of Type 3c diabetes, which comprises 8 percent of those with diabetes, and pancreatic cancer is not well defined and is a new area of investigation. Type 3c diabetes adults are a potential high-risk group for screening as 50 percent of diabetes associated with cancer is Type 3c; and in 20 percent of pancreatic cancer patients, the onset of diabetes occurs in when they are asymptomatic for cancer.

Dr. Rinaudo informed members that the NIDDK and NCI sponsored workshops in 2012 and 2013 to discuss Type 3c diabetes and the risk of pancreatic cancer, basic and translational studies in chronic pancreatitis, and risk factors linking the diseases. In addition, The NCI's 2014 Strategic Framework for

PDAC outlined goals to identify patients at high risk, develop methods to detect early stage disease and lesions and distinguish between low and high risks for neoplasms and adenomas, and determine the relationship between Type 3c diabetes and pancreatic cancer. Members were told that the CSCPPC structure would include a data coordinating center that served as a hub for adult and pediatric clinical centers, a repository for biospecimens, and specialized imaging and molecular profiling laboratories, and be overseen by a steering committee and NIH staff. Research objectives include: detecting and quantifying pancreatic fibrosis and cancer; determining the combinations of genetic and environmental factors that give rise to pancreatic cancer; studying high-risk patients to evaluate genomic, proteomic, and hormonal markers of early pancreatic cancer; and supporting surveillance studies and survivorship registries to understand factors that contribute to disparities in pancreatic cancer incidence among populations.

Subcommittee Review. Dr. Jeffrey A. Drebin voiced the Subcommittee's enthusiasm for the concept, and noted that chronic pancreatitis is: 1.) a fibrosis that predisposes to cancer; 2.)understudied; and, 3.) smoking related. The consortium model offers the best model to obtain tissue and allows the addition of groups through subcontracts. Dr. Drebin noted that the Subcommittee supported the collaboration with the NIDDK and NIAAA and appreciated that the NCI would have substantial input on the direction of the consortium. The potential use of claims databases, such as the SEER-Medicare Linked Database, to understand some of the associations as an additional mechanism for investigation within the consortium was encouraged.

The first year cost for the NCI is estimated at $2 M for 10 U01 awards, with a total cost of $10 M for 5 years.

Motion. A motion to concur on the Division of Cancer Prevention's (DCP) request for application/Cooperative Agreement (RFA/Coop. Agr.) entitled "Chronic Pancreatitis and Pancreatic Cancer Clinical Research or Consortium of the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CSCPPC)" was approved unanimously.

Division of Cancer Biology
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
(Limited Competition)—Dr. Ron Johnson

Dr. Ron Johnson, Program Director, Division of Cancer Biology (DCB), informed members that the NCI commenced its support for IARC monographs in 1982. Dr. Johnson stated that IARC monographs provide critical scientific evaluations of carcinogenic hazards to humans, including chemical and chemical mixtures, physical and biological agents, and occupational exposures and lifestyle factors. An advisory group prioritizes the agents based on the extent of human exposure, suspicion of carcinogenicity, public health relevance or concern, and new or unpublished studies. He stated that the monograph process includes comprehensive literature reviews of exposure and mechanistic data, cancer epidemiology studies, and cancer bioassays in animals by working groups; determination is based on the weight of evidence by three working group meetings each year of which the NCI supports two; and the volumes are available as PDFs. Members were told that agents that are of high concern and affect global/low-middle income countries are evaluated, and that priorities for 2015–2019 include bisphenol A (BPA), aspartame, indium tin oxide, and nicotine/e-cigarettes. Dr. Johnson noted that the IARC Monograph Program is used by health agencies and institutions worldwide to set policy for carcinogens and 109 Working Groups have evaluated more than 900 agents. He noted that this is a unique award to the NIH and that IARC collaborates with U.S. agencies in evaluations and exchanges of information. IARC differs from the NIEHS' National Toxicology Program (NTP) and EPA's Integrated Risk Information System (IRIS) in the number and diversity of agents being evaluated and the focus on agents of global concern, as well as IARC frequently being the first to make a determination for many agents.

Dr. Johnson said that the reissue concept is proposed as a limited competition because IARC is uniquely positioned to conduct the studies. The U01 mechanism will continue to facilitate interaction with the NCI, and activities will include recommendation of agents for evaluation, identification of resource individuals in the United States, and attend or participate in Working Group meetings.

Subcommittee Review. Dr. Shannon expressed the Subcommittee's support for the concept, noting the low cost and significant impact as shown by an IARC monograph produced 10 years ago on secondhand smoke that continues to be downloaded 20,000 times per year, has influenced regulations in California, and has been used in judicial proceedings. He added that by convening scientific experts to review the literature, the IARC monographs provide a reliable scientific source for policymakers to make informed decisions.

The first year cost is estimated at $.859 M for 1 award, with a total cost of $4.3 M for 5 years.

Questions and Answers

Dr. Beth Y. Karlan, Director, Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Director of Gynecologic Oncology, Department of Obstetrics & Gynecology, Cedar-Sinai Medical Center, and Professor, Obstetrics and Gynecology, David Geffen School of Medicine, UCLA, reminded members that the President's Cancer Panel (PCP) held a panel on communication in the digital age. Dr. Karlan encouraged engagement of the PCP in global dissemination of the monograph information.

In response to a query by Dr. Golub about the list of agents that need attention, Dr. Johnson explained that PIs consider approximately 60 to 80 priority agents and usually get to 80 percent of them in a 5-year cycle. He added that the IARC has the flexibility to expedite agents that become high priority.

Dr. Stein asked about efforts to make the IARC monographs digitally readable, including attaching session numbers for small molecules, controlled vocabulary terms, and other elements to help the monographs become part of the corpus of databases. Dr. Johnson responded that the monographs currently are available as PDFs and that the IARC is working on digital extraction of the literature to expedite the review process.

Dr. Torti commented on the dearth of scientific validity about the potential carcinogenic nature of agents, noting that the NCI and NIH can help provide scientific underpinnings for regulatory decisions.

Dr. Pietenpol asked about what is the redundancy in sources for this type of information. Dr. Johnson responded that the IARC monographs are considered the gold standard for global evaluation and examine approximately 450 agents. He added that U.S. policymakers also refer to the *Report on Carcinogens*, which focuses on 240 known or suspected carcinogen agents of domestic concern.

Motion. A motion to concur on the Division of Cancer Biology's (DCB) request for application/Cooperative Agreement (RFA/Coop. Agr.) (limited competition) entitled "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans" was approved unanimously.

XVI. NCAB CLOSED SESSION—DR. TYLER JACKS

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

The NCAB *en bloc* vote for concurrence with IRG recommendations was unanimous. During the closed session, a total of 2,292 NCI applications Requesting support of $1,208,734,287 and 16 FDA applications were reviewed.

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

Drs. Golub and Jacks thanked all of the Board members, as well as all of the visitors and observers, for attending.

There being no further business, the 3rd joint meeting of the BSA/NCAB was adjourned at 11:10 a.m. on Tuesday, 24 June 2014.

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