DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
160TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 6, 2011

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 160th regular meeting on 6 December 2011, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 6 December 2011, from 9:00 a.m. to 4:15 p.m., and closed to the public from 4:15 p.m. to 5:00 p.m. The NCAB Chair, Dr. Bruce A. Chabner, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, presided during both the open and closed sessions.

NCAB Members

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

Alternate *Ex Officio* NCAB Members

Dr. Michael A. Babich, CPSC
Dr. Patricia Bray, OSHA/DOL (absent)
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD (absent)
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP (absent)
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH
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. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Mr. John Czajkowski, Deputy Director for Management and Executive Officer
Dr. James Doroshow, Deputy Director for Clinical and Translational Research
Dr. Joseph Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Associate Director for Prevention
Dr. Ed Harlow, Special Assistant for Science Planning
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
Dr. 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. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Director, Center for Global Health
Mr. Michael Weingarten, Director, Small Business Innovation Research
Dr. Linda Weiss, Director, Office of Cancer Centers
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director
Dr. Barbara Wold, Director, Office of Cancer Genomics
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carlton Brown, Oncology Nursing Society
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Mr. Adam Clark, Lance Armstrong Foundation
Dr. Jeff Allen, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Mr. Matthew Farber, Association of Community Cancer Centers
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambarresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Steven Klein, National Science Foundation
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology

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

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TUESDAY, DECEMBER 6, 2011

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 13 SEPTEMBER 2011 MINUTES—DR. BRUCE A. CHABNER

Dr. Chabner called to order the 160th NCAB meeting. He 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. Chabner reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 13 September 2011 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

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

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

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

Dr. Harold E. Varmus, Director, NCI, greeted members and welcomed a new member, Dr. Tyler E. Jacks, Director, Koch Institute for Integrative Cancer Research, David H. Koch Professor of Biology, Massachusetts Institute of Technology. Dr. Varmus described recent news regarding the budget and activities of interest occurring across the NCI and NIH. He informed members that appointments to the President's Cancer Panel are underway, namely: Drs. Barbara K. Rimer, Dean and Alumni Distinguished Professor, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill; and Owen N. Witte, Director, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, University of California, Los Angeles, and Investigator, Howard Hughes Medical Institute.

Budget. Dr. Varmus reminded members that the NCI experienced a 1 percent budgetary decline in fiscal year (FY) 2011. Through specific reductions in funding to Cancer Centers and noncompeting renewal grants as well as across its portfolio, the NCI funded more than 1,100 grants and achieved a success rate of 14 percent, which is lower than the overall NIH success rate of 17 percent. Dr. Varmus told members that the FY 2012 budget remains under a Continuing Resolution (CR) and is approximately 1.5 percent lower than the FY 2011 level. He said that House Representative Denny Rehberg (R-MT), member of the House Appropriations Committee, visited the NIH campus, including the Clinical Center. The NCI currently is operating conservatively by paying its noncompetitive renewals at 90 percent and competitive renewals and competitive new awards at 80 percent. The success rate is at the 7th percentile, and intense discussions regarding grants that fall below that 7th percentile line are being held throughout NCI leadership levels. NCI leaders have agreed to emphasize the setting of priorities through the expansion, reduction, or termination of some programs rather than require additional wholesale reductions across the Institute.

The budget for FY 2013 is in the planning process, and the NCI's bypass budget will highlight progress made against six cancers not featured in previous years. Dr. Francis S. Collins, Director, NIH, requested that the NIH Institutes and Centers (ICs) submit three of their best new research proposals for inclusion in the NIH submission to the President's Budget. Dr. Varmus stated that most ICs have shifted in their approach to allocating funds to ensure support of the best science rather than reaching a targeted number of awards.

Provocative Questions Initiative. Dr. Varmus said that the NCI received more than 700 applications for the Provocative Questions request for applications (RFA), including more than 400 individual investigator applications (R01s). Approximately 100 of the applications were submitted by early-stage investigators and 150 by new investigators. Each of the RFA's 24 questions received responses. Dr. Varmus indicated that the initiative will continue to hold workshops, generate new questions, and have additional rounds of applications. The review format is under discussion but likely will consist of two phases: an initial review and an in-person study section review of the highest ranking applications. Dr. Varmus and Dr. Ed Harlow, Special Assistant for Science Planning, have written an article about the provocative questions exercise to encourage other funding agencies to stimulate the imagination of individuals and organizations and generate feelings of optimism and coherence in the face of economic difficulties.

Drug Shortages. Dr. Varmus informed members that the White House and Department of Health and Human Services (HHS) continue to be engaged in the drug shortage issue. President Barack Obama issued a statement on the topic, and both the U.S. Food and Drug Administration (FDA) and the HHS Office of Science and Data Policy have released several reports on the issue. There is bipartisan support in Congress to address the problem. Dr. James Doroshow, Deputy Director, said that one of the major generic manufacturers recently exited the market completely, and the shortages remain a significant concern.

Other NCI Activities. Dr. Varmus said that the Honorable Hillary Clinton, Secretary of State, visited the NIH campus and talked about a new three-step program to prevent and treat acquired immune deficiency syndrome (AIDS) by treating more people, endorsing circumcision with greater vigor, using other methods to prevent transmission, and establishing a broader program to cover more people who are infected with the human immunodeficiency virus (HIV), particularly in the developing world. In addition, Dr. Varmus met with Dr. Thomas R. Frieden, Director, Centers for Disease Control and Prevention (CDC), regarding common interests between the NCI and CDC, and this discussion will continue. An upcoming workshop on team science will provide a forum to discuss multi-team efforts that are interdisciplinary or involve multiple principal investigators (PIs), including inter-institutional collaborations, such as through NCI's new program project grants, the Survivors Taking Action and Responsibility (STAR) consortium, Stand Up to Cancer, or other stakeholder organizations. Dr. Varmus referred to The Cancer Genome Atlas (TCGA) as one model of successful team science. He also discussed the function of the NCAB, suggested opportunities to increase synergistic interactions with the NCI Board of Scientific Advisors (BSA), and invited members to share comments about holding semi-joint meetings with the BSA.

International Activities. Dr. Varmus also highlighted several international activities. A recent meeting of leaders of cancer research agencies from approximately 15 countries discussed common interests of tobacco control, genomics, and bringing genomics into clinical practice as well as opportunities to collaborate in the developing world. Dr. Varmus also visited Africa to learn more about what can be done to reduce the cancer burden in African countries and other poor countries; his trip encompassed Rwanda, which is strongly supportive of improvements in health and has an active vaccination program, and Uganda, where a new Cancer Center is being built with the help of investments by the U.S. Agency for International Development (USAID) and the Fred Hutchinson Cancer Research Center, an NCI-designated Cancer Center.

Human Papillomavirus (HPV). Dr. Douglas R. Lowy, Deputy Director, provided an updated report on the status of the NCI's HPV activities. He informed members that the Global Alliance for Vaccines and Immunization (GAVI Alliance) recently announced its intent to support HPV vaccination of young adolescent girls and cervical cancer screening of adult women in the developing world. This provides an opportunity for sustained support in low-resource settings, such as Rwanda.

The CDC's Advisory Committee on Immunization Practices (ACIP) recently changed the recommendation for vaccination for males, upgrading from permissive to routine for males aged 11-21 and remaining permissive for males aged 9-10 and 22-26. Dr. Lowy reminded members that the Merck vaccine is approved for both genders and the GlaxoSmithKline (GSK) vaccine is approved only for females. The rationale for the ACIP's recommendation is that low uptake among females implies limited immunity, approximately 30 percent of HPV-associated cancers in the United States occur in males, and a higher percentage of genital warts occur in males. Whereas Pap smear screening has reduced the incidence of cervical cancer substantially, HPV positive oral pharynx cancer is beginning to rival the incidence of cervical cancer; inguinal vulva, vaginal and penile cancers also are important. Consequently, an additional rational for the male vaccination is that men who have sex with men represent a separate community that will receive less protection from the vaccination of women. The ACIP also considered gender equity in its decision.

Lower uptake of the vaccine has been seen in the United States because of medical uncertainties at the time of FDA approval concerning rare serious adverse events for the target population, duration of protection, and the lack of protection against some HPV types that cause cervical cancer, as well as negative public response from efforts to make the vaccine mandatory in 2007 and concerns about promotion of sexual disinhibition. Dr. Lowy said that there has been an ambivalent reception in some medical circles for the vaccine, particularly following several editorials concerning the idea that the relationship between infection at a young age and development of cancer 20-40 years later is not known. The incidence of cervical cancer has reduced substantially in the United States during the past 35 years because of screening of precancerous lesions but adenocarcinoma, for which the HPV vaccine could provide greater benefits than cytological screening, has not seen a similar reduction. Dr. Lowy shared population-wide data of the vaccine's efficacy in Australia that showed high levels of protection against incident infection for women without preexisting infections. A recent publication from the Vaccine Safety Data Link Program provides additional reassurance of the vaccine's safety.

Future directions are to educate the medical community and general population with current information about the vaccine, including that protection is conferred by vaccinating young adolescents, the excellent immunogenicity with a high duration of protection, and the acceptable level of adverse events. Development of a second-generation vaccine with broader protection is ongoing. In addition, research to address other vaccine-related issues is encouraged.

Questions and Answers

Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., commented that steep fines may be a further disincentive for generic drug manufacturing rather than an incentive. Dr. Varmus acknowledged the risk and referred members to the HHS report, *Economic Analysis of the Causes of Drug Shortages*; he reminded members that, despite the FDA's prevention of some shortages, the incidence of drug shortages has risen during the past decade. Dr. Chabner suggested that, to ensure that adequate incentives remain, thoughtful restructuring of the industry is needed, particularly in regard to anticompetitive practices.

Dr. Chabner asked about the funding plan for the Cancer Centers and Specialized Programs of Research Excellence (SPOREs). Dr. Varmus indicated that the two programs are separate; he noted that the Cancer Centers' budget was reduced 5 percent last year and confirmed his intent to fully fund the Cancer Centers at the FY 2011 level. He said that the Cancer Centers have a fundamental role in NCI's work and is pleased with their increased role in cooperative group activities and bringing genomics into clinical care. The SPOREs Program will undergo examination similar to other team science activities.

Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, and Professor of Medicine, University of Maryland, commented that the public health community has not yet recognized that boys are at higher risk for HPV infection than girls. Dr. Lowy agreed and noted that many recommendations tend to be based on past history.

Dr. Olufunmilayo F. Olopade, Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, and Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine, encouraged the NCI to adapt lessons from the GAVI Alliance and the global health setting, including the commitment by Rwanda's Ministry of Health to vaccinate boys and girls. Dr. Lowy agreed that this is an interesting idea but cautioned that the price of the vaccine is a limiting issue. Dr. Varmus said that stakeholders have been discussing how to reduce the cost, including the development of a vaccine that covers nine strains of HPV, and added that the Rwandan government's commitment to improve public health is exemplary.

Dr. Sellers observed that rare extraordinary side effects often are featured in media, including medical journals, whereas an incredible safety profile is not, and he encouraged discussions with editors of highly renowned journals to describe the HPV issues and information accurately to the medical community. Dr. Chabner noted the influence of social and moral issues concerning unprotected sexual acts among younger people, suggested that discussion of the vaccine during a national political debate would help educate the public, and encouraged the NCI to prepare a peer-reviewed article to educate the medical community about the vaccine's safety and efficacy in the context of public health. Dr. Jacks commented that opinion editorials and policy statements will provide leadership to the public. Dr. Olopade encouraged the NCI Office of Communications and Education to support cancer education efforts that target the general public, infuse HPV information into the public school curricula, and result in improved adoption by the population for cancer prevention services.

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, and Director, Institute for Global Health, University of Southern California, asked about the optimal level of immunization for the mixed population setting. Dr. Lowy confirmed that modeling of genders individually and in aggregate has been discussed, and Dr. Varmus noted the complications brought by the multiplicity of diseases.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, encouraged the development of a consistent message to clinicians and the general public regarding screening and immunization, and she noted that public health research is needed to improve cervical cancer mortality rates among specific geographic areas and populations, including African Americans in the Mississippi delta and American Indians on reservations. Dr. Varmus pointed out that advocacy groups, including the Bush Foundation and the Lasker Foundation, have provided assistance in efforts to reduce cervical cancer incidence and mortality rates.

IV. NIH DIVERSITY REPORT—DR. LAWRENCE TABAK

Dr. Lawrence Tabak, Principal Deputy Director, NIH, updated members about the diversity of the NIH biomedical research workforce and the NIH's plans to further diversify its workforce. The NIH is motivated to increase its workforce diversity by a desire to attract the best minds to science. Dr. Tabak informed members that compared to the 2010 U.S. Census Bureau report and the U.S. full-time medical school faculty, Hispanics and African Americans are underrepresented among NIH principal investigators on research program grants (RPGs). The demographics of underrepresented minorities (URMs) in the educational pipeline illustrate the magnitude of the diversification challenge; in 2008, URMs represented one-third of the college-age population but only 17 percent of those earning a Bachelor's degree and 7 percent of those with a doctorate. There are many reasons why URMs are less likely than average to pursue advanced degrees in the biological sciences, chemistry, and physics, but graduate school

recruitment represents an opportunity to improve the situation. Addressing this problem is topical because the population of URMs is increasing in the United States; therefore, the rate at which those with Bachelor's degrees earn doctorates must double simply to maintain the status quo.

The NIH has commissioned several studies recently on the diversity of the workforce. These investigations evaluated diversity in academic medicine, sex differences in NIH extramural programs, and the racial and ethnic characteristics of NIH research awardees. Although the number of applications was small, researchers found that new investigator grant applications by African Americans were significantly less likely to be successful than those of whites. Examining the factors controlling success, the study determined that award probabilities depended on the funding rank of the applicant's institution, but within each rank African Americans did less well than whites in procuring funding. Only an extensive publishing history and prior review committee experience reduced the disparity for African Americans. African American and Hispanic applicants also were less likely to resubmit revised applications, and NIH-supported training increased award rates but was more effective for whites than African Americans.

The NIH is taking aggressive action to determine the causes of the differential funding success rates of URMs and develop effective interventions. As an agency, it is engaged in communication outreach to all stakeholders; has established an "Early Career Reviewers" program that allows self-nomination to diversify the institutions from which review panels are drawn; plans to conduct experiments to illuminate possible sources of bias in the review process; is encouraging academic institutions to strengthen pre-application mentoring programs for junior faculty; has funded grants to study interventions to strengthen the educational pipeline to improve workforce diversity; and has formed two high-level groups (the NIH Diversity Task Force, composed of internal NIH leaders, and the Advisory Committee to the Director [ACD] Working Group on Diversity in the Biomedical Research Workforce, providing an external perspective) to help the NIH strategize about the problem. The ACD Working Group on Diversity in the Biomedical Research Workforce has met four times, and after studying a large amount of data they concluded that there are pipeline issues that the NIH should consider but would require collaboration with other entities to address, and extramural and intramural challengers are unique. The Working Group is scheduled to brief the NIH Advisory Committee to the Director on December 8, 2011, and make final recommendations in June 2012.

Questions and Answers

Dr. Victoria L. Champion, Associate Dean for Research and Mary Margaret Walther Distinguished Professor of Nursing, Center for Research and Scholarship, Indiana University School of Nursing, and Dr. Chabner asked for more details to explain the statistics on Asians and Hispanics and suggested that a better understanding of why Asians are disproportionally represented in academic medicine and funding might provide a model for URMs. Dr. Tabak agreed and explained that the results for Asians and Hispanics are somewhat confusing because the Asian group included non-citizens, who faired more poorly than whites likely due to language barriers, and the Hispanic group included Spanish speakers of European origin, whose results did not differ from whites.

Dr. Chabner asked whether the lack of diversity in NIH's intramural program was similar to its extramural program. Dr. Tabak responded that there were very few African Americans and Hispanics in the intramural program and that a trans-NIH solution is needed. Dr. Varmus suggested that one approach to increase the diversity of the intramural staff is to revise the criteria used to assess scientific contributions by applicants so that there is less reliance on publishing in high-impact journals; he observed that URMs were well represented in NIH training programs but often chose post-training employment outside the NIH that offered higher salaries and stronger professional development opportunities.

In response to a question from Dr. Jacks about whether differences in original scores could account for differences in results for resubmissions, Dr. Tabak replied that these data were available but have not been analyzed. Dr. Olopade suggested that because resubmission greatly improves funding success, encouragement by mentors was important.

Dr. Olopade questioned whether the NIH had observed differences by racial and ethnic group in research topics and whether some areas might be less valued than others. Dr. Tabak answered that African Americans tended to apply disproportionately for grants in the behavioral and social sciences, particularly in disparities research, but did not have higher application success rates in those areas than overall.

Dr. Champion proposed that intervention in high school could be fruitful, including encouraging mentorships. Dr. Tabak agreed that it would be beneficial for the NIH to promote science at the primary and secondary school levels more strongly as a long-term strategy to improve the educational pipeline.

Dr. Varmus proposed scheduling an update on NIH diversity at a future meeting.

V. OVERVIEW: CENTER FOR CANCER GENOMICS—DR. BARBARA WOLD

Dr. Barbara Wold, Director, Office of Cancer Genomics, provided an overview for members of the Center for Cancer Genomics' mission to develop and apply cutting-edge genome science to better treat cancer patients and stated that she sought members' input to determine the best way to direct NCI's genomics efforts to provide advances in diagnosis, improve the understanding of pathways altered in cancer, direct drug development, and, ultimately, develop precision treatments. A key future challenge will be to capture genomics data and treatment outcomes from clinical care and make it available for the research community. The combinatoric nature of the disease and of treatments call for data on very large numbers of patients. The guiding questions are the following: What are the key science opportunities? What is the best and fastest path to the clinic? What are the bottlenecks at the levels of discovery, trial design, and standard of care? How should the results of clinical sequencing be captured? Dr. Wold reviewed major advances in the early genome era of 2001–2005 that arose from the development of new technologies, specifically: sequencing of pathways and gene classes, microarray studies and integrative genomics, and translocation discovery from genomic data.

In 2005, the NCAB Working Group on Biomedical Technology recommended the establishment of the Human Cancer Genome Project (HCGP) based on the premises that understanding the cancer genome is technologically feasible at reasonable cost and would have major implications for the understanding, diagnosis, and treatment of the disease. TCGA and the target program directed at childhood cancers were established to create and characterize a large sample collection to achieve the HCGP goal of a comprehensive description of the genetic basis of all major cancer types. TCGA has expanded rapidly, approaching its goal of providing by 2014 sufficient data for the exploration of the genetics basis of 20 major cancer types. TCGA data on the tumor and normal exome, and ribonucleic acid (RNA) transcriptome provide information on structural rearrangements, copy number changes, point mutations and indels, and gene expression. Numerous TCGA post-pilot publications are expected in 2012 on a range of cancers, including colorectal cancer, breast cancer, and acute myeloid leukemia. Post-pilot applications include whole genome deep sequencing beyond the exome, analysis of which will require further advances in bioinformatics. The link between cancer genetics and epigenetics is being revealed with the discovery of novel driver genes associated with these functions in multiple cancers.

Future NIH funding will support cancer genomics, but specific projects will sunset. TCGA is a major priority at present, but is scheduled to conclude in FY 2014. A similar trajectory is expected for the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program. Science opportunities in 2012 include adding rare tumors (not included in the initial TCGA and TARGET), analysis of more samples from patients that are members of minority groups (underrepresented in TCGA),

development of key mouse models comparable to human tumors, and validation of the use of formaldehyde-fixed, paraffin-embedded (FFPE) samples, an alternative to flash freezing that will simplify sample collection and preservation in clinical settings. FFPE samples have recently produced high-quality RNA and deoxyribonucleic acid (DNA) data that agree well with frozen sample results, although a reduced signal from exons in total RNA sequencing remains to be explained. Overall, RNA profiling is emerging as a relatively inexpensive option for phenotyping tumors in clinical settings. Proof of principle has been demonstrated for RNA profiling using a very small number of cells. This option of using samples as small as 10 or even a single cell holds promise of being clinically relevant in early disease, valuable for samples with mixed cell types, and cost-effective. The number of genes detected using smaller samples is less than with 30- or 100-cell pools, but valuable information still is obtainable using the smaller sample size, coverage is good across the transcript length, and microdissection techniques such as laser capture can be used to pinpoint specimens of interest. RNA profiling results have generic protocols for using FFPE samples and sequencing small cell numbers from fresh or frozen samples will likely be available in 2012, but merging the two techniques together remains a research challenge.

Dr. Wold described the early uses of large-scale sequencing in the clinical setting. Multiple pilot projects are ongoing, with key steps that include obtaining informed consent after genetic counseling, deciding what information to disclose to the patient, and using the data to help direct the patient's treatment, depending on the specifics of gene lesions discovered. Biopsy genomics data from a patient can be useful for designing clinical trials, such as screening for genetic trial eligibility and making informed decisions about grouping participants, and customizing treatment, in which the response to particular therapeutics can be predicted from tumor genomics. To address the problems that remain both at the research and clinical level with storing and analyzing the huge amount of data generated by DNA sequencing, including transfer speed as well as data capacity, the NCI funded the new Cancer Genomics Hub, which will store the data from TCGA and TARGET. Dr. Wold asserted that not only will discoveries using genomics and functional genomics shape drug development, diagnosis, and ultimately treatment, but that genomics data can and should drive the discovery process in the systems biology of cancer. Optimizing data access will allow discovery of new relationships through data mining, but at the same time data must be secure to ensure the protection of individual rights codified by the Genetic Information Nondiscrimination Act (GINA).

Questions and Answers

Dr. Cullen questioned how the large quantity of data generated by the development of faster and less expensive sequencing techniques and participation of large numbers of patients could be analyzed to produce real-world applications in the near future. Dr. Wold replied that computational techniques are being developed to better compress and analyze these data, and that these are critical endeavors over the next few years.

Dr. Olopade encouraged the NCI to address germline genetics because it could be driving somatic genetics and might be used in the future to develop prevention strategies. She suggested that genome-wide association studies (GWAS) and deep sequencing might uncover heritable genetic susceptibilities that interact with somatic mutations, and therefore germline and somatic genetics should be integrated. Dr. Wold answered that germline genomics has been studied intensively, but full integration of germline data in current genomic studies is made more challenging due to the ethical implications regarding patients' family members.

Dr. Jacks commented that patients are very willing to make their genetic material available for research. Dr. Wold replied that the NIH is indeed working with patient advocates to gain their further participation, while ensuring that patients are well informed about how their genetic information will be used.

Dr. Jacks suggested given that tumor heterogeneity and functional analysis are important scientific challenges critical to bridging the gap between genome sequencing and clinical applications, functional analysis is not emphasized enough in TCGA. Dr. Wold agreed that both are rich areas of research and suggested that techniques that analyze small samples will be valuable for studying spatial and temporal variation in tumors, and that functional analysis needs increasing emphasis.

Dr. Jacks asked about global participation in TCGA. Dr. Wold responded that the International Cancer Genome Consortium uses TCGA data extensively, but data sharing between countries, though critical, can be hindered by differences in policy and law regarding genome data among countries.

VI. U.S. PREVENTION TASK FORCE RECOMMENDATION ON PSA—DR. BARRY KRAMER

Dr. Barry Kramer, Director, Division of Cancer Prevention, provided background and an overview of the U.S. Preventive Task Force's (USPTF) recent draft guideline, which recommended against the routine use of prostate-specific antigen (PSA) for prostate cancer screening. The 30-day period of comment has just expired and the medical officer who administers the comments at the Agency for Healthcare Research and Quality (AHRQ) indicated that the draft guideline has drawn a substantial number of comments. These comments will be evaluated before a final recommendation is issued.

There are two core issues in screening and prevention when judging evidence to develop guidelines: (1) it is difficult to improve the health of healthy people; and (2) evidence of the benefit to healthy people must be very strong if there are risks involved in screening, since the target population of health people is often so large. For the PSA guidance, the target population is millions of men. For example, this concept is likely behind the recent decision by the FDA not to approve 5-alpha reductase inhibitors for the prevention of prostate cancer in healthy men. Similarly, in the case of prostate cancer screening, the USPTF gave a Grade D recommendation for PSA screening in its draft guideline. A Grade D is defined as a "moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits." The text from the draft report clearly indicates the Task Force's consideration of the balance of both benefits and harms, which is the primary issue for any public screening program. The determination of benefit versus harm in screening programs in healthy people is always a challenge.

Dr. Kramer illustrated examples of harms the USPTF considered in giving the Grade D recommendation for PSA testing. Screening tests may lead to high numbers of false positive tests in people without cancer. The false positive tests have led to unnecessary diagnostic workups, some resulting in bleeding and sepsis after biopsy, or perforation during in the case of colonoscopy or endoscopy. Screening may lead to detection of lethal cancer without changing the outcome for patients who have cancer. In such cases, screening can simply make the patient aware that they have cancer without decreasing the risk of dying of the cancer. A particularly important issue with PSA testing is the large number of nonlethal cancers diagnosed (i.e., over diagnosis) that leads to unnecessary cancer treatments, which can cause significant harm. Therefore, screening healthy individuals by PSA was viewed by the USPTF as providing little assurance to those who are otherwise healthy while exposing them to potential substantial harm by a test that did not meet adequate evidence standards to establish benefit.

Dr. Kramer reviewed the results of randomized controlled trials (RCTs) for prostate screening by PSA examined by the USPTF, including the NCI's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Study of Prostate Cancer (ERSPC). These trials began in the 1990s after early evidence from non-randomized studies suggested the benefit of PSA screening in healthy men. Results of screening 76,705 men in the PLCO after 10 years found there were actually more deaths (RR of 1.13, though not statistically significant) attributed to prostate cancer in the intervention arm than in the control arm, although data did not exclude the possibility of small benefits. At the same time, the ERSPC trial of 182,160 participants that included a core age group (55 to 69 years) for the prospective study found

fewer deaths in the screened arm than in the control arm (statistically significant, p = 0.04) after 10 years. Both the PLCO and ERSPC had design problems. A key problem of the PLCO was contamination and resulting statistical underpowering. The ERSPC was a series of trials rather than one single trial, with disparate design components, such as different cut points for PSA, different screening approaches, and different medical systems in the trial. Recently analyzed data from a 13-year follow-up in the PLCO (unpublished but presented with permission) indicates that the 10-year results have not changed; the number of men needed to be screened to avoid one death is infinite. With additional follow-up, the confidence interval around the primary outcome is narrowing. The USPTF also examined two meta-analyses of five RCTs addressing the issue of prostate cancer screening. The conclusion from both meta-analyses was that there was no proven benefit for PSA screening.

For the harm side of the equation examined by the USPTF, there were 13 percent false positives at a cut-off of PSA greater than 4 in the PLCO (after 4 years), with a 5.5 percent risk of biopsy. The ERSPC reported hematospermia (50%), hematuria (23%), urinary retention (0.4%), and fever (3.5%) in those undergoing biopsy. Surveillance, Epidemiology and End Results (SEER) Medicare data in the United States indicate that approximately 1.5 percent of men who undergo biopsy are hospitalized with infections related to the biopsy within 30 days of the biopsy. Data from Canada indicate a 3.5 to 4 percent rate of hospitalization in biopsy patients who underwent prostate biopsy and were found not to have cancer. For those treated for prostate cancer, additional harms exist, including urinary incontinence (20%) and impotence (> 30%), as well as age-related post-operative death (0.5%).

Dr. Kramer cautioned participants about the dangers of over-diagnosis that occurs in association with most screening tests. PSA as a diagnostic test has greatly increased the number of men diagnosed with prostate cancer, and data show increasing incidence with increasing use of the test. There is a large reservoir of silent prostate cancer, with a natural history that is not well understood. This has resulted in a pseudo-epidemic of prostate cancer in the United States. Approximately 1 million men have been diagnosed as a result of screening who otherwise would not have been diagnosed. There is also no clear difference in the reduction in prostate cancer mortality when comparing geographic regions of the United States that have had different levels of screening.

Dr. Kramer concluded the presentation with information from the Physicians Data Query (PDQ) database at the NCI. The conclusion in the PDQ is that the evidence is insufficient to determine whether screening for prostate cancer with PSA or digital rectal exam reduces mortality in prostate cancer. In addition, PDQ states that there is solid evidence that current prostate cancer treatments result in permanent side effects in many men. Members were referred to the NCI website (http://www.cancer.gov/cancertopics/pdq/screening/prostate/HealthProfessional) for a more detailed review of the data.

Questions and Answers

Dr. Samet commented that past USPTF recommendations on long-established screening procedures, such as those recently for PSA screening and mammography, have been criticized and discounted by some in the scientific community and the media reflexively. He also questioned the use of the term “insufficient evidence” rather than “no evidence of benefit,” as sufficient evidence pointed to a lack of benefit from PSA screening. Dr. Kramer said that the USPTF recognized the controversy that its grading would cause, and he noted that the PDQ designation of “insufficient evidence” was because the PLCO and ERSPC results were not definitively negative or positive, respectively. He added that the grade “D” was given in the context of testing in healthy people, and the lack of clear benefits or harms.

Dr. Sellers asked whether the rise in prostate cancer diagnosis as PSA testing increased could have been from re-screening of people, particularly in the PLCO trial. He also queried about the number of cancers picked up at the height of the statistical peak that were clinically relevant incident cancers. Dr. Kramer responded that the initial PSA screening tests likely picked up long-growing prostate tumors that

would not have been diagnosed for many years, noting that cancers detected by PSA screening likely include those that were slow-growing, fast-growing, or indolent. He posited that many of those found during the peak years were ones that had existed for a long time and likely would never have caused a problem.

Dr. Chabner commended Dr. Kramer and the PDQ panel for their statement and asked about plans to study subgroups. Dr. Kramer agreed that the PDQ statement is well worded, but he also concurred with the USPTF caution because stronger evidence is needed if large numbers of healthy men are going to be screened and could suffer harm depending on the results of the screening. Although it currently is not possible to identify those who may benefit from PSA testing, a *post hoc* analysis of PLCO data did not clearly indicate that comorbidity could distinguish between those who might benefit or not benefit. Because enthusiasm for screening among the population is high and likely to persist, a new molecular test is needed that can identify those cancers that are likely to progress and those that can be left untreated.

Dr. Champion asked if they knew the number of men in the PLCO control group who had PSA screening in the trial. Dr. Kramer responded that this information is not known for the entire trial, but an analysis showed no differences in results among those who had previously been screened and those who had not.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, noted that these trials represent the way screening was conducted as much as 20 years ago and asked whether the more sophisticated screening methods used today, such as PSA velocity, were considered by the USPTF and PDQ. In addition, he noted that of those men who died of prostate cancer in the Goderberg study, nearly 40 percent were diagnosed in their first screening, which means they already had late-stage cancer, and survival rates would have increased if the screening had been performed earlier. Dr. Kramer agreed that the issue is important and a key element is determining a positive versus negative test. He added that new methods might also cause more harm, such as lowering the PSA threshold below 4.0 that was used in the PLCO; a lower threshold means more men are treated and more harm may actually be incurred at a lower threshold. Dr. Atala pointed out that the two best studies, ERSPC and Goteburg, saw a 20 and 44 percent reduction in prostate cancer mortality, respectively, and that these results become diluted when these data are combined with other studies in the meta-analyses. In addition, the SEER data showed a reduction of greater than 40 percent since the PSA screening era during a time period that saw little change in treatment for prostate cancer. Dr. Kramer replied that a number of changes have occurred in treatment since the advent of PSA testing, including more radical prostatectomies; in addition, adjunct radiation therapy with hormones have resulted in approximately a 40 percent relative reduction in the risk of death from prostate cancer. Therefore at least some of the decrease in mortality may be attributable to advances in therapy rather than screening.

Dr. Marcia R. Cruz-Correa, Associate Professor of Medicine and Biochemistry, University of Puerto Rico, and Basic and Translational Science Director, University of Puerto Rico Comprehensive Cancer Center, asked about differences in race regarding prostate cancer mortality. Dr. Kramer responded that African Americans have a higher risk of the disease and mortality. However, it is not known if African Americans, or other racial or ethnic groups, have greater benefits (or harms) from PSA testing.

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology and Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, commented that the PSA controversy has raised more questions than have been answered, and a certain amount of confusion confronts the clinician in trying to advise patients. He referred to the Baltimore Longitudinal Aging study, which is unique because samples were run on the same day with the same PSA analyzer and it was possible to see PSA rising over time until some participants were diagnosed with metastatic disease. Dr. Coffey observed that the outcry from the

advocacy groups responding to the USPTF guidelines results from longstanding skepticism about conclusions developed from governmental bodies or university committees. Dr. Sellers suggested that it would be constructive to agree that the PSA test is not the ideal test and begin developing a more accurate and useful test for the future. Dr. Coffey agreed but cautioned that too many patients undergo prostate cancer operation, without knowledge of a clear benefit.

Dr. Olopade noted that the challenge for conducting population studies in a diverse health system, such as that of the United States, is that quality of care and quality of follow-up is not standardized, with the consequence of uninterpretable results; a health care system governed by quality measures that are enforced throughout the system is desirable.

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

***Ad hoc* Subcommittee on Global Cancer Research.** Dr. Olopade provided a report of the Subcommittee's meeting. The Subcommittee appreciated NCI's establishment of the Center for Global Health (CGH) and thought that this was an opportune time for the NCI to conduct more, impactful international work. The Subcommittee discussed NIH research training program grants (D43s), which have been used for years by the Fogarty Center to train scientists locally and international sites. One of the first D43s that the NCI instituted was the HIV-associated malignancies mechanism. Dr. Olopade noted that it was obvious at a recent African Organisation for Research and Training in Cancer (AORTIC) meeting that attendees who had D43 grants were among the most cohesive in their ability to conduct research in research-poor settings. She added that the NCI had good representation at AORTIC, and that the meeting might not have been held without this support, given the current political climate in Egypt. The D43 is a good mechanism to increase research productivity.

Dr. Edward L. Trimble, Director, Center for Global Health, presented to the Subcommittee ideas about current and potential opportunities to promote research. He sought advice about whether to fund more D43 grants in non-HIV, non-communicable disease areas. The D43 grant is held in concert with Cancer Centers, which is an increasing presence in developing countries, and the Subcommittee discussed ways to increase this mechanism. Dr. Trimble also presented ideas about other collaborative engagements, such as USAID's investment in a new cancer center in Uganda. The Subcommittee discussed opportunities to leverage similar activities with partner institutions in other countries. Other ideas related to Southeast Asia and the Pacific Islands. Questions were asked about whether the NCI should maintain broad coverage in the global arena or narrowly focus where to build research capacity and the type of infrastructure to support.

Interesting opportunities for collaborative work involve the Pink Ribbon/Red Ribbon alliance as well as the GAVI Alliance's interest in disseminating information on HPV, cervical cancer, and head and neck cancers. Other opportunities include: collaboration with the Fogarty Center to expand the medical education partnership initiative, a major activity to partner with medical institutes in low-resource settings (e.g., sub-Saharan Africa); activities related to the framework for tobacco control; and international training, particularly for nursing in oncology, other health professionals who are needed for cancer control globally and to conduct clinical trials in low-resource settings, and other health professionals who are needed for cancer control globally.

Discussion

Dr. Varmus told members that a CGH workshop is planned to discuss how to shape a research program for the Center based on current NCI international programs and support. In terms of capacity building, the NCI has provided training programs (i.e., human capacity) but has not provided support for facilities or other capacities. He expressed uncertainty about the advantage of providing training in the

absence of a research commitment. However, many NCI-designated Cancer Centers have developed partnerships in developing countries, especially in Africa, that the NCI can further support, such as by building registries, developing national cancer plans for several countries to provide a model for other countries, and building a research program that is based on some of the joint arrangements between the NCI-designated Cancer Centers and Centers in Africa.

Dr. Olopade said that the D43 mechanism addresses human capacity. She shared the Subcommittee's suggestion that researchers should work with the resources that are available at their home countries and conduct research despite the limited infrastructure; questions can still be answered, as seen by the research on HIV/AIDS-associated malignancy that is conducted in Uganda. In addition, the NCI's support of research programs should leverage local infrastructure when possible, such as the USAID-funded cancer center in Uganda. Dr. Lowry said that the Subcommittee meeting was focused on training and building the capacity of people and that the NCI might leverage resources to have an even greater impact.

Dr. Chabner asked about plans for a Subcommittee follow-on meeting and ways to involve younger researchers in NCI's global health efforts. Dr. Olopade provided several examples of interactions among U.S. and African junior faculty, noting an increase of co-learning by both investigators and supporting more of such collaboration through the D43 mechanism. She said that the Subcommittee will meet again prior to the next Board meeting.

Motion. A motion to accept the summary report of the 5 December 2011 *ad Hoc* Subcommittee on Global Cancer Research meeting was approved unanimously.

VIII. STATUS REPORT: CENTER FOR CANCER RESEARCH—DR. ROBERT WILTROUT

Dr. Robert Wiltrout, Director, Center for Cancer Research (CCR), provided an overview of the CCR and told members that the presenters would relate the story of how CCR investigators uncovered erroneous science with an impact on public health and NCI efforts to increase collaborations and use of the NIH Mark O. Hatfield Clinical Research Center (Clinical Center). Dr. Wiltrout reminded members that the CCR integrates basic, translational, and clinical research to make cancer preventable, curable, or manageable. The CCR applies information that is generated by interdisciplinary interactions to inform the larger biomedical research community and ultimately positively affect patients with cancer and HIV. The Clinical Center functions as a comprehensive translational research center that promotes high-quality, basic science and moves those discoveries into the clinic as quickly as possible. CCR investigators are encouraged to conduct high-risk, high-impact research, including some studies that require long-term support that would not be funded through other mechanisms.

Dr. Wiltrout explained that the CCR's research structure is composed of basic (30%), translational and clinical (55%), and HIV/AIDS (15%), and supports activities that span the NCI and NIH. Among the foremost aspects of the NCI intramural program are: support for high-risk, high-impact research; a culture that fosters interaction between disciplines and encourages efficient translation of knowledge between bench and bedside; commitment to developing new technologies; and access to the world's largest cancer focused clinical research center. The Clinical Center also has a mandate to study rare cancers and underserved patient populations, and it promotes collaboration and training. In addition, the CCR has the flexibility to rapidly reallocate resources at times when the NCI can make definitive contributions.
Dr. Wiltrout next introduced the speakers: Drs. Stephen Hughes, Director, HIV-Drug Resistance Program, CCR; and Lee Helman, Scientific Director for Clinical Research, CCR.

The Rise and Fall of Xenotropic Murine Leukemia Virus-Related Virus (XMRV). Dr. Hughes described to the members the NCI's response to reports that XMRV, a murine leukemia virus (MLV)-related virus first isolated from a human prostate tumor line, might be linked to chronic fatigue syndrome

(CFS) and prostate cancer. XMRV is part of the murine leukemia virus family, which are cancer-causing viruses in animals, as well as being closely related to endogenous viruses found in mice and gammaretroviruses, which infect primates. Concerns about protecting the blood supply from a potential pathogen prompted a rapid response from the scientific community, and the NCI was well-positioned to lead research because of its expertise in developing assays to detect HIV and interest in prostate cancer. Dr. Hughes said that in 2009, the NCI HIV Drug Resistance Program (DRP) and NCI-sponsored extramural researchers began developing assays and reagents for XMRV detection, and the NCI sponsored a workshop and put in place an Action Plan on XMRV. A timeline of NCI XMRV research indicates that by the late summer of 2011, only 18 months after the effort began, there was good evidence that XMRV was not a human pathogen. DRP contributions included failure to detect XMRV antigens in approximately 600 prostate cancers, determining that recombination between endogenous murine proviruses likely gave rise to XMRV, which subsequently infected a human prostate cancer xenograft used to develop the 22Rv1 prostate cancer cell line. DRP investigators also found that the XMRV detected in CFS patient samples likely was due to laboratory contamination. This last result arose when new plasma samples from "XMRV-infected" CFS patients were analyzed, and these contained only non-XMRV mouse viruses or XMRV that was nearly identical to that which contaminated the 22Rv1 cell line.

Dr. Hughes summarized for members the research results that led the scientific community to conclude that XMRV is not a human pathogen: DNA sequencing showed that XMRV likely arose from recombination of two endogenous mouse viruses; XMRV is susceptible to human messenger RNA (mRNA) editing in cell culture and is rapidly cleared from the serum of an infected monkey; new samples from CFS and prostate cancer patients showed no XMRV infection; all "patient-derived" XMRV viruses isolated were very similar; and some of the reports of XMRV in patient samples were due to mouse DNA contamination and others were due to laboratory XMRV contamination. Although XMRV was not a human pathogen, the NCI was prepared to respond to the potential public health threat of a new pathogenic retrovirus, as shown by the NCI's rapid progress in developing assays to detect XMRV RNA, DNA, and replication as well as in identifying potential anti-XMRV drugs by screening those developed to combat HIV and solving XMRV enzyme structures.

Questions and Answers

Dr. Chabner asked whether the original report about XMRV provided any indications of scientific mistakes. Dr. Hughes responded that issues can be pointed out in retrospect, but that it is difficult in scientific work to come up with a believable negative result. The success in the XMRV story is that the evidence has dissipated the perception of the virus as a human pathogen. Dr. Varmus emphasized the importance of determining the origin of XMRV and assuring that the virus was not a cause of chronic fatigue syndrome, and he noted that collaborative efforts with the NCI; National Institute of Allergy and Infectious Diseases (NIAID); National Heart, Lung, and Blood Institute (NHLBI); and NIH Clinical Centers are underway to validate the findings. He added that there is significant public health interest in this story on the part of the HHS and Dr. Francis Collins, NIH Director, and that isolating the unique properties of the XMRV as a recombination pattern then being used as a fingerprint demonstrates the importance of truly understanding the virus.

New Approaches for Intramural-Extramural Collaborations. Dr. Helman provided an overview of the NIH Mark O. Hatfield Clinical Research Center (Clinical Center) and described two programs aimed to increase use of the Clinical Center. The Clinical Center opened in 1953, was expanded in 2005, and received the Lasker-Bloomberg Public Service Award in 2011. It has 240 inpatient beds, 82 day-hospital stations, with 1,200 credentialed physicians and more than 400,000 patients and volunteers involved in the clinical research studies, as well as dentists, Ph.D. researchers, nurses, and allied health professionals. The Clinical Center is wholly dedicated to research, has high flexibility as a facility, and provides onsite lodging for pediatric and adult patients. Patient cohorts include more than 400 rare disease

cohorts, and patients come from all 50 states and around the world. There are approximately 10,000 new research participants each year.

Use of the NIH Clinical Center by Extramural Investigators for Collaborative Partnerships. The Clinical Center stands as a unique resource through its extensive training, Molecular Imaging Clinic, NIH Center for Interventional Oncology, and Clinical Molecular Profiling Core. Challenges for the Clinical Center include accelerated costs with decreasing budgets, a need to better serve the extramural community using the facility in collaborative work, and better use as a training ground for clinical researchers. In addition, there is an overall under-utilization of inpatient beds; although the NCI averages 85 percent utilization and uses 38 percent of all inpatient days, the NIH-wide use of the Clinical Center was 70 percent in 2010. A Congressionally mandated Scientific Management Review Board (SMRB) recommended that the Clinical Center serve as a state-of-the-art national resource with resources optimally managed to enable both internal and external investigator use. NIH leadership recognized that making the Clinical Center a resource available to the extramural community is the greatest challenge.

Dr. Helman told members that the NIH published a Request for Information (RFI) in October 2011 and is planning to release a Request for Proposals (RFP) based on responses to the RFI. The RFP will be a cooperative agreement supporting a bench-to-bedside program and involves basic and clinical researchers within the intramural and extramural communities. Teams will include at least one NIH intramural and one extramural investigator, and will have full access to the NIH Clinical Center resources.

Questions and Answers

Dr. Chabner encouraged the inclusion of industry as a partner, noting that industry lacks the access to patients and experienced clinical researchers that the Clinical Center offers. Dr. Varmus said that such interactions do occur through industry's provision of agents and other biologicals as well as Cooperative Research and Development Agreements (CRADAs) between NCI intramural investigators and industry partners.

Dr. Chabner observed that this collaboration would be an attractive way of conducting studies on rare cancers or other unique groups of patients. He added that neurofibromatosis type 2 (NF2) patients receiving anti-angiogenic treatment at the Massachusetts General Hospital would benefit through this interaction, and he also suggested that this partnership might provide the best vehicle to study rare mutations found in lung cancer, as 1 percent of the patients have *HER2* amplification and one-half percent have *BRAF* polymorphisms, and a local center cannot accrue sufficient numbers of patients to support a clinical trial. Dr. Helman agreed and described how a study of pediatric gastrointestinal stromal tumors (GIST) benefited from extramural-intramural collaboration. Dr. Varmus said that the NIH has struggled for 15 years with how to help the entire clinical research community understand that the Clinical Center has remarkable resources and is open for collaborative work. Dr. Helman noted that extramural investigators benefit from such partnerships in that they remain engaged and in control of their trial and are assured that their patients receive the proper care. Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, and B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, supported this collaboration as an efficient use of funds, particularly for orphan diseases, and commented that the Clinical Center resource would allow extramural clinical investigators to proceed with trials that they otherwise would be unable to conduct.

Dr. Jacks observed that the value of this extramural-intramural partnership extends to the basic scientist with a concept who needs partnerships and technologies to conduct the translational work; the Clinical Center provides the ability to follow the patient intensively over time, which is more difficult in an academic setting. Dr. Helman said that the Clinical Center has invested in technologies, particularly imaging, to better support the research, and that the NCI would welcome basic scientists with an interesting clinical challenge.

Dr. Olopade queried about funding for the partnerships. Dr. Varmus indicated that the NCI will address this as needed, noting that the demand has not increased despite many efforts to increase external utilization of the Clinical Center. Dr. Kaur said that demand would be a good problem to have to select the unique opportunities for this joint collaboration.

Dr. Sellers asked about the NCI's level of interest in reformatting therapeutic antibodies into pet-based nanobodies or dibodies. Dr. Helman responded that the Clinical Center is well set up to do this work and has completed some of it.

Dr. Richard Pazdur, Division Director, Division of Oncology Drugs, FDA, asked about the buy-in from the Clinical Center staff regarding this collaboration. Dr. Helman said that this concern was addressed by developing it as a partnership; the Clinical Center investigators are intellectually curious and appreciate the opportunity to collaborate with good scientists in the extramural community.

NIH Lasker Clinical Research Scholars Program. Dr. Helman reminded members that the purpose of the Lasker Program is to support research during the early-stage careers of independent clinical researchers as well as provide a unique bridge between the intramural and extramural research communities. It includes two phases: (1) 5-7 year appointment as an NIH intramural tenure-track investigator with an independent research budget; and (2) successful scholars, who either apply for a tenured position at the NIH or apply for up to 5 years of NIH support for their research at an extramural research facility. The translational clinical researchers after fellowship training would be competitive for tenure-track positions and have the ability to do independent research.

Program partners include the Lasker Foundation as well as intramural and extramural support from the NIH. The Lasker Foundation participates in the selection and mentoring processes and provided financial support for the 2011 launch that allowed the scholars to attend the Lasker awards ceremony and to participate in the annual meeting. It also highlights schools on its website. The Program conducts competitive, merit-based reviews on an initial, interim, and final schedule. Dr. Helman said that there were 15 applicants, including one oncology applicant, in FY 2011, of which 2 candidates are under consideration. Changes to the application for FY 2012 include a deadline of late January, a reduction from 12 to 6 pages, and a discussion of how proposed research will utilize the Intramural Research Program (IRP) environment. In addition, applicants must be within 10 years of completing their core residency. Dr. Helman invited members to share their thoughts on how the NCI might attract a more robust pool of oncology applicants to the Lasker Program.

Questions and Answers

Dr. Varmus expressed appreciation to the Lasker Foundation for lending its name to the scholar program, which is an ideal way to start a career in clinical research. He noted that the program has not found traction in the larger community, in contrast to the highly successful "NIH Earl Stadtman Investigators" recruitment program, and said that the NCI has difficulty recruiting clinical investigators at the mid or higher levels.

Dr. Waun Ki Hong, Professor and Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, asked whether the Lasker Program is open to applications from physician scientists and clinical investigators. Dr. Helman responded affirmatively and stated that an investigator is not required to have a laboratory but can establish a clinical research program.

Dr. Chabner said that his institution works hard to keep their excellent investigators, and a shift to the NIH may not be the easiest transition from a place where they are productive and have ongoing relationships; his institution can add facilities to accommodate more investigators, whereas the NIH Clinical Center and clinical programs are more limited.

Dr. Sellers requested clarification about the timeframe in the fellowship-to-faculty process that the Lasker Program is targeting for recruitment. Dr. Helman confirmed that the target is postdoctoral students in the process of completing their fellowship. Dr. Varmus said that a successful recruitment program would involve a Lasker emissary on major campuses prompting incipient clinical researchers at the appropriate time to apply for this program. Dr. Atala lauded the program, observed that it might take time for news about the program to spread, and encouraged the NCI to recruit earlier in the fellowship. Drs. Cruz-Correa and Olopade concurred with an earlier recruitment timeframe, including recruitment at the predoctoral level and working with training program directors to reach oncology fellows who wish to conduct clinical research but have no support for that training.

Members discussed additional recruitment approaches. Dr. Kaur said that her institution offers a clinical investigator career track that includes the flexibility to acquire skills elsewhere for 1-2 years, and she suggested that the NCI might adopt a similar approach. Dr. Cullen suggested that an effective approach may be to support the last year of training with the provision that the fellow then enters the intramural program. Dr. Chabner noted that the Cancer Education Consortium provides a multi-day training program of fellows, at which the NCI might present the Lasker Program for career consideration.

IX. STATUS REPORT: DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS—DRS. JOSEPH FRAUMENI, JR., NEAL FREEDMAN, AIMEE R. KREIMER, STEPHEN CHANOCK, AND ROBERT N. HOOVER

Dr. Joseph Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), reminded members that the DCEG's mission is to incorporate advances in genomic and other technologies as biomarkers into epidemiologic studies that inform, proving new strategies, clinical practice, public policy and biological concepts. The Division encompasses national and international topics, with rapid and coordinating response to emerging scientific questions and public health concerns by examining epidemiology and biomarkers as well as developing strategic partnerships that cut across the NCI, NIH, and other organizations. DCEG manages the NCI Cohort Consortium, an intramural-extramural partnership with 40 cohorts and nearly 5,000 subjects. Its research programs are integrated with a training program to develop the next generation of scientists in the field. Dr. Fraumeni next introduced the DCEG investigators who presented in their fields of study: Drs. Neal Freedman, Investigator, Nutritional Epidemiology Branch; Aimée R. Kreimer, Investigator, Infections and Immunoepidemiology Branch; Stephen Chanock, Chief, Laboratory of Translational Genomics, and Director, Core Genotyping Facility; and Robert N. Hoover, Director, Epidemiology and Biostatistics Program.

The Changing Risks of Bladder Cancer Related to Tobacco Smoking. Dr. Freedman presented information about the strengthening trend in the association of tobacco smoking with bladder cancer that has emerged since the 1970s. Tobacco smoking is a persistent problem in the United States even though the link between tobacco and many types of cancer, including bladder cancer, is well established. Tobacco use has changed over time, with women now smoking at rates similar to men, modifications to cigarettes that might affect exposure, and the use of new tobacco products. The bladder is exposed to tobacco carcinogens through excretion in urine. There are 70,000 bladder cancer cases per year in the United States. New England has a relatively high rate of bladder cancer mortality compared to the rest of the United States, as shown in the NCI Atlas of 1950-1994 data and confirmed in the New England Bladder Cancer Study, which found an unexpectedly high fivefold increase for current smokers. Based on 1970s studies, the risk

was expected to have been only 2-3 times higher. The higher risk is consistent with a trend showing a strengthening association between bladder cancer and smoking that has been observed in case-control studies, starting in the late 1970s.

Dr. Freedman described the design and results of the recent NIH-AARP prospective study that he led on the changing risks of bladder cancer related to tobacco smoking. Participants were 500,000 members of the AARP, aged 50-71, who were followed for 11 years (from 1995 to 2006). During that time, there were 4,500 incident bladder cancers. Current smokers had a fourfold higher risk of developing bladder cancer than nonsmokers, which is consistent with the temporal trend observed in cohort studies showing an increase in bladder cancer risk among smokers over time.

Dr. Freedman offered several hypotheses to explain this trend: the use of reconstituted rather than leaf tobacco resulting in more carcinogens in tobacco smoke, the unintended consequence of cigarette filters leading to deeper inhalation, other exposures changing over time, changes in smoking habits, and better diagnosis. Future work includes investigating bladder cancer and tobacco association in other populations, examining trends in other cancers in the AARP cohort, and considering the larger context of other diseases and tobacco products (e.g., smokeless tobacco, water pipes, electronic cigarettes, dissolvable tobacco) that have unknown risk profiles. The 2009 Family Smoking Prevention and Tobacco Control Act gave the FDA authority to regulate the manufacture, distribution, and marketing of tobacco products, and the NIH and the FDA have formed a partnership to support research relevant to tobacco regulation.

Questions and Answers

Members discussed approaches to expand and refine the study of the association between bladder cancer and tobacco smoking. Dr. Olopade suggested that cohorts such as the Middle East Cancer Consortium (MECC) could be added. Dr. Samet observed that biomarker data, such as nitrosamine levels as a surrogate for tobacco exposure, could be incorporated. Dr. Aubrey Miller, Senior Medical Officer, National Institute of Environmental Health Sciences, NIH, suggested exploring the impact of co-carcinogens, such as menthol, on the carcinogenic effects of tobacco. Dr. Freedman agreed that the MECC and National Health and Nutrition Examination Survey (NHANES) cohorts could provide valuable data. Dr. Kaur noted that data among Native Americans and Alaska Natives showed no change in bladder cancer rates.

Dr. Pietenpol asked whether an explanation for elevated bladder cancer mortality in New England had been found. Dr. Freedman explained that many residents used well water that had elevated arsenic levels and that this may explain the higher rates.

In response to a question by Dr. Sellers about how changes in diagnostic methods would be assessed, Dr. Freedman responded that he and his colleagues were just beginning to approach this problem, and one difficulty was likely to be the determination of tumor invasiveness.

Dr. Coffey and Dr. Pietenpol asked questions about how much of the risk for bladder cancer was attributable to smoking as compared to co-morbidities or HPV. Dr. Freedman answered that 50 percent of all bladder cancers were attributable to smoking, as were 90 percent of all lung cancers.

Dr. Atala asked about biomarkers for bladder cancer, but Dr. Freedman indicated that currently there are none.

Recent Findings From the NCI Costa Rica HPV-16/18 Vaccine Trial. Dr. Kreimer presented information about the design and recent findings from the NCI Costa Rica HPV-16/18 vaccine trial. The study is a prospective, community-based, blind, randomized trial comparing vaccination with three doses during 6 months of the HPV-16/18 vaccine to controls receiving the Hepatitis A vaccine with the

endpoints of persistent cervical and anal HPV-16/18 infections. Participants were 7,466 women, 18-25 years old, enrolled between June 2004 and December 2005, with annual follow-up visits for 4 years. Cervical samples were collected at all visits, and anal and oral specimens were collected at the 4-year visit. The initial 4 years of the trial were completed in December of 2010, and long-term follow-up for an additional 6 years is ongoing. The initial findings of the NCI confirmed the results of commercial trials on the prevention of cervical HPV infections among uninfected women, with a 91 percent vaccine efficacy among the Costa Rican cohort. Further findings from the Costa Rica vaccine trial were that the HPV vaccine was not efficacious for women who had HPV-16/18 infection at the time of vaccination; it has a safety profile similar to that of other licensed vaccines, although it is not recommended for pregnant women; and it was effective against HPV-16/18 as well as some non-vaccine HPV types, having the highest impact when given prior to sexual initiation. No significant differences in efficacy were found between administration of two or three doses of the vaccine or even when it was given as a single dose.

The vaccine also offered similarly strong protection against anal HPV-16/18 infection. U.S. data show that both cervical and anal cancer are almost exclusively associated with HPV. Cervical cancer currently dominates the worldwide burden of HPV-associated cancers, but due to widespread cervical cancer screening and rising incidence of other cancers associated with HPV infection (i.e., anal cancer and oropharyngeal cancer), the gap between the burden of cervical cancer and other HPV-associated cancers is narrowing in the United States.

Upcoming research includes evaluating the efficacy of an oral HPV-16/18 vaccine and its long-term safety and duration of protection, identifying immunological markers of protection, and studying the national history of HPV infection in a vaccinated cohort.

Questions and Answers

Dr. Cullen asked about the correlation between anal and cervical HPV infections. Dr. Kreimer responded that infection at both sites was correlated, and anal HPV infection was linked to the practice of anal sexual behaviors.

In response to Dr. Olopade's question of whether additional cohorts were being considered for study, Dr. Kreimer said that while our data findings were likely generalizable to other populations such as those in the United States, and studies in populations with substantial co-morbidities and compromised immune systems might be warranted, particularly as it relates to efficacy for fewer than three doses.

The Aging Genome: Genetic Mosaicism and Its Relationship to Cancer. Dr. Chanock described GWAS discoveries that suggest that genetic mosaicism increases with age, mosaicism may be a risk factor for adult epithelial cancers, and GWAS data can be used to detect early or pre-leukemic states. Genetic mosaicism is defined as the co-existence of distinct subpopulations of cells regardless of clonal or developmental origin. Dr. Chanock reminded members that GWAS have been effective in associating new regions in the genome with diseases and traits. Results from GWAS have been particularly beneficial for cancers, such as prostate cancer, for which epidemiologic risk factors have been difficult to ascertain. GWAS have provided mechanistic insights pertaining to the etiology of complex diseases, gene-environment interactions, and pharmacogenomics. Challenges remain for using genetic markers to predict risk when making individual or public health decisions, however, because common variants represent only a fraction of genetic contributions to risk.

During the past 6 years, 189 NCI-supported researchers from 48 participating institutions have scanned 80,000 samples in 13 GWAS, generating more than 76 trillion genotypes. One serendipitous discovery was the observation of large chromosomal abnormalities, structural variation, and aneuploidy in germline DNA. These chromosomal aberrations were characterized by extensive regions in the genome (greater than 2 megabase pairs [Mb]) where there was amplification or deletion of genetic sequences or a

loss of heterozygosity (LOH) event. Moreover, these chromosomal alterations were present in only a subpopulation of cells, indicating that the cells were genetically mosaic. Extreme mosaicism underlies developmental disorders and catastrophic diseases, and genetic instability and somatic alterations have been implicated in cancer etiology.

Dr. Chanock stated that when genetic mosaicism was analyzed across all 13 GWAS, mosaic events were detected at a much higher rate than expected. Approximately 1 percent of the more than 57,000 cases of cancer and cancer-free controls contained at least one event. Although large chromosomal alterations have been well studied in somatic cells, until this analysis these events were believed to occur rarely in the germline. The researchers discovered that genetic mosaicism was a very rare event in normal children but occurred with increasing frequency as subjects became older, making age the strongest predictor of this type of abnormality. There was a higher frequency of genetic mosaicism in men compared to women, but no associations were found with ancestry, smoking, or DNA sample source (i.e., blood vs. buccal). Certain genomic locations represented a preponderance of the observed copy-neutral LOH as well as the gain or loss of genetic information. A few of the frequently altered regions, including locations on chromosomes 13 and 20, contain genes implicated in hematopoietic malignancies.

The occurrence of genetic mosaicism was associated with the incidence of cancers, particularly kidney and lung epithelial malignancies. The elevated frequency of mosaicism also was striking in incidental and secondary hematologic cancers such as leukemia. Importantly, the DNA samples for the GWAS analyses were obtained more than 5 years before hematologic cancer diagnosis, suggesting that detection of genetic mosaicism through GWAS might be useful as a biomarker for predicting the onset of particular leukemic or pre-leukemic states. Interestingly, there also were individuals who had multiple sites of genetic mosaicism yet remained cancer-free. This indicates that not all mosaic events will be predictive of cancer and highlights the importance of determining the relationship between mosaicism and disease. Dr. Chanock concluded by saying that researchers are conducting longitudinal GWAS to consider whether mosaicism varies over an extended period of time and are seeking insights into the mechanisms that link mosaicism to cancer.

Questions and Answers

Dr. Olopade asked whether the study examined myelodysplastic syndrome and secondary leukemias in a breast cancer cohort. Dr. Chanock responded that GWAS can include any cohort of sufficient size, adding that in the study he described secondary malignancies were suggestive but showed relatively small numbers.

Adverse Health Outcomes in Women Exposed *In Utero* to Diethylstilbestrol. Dr. Hoover presented research that identified adverse health outcomes in women exposed to the potent estrogen diethylstilbestrol (DES) *in utero*. In the late 1960s, physicians began treating 8 young women who had clear cell adenoma carcinomas of the vagina, a condition that was rare but previously had presented only in elderly women. DES had been given to pregnant women in the belief that it would prevent complications of pregnancy. Epidemiologists linked the cancer definitively to DES exposure *in utero* in 7 of the cases, with none of the 32 unmatched controls exposed; following this, the FDA banned the use of DES during pregnancy. DES was the first identified transplacental carcinogen and provides a laboratory model for late effects of hormones and other agents. It has become a key tool to investigate endocrine disruptors, epigenetic changes, and transgenerational carcinogenesis.

DES was the first synthetic estrogen manufactured in 1938, with use in clinical settings in 1940 to prevent complications of pregnancy. It was actually subjected to four clinical trials in the early 1950s, which showed no evidence of efficacy, but continued to be used because of an aggressive marketing campaign and the lack of requirement that drugs be efficacious to be prescribed. Research on the adenocarcinoma peaked in the late 1970s, and by the late 1980s two long-term adverse health outcomes of

DES exposure were well established: vaginal adenocarcinoma and pre-term birth in the women exposed *in utero*. Laboratory research continued in the1990s through studies of combined cohorts of exposed and non-exposed mothers, sons, and daughters; in all, four cohorts were conducted at nine centers, and in total provided more than 5,000 women with documented exposure to DES while *in utero* and approximately 2,400 well-matched comparison subjects. Studies of these cohorts during the past 17 years found additional adverse health outcomes, including: cervical dysplasia; excessive breast cancers after age 40; significant problems with infertility and pregnancy; and clear evidence that age distribution of menopause has shifted to an earlier age.

In addition to significant adverse outcomes, the risks involved are substantial. Adenocarcinoma risks are approximately 40 times higher than expected based on population rates. Hazard ratios are twofold for breast cancer, cervical intraepithelial neoplasia, and infertility. For pregnancy outcomes, hazard ratios rise to fivefold for preterm delivery and eightfold for neonatal deaths. For the first time, Dr. Hoover's team was able to calculate absolute risks, that is, the proportion of women who would develop one of these outcomes by age 55. DES has a high adverse-event burden, as shown by comparing cumulative risks for adverse health outcomes for the exposed and unexposed, including increased risk of rare events such as clear-cell adenocarcinoma (40-fold increase) and a 1 in 10,000 chance of getting adenocarcinoma if exposed to DES, but also twofold to threefold increased risk for common events such as cervical intraepithelial neoplasia, infertility, and preterm delivery.

Retrospective analyses were conducted of clinical records from two cohorts in the 1970s that recorded the presence or absence of vaginal adenosis. Vaginal adenosis is a pathognomonic of DES exposure and serves as a precursor of the clear cell adenoma carcinomas. It was found to be a good marker for effective biological dose. Analyses also revealed good evidence of dose response in terms of cumulative risk, including an excess risk of breast cancer in those women aged 40 or older who were exposed to DES *in utero*.

Dr. Hoover said that the conclusion of this research is that *in utero* exposure to DES is associated with high lifetime risk of a broad spectrum of health outcomes. The cumulative risks, in terms of multiplicity and total amount of women involved, are unprecedented for the long-term side effects of drugs given to normal individuals. Lessons from the DES experience and research include the value of clinical trials, early life and gestation are vulnerable time periods, alert clinicians and mothers notice the unusual, and a systematic long-term post-marketing surveillance of drugs is needed.

Questions and Answers

Dr. Kaur asked whether similar data were available regarding urogenital problems experienced by DES sons. Dr. Hoover responded that the sons have some minor urogenital anomalies, maldescent and epididymal cysts, and a twofold excess of testicular cancer, but no effect on male fertility and no significant other adverse outcomes; the sons have reached an age where prostate cancer may be a risk, and investigators currently are following up on this.

Dr. Atala asked what strategies have been developed to handle other epidemiologic manifestations, and he noted the resurgence in the use of DES for its anti-angiogenic properties. Dr. Hoover acknowledged the difficulties in conducting effective post-marketing surveillance of drugs.

X. CLOSED SESSION—DR. BRUCE A. CHABNER

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

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

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

XI. ADJOURNMENTCDR. BRUCE A. CHABNER

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

There being no further business, the 160th regular meeting of the NCAB was adjourned at 4:15 p.m. on Tuesday, 6 December 2011.

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

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