DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
163rd NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
November 29, 2012

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

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BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 163rd regular meeting on 29 November 2012, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Thursday, 29 November 2012, from 9:00 a.m. to 2:45 p.m., and closed to the public from 3:00 p.m. to 4:03 p.m. The NCAB Chair, Dr. Tyler E. Jacks, Director, Koch Institute for Integrative Cancer Research, David H. Koch Professor of Biology, Massachusetts Institute of Technology, presided during both the open and closed sessions.

NCAB Members

Dr. Tyler E. Jacks (Chair)
Dr. Anthony Atala
Dr. Bruce A. Chabner
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Marcia R. Cruz-Correa (absent)
Dr. Kevin J. Cullen
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong
Mr. Robert A. Ingram (absent)
Dr. Judith S. Kaur
Ms. Mary Vaughan Lester
Dr. H. Kim Lyerly
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
Dr. Vincent J. Cogliano, EPA (absent)
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA
Dr. Craig D. Shriver, DoD
Dr. Michael Stebbins, OSTP (absent)
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH (absent)
Dr. Sharlene Weatherwax, DOE

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Harold Varmus, Director, National Cancer Institute
Dr. Jeff Abrams, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. 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. 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. George Komatsoulis, Acting 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. 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

TABLE OF CONTENTS

THURSDAY, 29 NOVEMBER 2012

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I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 5 SEPTEMBER 2012 MINUTES—DR. TYLER E. JACKS

Dr. Jacks called to order the 163rd 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. Jacks 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 5 September 2012 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. TYLER E. JACKS

Dr. Jacks called Board members' attention to future meeting dates. He said that the date for the February 2013 NCAB meeting may be changed; members will be kept informed.

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

Dr. Harold E. Varmus, Director, NCI, welcomed members and reflected on the passing of former congressman The Honorable Arlen Specter of Pennsylvania. Dr. Varmus noted that Mr. Specter had served as the ranking Republican on the United States (U.S.) House Appropriations Committee for many years, provided notable support for the Nation's cancer research enterprise, and experienced three types of cancer in his lifetime. Recruitment continues for Directors of the NCI Division of Cancer Epidemiology and Genetics (DCEG), Center for Cancer Genomics (CCG), and Center for Biomedical Informatics and Information Technology (CBIIT) as well as for the Medical Oncology Branch. Members were informed that the National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA), which were to merge into one entity, will remain as distinct institutes but with more functional integration of efforts. Dr. Varmus announced that a Subcommittee on Cancer Centers Working Group will address budgetary and policy issues related to the funding process and how applications are written and reviewed.

NCI Budget and Legislative Concerns. Dr. Varmus informed members that the recent national elections have resulted in changes to Congress that will affect the NCI, including a new Chair of the House Labor, Health and Human Services, Education, and Related Agencies Committee. The NCI continues to operate under a Continuing Resolution through March 2013 and has implemented conservative strategies in the payment of noncompetitive grants and other funding considerations. The NIH is preparing its Fiscal Year (FY) 2014 budget submission, and the NCI has provided several new activities to include in the submission. Dr. Varmus described the NCI's approach to funding applications and emphasized that there is no mandated percentile for funding grants. Members were shown that funding for individual investigator (R01 and R21) grant applications are at the same level in FY 2012 as it was in FY 2011; the overall success rate of all competing research project grants was14 percent. Dr. Varmus said that a proposed pancreatic cancer bill was revised to focus more broadly on recalcitrant cancers. The bill has passed the House and is on hold in the Senate; the NIH has responded to questions from the Senate regarding the bill's topic.

NCI Activities of Interest. Dr. Varmus informed members that he attended the inauguration of the Cancer Center at the University of Kansas as an NCI-designated center. He noted his international

travels to promote cancer research globally, including Indonesia and Mexico, and discussions with the U.S. Agency for International Development (USAID) to discuss potential collaborative activities. Dr. Varmus also reviewed other activities of interest, including the Frederick National Laboratory for Cancer Research (FNLCR), status of the Provocative Questions initiative (PQ), and an imminent 1-day meeting sponsored by the Center for Cancer Genomics (CCG) on the future of cancer genomics beyond the work of The Cancer Genome Atlas (TCGA) program. Dr. Varmus presented highlights of recent workshops of interest, including: 1) one on pancreatic cancer; 2) a second annual meeting of global leaders of major cancer research funders, with a white paper in preparation on national registries, prevention, and data sharing opportunities; 3) a workshop on "precision medicine" in which the Exceptional Cases Initiative was discussed; and, 4) a phenotype-to-genotype workshop, to be described in further detail by Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and based on the *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* report from the Institute of Medicine (IOM).

Human Papillomavirus (HPV) Vaccination and Cervical Cancer Control. Dr. Douglas R. Lowy, Deputy Director, updated members about issues related to HPV vaccination and cervical cancer control. Dr. Lowy recognized the effect of the NCAB's and Dr. Varmus' support in facilitating efforts in this field. He noted that the President's Cancer Panel (PCP) currently has focused on HPV vaccination, mostly in the United States, where fewer women are being immunized than in other parts of the world and that a problem exists regarding women receiving booster dosages. PCP meetings held in July, September, and November 2012, were attended by several NCAB members. The fourth PCP meeting that will be held in April 2013 will focus on global HPV vaccination. Innovative ideas that have resulted from these meetings include: 1) booster vaccinations provided through pharmacies to facilitate the completion of the vaccination; and, 2) use of primary age rather than cytology for cervical cancer screening. Dr. Lowy noted that increasing the uptake of the vaccine and ensuring vaccination completion could safely lengthen the time between screening intervals, strengthen "herd" immunity, and thus reduce by 15 percent HPV disease-associated annual costs, which are estimated at $6.5 B. Members were informed that the NCI and the U.S. Food and Drug Administration (FDA) have held preliminary discussions to ameliorate the issue of under-screened women who are at risk of cervical cancer, including the possibility of a clinical trial that incorporates self-collection of vaginal samples. In addition, the two meetings held in 2012 by the Lasker Cervical Cancer Initiative focused on cervical cancer in the developing world and provided comprehensive cervical cancer control (i.e., prevention, screening, treatment, palliation). Ex-President Calderón of Mexico implemented HPV vaccination of all 5th grade girls in Mexico.

Update on the National Cancer Trials Network (NCTN). Dr. Doroshow informed members that the application deadline for the NCTN is in 6 weeks, with the review process to be completed by June 2013. Dr. Doroshow told members that the NCI's phenotype-to-genotype efforts will be molecular identification studies, drawing patients from past trials conducted mostly by NCI-designated Cancer Centers with response rates under 10 percent in a particular histology. The intent is to better understand how the drugs worked and elucidate the reasons for their efficacy or inefficacy.

Questions and Answers

Dr. Jacks asked about the decisionmaking process for awards, including when high-ranked projects are not funded and lower ranked projects are funded. Dr. Varmus indicated that the NCI's interest is to maintain a balanced research portfolio that meets the needs of all the Divisions.

Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., commented on the score distribution. Dr. Varmus responded that each Study Section, which reviews applications for all NIH Institutes and Centers (ICs), may only have 30 percent of the NCI applications in the 10th percentile, and thus, the distribution may appear uneven for some ICs.

Dr. Jacks observed that the perception in some parts of the scientific community is that the NCI paylines are extremely low. Dr. Varmus responded that the perception of an absolute 7 percent payline cutoff for the NCI is not true, but confusion may result from the percentile assigned by the Study Section evaluations versus the zone of likely funding, which can be interpreted as a percent.

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, asked about the number of grants awarded to new investigators. Dr. Varmus re-affirmed the NCI's commitment to fund new investigators, with a strategy of funding applications from new investigators at a lower percentile than applications from those who have received funding in the past.

Dr. Bruce A. Chabner, Director of Clinical Research, Massachusetts General Hospital Cancer Center, asked why any trial would be planned today without genotyping patients. Dr. Doroshow responded that moving forward this could be accomplished, although genotyping does not guarantee identification of all mutations. Dr. Varmus, while recognizing the complexity of the issue, stated that unexpected mutations for which investigators are not screening likely will influence patient outcomes. Dr. Sellers commented that the research community is in a period of incomplete information during which the unexpected will happen, knowledge will continue to grow, and a better understanding of genotype and mutations will lead to better targeted therapies. Dr. Doroshow added that there also is a lack of complete knowledge of the action of the agents being used for cancer therapy.

Regarding HPV vaccines, Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, Professor of Oncology, Mayo Clinic, suggested that much as there is a need for knowledge about patients who do not respond to cancer therapeutics, much can be learned from populations that do not respond to vaccines, and she asked about the current state of HPV vaccination for head and neck cancers. Dr. Lowy responded that the issue in head and neck cancer is that there is a lack of a precursor lesion as in cervical cancer. It is known that HPV vaccination can prevent oropharynx HPV infection, but data are not clear whether prevention of these HPV infections meets a virologic endpoint, as it does in anogenital cancers. He noted that this makes it more difficult to obtain FDA approval for HPV vaccination post-licensure for head and neck cancers.

Dr. Olopade questioned the focus on "n-of-1" outliers in therapeutic trials if it means discounting otherwise effective agents and failing to communicate that information. Dr. Varmus replied that the NCI recognizes both that many clinicians see conventional therapies curing some people, and that the genotype-to-phenotype aspect applies to conventional therapy, not simply to just targeted therapy. The perception that an agent is not successful because it only produces an average of 6 months extended life does not highlight the fact that many patients live 2 years, and others do not respond at all. Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, Professor of Medicine, University of Maryland, added that he can cure 40 to 50 percent of his patients with $250 worth of cisplatin and some radiation, but it is not known what is genotypically different about those patients than the others who do not respond. Dr. Varmus acknowledged the often curative effects of chemotherapy as well as the perception of high toxicity during treatment based on past experience.

IV. REVIEW OF THE DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS (DCEG) —DR. JONATHAN M. SAMET

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, Director, Institute for Global Health, University of Southern California, Los Angeles, CA, provided an update from the NCI Director's Advisory Panel on the DCEG.

After reviewing the mission, organizational chart, and personnel demographics of the DCEG, Dr. Samet summarized the DCEG's role as a national agency that provides consultation, advice, and review for government agencies on cancer. Past activities have included responding to Congressional requests for mandated reports on saccharin and bladder cancer, electromagnetic radiation and childhood leukemia, and cell phones and brain cancer.

Dr. Samet reviewed the charge to the Advisory Panel from Dr. Varmus, members of the panel, and the approach taken by the Panel. DCEG leadership provided overview materials on major projects and publications as well as 5-year strategic plans for DCEG and its branches. Panel members also met with DCEG and branch leadership, as well as with Directors of other NCI Divisions, to gain their input into the review process. Dr. Samet presented key findings from the Panel, including confirmation that under Dr. Joseph Fraumeni's leadership, DCEG has been the world's leader in cancer epidemiology and has played a major role in cancer genetics. In addition, DCEG has developed relevant consortia for investigating cancer genetics, DCEG is a major supporter of training for cancer epidemiology and genetics, and DCEG Branches have long-established research programs with broad reach. Major recommendations from the Panel include an enhanced focus by the next DCEG Director on genomics and translation and a broader strategy for integration of DCEG across all Divisions within the NCI.

Dr. Samet described the Panel's findings related to issues for enhancing translation of DCEG programs for cancer genomics. There are limits to how DCEG can translate findings of genome-wide association studies (GWAS) and next-generation technologies; however, increasing collaborations between DCEG and other NCI Divisions on cancer genomics can help to ameliorate current limits. The Panel also found that DCEG could benefit from a clinical perspective to enhance the emphasis on clinical translation. Another barrier is the absence of an overall NCI-wide strategy for translating genomic findings.

The presence of a strong international component in the DCEG has allowed the Division to enhance research and capacity building. Dr. Samet emphasized that the Panel strongly recommended that the DCEG strengthen its engagement with the Center for Global Health (CGH). He then summarized findings from the Panel regarding the next DCEG Director. The Panel strongly recommended that the new Director have a broad background and extensive grounding in epidemiology, be able to keep the DCEG at the cutting edge of "omics" technologies, promote translation, have a commitment to training and mentorship, and be able to successfully fill the role of being a global leader in the field with a vision for the future.

Questions and Answers

Dr. Olopade commented on the emphasis on epidemiology in DCEG's presentation while at the same time making a strong argument about the need for a new Director who can provide a bridge to translation, especially in the field of genomics. Dr. Samet said that it is important to have a new Director who understands translation, but epidemiology remains the basic research foundation of the DCEG.

Dr. Sellers asked if the DCEG is seeking more diverse cohorts in the United States, given the rapidly changing demographics of the country. Dr. Samet agreed that cohorts now are used in many different ways that were not anticipated previously, and cohort designs remain a topic of intense discussion at the NCI.

Dr. Jacks asked for further clarification on the history of DCEG international interactions and guidance on how involvement with the CGH can be increased. Dr. Samet responded that in the past, DCEG international activities have been based on specific opportunities for specific diseases, such as

HPV and cervical cancer, or through interactions with individual investigators; the DCEG and CGH will collaborate as opportunities arise.

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, commented on lessons learned from migration studies of prostate cancer, such as that China has a low rate of prostate cancer, but Chinese men who migrate to the United States have a dramatic rise in prostate cancer incidence in the second generation. Epidemiology has not been able to provide a clear insight for why this occurs. He asked how the DCEG can design studies to answer these types of fundamental questions. Dr. Samet noted that migration was on the list of questions for the PQI. Migration and health is a difficult research topic and may be addressed by developing the right kinds of cohorts. This reinforces the need to have close collaborations with international investigators and the type of thinking that needs to be a part of the vision of the new DCEG Director.

Dr. H. Kim Lyerly, Vice President/Global Head of Oncology, George Barth Geller Professor of Cancer Research, Professor of Surgery, Duke University School of Medicine, asked how the DCEG can handle studies in which there is an interface with cohorts with multiple disease risk factors for chronic diseases, such as seen in obesity, as well as opportunities for population-based genomic studies or commercial ventures in this area. Dr. Samet acknowledged the challenge as the DCEG tries to develop cohorts with as many platforms for disease conditions as possible, with particular issues in phenotyping individuals for multiple diseases. There are many examples of cohorts developed for one purpose that were used later for very different purposes (e.g., Nurses' Health Study); new approaches founded on developing broad-based, population-based cohorts that can be used for multiple diseases are needed.

Dr. Kaur noted that the example of HPV vaccine development and the role epidemiology played in this success may indicate a shift from infectious disease-related epidemiology to noncommunicable disease-related epidemiology and require a new research paradigm with new types of cohorts. Dr. Samet agreed, noting that IOM's recent precision medicine report recognized the need for large-scale informatics platforms that allow epidemiologists to follow individuals over a lifetime. He added that the DCEG could have an important role in providing leadership on this issue.

Dr. Chabner reflected on the limited results from GWAS, especially in terms of how to apply GWAS findings to the clinic or to address biological questions, and asked for further clarification on whether there are examples of GWAS increasing the understanding of disease or risk factors for disease. Dr. Samet said that GWAS was an important and critical step for understanding genetic components of disease. Dr. Olopade explained that GWAS had an important role in her research on the gene *p53* and risk prediction. Dr. Chabner added that GWAS may be beneficial in finding mutations through, but it is a limited tool for application to the clinic. Dr. Sellers commented that GWAS has been a disappointment because phenotype characterization does not correspond exactly to genotypic characterization, and the resolution of GWAS is not sufficient. He described studies in Icelandic populations that suggest the importance of somatic-genetic chancers and encouraged DCEG to consider how best to link germline genetics with somatic genetics from TCGA. Dr. Varmus indicated that this issue will be discussed at a meeting tomorrow because there is interest in having a better understanding of the determinants of penetrance of mutations and the connection between somatic and germline mutations.

Dr. Coffey asked about the extent to which the field of epidemiology must be modified based on the large amounts of new microbiome information being generated by researchers. Dr. Samet responded that new technologies and the emphasis on new sources of data, such as that from the microbiome, metabolome, and other "omics" approaches, will generate vast amounts of data; a challenge remains to

develop future cohorts based on the ability to collect "omics" information. This reinforces the need for large-scale informatics to be able to collect and analyze large amounts of data.

Dr. Jacks asked about current linkage and future organization between intramural research and the extramural community. Dr. Samet responded that there are many interactions, from informal to formal, and this addresses the issue of different types of clinical and translational efforts and the organizational structure this will require. The DCEG has focused on the etiology of disease, but there needs to be recognition that disease exists on a continuum, and each step on the continuum should be addressed.

V. STATUS REPORT: PANCREATIC CANCER WORKING GROUP—DR. JAMES L. ABBRUZZESE

Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, updated members on the status of the Pancreatic Cancer Working Group and its recent workshop. Dr. Abbruzzese reminded members that pancreatic cancer is one of the cancers receiving increased attention because of challenges in detection and treatment, despite some recent progress. Pancreatic cancer is the fourth leading cause of cancer mortality among men and women and expected to rise to the second leading cause of cancer mortality after lung cancer. He summarized the challenges in treatment (e.g., resection, chemotherapy) and risk factors. Recent studies have indicated that there is a small subset of patients with somatic mutations, such as in BRCA2, who may be responsive to classical chemotherapeutic agents. Dr. Abbruzzese said that data on risk factors for pancreatic cancer suggest the opportunity for a concerted prevention effort to reduce the incidence of disease. Smoking and metabolic conditions, such as obesity and diabetes, are associated with approximately 50 percent of the cases of pancreatic cancer. Inherited syndromes are associated with lesser numbers of patients, and increasingly, those with mucinous pancreatic cysts have been identified as at a higher risk for pancreatic cancer.

Recent progress in translational efforts for pancreatic cancer has included histological and molecular characterization of precursor lesions, descriptions of mutational profiles, and development of genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDX). Dr. Abbruzzese provided an overview of recent clinical progress in screening patients with known high-risk germline mutations and effective integration of currently available treatment modalities (e.g., surgery, radiation, and chemotherapy).

Dr. Abbruzzese informed members about the Clinical Trials and Translational Research Advisory Committee (CTAC) Pancreatic Cancer Working Group and the "Pancreatic Cancer: Scanning the Horizon for Focused Interventions" workshop held in October 2012. The purpose of the working group is to develop strategies and recommendations that will help the NCI in its efforts to reduce the incidence and mortality rates of adenocarcinoma of the pancreas. Specific goals were outlined, including increasing collaborations among centers investigating pancreatic cancer, developing recommendations to take advantage of new investment opportunities, and providing advice on the NCI plan to implement the recommendations. The workshop focused on the three greatest areas of need for pancreatic cancer research: (1) identifying cohorts of individuals at high risk; (2) determining if high-risk patients can be identified for pre-invasive pathological precursors (i.e., mucinous pancreatic neoplasia [MCN] or intrapancreatic mucinous neoplasm [IPMN]) or early cancer; and (3) developing effective systemic therapies. Breakout sessions were organized around the three areas of need. Dr. Abbruzzese informed members about provocative questions addressed during the workshop, such as why some pancreatic cancers occur in some patients without risk factors or genetic abnormalities and why some identical mutations (e.g., *CDKN2A*) result in pancreatic cancer in some patients and melanoma in others.

Dr. Abbruzzese informed members of the four high-level recommendations resulting from the workshop, which included specific recommendations for the two patient populations that have been defined as at increased risk for pancreatic cancer. For people with new-onset diabetes, the recommendation is to develop a means to identify the approximately 1 in 125 patients with new-onset diabetes who have early pancreatic cancer; for patients with specific germline mutations or familial pancreatic cancer, the recommendation is to develop screening methods to identify those patients with heritable pancreatic cancer (specific germline mutations or pancreatic cancer families) or mucinous pancreatic cysts (MCN and IPMN) who will progress to invasive pancreatic cancer and require surgical intervention. Other recommendations are to develop strategies that neutralize the driver oncogene *KRAS* and to accelerate clinical and preclinical therapeutic approaches that target the immune and nonimmune components in pancreatic tumors. The next steps for the committee will be to investigate how to address the recommendations.

Questions and Answers

Dr. Coffey noted that progress has been made recently in immunotherapy to show that chromosome instability instigates *CD47* to allow the cancer cell to fight the immune system. He asked if this occurs, as well as activation of cytotoxic lymphocytes (CTLs), in pancreatic cancer. Dr. Abbruzzese replied that chromosomal/genomic instability is significant in pancreatic cancer, and that CTLs are activated in pancreatic cancer cells; how to activate the immune system in pancreatic cancer is a significant challenge. Dr. Coffey replied that stromal changes are becoming more interesting in cancer research, especially the shortening of the telomere, which occurs in epithelial cells; he wondered if this has been investigated in pancreatic cancer and suggested that the ENCODE (Encyclopedia of DNA Elements) process be used for pancreatic cancer. Dr. Jacks replied that there is some evidence in a mouse model of pancreatic cancer that some of the stroma is differentiated from the tumor.

Dr. Chabner said that in animal models investigators are trying to detect circulating pancreatic cancer cells; another approach is to aspirate IPMN to see if *KRAS* is present, which could be used as a marker for resection. Dr. Abbruzzese suggested that the number of circulating cells is low, but circulating DNA may be a more robust use as a biomarker. As for *KRAS*, significant research is being conducted on cysts to distinguish cyst type (mucinous or serous) by the mutations in *KRAS* and two other genes. Identifying mucinous cysts, which are the most clinically relevant, would be a significant step forward

Dr. Olopade commented that the presence of *BRCA1* and *BRCA2* in pancreatic cancer is almost as predictive as these genes in ovarian cancer. Because there are large cohorts of women with these genes, it seems practical to enlist these cohorts in pancreatic cancer research. Dr. Abbruzzese agreed that this group, as well as those with IPMN, may be ideal for investigating novel screening and biomarker approaches. Screening today only identifies approximately 40 percent of those patients with changes that may lead to pancreatic cancer, and more research needs to be conducted in this area. Dr. Samet wondered about establishing cohorts of smokers or people with diabetes.

Dr. Jacks asked if the knowledge that *KRAS* appears to be present in all pancreatic cancer tumors should lead to specific NCI research activities related to the recommendations from the working group. Dr. Abbruzzese replied that the Working Group will consider this and that discussions are underway with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Dr. Chabner suggested that in the NCI's response to Congress, consideration should be given to responding that *KRAS* is one of the problems, not pancreatic cancer *per se*. Dr. Sellers added that this is an exciting time for pancreatic cancer research, especially because there are therapeutic agents that target the *KRAS* pathway, with Phase 1 and Phase 2 trials underway. Dr. Varmus replied that the NCI intends to respond to Congress on the issues that they have queried. He thanked Dr. Abbruzzese for his leadership of

the working group and the excellent workshop. He noted that the NCI's investment in pancreatic cancer research has increased threefold in the last decade and is beginning to show results. Dr. Varmus further emphasized that prevention can have a significant impact on reducing the mortality rates from pancreatic cancer.

VI. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH: NEW INITIATIVE—DR. DAVID C. HEIMBROOK

Dr. David C. Heimbrook, Chief Executive Officer, SAIC-Frederick, provided an update of new initiatives at the FNLCR, an NCI Federally Funded Research and Development Center (FFRDC) managed by SAIC-Frederick. Dr. Heimbrook said that the FNLCR is the only FFRDC dedicated to biomedical research, and provides advanced integrated biomedical resources to government, academic, and commercial scientists. Dr. Heimbrook reviewed FNLCR's collaborations, material transfer agreements (MTAs), and partnerships since 2008, and, as an example, described the Nanotechnology Characterization Laboratory (NCL), which was established in 2004 as an interagency collaboration among the NCI, FDA, and National Institute of Standards and Technology (NIST). The NCL provides support for the development of diagnostic and therapeutic nanoparticles, and it conducts physicochemical characterization, safety and *in vitro* studies, and *in vivo* characterization for nanomaterials to inform regulatory agencies and developmental programs. The FNLCR also supports the Division of Cancer Treatment and Diagnosis (DCTD) Experimental Therapeutics (NExT) Program to create a coordinated cancer therapeutics discovery and development pipeline with the external scientific community.

Dr. Heimbrook provided background on the establishment of the NCI-Frederick Advisory Committee (NFAC), charged by Dr. Varmus with reviewing the overall research program and making recommendations on the best use of FNLCR's infrastructure and capabilities. The NFAC is chaired by Dr. Zachary Hall, University of California, San Francisco, and has met three times since it was established. The NFAC endorsed the creation of a contractor Cooperative Research and Development Agreement (cCRADA), which allows the FNLCR to develop increased external partnerships for research, development, and testing. It was noted that the NCI approves all interactions with external partners regarding the cCRADA.

Dr. Heimbrook informed members that a new initiative, "Big Ideas," is critical for establishing the FNLCR as a true national laboratory for cancer research, similar to that of the Los Alamos National Laboratory, the Fermi Laboratory, or the Lawrence Berkeley National Laboratory in their respective fields. He said that this initiative is led by NCI leadership and the NFAC. Two of these initiatives are at the top of the list. Dr. Heimbrook asked Drs. Varmus and Doroshow to describe these two important initiatives. Dr. Varmus described the "Big Idea" regarding a focused research initiative for developing new approaches for targeting oncogenic *ras*, which has been discussed in terms of pancreatic cancer but also has applications in colorectal, lung, prostate, and other cancers. The concept is to find currently available resources to redirect research on oncogenic *ras*. A working group has been formed and is co-chaired by Dr. Varmus and Dr. Frank McCormick, Director of the University of California, San Francisco, Comprehensive Cancer Center. Dr. Doroshow described the second "Big Idea" concept that involves preclinical models and the comparison of various *in vivo* and *in vitro* models to assist in the development of robust standards and improve their predictive utility. This project can be

conducted as a public/private partnership to develop a repository of xenografts for academic and industry researchers. A pilot genetically-engineered mouse model (GEMM) study also is planned that will use patient biopsies to conduct genomic studies, and the final project is envisioned as developing a better way to characterize patient-derived xenografts (PDX) molecularly.

Dr. Heimbrook elaborated on the FNLCR resources (e.g., technologies) and infrastructure, as well as the funding mechanisms, to support the "Big Ideas" projects. An addition to the resources at the FNLCR is the Advanced Technology Research Facility (ATRF), which opened in June 2012 in Frederick, MD. The ATRF adds to the capabilities of the FNLCR to support state-of-the-science projects. To provide the NCI leadership at the FNLCR, Dr. Varmus may appoint an NCI FNLCR Director to work with SAIC-Frederick leadership to move projects forward in a timely manner. The organization of the "Big Idea" projects is envisioned as a "hub-and-spoke" model that includes the FNLCR, academia, and industry scientists.

Questions and Answers

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, asked if the NCI is reaching out to the Jackson Laboratory (JAX) for PDX. Dr. Varmus said the NCI is working with JAX to build the PDX expertise required and also is reaching out to many other institutions to secure partnerships. Dr. Pietenpol added that JAX also is in contact with NCI Cancer Centers to secure tumor specimens. Dr. Sellers said that the pharmaceutical industry can develop their own PDX and GEMM projects, but academic institutions may have more difficulty because of the cost. Dr. Varmus recognized that this is an important issue in drug development, and discussions at a recent meeting held by Dr. Francis Collins, NIH Director, on target validation raised this issue. Dr. Sellers suggested that the NCI consider ways to empower the academic institutions for PDX development and research, and Dr. Jacks agreed, observing that a repository should be available to the academic community. He also asked if there were precedents in cancer research for the "hub-and-spoke" organizational concept for the FNLCR. Dr. Varmus replied that there may or may not be a precedent, but the current focus is on understanding how the other national laboratories are organized. A meeting has been scheduled with administrators from the Lawrence Berkeley National Laboratory to see how they operate and the types of external interactions that they have.

Dr. Sellers asked if NeXT has internal Good Manufacturing Process (GMP) capabilities. Dr. Doroshow responded there is a small GMP laboratory for biologics but not for each step of the drug development process.

Dr. Coffey commented that the FNLCR may be able to investigate chromatin in the nucleus of cells as part of the preclinical testing program. He indicated that interesting work is occurring in this area in many places within the United States and internationally, and a study such as this would lend itself to the "hub-and-spoke" organizational model.

Dr. Chabner asked what projects likely would experience reduced funding due to the new "Big Ideas" initiatives. Dr. Heimbrook responded that the ideas are currently conceptual, and so

funding models are not yet clear. It is anticipated that funding for the "Big Ideas" would derive from the current FNLCR budget, which may require re-prioritization of some on-going efforts and redirection of existing staff. Some of these on-going efforts could be outsourced to minimize impact on programs.

VII. ONGOING AND NEW BUSINESS—DR. TYLER E. JACKS

***Ad hoc* Subcommittee on Global Cancer Research.** Dr. Olopade, Subcommittee Chair, told members that the Subcommittee met and discussed developing partnerships in global health, with emphases on the U.S. Government portfolio and the CGH. The Subcommittee heard presentations from Dr. Sudha Sivaram, The Johns Hopkins School of Public Health, and Dr. Brenda Kostelecky, NCI, on investments that U.S. Government agencies have made in global health, scientific areas of overlap between agencies, and available infrastructure for cancer control planning that uses data from the NIH Research Progress Online Reporting Tool (RePORTER), as well as U.S. government agency documents. They focused on India, Kenya, and Columbia and suggested that the Subcommittee will need additional time to assess data from five other countries. The Subcommittee also heard from Dr. Ted Trimble, Director of the CGH, NCI, on strategic priorities of the CGH. The Subcommittee identified seven priority areas that could be transformative: (1) cancer control planning and implementation; (2) research on cancers associated with chronic infection; (3) research on modifying common risk factors for noncommunicable diseases; (4) research on ecological-niche cancers; (5) building capacity for global cancer research; (6) development of low-cost technology for cancer detection and diagnostics; and (7) expanding partnerships. A suggestion was made that the CGH should select a few of the priority areas to focus on initially and develop more in-depth plans for research projects that include appropriate resources. Dr. Samet added that training is an area that crosses each of the priority areas and should be included in any strategic planning. Dr. Varmus commented that some of the new initiatives of the CGH have influence beyond resources to leverage in a number of countries, such as the recent experiences in Indonesia and Turkey on tobacco control. The NCI Cancer Centers also are heavily involved in international cancer research, such as their involvement with the cancer center in Kampala, Uganda. These types of collaborations may be able to be funded through supplements, which is a novel way to increase the NCI's investment.

***Ad hoc* Subcommittee on Communications.** Dr. Victoria L. Champion, Distinguished Professor of Nursing & Edward W. and Sarah Stam Cullipher Endowed Chair, Associate Director of Cancer Control and Population Sciences, IUSCC, and Subcommittee Chair, told members that the Subcommittee last met in 2008 and that the current meeting served as an orientation and organizational meeting. They identified areas within the NCI organization focused on communications and heard from Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), and Dr. Lenora Johnson, Director, Office of Communications and Education (OCE), NCI. Subcommittee members requested more information on the OCE for their next meeting. Dr. Champion summarized that there are two components of the NCI's communication activities: 1) those dealing with all areas of communication to constituents, and 2) peer reviewed research. The Subcommittee, after lengthy discussion, determined that the first area of focus should be the structure encompassing communication with all constituents. The next meeting of the Subcommittee will be in February 2013, at which time they will decide on strategies to evaluate the communication structure within NCI including a review of the NCI budget for communications. The Subcommittee also will consider how the NCI may coordinate its communications efforts with the American Cancer Society.

Motion. A motion to accept the summary reports of the 28 November 2012 *Ad hoc* Subcommittee on Global Cancer Research meeting and the *Ad hoc* Subcommittee on Communications was approved unanimously.

Organization of the Center for Cancer Training (CCT). Mr. John Czajkowski, Deputy Director for Management and Executive Officer, NCI, informed members of the need to establish the CCT as an official organization within the Institute. According to NIH policy, in order to implement such an organizational change, it has to be discussed in two public meetings in order to allow for comments. NCI chose the NCAB and Board of Scientific Advisors (BSA) meetings for this purpose in order to apprise members of the proposal, and the BSA was told of the change at its November 5, 2012, meeting. This change will have no impact on CCT's mission, staffing, or organization. There were no comments from NCAB members or the public on this proposal.

Establish the Cancer Centers Working Group and the Working Group to Provide Input From Stakeholders and Global Experts for NCI's Center for Global Health. Dr. Jacks referred members to the charge for a Working Group for the Cancer Centers, which will be convened under the NCAB Subcommittee on Cancer Centers. In addition, Dr. Jacks referred members to the charge for an *Ad hoc* Working Group to Provide Input From Stakeholders and Global Experts for the NCI's Center for Global Health, which will be convened under the NCAB *Ad hoc* Subcommittee on Global Cancer Research.

Motion. A motion to form the NCAB Cancer Center Working Group and the *Ad hoc* Working Group to Provide Input From Stakeholders and Global Experts for the NCI's Center for Global Health was approved unanimously.

Future Agenda Items. Dr. Jacks requested that members submit agenda topics for future meetings. Dr. Chabner said that he would like to suggest a future session on screening.

Dr. Varmus recognized Ms. Margaret Crowley, who has served in the role of "Verbatim Recorder" for NCAB and BSA meetings for the past 30 years. Ms. Crowley is retiring after this meeting and Dr. Varmus asked for a round of applause from NCAB members.

VIII. DIVISION OF CANCER PREVENTION UPDATE—DR. BARRY KRAMER

Dr. Barry Kramer, Director, Division of Cancer Prevention (DCP), provided an update on DCP activities since his last presentation to members in February 2012. Dr. Kramer informed members that substantial progress has been made on the seven DCP initiatives that comprised his vision for the DCP, as described at the previous meeting. To begin the review, Dr. Kramer informed members that results of the analysis for the colorectal cancer (CRC) component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial has been published in the *New England Journal of Medicine* (*NEJM*), reporting a 21 percent relative reduction in the incidence of proximal and distal CRC and a 26 percent relative reduction in distal CRC mortality between the regular screening by flexible sigmoidoscopy arm versus the usual care arm of the study. Other progress for clinical studies and large trials include the issuance of a Program Announcement (PA) for using the PLCO biospecimen resource for research on cancer etiology and early detection. In addition, public use datasets and a website, which includes an imaging library, have been developed for the PLCO and the National Lung Screening Trial (NLST). For communicating results of the NLST, DCP generated a one-page summary published in the *NEJM* that describes the study cohort, study findings, and take-home messages.

Dr. Kramer described progress in agent development, overdiagnosis, and cancer immunoprevention. Progress in agent development includes the implementation of the PREVENT Cancer Preclinical Drug Development Program, with 12 applications awarded for 6 new drugs, 3 surrogate biomarkers, and 3 vaccines. The Phase 0-1-2 Early Phase Prevention Trials contracts were recompeted and awarded. Trials completed this year included those for atorvastatin, sulindac, and inulin in CRC;

polyphenon E/green tea in prostate and bladder cancers; zileuton plus celecoxib in lung cancer; and resveratrol and atorvastatin in breast cancer. Another ongoing initiative in agent development is the construction of models for predicting outcomes of animal tumor assays from the results of short-term morphological assays in preclinical models. The model has been applied to six morphological assays. Progress on initiatives for overdiagnosis included a workshop that resulted in recommendations for scientific next steps in basic and translational research. DCP also has co-sponsored a PA with DCTD for preclinical and clinical studies that correlate cancer imaging methods with biomarkers to detect cancers at the earliest stages, reduce false-positive tests, and detection of non-life-threatening tumors. DCP and the Division of Cancer Biology (DCB) are collaborating to propose a consortium to build on existing resources and collaborate with other groups to characterize cellular and molecular patterns of indolent versus potentially lethal lesions, and determine the cellular and molecular phenotypes of early lesion cells and the associated microenvironment. The DCP Early Detection Research Network (EDRN) has a pilot project to discover and develop biomarkers or molecular signatures that can distinguish indolent cancers from progressive cancers in prostate, breast, and lung cancers. Progress on cancer immunoprevention includes three studies on vaccines, including a multi-antigen vaccine for prevention of MNU-induced ER+ rat mammary cancers, characterization and testing of potential antigens for immunization against murine colon cancer, and development of a Plac-1 vaccine for breast cancer prevention. In addition, a PA for the detection of pathogen-induced cancers, which account for an estimated 20 percent of cancers, has been issued to develop molecular signatures for risk, progression, and early detection of these cancers.

Dr. Kramer informed members about progress on international collaborations, including the China Cancer Screening Trial Feasibility Study, which will attempt to replicate NLST results in an urban Chinese population. Tobacco use in China is high, but China does not want to institute population-wide, low-dose helical computed tomography scans for lung cancer screening unless the NLST results can be confirmed in their population. This is an important initiative because of differences in the histology of lung cancer between the two countries, for example, adenocarcinoma is the most common lung cancer in the United States, but squamous cell carcinoma is more common in China. Another important collaboration with China is the translation of the Physician Data Query system statements of relevance into Chinese; the DCP is working with the NCI Office of Communication and Education on this project, which is fully funded by China.

The last two DCP initiatives are the Cancer Prevention Fellowship Program, which has seen a doubling of participation since 2007, and an initiative on new approaches to clinical prevention trials, which will investigate ways to identify and definitively test new drugs. An area of interest in new approaches to clinical prevention trials is repurposing drugs, such as metformin and aspirin, that modify cancer pathways but have been tested only in trials of nonmalignant conditions. The DCP has provided funds to the NIDDK to study metformin in the Diabetes Prevention Program Outcome Study (DPPOS) for cancer endpoints, especially in obesity-related cancers. The DCP also is providing funds to the National Institute on Aging to collect biospecimens from the Aspirin in Reducing Events in the Elderly (ASPREE) study, which is testing aspirin in 19,000 healthy people 70 years of age and older. Another project for new approaches to clinical prevention trials is developing reciprocal control design for trials in which participants in each arm of a trial receive an intervention for a particular disease but also serve as controls for a different intervention and disease in the other arm.

The DCP also is establishing the NCI Community Oncology Research Program (NCORP), a new community-based program to align the Community Clinical Oncology Program Network (CCOPs and Minority-Based CCOPs) and the National Community Cancer Centers Program (NCCCP).

Questions and Answers

Dr. Coffey commented that he is always puzzled by the fact that 90 percent of smokers do not get lung cancer. Dr. Kramer responded that it is not known why this is so, but smokers who have chronic obstructive pulmonary disease (COPD) have a higher risk of progressing to lung cancer than smokers who do not have COPD.

Dr. Waun Ki Hong, Professor, Head of the Division of Cancer Medicine, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, applauded Dr. Kramer for the DCP collaborations with the DCB and encouraged further collaboration with the DCEG and other partners to better understand the correlation of germline mutations and somatic mutations in target tissue. Dr. Kramer noted that he made a joint presentation for a proposal on this topic with Dr. Dinah Singer, Director, DCB, at the Scientific Program Leaders Retreat to illustrate what each Division is doing for the project. He added that at the suggestion of DCEG's Dr. Peggy Tucker, the DCP will collect buccal cells from the ASPREE study for normal DNA from a nonmalignant site to conduct the studies Dr. Hong suggested.

Dr. Samet stated that the NLST also produced patient guides in conjunction with the American College of Chest Physicians and the American Lung Association, and he added that opportunities may arise to discover what occurs when a new screening test comes into the marketplace, such as how patients and physicians use different information sources about a new test. Dr. Kramer responded that there is no organized cancer screening activity in the U.S. health care system; instead, the approach taken is termed "opportunistic." The DCP is conducting a post-*hoc* analysis of the NLST, led by Dr. Paul Pinsky, to try to identify those people who would benefit most from lung cancer screening. In addition, the new NCORP will be involved with cancer care and delivery, which can address screening. Dr. Croyle added that questions about screening are paramount in all cancer types, and the lessons learned regarding mammography screening for breast cancer are instructive; after the screening trials of breast cancer, dissemination of the findings required a concerted communication effort before mammography was included as part of a common breast health program.

Dr. Kaur asked how changing demographics will be addressed moving forward for cancer clinical trials. She also wondered what percentage of those participating in the NIDDK DPPOS belong to ethnic or minority groups. Dr. Kramer said he did not know, but in most prevention studies in the past, ethnic and minority populations generally were underrepresented.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, asked if there would be an update study on prostate screening from the PLCO similar to the ones for CRC and lung cancer. Dr. Kramer responded that subgroup analysis has been completed for prostate cancer from the PLCO, and results indicated no difference in outcomes between groups. Because the PLCO and NLST are a plentiful source for characterized biospecimens, this offers an opportunity to assess whether it is possible to identify risks for cancer. A lesson learned so far is that a substantial percentage of overdiagnosed cancers result from screening.

IX. NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM (NCORP)—DR. WORTA McCASKILL-STEVENS AND DR. STEVEN CLAUSER

Dr. Worta McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, DCP, informed members that the NCORP is the new community program that is derived in part from the realignment of the CCOP, MB-CCOP, and NCCCP. The NCORP was designed to build a community-based network to support a wide range of clinical, cancer disparities, and cancer care delivery research (CCDR). Clinical trials will continue to be a core function of the community-based program, but additional research priorities and opportunities will be focused on health services, behavior,

dissemination, and outcomes research. Dr. McCaskill-Stevens reviewed the core elements of NCORP, with a strengthened research capacity at the community level and involvement of clinicians and patients inside and outside the clinical trial system as well as a focus on integrating cancer care disparities research, care delivery research, and clinical trials. Public/private partnerships will have special emphasis with the NCORP.

Dr. McCaskill-Stevens reviewed the eligibility requirements for NCORP centers, including a history of participating in cancer research with a capacity to conduct clinical research, an infrastructure conducive to CCDR, available study populations, and support from senior leadership of the organization. The three types of NCORP community sites include: (1) a site that can conduct cancer control, prevention, and treatment clinical trials with a minimum requirement to support CCDR and cancer disparities research; (2) a site that serves large minority and/or underserved populations with a commitment to mentor other sites within the network in this area; and (3) a site that has the capability to accrue large numbers of patients to clinical trials with the expanded capacity for CCDR and cancer disparities research. The research base components must be able to provide research development and infrastructure support for cancer clinical trials and CCDR.

The NCOP will be housed in the DCP and will have external and internal advisory committees. Funding will be provided through the U-10 Cooperative Agreement mechanism for a period of 5 years for both the community sites and research bases. Clinical trials will be conducted with the NCI NCTN, Cooperative Groups, and the DCP Research Bases. Currently, there are three proposals for organizational options for CCDR research: (1) integrated into each Research Base within the NCI NCTN; (2) integrated as part of one Research Base within the NCI NCTN; or (3) a stand-alone entity as a CCDR Research Base.

Dr. McCaskill-Stevens informed members of the research agendas for NCORP clinical trials, NCORP CCDR, and NCORP disparities research. The NCORP clinical trial agenda will incorporate emerging science and novel trial designs for treatment, cancer control, prevention, and screening. An expanded research portfolio will include trials on overdiagnosis and underdiagnosis, post-treatment surveillance, precancerous lesions, and mechanisms of treatment and cancer-related toxicities. The NCORP provides an opportunity to integrate studies to enhance accrual of racial/ethnic populations and other underserved populations in clinical research. The NCORP CCDR research agenda will ensure that optimal evidence-based therapies and system supports are available, and build the evidence base for how clinical practices and organizational processes and policies improve patient outcomes. Some examples of this strategy for CCDR research are studies of alternative models for organizing and supporting multi-modality therapy through multidisciplinary treatment programs, and studies of optimal approaches to incorporate patient-reported outcomes. This approach will build data capabilities to assess organizational approaches to improve cancer care for the underserved. The research agenda for NCORP cancer disparities research includes promoting participation of underserved populations and incorporating specific disparities research questions in clinical trials and CCDR. The NCORP also can increase capacity by working with NCI's Center to Reduce Cancer Health Disparities (CRCHD) to help enlist and educate underserved communities about health disparities.

Dr. McCaskill-Stevens provided a list of current NCORP activities and the timeline, which includes an internal NCI concept review in February 2013, and a Funding Opportunity Announcement (FOA), to be released in the fall of 2013, with awards in early 2014.

Questions and Answers

Dr. Olopade wondered how the NCORP might leverage genomics research to reduce health disparities and encouraged the NCI to incorporate targeted treatment into NCORP clinical trials.

Dr. Cullen asked if assessments were conducted on the strengths and weaknesses of the NCCCP, CCOP, and MB-CCOP before developing the NCORP. Dr. Kaur wondered if the NCORP is the consolidation of three existing programs or a new program. Dr. McCaskill-Stevens responded that these are challenges for the NCORP, but they will be consulting with those in the genomics field to determine how best to integrate genomics research to expand the populations being served. The NCORP also will be seeking advice on the best methods for including targeted treatment in clinical trials. Assessments of each program have been completed over time, but as the NCI moves into a different era for clinical trials (e.g., reduced resources), the NCORP will be evaluating infrastructure needs and what it will take to enhance community programs.

Dr. Champion asked about strategies to increase behavioral and outcomes research, especially in terms of accrual. Dr. Steven Clauser, Chief, Applied Research Program, Outcomes Research Branch, DCCPS, responded that the NCI portfolio is being surveyed to determine past and ongoing activities as well as opportunities for future research to identify priority areas that can be addressed realistically within the budget and existing resources.

Dr. Chabner asked if issues found in the past review of the NCCCP, including lack of accrual information on ethnicity and race, as well as a general lack of administrative oversight, will be addressed in the organization of the NCORP. He also noted that the NCCCP was funded through the Frederick contract and asked how the NCORP will be funded. Dr. Clauser responded that one of the basic problems with the NCCCP was that it had too broad a mandate; the NCORP will focus on research, not expanding all types of program delivery aspects, as was included in the NCCCP mandate. Dr. McCaskill-Stevens added that the NCORP is funded through the U-10 mechanism under a new Request for Application (RFA).

Dr. Jacks asked about the interface between the NCORP and NCI-designated Cancer Centers, particularly for community outreach efforts, as well as any involvement of the Veterans Administration (VA). Dr. McCaskill-Stevens responded that in the CCOPs, VA sites were eligible and noted that because the re-organization of the three existing programs, some of the committees for outreach have been combined for efficiency.

X. CLOSED SESSION—DR. TYLER E. JACKS

"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. ADJOURNMENT—DR. TYLER E. JACKS

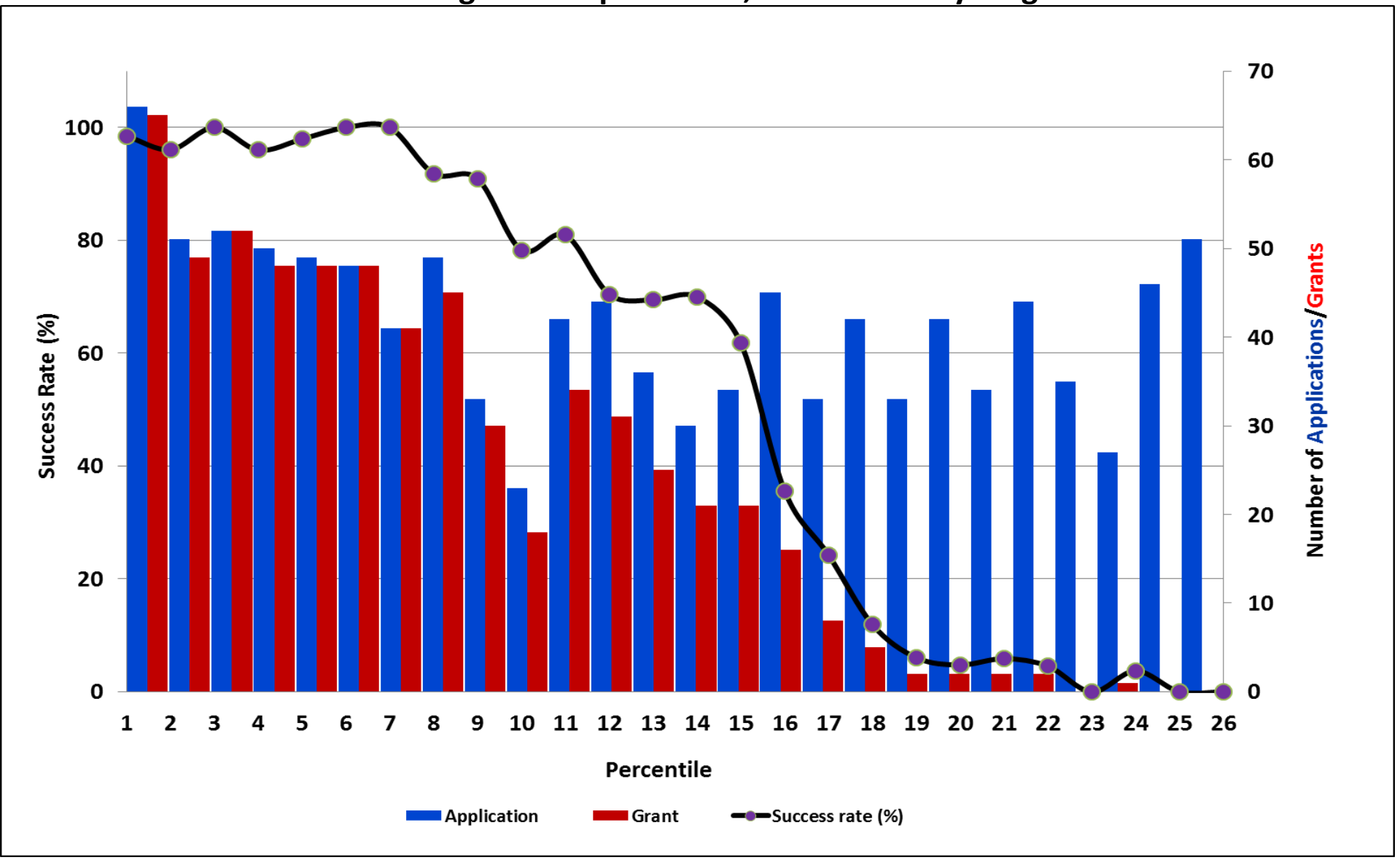
Dr. Jacks thanked all of the Board members, as well as all of the visitors and observers, for attending.

There being no further business, the 163rd regular meeting of the NCAB was adjourned at 4:03 p.m. on Thursday, 29 November 2012.

Date	Tyler E. Jacks, Ph.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary

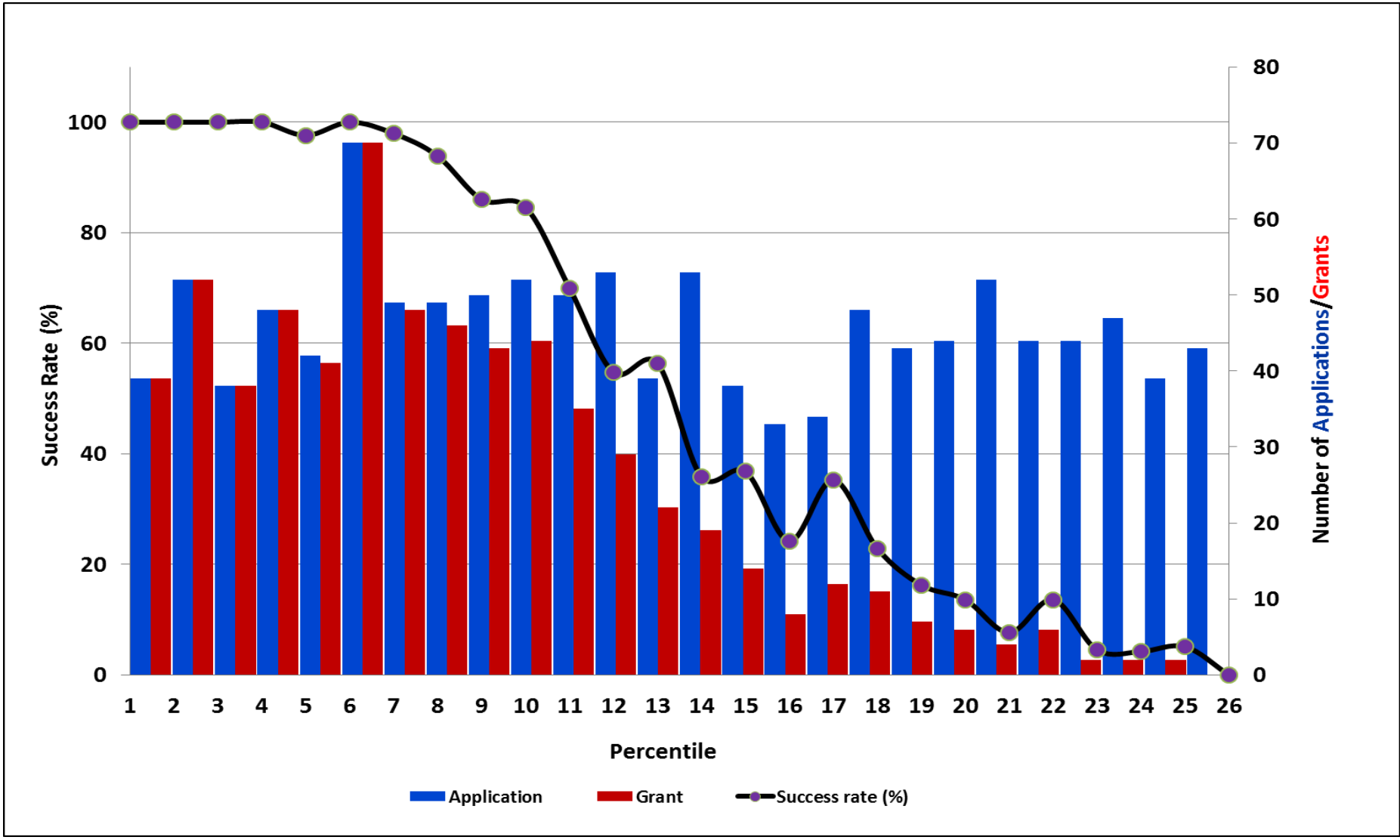
NCI FY2012: "Percentiled" R01 Applications, Awards, and Success Rates

All Investigators: Experienced, New and Early Stage



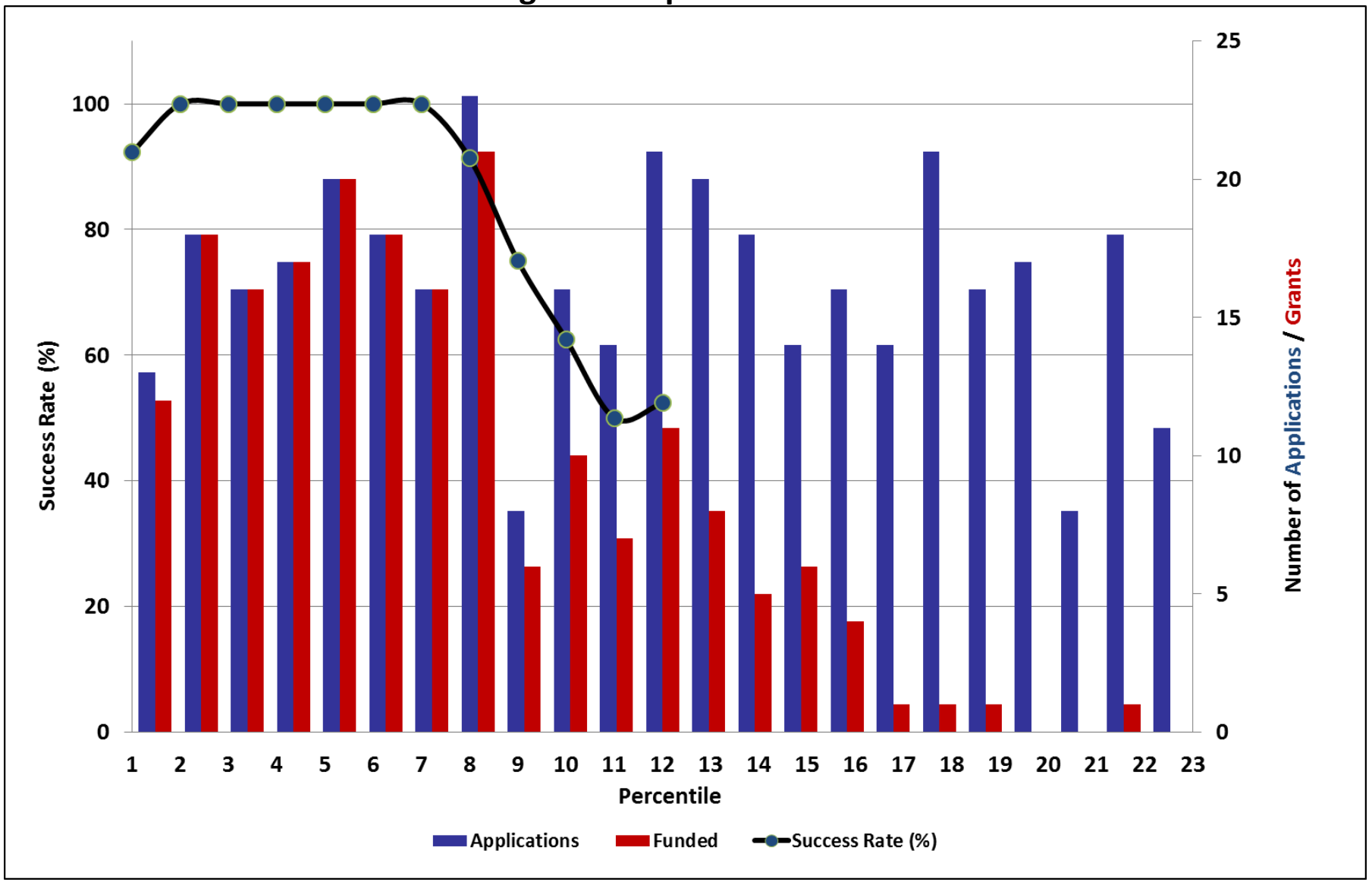
NCI FY2011: "Percentiled" R01 Applications, Awards, and Success Rates

All Investigators: Experienced, New and Early Stage



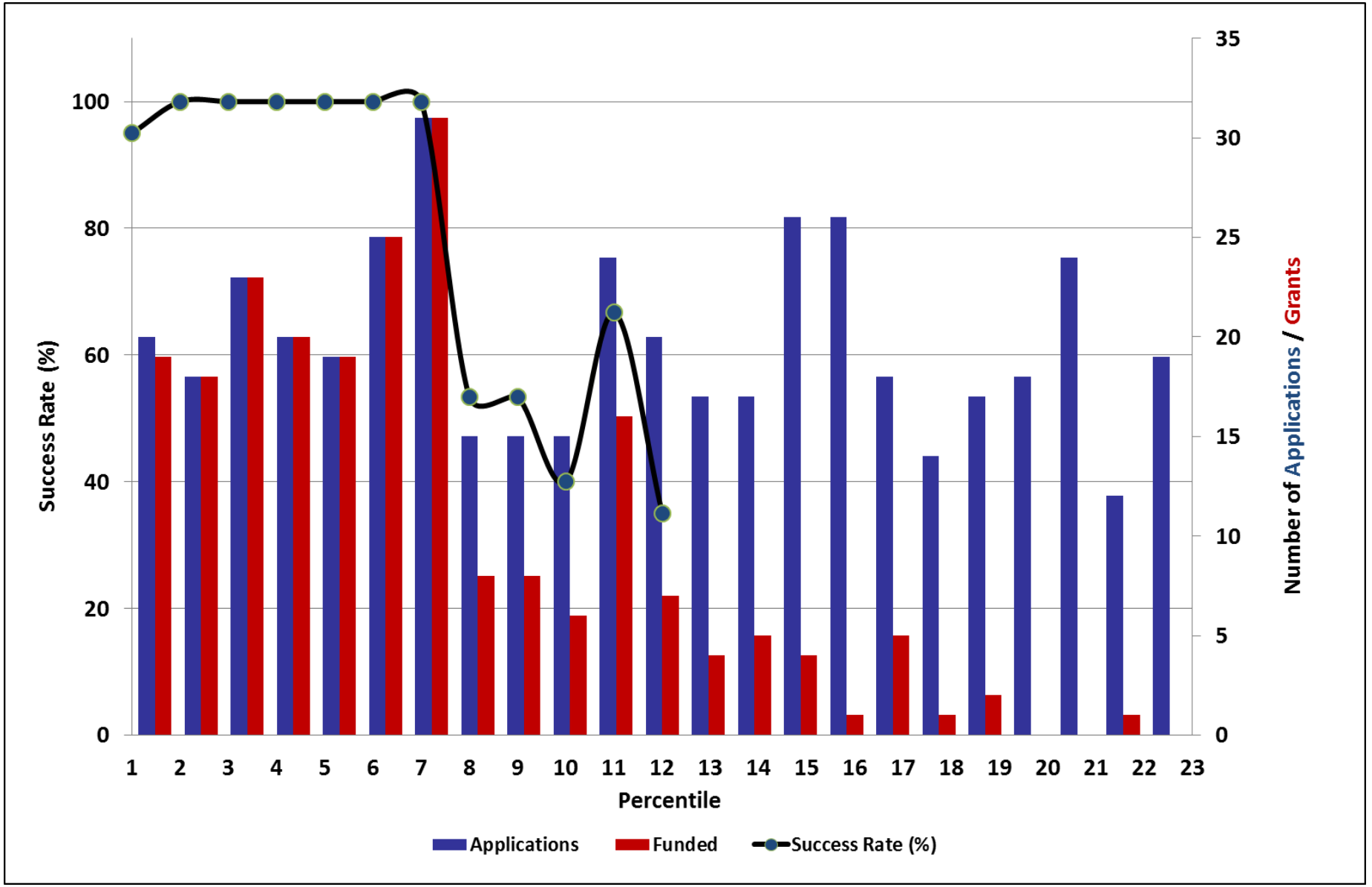
NCI FY2012: R21 Applications, Awards, and Success Rates

All Investigators: Experienced and New



NCI FY2011: R21 Applications, Awards, and Success Rates

All Investigators: Experienced and New



Fiscal Year 2012: Success Rates (investigator-initiated R01's and R21's)

	Total Applications	Number With Percentiles Of 25 or better	Number With Percentiles Of 10 or better	Funded	Success Rate
R01 – All Investigators	4,143	1,029	462	618	15%
Experienced Investigators - Total	2,849	777	356	466	16%
Type 1	2,345	556	245	316	13%
Type 2	504	221	111	150	30%
New Investigators	1,294	252	106	152	12%
Early Stage Investigators	564	129	59	86	15%
R21 – All Investigators	1,911	411	165	200	10%
Experienced Investigators	751	194	73	87	12%
New Investigators	1,160	217	92	113	10%

Fiscal Year 2012 vs. 2011: All Competing Research Project Grants

	FY 2012		FY 2011	
	Funded	Success Rate	Funded	Success Rate
R01 – Unsolicited	620	15%	655	15%
R21 – Unsolicited	200	11%	223	10%
R03	101	20%	72	17%
Solicited R01/R21	88	8%	68	14%
*Other RPGs	78		88	
Total Competing RPGs:	1,085	14%	1,106	14%

*Other RPGs include R03, R15, P01, U01 and UM1.

REPORT FROM THE NCI DIRECTOR'S ADVISORY PANEL ON THE DCEG

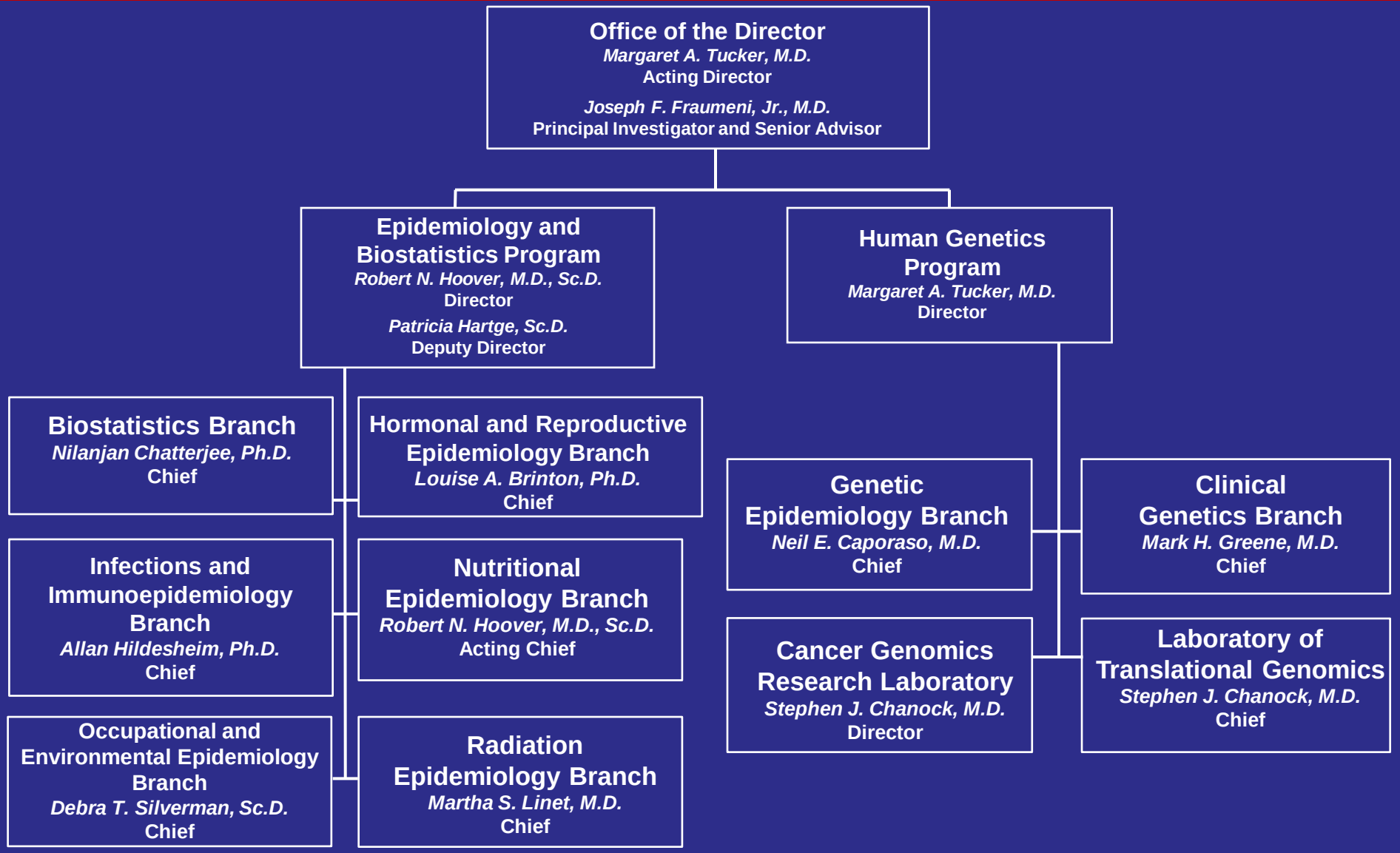
Presentation to the NCAB

Jonathan M. Samet
Department of Preventive Medicine
University of Southern California

DCEG Mission

- **Conducts broad-based, high quality, high impact research;**
- **Maintains a national and international perspective, giving priority to emergent issues identified through clinical, laboratory, and epidemiologic observations, as well as to public health concerns identified by the Institute, Congress, regulatory agencies, and other appropriate bodies;**
- **Develops infrastructures, resources, and strategic partnerships in molecular epidemiology across NCI, NIH, and the extramural community; and**
- **Trains and mentors the next generation of scientists in cancer epidemiology and related fields.**

DCEG Organizational Chart



DCEG Personnel Demographics

	Permanent					Not Permanent		
	PIs							
Branch	Tenured	Tenure-Track	Staff Scientists & Clinicians	Research Fellows	Other Staff	Special Volunteers & Fellows	Contractors	Total
BB	7	4	2	3	2	12	3	33
CGR	0	0	0	0	0	0	49	49
CGB	2	2	4	2	3	4	3	20
GEB	5	1	3	1	4	12	1	27
HREB	2	4	1	2	2	16	5	32
IIB	5	5	0	1	1	14	3	29
LTG	1	3	1	3	6	16	1	31
NEB	4	4	2	4	1	12	2	29
OD\EBP\HGP	5	0	3	0	16	4	4	32
OEEB	5	4	7	3	3	11	4	37
REB	3	2	9	3	3	11	2	33
TOTAL	39	29	32	22	41	112	77	352

DCEG as National Agency

- **Consultation/advice/review for government agencies on cancer**
- **Population rates and trends in SEER**
- **Radiation effects/protection policies**
  - **National and international advisory/lead roles**
  - **Multinational followup of radiation exposures**
- **Common exposures of concern- Congressional Mandates**
  - **Saccharin and bladder cancer**
  - **Power frequency EMF and childhood leukemia**
  - **Cell phones and brain cancer**

DCEG as National Agency (continued)

- **Potential toxic exposures**
  - **Tobacco/alcohol**
  - **Occupational exposures (e.g. formaldehyde, benzene)**
  - **Carcinogenic late effects of medications**
- **Emergent public health issues**
  - **AIDS related malignancies**
  - **Preventive care for BRCA1/2 carriers**
  - **Fukushima**

Charge from Dr. Varmus

- The current structure of DCEG.
- The reach and quality of its research portfolio.
- The positioning of DCEG within NCI.
- The relationship of DCEG to other divisions within NCI, particularly the Division of Cancer Control and Population Sciences (DCCPS).
- The disciplinary make-up of its investigators and the scope of its research. Are there critical gaps?
- Its relationships to the new Center for Global Health and the Center for Cancer Genomics
- The characteristics/background for the next director.
- The current leadership team.

Advisory Panel Members

Jonathan M. Samet, MD, MS (Chair)

Christine Ambrosone, Ph.D.

Paolo Boffetta, M.D., M.P.H.

Graham Casey, Ph.D.

Graham A. Colditz, MD, DrPH

Elizabeth A. Platz, Sc.D., M.P.H.

Gary L. Rosner, Sc.D.

Michael J. Thun, M.D., M.S.

Panel Approach

- Materials provided in advance: overview materials on make-up, major projects, major publications, and five-year strategic plans for DCEG and branches.
- Meetings with DCEG and Branch leadership.
- Meeting with Directors of other Divisions.

Key Findings--Overall

- Under Joe Fraumeni's leadership DCEG has been the world's leading group in cancer epi.
- DCEG has played a critical, global role in cancer genetics, including developing consortia.
- DCEG is a major training site for cancer epidemiology and genetics.
- DCEG's Branches have long-established research programs with broad reach.

Structure and placement of DCEG within NCI

- Current structure assures “place and identify of cancer epidemiology” and an independent intramural program should be maintained.
- Differences in culture and funding across NCI divisions may impede more and faster translation.
- Issues related to translation should be addressed by the next DCEG director.
- Need for broader strategy of integration across divisions.

Cancer Genomics: Enhancing a "Good Thing"

- The success of DCEG in cancer genomics points to issues to be addressed to enhance translation:
  - Limits to translational capacity to follow-up on findings of GWAS and next-gen technologies.
  - Limited collaborations between DCEG and other divisions around cancer genomics.
  - DCEG has few clinicians and emphasis on clinical translation is limited.
  - No overall NCI-wide strategic plan for moving from genomics findings to application.

Strategic Research Directions

- Variable approaches to strategic planning across branches.
- Need to have a unified approach across branches and set priorities based on broader needs.
- Look at how to move across exposure-based boundaries.

Center for Global Health

- DCEG has long worked internationally, carrying out research and capacity-building.
- Teaming of the new Center with DCEG should be synergistic.
- Pro-active engagement with new center is recommended.

Characteristics/Qualities for Next Director

- Broad breadth and strong grounding in epidemiology.
- Able to keep DCEG at the cutting edge in “omics”--visionary.
- Promote translation.
- Commitment to training and mentorship.
- Able to take on the role “of being a global leader in the field.”

Pancreatic Cancer

Recent Progress and a Look Forward

Pancreatic Adenocarcinoma

- Highly lethal tumor
- 2% of All Cancer Cases
- 5% of All Cancer Deaths
- 4th Leading Cause of Cancer Death
  - Lung
  - Colorectal
  - Breast
  - Pancreas

Pancreatic Adenocarcinoma

- Cure is rare and only seen in resected patients.
- 100 Patients:
  - 15 - 20 patients will have resectable tumors.
  - Of these, 1 in 5 have long-term survival.
  - 3 - 4% five year survival.
- Tumors are resistant to chemotherapy and radiation.
  - The mechanism(s) of resistance are diverse.
- Survival for most patients is measured in months.
- Primary prevention is paramount!

Pancreatic Cancer Risk Factors

Environmental

- Cigarette smoking (~25%)
- ETOH/chronic pancreatitis

Metabolic (>25%)

- Diabetes
- Obesity

Genetic

- Pancreatic cancer families
- Hereditary syndromes

Mucinous pancreatic cysts

- Mucinous Cystic Neoplasm
- Intrapancreatic mucinous neoplasm (IPMN)

Recent Translational Progress

- Initial histologic and molecular characterization of precursor lesions.
- Initial descriptions of mutational profile of pancreatic cancer.
- Development of GEMMs and patient-derived xenografts (PDX).
- Importance of tumor-related stroma (stellate cells & immunocytes).
- Recognition of the role of diabetes and obesity in pancreatic cancer risk and survival.

Recent Clinical Progress

- Initial screening efforts for patients with FPC or known germ-line mutations conferring risk.
- Understanding the natural history of mucinous cystic neoplasms and development of criteria for surgical resection.
- Recognition that development of targeted agents will require understanding pancreatic cancer cellular heterogeneity.
- Effective integration of currently available modalities (surgery, radiation, chemotherapy).

CTAC Pancreatic Cancer Working Group

Purpose: Develop strategies and recommendations that will advise NCI on ways to reduce the incidence and mortality rates of adenocarcinoma of the pancreas.

Goals:

- Develop strategies to increase the extent of collaboration between centers studying pancreatic cancer. This may include:
  - Increasing tissue acquisition in association with high-quality clinical data to facilitate greater genetic and biochemical characterization of the disease;
  - Assessing recent progress in the field;
  - Scanning the horizon for future developments in medical science.
- Developing recommendations to capitalize on new investment opportunities.
- Provide advice on the NCI plan to implement the recommendations.

Pancreatic Cancer: Scanning the Horizon for Focused Interventions

October 23-24, 2012

Critical Questions - Areas of Greatest Need

- Can we identify cohorts of individuals at high risk?
- Can we screen patients deemed to be at high risk and identify pre-invasive pathologic precursors or very early cancer?
- Can we develop effective systemic therapies?

Other Provocative Questions

Why does pancreatic cancer occur in some patients with no known risk factors or genetic abnormalities?

Why do identical mutations (e.g. CDKN2A) result in pancreatic cancers in some patients and melanoma in others?

Can aspirin and/or metformin prevent or control pancreatic cancer?

Why do some patients with pancreatic cancer respond remarkably to treatment while most others do not?

Breakout sessions

- Epidemiology and Risk Assessment Research
- Pathology, Screening and Early Detection Research
- Therapeutic Research

Develop Precise Near-term Goals

- Are we in a position to test the clinical usefulness of available biomarkers to risk-stratify patients deemed at moderate risk based on clinical criteria?
  - New-onset diabetes
  - Obesity/metabolic syndrome
  - Mucinous cystic neoplasms
- What can be done to improve the screening of patients with high risk germ-line mutations or pancreatic mucinous cysts that are precursors to invasive pancreatic cancer?

Develop Precise Near-term Goals

- Can we specify efficacy criteria that should be generated during pre-clinical testing of a novel therapeutic before testing the agent in patients with advanced pancreatic cancer?
- Using available model systems can we precisely identify the molecular or biochemical characteristics of the pancreatic cancer patient population likely to respond to the targeted intervention in the clinic?

High Level Recommendations

Two patient populations can currently be broadly defined that are at increased risk for pancreatic cancer:

1) New-onset diabetics
   - **Develop a means to identify the approximately 1/125 patients with new-onset diabetes who have early pancreatic cancer.**

2) Patients with specific germ-line mutations, familial pancreatic cancer, or mucinous pancreatic cysts
   - **Develop screening methods to identify those patients with heritable pancreatic cancer (specific germ-line mutations or pancreatic cancer families) or mucinous pancreatic cysts (MCN and IPMN) who will progress to invasive pancreatic cancer and require (surgical) intervention.**

High Level Recommendations

3) Develop strategies that neutralize the driver oncogene KRAS.

4) Accelerate clinical and preclinical therapeutic approaches that target the immune and non-immune components in pancreatic tumors.

Pancreatic Cancer: Scanning the Horizon for Focused Interventions

- Comments and Discussion regarding the pancreatic cancer initiative.

- **Additional Discussion:**

  Are there other cancers or cancer properties (e.g. metastasis or genomic instability) that could benefit from focused attention by a working group?

Frederick National Laboratory
for Cancer Research



Frederick National Laboratory for Cancer Research : New Initiatives

Presentation to the National Cancer Advisory Board

David C. Heimbrook, Ph.D.

CEO, SAIC-Frederick, Inc.

Nov. 29, 2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute
Frederick National Laboratory is a Federally Funded Research Center, operated by SAIC-Frederick, Inc., for the National Cancer Institute.

Frederick National Laboratory

Presentation Outline

- Our Identity and Mission
- Exemplifying the impact of Frederick National Laboratory programs
- NCI-Frederick Advisory Committee guidance for the future of Frederick National Laboratory

Overview of Frederick National Laboratory for Cancer Research

FNLCR is the only Federally Funded Research and Development Center (FFRDC) dedicated to biomedical research

- Proudly operated by *SAIC-Frederick, Inc*. on behalf of the National Cancer Institute

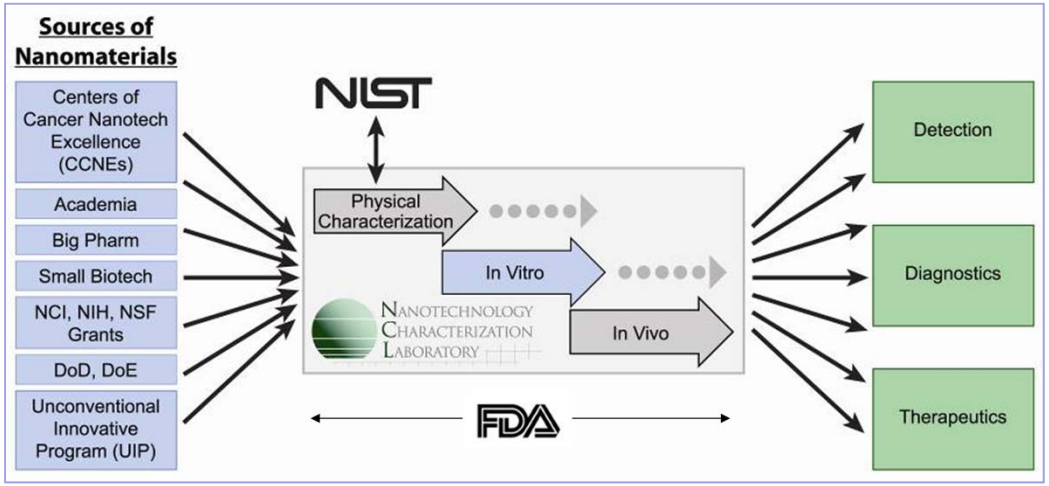
Main campus is on 70 acres at Ft. Detrick, MD

- Co-located with intramural NCI researchers and other NCI activities
- Additional FNLCR scientists at Bethesda and Rockville sites

FFRDC status enables us to nimbly provide advanced integrated biomedical resources and know-how to government, academic, and commercial scientists without competing interest

Nanotechnology Characterization Laboratory (NCL)

- NCL was established in 2004 as an interagency collaboration among NCI, NIST, and FDA. The lab's mission is to accelerate the translation of promising nanotech cancer drugs and diagnostics
- NCL performs preclinical characterization of nanomaterials, including:
  - physicochemical characterization
  - in vitro experiments
  - in vivo testing for safety and efficacy



90% of NCL's efforts support the extramural community

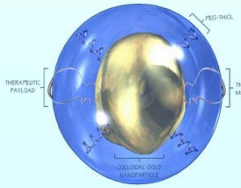
Success Stories:
NCL-aided Submissions to Clinic

AZAYA THERAPEUTICS

- **ATI-1123** : PEGylated nanoliposomal formulation of docetaxel
- Phase I safety study in patients with advanced solid tumors complete in 2012.

IND 2009

CYTIMMUNE SCIENCES INC



Phase 1 Completed 2008

- **AurImune®** : PEGylated colloidal gold nanoparticle-TNFα conjugates
- Phase II study in combination with Taxotere to start in 2012.

- **BIND-014** : docetaxel-encapsulated PLGA nanoparticle-aptamer conjugates
- Binds PSMA expressed on prostate cancer cells
- Phase I safety study in patients with advanced or metastatic cancer ongoing.

BIND BIOSCIENCES

IND 2011

Nanospectra

- Silica-core gold-shell particle for photothermal ablation with NIR irradiation
- Pilot safety study in head and neck cancers ongoing; efficacy study in lung tumors to start in 2012.

IDE 2008

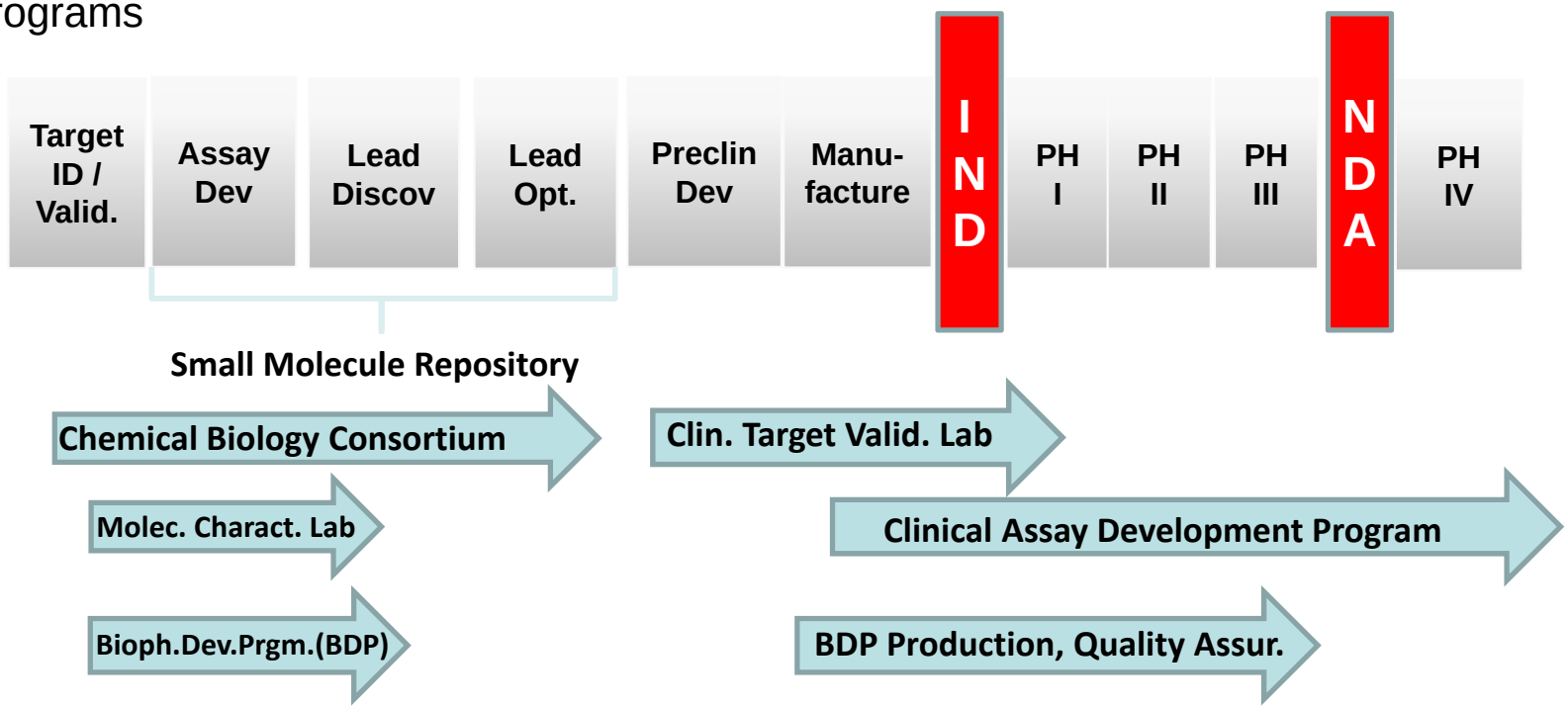
ProNAi

IND 2010

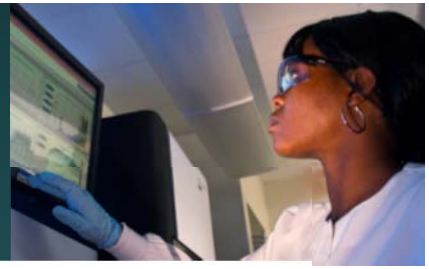
- **PNT2258 :** liposome-encapsulated oligonucleotide for breast and lung cancer.
- Phase I safety study in patients with advanced solid tumors ongoing.

The NCI Experimental Therapeutics Program (NExT)

- NExT is led by the Division of Cancer Treatment and Diagnosis to create a coordinated cancer therapeutics discovery and development pipeline with the external scientific community
  - Projects evaluated by extramural Special Emphasis Panel
- SAIC-F provides operational and dedicated technical support to all phases of NExT programs



NCI-Frederick Advisory Committee
Building for the Future



- **NFAC charge - review the state of research at FNLCR and make recommendations for the best use of its capabilities and infrastructure**
- **15 member committee**

Zachary Hall, Ph.D. Former Director, NINDS Former President; Institute of Regenerative Medicine, UCSF
Emeritus Professor, UCSF

Chair

C. Barrett

D. Botstein

L. Garraway

J. Gray

B. Hahn

M. Justice

T. Look

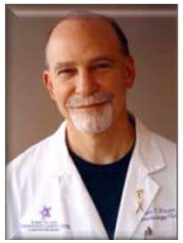
L. Marnett

J. Mesirov

G. Nolan

K. Olden

J. Pietenpol



S. Rosen

C. Willman

Expanding the Partnering Base

Development of Contractor Cooperative Research and Development Agreement (c-CRADA)

- **Enables SAIC-Frederick to partner directly with extramural scientists and organizations for access to our science and technology know-how**
- **Use full CRADA authority under CRADA statutes**
  - c-CRADAs for Research, Development, and Testing collaborations
  - “Technical Service Agreement” for tactical evaluation of proprietary partner materials, SIV assays, etc.
- **Intellectual property rights**
  - SAIC-F is the custodian of joint or sole IP emerging from the CRADA
  - SAIC-F can provide an advanced understanding of IP / Commercialization rights
  - Any royalty streams support FFRDC R&D efforts
- **Processes**
  - Focus on speed
  - Local government review and approval with external input as appropriate

New Partnering Initiatives

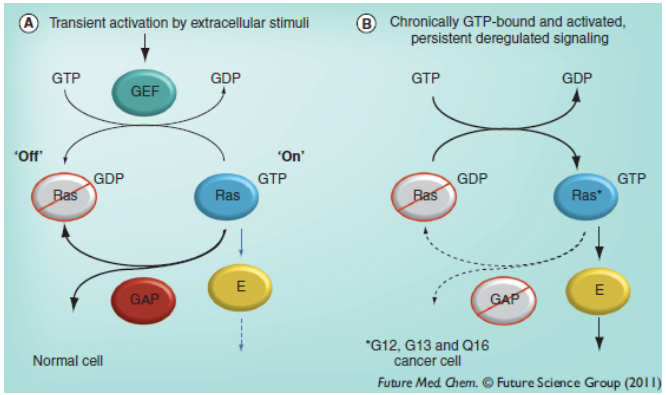
Expanding access to FNLCR Resources

- **Contractor Cooperative Research and Development Agreements (cCRADA)**
  - Four partnerships received initial concept approval
  - Five additional agreements in development
- **Technical Service Agreement (TSA)**
  - Seven distinct assays approved for external offering
  - Three additional assays submitted for approval, 11 in preparation
  - One agreement signed with UCSF, 4 in progress
- **External-facing FNLCR website operational and evolving**
  - http://frederick.cancer.gov/

FNLCR New Initiatives: “Big Ideas”

Fulfill the “National Laboratory” vision

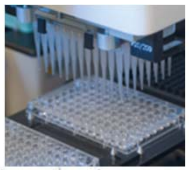
- Ideas contributed by NCI, FNLCR, and external workgroups
  - **Ras Therapeutics** (*Dr. Varmus*)
    - Identify and validate new therapeutic approaches targeting oncogenic Ras



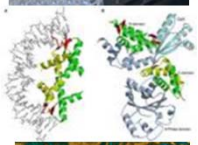
  - **Preclinical models** (*Drs. Doroshow and Wiltrout*)
    - Systematic comparison of the constellation of preclinical efficacy models to develop robust standards and improve predictive utility

Implementing the “Big Ideas” at FNLCR

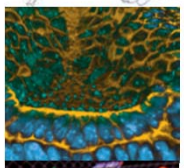
We have essential needs…



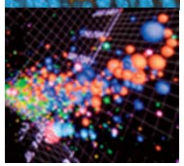
Genetics and Genomics



Proteins and Proteomics



Imaging and Nanotechnology

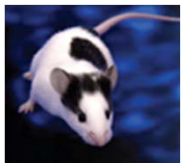


Advanced Biomedical Computing

Lab Space

…integrated into a brand new state-of-the-art Research Facility

Advanced Technology Research Facility
Opened June 2012



Integrated *in vivo* support at Frederick & Bethesda

Implementing the “Big Ideas” at FNLCR

- **Leadership**
  - Appointment of NCI FNLCR Laboratory Director to work with SAIC-Frederick leadership
- **Scientists**
  - “Hub-and-spoke” model – FNLCR, academia, industry
    - Redirect some FNLCR scientists supporting intramural core services
    - Dedicated laboratory space at new Advanced Technology Research Facility
- **Support**
  - Redirect necessary support from current FNLCR budget
    - “In-kind” personnel, plus contracts
- **Timing**
  - As soon as the scientific workplan for each project is developed

Conclusions

- **Frederick National Laboratory for Cancer Research** is a unique resource within the national biomedical research community
- **Program partnerships** facilitate basic and translational research achievements
- **New partnering opportunities** expand the impact of FNLCR science
- **New "big idea" research programs** will strengthen the identity and impact of FNLCR as a National Laboratory

National Cancer Institute

Division of Cancer Prevention Update

National Cancer Advisory Board
November 2012

Barry Kramer, M.D., M.P.H.
Director
Division of Cancer Prevention
National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Scientific Directions – November 2012

1. Clinical Studies and Large Trials
2. Agent Development and Decision-Making
3. Overdiagnosis and Precancerous Lesions
4. Cancer Immunoprevention
5. International Collaborations
6. Cancer Prevention Fellowship Program
7. New Approaches to Clinical Prevention Studies

1. Clinical Studies and Large Trials

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 21, 2012 VOL. 366 NO. 25

Colorectal-Cancer Incidence and Mortality with Screening Flexible Sigmoidoscopy

Robert E. Schoen, M.D., M.P.H., Paul F. Pinsky, Ph.D., Joel L. Weissfeld, M.D., M.P.H., Lance A. Yokochi, M.D., M.P.H., Timothy Church, Ph.D., Adeyinka O. Laiyemo, M.D., M.P.H., Robert Bresalier, M.D., Gerald L. Andriole, M.D., Saundra S. Buys, M.D., E. David Crawford, M.D., Mona N. Fouad, M.D., Claudine Isaacs, M.D., Christine C. Johnson, M.D., Ph.D., M.P.H., Douglas J. Reding, M.D., M.P.H., Barbara O'Brien, M.P.H., Danielle M. Carrick, Ph.D., Patrick Wright, B.S., Thomas L. Riley, B.S., Mark P. Purdue, Ph.D., Grant Izmirlian, Ph.D., Barnett S. Kramer, M.D., M.P.H., Anthony B. Miller, M.D., John K. Gohagan, Ph.D., Philip C. Prorok, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

Clinical Studies and Large Trials
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial: Colorectal Cancer Results

Flexible sigmoidoscopy at baseline and year 3 or year 5 vs. usual care (155K participants)

- **21% relative reduction in incidence for screened group (proximal and distal): 3 per 1,000 persons over 10 years**
- **26% relative reduction in colorectal cancer mortality for screened group (distal only): 1 per 1,000 persons over 10 years**

Clinical Studies and Large Trials

Screening Trial Resource Availability

PAR Approved for utilizing the PLCO biospecimen resource to bridge gaps in cancer etiology and early detection research

- **Promotes use of resource by streamlining permission and adding funding for projects**

Public use data sets and website for PLCO and National Lung Screening Trial (NLST) data available

http://biometry.nci.nih.gov/CDAS

- **Cancer Data Access System to manage data release**
- **Website gives summary materials & access info**

NEJM, Nov 2012

Patient and Physician Guide: National Lung Screening Trial (NLST)

What is the purpose of this guide?
To explain the benefits and harms of low-dose computed tomography (CT) screening for lung cancer in people at high risk for the disease. The NLST showed a reduction in deaths from CT screening compared to chest X-ray screening. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial recently showed that chest X-ray screening (compared to no screening) did NOT reduce the chance of dying from lung cancer.

Who participated in the NLST?
Current or former cigarette smokers within the past 15 years, 55 to 74 years of age, with at least 30 pack-years of smoking [Pack-years = packs per day x number of years smoking]. Participants must have had no symptoms or signs of lung cancer or other serious medical conditions, and be medically fit for surgery.

Study Findings: Low-dose CT versus Chest X-ray screening

53,454 current and former smokers were randomly assigned to be screened once a year for 3 years with low-dose CT or chest X-ray. Here's what happened after an average of 6.5 years:

	Low-dose CT 26,722 people		Chest X-ray 26,732 people
Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?			
4 in 1,000 fewer **died from lung cancer**	13 in 1,000	*versus*	17 in 1,000
5 in 1,000 fewer **died from all causes**	70 in 1,000	*versus*	75 in 1,000
Harm: What problems did CT scans cause compared to chest X-ray?			
223 in 1,000 more had at least one **false alarm**	365 in 1,000	*versus*	142 in 1,000
18 in 1,000 more had a **false alarm leading to an invasive procedure**, such as bronchoscopy, biopsy, or surgery	25 in 1,000	*versus*	7 in 1,000
2 in 1,000 more had a **major complication** from Invasive procedures	3 in 1,000	*versus*	1 in 1,000

"Take home" messages

Lung cancer screening with CT scans is the only screening test shown to lower the chance of dying from lung cancer. The effect of screening may vary depending on how similar you are to the people who participated in the study. The benefit of screening may be bigger if your lung cancer risk is higher. The harm may be bigger if you have more medical problems (like heart or severe lung disease), which could increase problems from biopsies and surgery.

For perspective, the reduction in deaths from lung cancer with CT screening is larger than the reduction in deaths from the target cancers of other common screening tests, such as mammograms for breast cancer.

There is a tradeoff: CT screening decreases your chance of death but increases your chance of having a false alarm.

If you choose to have CT screening, it is important to have it done at a medical center with special expertise in lung cancer screening and treatment.

Most important thing you can do

DON'T SMOKE. Regardless of your screening decision, avoiding cigarettes is the most powerful way to lower your chance of dying overall or suffering or dying from a variety of diseases, such as lung cancer, emphysema, heart or vascular disease. For example, at age sixty-five, 89 in 1,000 male current smokers will die of lung cancer in the next 10 years versus 4 in 1,000 never smokers. For women, the corresponding figures are 55 in 1,000 versus 5 in 1,000.

For help quitting, call 1-800-QUIT-NOW.

Agent Development

The PREVENT Cancer Program implemented and the first two semi-annual application cycles completed (42 applications)

12 applications approved and task orders awarded

- **New drugs (6)**
- **Surrogate biomarkers (3)**
- **Vaccines (3)**

Agent Development and Decision-Making
Early Phase Prevention Trials

Phase 0-I-II Cancer Prevention Trials contract recompeted and awarded

- **Primary mechanism for early phase trials**
- **Identify & test biomarkers of efficacy**
- **Develop trial models for identifying agents**

Contract trials completed this year

- **Atorvastatin, sulindac, inulin in colorectal cancer**
- **Polyphenon E/green tea in prostate, bladder cancer**
- **Zileuton + celecoxib in lung cancer**
- **Resveratrol, atorvastatin in breast cancer**

Making Better Decisions About Agents

Overarching Goal: Determine positive and negative predictive values of preclinical models for clinical development

- **Constructed a model for predicting the outcome of long-term animal tumor assays from the results of short-term morphological assays**
- **Applied to 6 morphological assays**

3. Overdiagnosis & Precancerous Lesions

Overdiagnosis Workshop & Initiative

Workshop led to recommendations for scientific next steps in basic and translational research

EDRN pilot project to discover and develop biomarkers or molecular signatures that can distinguish indolent cancers from progressive cancers

- **Includes prostate, breast, and lung cancers**

Overdiagnosis and Precancerous Lesions

Companion Imaging & Biomarkers PAR

Co-sponsored with Division of Cancer Treatment and Diagnosis

PAR for pre-clinical and clinical studies that correlate cancer imaging methods with biomarkers to:

- **Detect cancers at the earliest stages**
- **Reduce false-positive tests**
- **Reduce overdiagnosis of cancer**

Overdiagnosis and Precancerous Lesions
Overdiagnosis Research Consortium

Joint project with Division of Cancer Biology

Propose a consortium to build on existing resources and collaborate with other groups

- **Characterize cellular and molecular patterns of indolent vs. potentially lethal lesions**
- **Determine the cellular and molecular phenotypes of early lesion cells and associated microenvironment**

4. Cancer Immunoprevention
Vaccine Studies from PREVENT

- A multi-antigen vaccine for prevention of MNU induced ER+ rat mammary cancers
- Characterization & testing of potential antigens for immunization against murine colon cancer
- Plac-1 vaccine for breast cancer prevention

Cancer Immunoprevention
PAR for Detection of Pathogen-Induced Cancer

- **> 20% of cancers are associated with microbial pathogens**
- **Premise: infectious pathogens and host cells play a joint role in modulating cancer-related pathways**
- **Goal: to develop new molecular signatures for risk of progression and early detection of pathogen-induced cancer**

5. International Collaborations
China Cancer Screening Trial Feasibility Study

Confirm NLST results in urban Chinese population

- **Differences in the histology of lung cancer, genetics, and health care systems in China vs. U.S.**

- **Feasibility study in 4 cities for a long-term randomized 3-arm screening trial**
  1. **Helical chest CT exam annually**
  2. **Helical chest CT biennially**
  3. **Annual screening for liver disease/cancer**

International Collaborations
Translating PDQ into Chinese

- Joint project with NCI Office of Communications and Education and three medical centers in China
- Pilot: a subset of the PDQ health professional summaries to be translated and made available to medical professionals and students

6. Cancer Prevention Fellowship Program

- **Applications more than doubled since 2007**
- **Class of 2013 will have 11 fellows (a 10% success rate)**
- **NIH Evaluation Set-Aside funds awarded to conduct a comprehensive evaluation of career paths and outcomes of former Fellows**

Non-Cancer Trials to Find Prevention Signals

Diabetes Prevention Program Outcome Study (DPPOS) Collaboration with National Institute of Diabetes and Digestive and Kidney Diseases

- Examine if metformin or lifestyle intervention can modify cancer incidence, especially in obesity-related cancers (breast, colon & rectum, endometrium, pancreas, esophagus, gall bladder, and kidney)

Aspirin in Reducing Events in Elderly (ASPREE) Study with National Institute on Aging & Australian govt.

- Funding collection of biospecimens from this randomized trial testing aspirin in 19,000 healthy people age 70 and older

New Approaches to Clinical Prevention Studies

Reciprocal Control Design for Trials

- Large numbers of participants must be followed for years in definitive prevention and early detection trials

- The reciprocal control design to increase efficiency
  - Participants in each arm receive an intervention for a particular disease but also serve as controls for a different intervention and disease in the other arm

- Panel Session at the Society for Clinical Trials Annual Meeting, May 2013: "The Reciprocal Control Design for Trials in the Early Detection and Prevention of Disease"

New Approaches to Clinical Prevention Studies

NCI Community Oncology Research Program (NCORP)

Two existing community-based cancer research programs

- **Community Clinical Oncology Program Network (CCOPs and Minority-Based CCOPs)**
- **National Community Cancer Center Program (NCCCP)**

Planning a new community-based program to align these programs to expand the scope of research

- **Clinical trials**
- **Cancer care delivery & health services research**
- **Cancer disparities research**

National Cancer Institute

National Cancer Institute Community Oncology Research Program (NCORP)

National Cancer Advisory Board

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NCORP – Concepts and Goals

- Develop a single community program derived in part from the realignment of the Community Clinical Oncology Program (CCOP), Minority-Based CCOP (MB-CCOP), and NCI Community Cancer Centers Program (NCCCP)
  - Build on their strengths

- Build a community-based network to support a wide range of clinical, cancer disparities, and cancer care delivery research (CCDR)
  - Clinical trials will continue to be a core function
  - Additional research priorities/opportunities in health services, behavioral, dissemination, and outcomes research

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NCORP – Core Elements

- Community-based organizations with a variety of research capacities linked to the NCTN
- Develop and support oncology practices within varied organizational settings as a collaborative network
- Research includes clinicians, patients within and outside of clinical trials, and organizations
- Public-private partnership, including a commitment of management to co-investment
- A focus on integrating cancer care disparities, care delivery research, and clinical trials

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Eligibility for NCORP Community Sites

- Capacity to participate in cancer research
  - Clinical research experience
  - Cancer care delivery research infrastructure
  - Available study populations
  - Senior leadership/organizational support

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NCORP Components

NCORP Community Components

- NCORP – General
  - ✓ Clinical trials (cancer control/prevention/treatment) + minimum requirement to support CCDR and cancer disparities research
- NCORP - Minority and Underserved
  - ✓ Serve large minority/underserved populations
  - ✓ Commitment to mentor other sites within the network for enhancing minority/underserved participation in research
- NCORP - Comprehensive
  - ✓ High clinical trial accrual + expanded capacity for CCDR and cancer disparities research

Research Bases

Research development and infrastructure support

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NCORP Research Components

Research Bases

- Research development and infrastructure support
  - Cancer Clinical Trials
  - Cancer Care Delivery Research
  - Cancer Disparities Research

NCORP Proposed Research Structure

- NCORP will be housed in the Division of Cancer Prevention
  - Collaborations with DCP, DCTD and CRCHD
- External and Internal Advisory Committees
- Funding: U-10 Cooperative Agreements for 5 years
  - Community Sites and Research Bases
- Organizational Structure for Clinical Trials
  - NCI-NCTN Cooperative Groups and DCP Research Bases
- Organizational Options for CCDR Research
  1. CCDR integrated into each Research Base/NCI Clinical Trials Network;
  2. Coordinating Center for CCDR integrated as part of one Research Base/NCI Clinical Trials Network; or,
  3. A dedicated CCDR Research Base

NCORP Clinical Trials Research Agenda

- Incorporate emerging science and novel trial designs into treatment, cancer control, prevention, and screening research

- Expanded research portfolio:
  - Overdiagnosis & underdiagnosis
  - Post-treatment- surveillance
  - Precancerous lesions
  - Mechanism of treatment and cancer-related symptoms

- Integrate studies to enhance accrual of racial/ethnic and other underserved populations into clinical trials

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NCORP Cancer Care Delivery Research Agenda

- Assure that optimal evidence-based therapies and system supports are available in routine practice
- Build the evidence-base for how clinical practices and organizational processes & policies improve patient outcomes
  - Studies of alternative models for organizing and supporting multi-modality therapy through multidisciplinary treatment programs
  - Studies of alternative patient/family navigation models to improve the coordination and outcomes of cancer care
  - Studies of optimal approaches to incorporate patient reported toxicities (e.g., PRO-CTCAE)
- Build data capabilities to assess organizational approaches to improve cancer care for the underserved

NCORP Cancer Disparities Research Agenda

- Promote participation of underserved populations in clinical trials and cancer care delivery research

- Incorporate specific disparities research questions into clinical trials and cancer care delivery research
  - Health care system factors
  - Health-related quality of life
  - Social determinants
  - Environment/physical determinants
  - Biological factors
  - Behavioral factors
  - Protective and/or Resiliency factors
  - Co-morbidities
  - Biospecimen education & collection

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NCORP – Current Activities

- Analysis of programmatic requirements
- Analysis of research capacity for CCDR at the site level
- Analysis of research capacity and priorities for CCDR at the Research Base level
- NIH-wide portfolio analysis for CCDR and cancer disparities
  - Funded Grants
  - Research Initiatives
- Baseline clinical trial accrual requirements

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NCORP Tentative Timeline

- Engage stakeholders for comment through 2012.
- A concept for internal NCI review in February 2013 and for NCI Board of Scientific Advisors in March 2013.
- Funding Opportunity Announcement for release in the Fall of 2013 with a goal of making awards in early 2014.

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We Would Like to Hear From You!

NCORP is a “work in progress.”

We welcome comments and feedback from you on the proposed program.

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