

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
2ND JOINT MEETING OF THE BOARD OF SCIENTIFIC ADVISORS AND
THE NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
June 24–25, 2013**

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

**NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
June 24–25, 2013**

The Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) convened for the 2nd Joint Meeting on 24–25 June 2013, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, 24 June 2013, from 9:00 a.m. to 5:35 p.m. and Tuesday 25 June 2013, from 9:00 a.m. to 11:00 a.m. and closed to the public on Tuesday 25 June 2013, from 11:00 a.m. to 12:00 p.m. The BSA Chair, Todd R. Golub, Chief Scientific Officer, The Broad Institute of Harvard University and Massachusetts Institute of Technology, presided during the open and closed sessions.

BSA Members

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

Dr. Irving L. Weissman (absent)

NCAB Members

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

Alternate *Ex Officio* NCAB Members

Dr. Michael A. Babich, CPSC
Dr. Patricia Bray, OSHA/DOL
Dr. Vince Cogliano, EPA
Dr. Michael Kelley, VA
Dr. John Balbus, NIEHS
Dr. Richard Pazdur, FDA
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. Louis Staudt, Director, Center for Cancer Genomics
Dr. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Director, Center for Global Health
Dr. Margaret A. Tucker, Acting Director, Division of Cancer Epidemiology and Genetics
Mr. Michael Weingarten, Director, Small Business Innovation Research
Dr. Linda Weiss, Director, Office of Cancer Centers
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wyszneuckas, Executive Secretary, Office of the Director
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy

Liaison Representatives

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

Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Dr. Patricia Mullan, American Association for Cancer Education
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Ms. Pamela Wilcox, American College of Radiology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council
Lance Armstrong Foundation—no representative

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MONDAY, JUNE 24, 2013

I. CALL TO ORDER AND OPENING REMARKS—DR. TODD R. GOLUB

Dr. Todd Golub called to order the 2nd Joint BSA and NCAB meeting and welcomed members of the Board, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Golub reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

II. FUTURE BOARD MEETING DATES—DR. TODD R. GOLUB

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

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

Dr. Harold E. Varmus, Director, NCI, welcomed NCAB and BSA members to the second joint meeting of these Boards. Dr. Varmus reviewed the agenda and announced that the NCI has completed its move to the Shady Grove facility, which provides a gold standard for green technology. He reflected on the passing of the longstanding NCI scientist Dr. Michael Potter.

Personnel. Members were informed that Dr. Louis Staudt is the new Director of the Center for Cancer Genomics (CCG). Dr. Varmus expressed appreciation to Dr. Stephen Chanock for his assistance as co-Acting Director and noted Dr. Kenna Shaw's departure from The Cancer Genome Atlas (TCGA) project. He announced that Dr. Warren Kibbe, the Director of Cancer Informatics, The Robert H. Lurie Comprehensive Cancer Center, Northwestern University Biomedical Informatics Center (NUBIC), will be the new Director of the Center for Biomedical Informatics and Information Technology (CBIIT) starting on October 1, 2013, and acknowledged the work of Dr. George Komatsoulis as CBIIT's Acting Director. In addition, members were told that Mr. Patrick McGarry was the new Director of NCI's Budget Office, and recruitment continues for a Director of the Division of Cancer Epidemiology and Genetics (DCEG).

Budget. Dr. Varmus informed members that the NCI's FY 2013 budget was \$4.788 billion (B), which reflects a 5.8 percent decrease from the 2012 level and includes reductions due to sequestration, NIH taps, and a 1 percent tap for the Department of Health and Human Services (DHHS) Secretary's transfer authority fund. Dr. Varmus stated that the NCI has been transparent throughout the budgetary process, including through a letter to grantees. He explained the Institute's challenges in managing the budget reduction while maintaining the number of new and competitive grants. He noted that the number of applications from new investigators had decreased. Dr. Varmus referred to the HHS decision that no layoffs or salary reductions would occur in its agencies because of sequestration but stated that fixed costs comprise 20 percent of the NCI's budget and that sequestration has resulted in significant restrictions to NCI staff, including travel and meetings. He encouraged the Boards to consider preparing a letter to the HHS Secretary regarding the elaborate meeting approvals required and travel restrictions that pose challenges to NCI staff in completing their work.

Members were informed that the FY 2014 President's Budget (PB), released late, proposes a 1.5 percent increase above the FY 2012 level. The House and Senate proposals for 2014 differ starkly, with the House allocations total being \$90 B less than Senate allocations, including \$30 B less for those areas overseen by the Senate Health, Education, Labor, and Pensions Committee. Senator Barbara Mikulski (D-MD), Chair of the Appropriations Committee, favors reversing sequestration, but further

sequestration would be applied if no resolution occurs. Dr. Varmus said that hearings were held by the Senate Committee on Health, Education, Labor, and Pensions on May 5, 2013, as well as a House hearing on the effects of sequestration on the HHS in early March. Members were told that the House Appropriations Subcommittee expressed interest in several NIH-wide activities, including the Institutes and Centers' (ICs) communication and education offices, the award process, the balance between peer review and programmatic assessment, and adherence to anti-lobbying provisions. Dr. Varmus stated that recent visits to the NIH campus by Senators Harry Reid (D-NV), Benjamin Cardin (D-MD), and other congressional members included visits to Drs. Staudt's and Marshall Lindehan's laboratories.

Dr. Varmus said that there has been Congressional interest regarding claims that replication of data produced via NIH funding does not always occur. NIH efforts on this issue include an NIH workshop, with a trans-NIH committee chaired by him and Dr. Storey Landis, Director, National Institute for Neurological Disorders and Stroke (NINDS), and a presentation of findings to the IC Directors. Members were told that the House Subcommittee on Research held a meeting on science integrity and transparency, with Dr. Bruce Alberts, past Editor of *Science*, presenting on the data process, ways to improve data sharing, and the reliability of scientific products. Dr. Varmus noted that Dr. Lisa McShane, NCI, has had a significant role in developing checklists for clinical and preclinical data; many clinical journals now use checklists to ensure adequate scrutiny and ensure that proper methodology has been employed. IC Directors will be given an update at their upcoming meeting, including various training programs, such as ethics and methods to use data responsibly.

News of Interest. A new global alliance to digitally coalesce the burgeoning clinical and genomics data on medical topics, including cancer, is being formed. Dr. Varmus described an initial meeting held in New York City in January 2013, to begin to form such an international alliance to make data accessible, interoperable and standardized and to develop appropriate governance structures. Dr. Varmus told members that a white paper that had guided the meeting was prepared by a small group which included Dr. Charles Sawyers, Chair, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center. After the meeting the paper was revised and NIH ICs and other organizations were invited to provide letters of intent to join the coalition. Currently, more than 80 institutions from 14 countries are engaged. On June 11, there was widespread, generally positive coverage that a number of institutions including NIH and NCI intend to join the alliance, which will work toward developing models of data governance and standards. Dr. Varmus referred members to a related activity, the NCI Cloud pilot, which would be discussed later.

Dr. Varmus described two recent Supreme Court decisions that have an impact on biomedical science (*Society vs. Myriad Genetics*; and the *Federal Trade Commission vs. Actavis*). On June 13, the Court yielded a unanimous verdict that opposed the patenting of naturally occurring genes on the grounds that a discovery by Myriad Genetics was laudable but that nothing was invented. Myriad's rights on cDNA remains an eligible patent. Dr. Varmus noted that Dr. Robert Nussbaum, University of California at San Francisco (UCSF), is working to accumulate data from those who paid for BRCA1 and BRCA2 gene tests, as Myriad dominated the testing of mutations for those genes and has collected much genomic and clinical data that are not shared. The Supreme Court also ruled that federal regulators may challenge in court the arrangements of patent holders on a drug and generic drug manufacturers at the time when loss of patent protection is about to occur.

Dr. Varmus informed members that NCI's semiannual leadership retreat will occur on July 23, with some members of the boards in attendance. Part of the retreat will be dedicated to a follow-up discussion of internal NCI information technology management. A larger portion of the retreat will be devoted to a broad discussion to ask: What are the essential ingredients of the current research climate, and how can NCI improve it, even in the short term? Can NCI rearrange and redesign its practices, including grant mechanisms, training programs, and review procedures for grant applicants, to better fit

the current climate? Dr. Varmus also called attention to NCI's pilot program to assess the consequences of asking grant applicants to provide on their biosketches a set of information points describing their five most major contributions to their science field.

Dr. Doroshov, Deputy Director for Clinical and Translational Research, updated the members about the recalcitrant cancer bill. He noted that members of the 2012 Recalcitrant Cancer Workshop approved the report, which recommends four initiatives: (1) examine the interaction of pancreatic ductal adenocarcinoma (PDAC) with new onset diabetes further; (2) assist in the development of biomarkers for mucinous lesions of the pancreas that are frequently associated with the subsequent development of PDACS; (3) support an enhanced immunotherapeutic approach to pancreatic cancer; and, (4) enhance the approach to RAS-specific therapeutics. Dr. Doroshov informed members that the NCI held a joint meeting with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to develop recommendations regarding the significant increase in the co-existence of chronic pancreatitis and the development of new PDAC.

Members also were informed about an upcoming workshop on new approaches to small cell lung cancer. Treatment for this disease has remained unchanged for more than 25 years, and the workshop on 9 July 8-9, 2013 will be chaired by Dr. John Mina, University of Texas (UT) Southwestern. Dr. Varmus stated that small cell lung cancer just about meets the criteria for recalcitrant cancer as defined in the recalcitrant cancer bill.

Dr. Douglas Lowy, Deputy Director, informed members that the NCI leadership is considering a reissuance of the Innovative Molecular Analysis Technology (IMAT) program, and a request for information (RFI) has been published to canvas the biomedical arena to see what high technological changes that, if they could occur, would be game changers for cancer research or clinical care.

Questions and Answers

Dr. Kevin Shannon, Roma and Marvin Auerback Distinguished Professor in Molecular Oncology, University of California, San Francisco, wondered whether Board members should prepare a revised biosketch. Dr. Varmus said that he prepared his own and several colleagues have as well. He welcomed suggestions and volunteers for the pilot assessment project.

Dr. Golub asked for further information about the reduction in the number of applications. Dr. Varmus replied that applications from new investigators decreased for R01s and increased for R21s, but that it is too early to interpret any trends.

IV. PRESIDENT'S CANCER PANEL REPORT—DR. BARBARA K. RIMER

Dr. Barbara K. Rimer, President's Cancer Panel (PCP, the Panel) Chair and Dean and Alumni Distinguished Professor, Gillings School of Global Public Health, The University of North Carolina, provided an update on the Panel's 2012–2013 workshop series titled "Accelerating Progress in Cancer Prevention: The HPV Vaccine Example" and described the next focus for the Panel's activities. Dr. Rimer reminded members that the PCP's workshop series addressed issues related to increasing HPV vaccine uptake both domestically and globally.

Dr. Lowy summarized a recent study that found a dramatic decrease in the prevalence of vaccine-type HPV among females in the target age group for vaccination during the vaccine era relative to the previous 4 years. This decrease in prevalence is impressive as only approximately one-half of eligible girls received one dose of the HPV vaccination, and only one-third received the full three doses. Analysis of vaccine types showed a two-fold decrease in prevalence for HPV 6 and 16, the most common HPVs in

the 2003–2006 time period, compared to HPV types that are not protected by the vaccine. Similar responses were seen for HPV 11 and 18. Dr. Lowy hypothesized that the dramatic decline of vaccine-type HPV prevalence was due to a combination of two factors: one dose of the vaccine provides more protection than anticipated; and vaccination among this group of individuals tended to select for those young women who were sexually active.

Dr. Rimer provided details about the fourth PCP workshop titled “Challenges of Global HPV Vaccination” and expressed gratitude for the efforts of the co-chairs : Drs. Edward L. Trimble, Director, NCI Center for Global Health (CGH); Olufunmilayo F. Olopade, NCAB member, Associate Dean for Global Health, and Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine; and Rima Khabbaz, Deputy Director for Infectious Diseases, Centers for Disease Control and Prevention (CDC). The workshop focused on the global epidemiology of HPV infection and vaccination coverage; global HPV vaccine policy and financing; and global vaccination program development, implementation, monitoring, and evaluation. There were 22 participants from various global regions and organizations, including: the GAVI Alliance; Program for Appropriate Technology in Health (PATH); Pan American Health Organization (PAHO); and the World Health Organization (WHO). Dr. Rimer described three main points from the workshop. They were: effective communications are critical around the world; concise messages from credible sources increase vaccine uptake; and the failure to counteract negative messages is detrimental to uptake, particularly in developing countries. Two other key points from the workshop were that financial resources and infrastructure are implementation barriers in low and middle-income countries, and that the United States should continue to support programs like GAVI that make HPV vaccines available in low-resource areas. In spring 2013, GAVI announced that it would make the HPV vaccine available for approximately \$4.50 per dose compared to a standard \$100 per dose, a significant boost to global vaccine availability. Many countries have effective HPV-vaccine uptake campaigns and the United States could implement successful strategies from these countries such as the use of vaccine-champions and strong public health messages that promote HPV vaccination. Research on health delivery systems should also be supported.

The Panel has begun preparing its report, which will be ready in the late summer. The report will include cross-walks to show how the PCP’s recommendations complement those of the CDC, the National Vaccine Plan, and Healthy People 2020. In addition to the print version, the Panel will release a mobile and desktop version of the. Panel staff is also working on developing ways to track and evaluate the report’s effectiveness and reach.

Members were informed that for the 2013-2014 series, the Panel’s will focus on “Emerging Media and Cancer Prevention.” With the massive shift in how people obtain information, emerging media facilitates access to information about how to prevent, detect, diagnose, and treat cancer. The rapid pace of technological innovation creates a growing gap between public health messages and the public’s use of new media. Likewise, Twitter can be a powerful tool, as seen by movie celebrity Michael Douglas’ recent tweet connecting his throat cancer to HPV. The PCP is considering the question of how to accelerate the use of emerging media for cancer control and improve the reach of communication about cancer prevention to diverse audiences as well as between physicians and patients. The topic will benefit from PCP member Hill Harper’s celebrity status. A planning workshop will involve a spectrum of leaders and innovators to discuss: strategies to overcome barriers to health organizations’ use of emerging media to improve health and reduce communication inequities; how to increase individuals’ access to emerging media; and opportunities to link electronic health records with individualized health messages.

Questions and Answers

Dr. Rimer made reference to the recent Supreme Court decision overturning the anti-prostitution condition for researchers receiving funding from the federal government, which is important for AIDS

research.

In response to a question, Dr. Lowy stated that the HPV vaccine study's findings represent almost entirely the Merck vaccine as the GSK vaccine was approved by the U.S. Food and Drug Administration (FDA) in 2009 and would not have contributed to any substantial percentage of the vaccines.

Dr. Mack Roach, Chair, Department of Radiation Oncology, UCSF, Helen Diller Family Comprehensive Cancer Center, asked for further details about the high prevalence of three types of HPV (53, 84, 89) shown in the study among the "other nonvaccine types." Dr. Lowy replied that prevalence shown likely has to do with variation and not exposure relative to a particular vaccine; the study did not find a notable increase in nonvaccine types.

Dr. Lowy informed the members that Merck is conducting Phase II trials of a vaccine for nine HPV types and hopes to publicly present interim results at the end of this year. The vaccine would target HPV 6 and 11, which account for approximately 90 percent of genital warts; HPV 16 and 18, which are the two most prevalent oncogenic types; and the five next most common oncogenic types.

Dr. Andrea Califano, Director, Columbia Initiative in Systems Biology, Institute of Cancer Genetics, Columbia University Medical Center, asked about whether global statistics were available for all the other HPV types. Dr. Lowy responded that the study's data clearly show that the reduction is specific to the HPV targeted by the vaccine. One notable exception is HPV 31, which in Merck's Phase III trials has been shown as pharmacogenetically related to HPV 16 and showed partial cross-protection. He indicated that the paper could be forwarded to the members.

Dr. Joshua LaBaer, Chair, The Directorate, Biodesign Institute, Arizona State University, asked how one might ensure that people get the best sources for information about cancer. Dr. Rimer replied that this is a question for the planning workshop. Tools to help people understand how to use the information currently are available.

Dr. Beth Karlan, Director, Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, David Geffen School of Medicine, University of California, Los Angeles (UCLA), encouraged adoption of a school-based vaccination approach in light of the riveting data on the HPV vaccine efficacy and the success experienced in Australia with this approach. Dr. Rimer agreed and stated that the Panel's report will include a recommendation for school-based vaccination. She added that another recommendation is that the discussion about the HPV vaccine should be reframed as cancer prevention, not sexually-transmitted disease prevention.

Dr. Victoria L. Champion, Associate Dean for Research, Indiana University School of Nursing, noted the overlap with the NCAB *Ad Hoc* Subcommittee on Communications, which is charged with looking at how the NCI communicates. Dr. Rimer agreed that there are opportunities for collaboration and that the PCP would communicate with the Division of Cancer Control and Population Sciences (DCCPS) as well.

Dr. Charles L. Sawyers, Chairman, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, commented that people pay attention to Twitter as shown by the American Association for Cancer Research's (AACR) Rally for Medical Research event, which trended on Twitter just below Margaret Thatcher who died that day, and asked whether Twitter statistics make an impact on Congress. Dr. Varmus responded that Congressional representatives will respond to trends in constituent phone calls, but attention to Twitter statistics depends on the media savvy at individual offices. Dr. Rimer indicated that Twitter statistics indicate people's interest in an issue.

Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., encouraged the NCI to develop a plan for immediate responses to countering incorrect cancer information that is disseminated via Twitter. Dr. Rimer replied that the workshop will discuss such communication aspects, and that all responses should be balanced. Dr. Varmus said that this issue is much broader than the NCI and that he would raise the topic with NIH leadership; the issue of misinformation is common in the infectious disease arena. Dr. Rimer acknowledged that Twitter is an important influence and can reach millions of people instantly with negative messages.

Dr. Marcia R. Cruz-Correa, Basic and Translational Science Director, University of Puerto Rico Comprehensive Cancer Center, asked about HPV vaccine uptake data for minority groups and suggested that uptake messages be tailored to minority groups who are high users of smart phones. Dr. Rimer noted that HPV vaccine uptake is higher among minorities for the first dose, and that the PCP's recommendation to increase full uptake is to increase the accessibility through vaccine delivery at pharmacies and schools.

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

On behalf of the NCI, Dr. Varmus recognized the contributions made by members of the BSA whose terms of office expired. He expressed appreciation for their service and dedication over the course of their terms. Retiring BSA members: Drs. Robert B. Diasio, Director, Mayo Clinic Cancer Center, and William J. and Charles H. Mayo Professor, Professor of Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics and Oncology, Mayo Clinic; and Louise C. Strong, Sue and Radcliff Killam Chair, Professor Genetics, Department of Genetics, The University of Texas M.D Anderson Cancer Center.

VI. RAS PROJECT—DRS. DAVID C. HEIMBROOK AND FRANK MCCORMICK

Dr. Varmus provided the context for the RAS Project. Following an NCAB recommendation, the NCI established a high-level advisory board (NCI Frederick Advisory Committee, NFAC) chaired by Dr. Zach Hall to advise on the NCI's activities at the Frederick National Laboratory. In addition, the NCI helped in the recruitment process of Dr. David C. Heimbroom, CEO of SAIC-Frederick, and renamed the Frederick enterprise the Frederick National Laboratory for Cancer Research (FNLCR) to provide greater prominence and credibility as the HHS' only federally funded research and development center (FFRDC) laboratory. The NFAC encouraged the FNLCR to improve its website, increase the transparency of its activities and plans, and undertake several large projects, including a proposal on RAS. Dr. Frank McCormick, UCSF, co-chaired an extramural RAS workshop in February 2013.

Drs. Heimbroom and McCormick described the RAS Program at Frederick. There are four types of rat sarcoma viral oncogene homolog (RAS), a protein that regulates signal transduction in cells: Harvey, Kirsten (A and B), and neuroblastoma. Mutated RAS is found in 33 percent of human cancers, currently is undruggable, and enables resistance to many existing cancer therapies. The concept for the RAS project at the FNLCR began with the NFAC's encouragement to identify the FNLCR's national missions, followed by a discussion of the program concept with the NCAB and BSA, a RAS workshop held in San Francisco, CA, in February 2013, and the development of a budget along with operational and scientific plans. The FNLCR performs a full spectrum of biomedical research and development activities, with specialties in genomics, proteomics, metabolomics, bioinformatics and imaging, nanotechnology, animal models, tumor cell biology and virology, and immunology and inflammation. All FNLCR assets and expertise are available to the RAS Program. The RAS Program is envisioned as a hub-and-spoke structure, with the FNLCR serving as a central point in interactions among NCI-supported extramural and intramural laboratories, biotechnology and pharmaceutical companies, and contract research. Partnerships

can be supported through various contractual agreements, including material transfer, technical services, and collaboration, as well as cooperative research and development agreements (CRADAs). Funding for the RAS Hub will total \$10 M each year and come from the reprioritization of ongoing activities within the existing FFRDC, and the RAS spokes will be funded through subcontracts or self-funded by biotechnology and pharmaceutical companies. Oversight will be provided by an NFAC *Ad Hoc* working group and NCI leadership.

Members were told that a clinical need for the RAS Project exists. There is a high incidence of RAS mutations in cancer, no drugs that target RAS proteins directly or indirectly, no effective therapies for RAS-driven cancers, and RAS cancer has been excluded from treatment with some targeted therapies. Opportunities include new ways of targeting undruggable proteins, performing structural analysis, and interrogating signaling networks, as well as using the power of RNAi for target identification and therapy, harnessing the immune system, and improving the therapeutic utility of mouse models. RAS mutations are found in human cancers, including in 95 percent of pancreatic, 45 percent of colorectal, and 35 percent of human lung adenocarcinoma cancers, as well as in acute myeloid leukemia (AML), melanoma, and bladder cancers. Members were informed that significant gaps in knowledge exist, including that there are no structures of mutant KRAS proteins with regulators or effectors, clinical data show that different alleles have different clinical outcomes but the cause is unknown, it is not known which effectors are important in established cancers or which cancer remains RAS-dependent once they are established, signaling complexes are uncharacterized, and how to target KRAS cancers for drug delivery or immune therapy through nanoparticles is unknown.

Dr. McCormick described five project areas that were identified during the February 2013 workshop, and indicated that the paradigm for each would involve a brainstorming session at Frederick with several key players to determine how to accomplish the project and which parts are conducted at the FNLCR and by partners: (1) Project One focuses on allele-specific compounds that are most prevalent in human cancer, including G12D, G12C, G12V, and G13D. Because these alleles have different clinical outcomes, the aim is to determine which effectors each of these engages, solve structures of mutant protein complexed with relevant effectors and regulators, and identify new opportunities for small molecule intervention from these structures. The prevalence of KRAS mutations in colorectal, lung, and pancreas cancers is high and targeting any of these alleles would be a significant step forward; prevalence in these cancer patients in the United States totals an aggregate of 29,500 in G12C; 50,520 in G12D; 36,500 in G12V; and 13,440 in G13D. Dr. McCormick reviewed the distinction between biological and clinical properties of KRAS alleles compared to more common alleles. For example, G12C and G12V have a worse clinical outcome than G12D, and G13D responds to EGF receptor inhibition whereas G12 mutants are excluded from this therapy. (2) Project Two, KRAS selective compounds, will investigate compounds that affect KRAS but do not distinguish between different mutant alleles. There is evidence in mouse models that ablating KRAS is not detrimental. KRAS proteins are modified in many ways, which provide opportunities for a chemical attack on KRAS. Dr. McCormick described an assay by Dr. Mark Philips that strips KRAS of the plasma membrane, which the FNLCR could adopt and work with industry in this project, as an example of a spoke in the “Hub-and-spoke” model. (3) Project Three identifies single proteins in plasma membranes. KRAS proteins act as dimers. The platform could be extended to analyze the nature of KRAS complexes in cancer cells and develop screens for disrupting the complexes. (4) Project Four is to map the surface of KRAS cancer cells. Knowing the protein composition of the cell membranes will allow the identification of peptides that could be targeted by immunotherapy as well as proteins that could internalize nanoparticles for drug delivery. The community has interest in this project, which would use mass spectrometry, phage display, and bioinformatics to characterize the surface of a KRAS cancer. (5) Project Five focuses on next-generation synthetic lethal screens in three-dimension models and *in vivo*. Engineered mice would facilitate screens to test combinations of siRNAs, shRNAs, and small molecules.

Questions and Answers

Dr. Golub said that a common misconception has been that the biopharmaceutical industry has addressed RAS in all possible avenues. He requested further details about interaction with industry and confidentiality issues. Dr. Heimbroke answered that industry could work with FNLCCR through a CRADA, and any intellectual property that emerged from the joint collaboration would be negotiated. Dr. McCormick stated that leadership is considering workshops with biotechnology companies to determine further details about producing useful material for industry, facilitating interactions, and protecting property rights. Dr. Varmus reminded members that the contractor-CRADA is a mechanism advocated by the NFAC.

Dr. Gregory Verdone, Erving Professor of Chemistry, Department of Stem Cell and Regenerative Biology, Harvard University, expressed strong support for this project and said that the chemistry community has not learned how to target 80 percent of human proteins. He suggested that success in showing that RAS is targetable in animal models could change the mindset of the drug development community.

Dr. Stanton L. Gerson, Shiverick Professor of Hematological Oncology, Case Western Reserve University, and Director, Siedman Cancer Center, University Hospitals Case Medical Center, applauded the effort and asked whether the project emphasis is on proteins proximate to the RAS mutations or in downstream processes, and if efforts have been undertaken not just to catalog RAS mutations but to prevent them. Dr. McCormick said that workshop attendees indicated their preference to target mutant proteins directly, which is the focus of Project One. Dr. Heimbroke added that some drugs work downstream; the siRNA project will seek targets by looking in an unbiased way for targets in combination with the mutation in RAS. Dr. Varmus indicated that the prevention of RAS mutations falls outside of the project's purview but recognized that causes and mechanisms of RAS mutations that transform normal cells to cancer cells are important for cancer prevention.

Dr. Califano said that the generation and molecular profiling of certain agents, including isogenic cell lines, would encourage many laboratories that are producing non-coordinated data to work in a coordinated fashion. He also recommended that the RAS Program dissect the cellular regulatory process to elucidate the activation of effectors and identify the co-mutation(s) that make RAS more or less aggressive in tumors. In addition, the FNLCCR should consider adopting a "bucket" approach to RAS studies, similar to *Nature*.

Dr. Bruce W. Stillman, President and Chief Executive Officer, Cold Spring Harbor Laboratory, encouraged the FNLCCR to coordinate efforts with the Lustgarten Foundation and other groups that are funding similar projects. He cautioned that the NCI may be faced with grant applications that request much more funding than is found in the traditional R01 application.

Dr. Sellers commented that the RAS Program could serve as a model for future projects, such as on transcription factors, as well as cloud-sourced science, and provide a venue for investigations on worthwhile but "non-sexy" projects. He suggested that the Program could create an online community that posts real-time work in chemistry and structure-activity relationships (SAR) for discussion among investigators. Dr. McCormick remarked on the dearth of understanding about the robust chemistry of the RAS proteins and reflected on interactive networking that occurred with the February 2013 workshop.

Dr. Judy E. Garber, Director, Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Professor of Medicine, Harvard Medical School, asked about the Program's intentions to attract and provide access to RAS information to non-RAS investigators and whether the support to current RAS investigators would be shared in a broader way. She also cautioned about how success is defined, given

that this is a large project. Dr. Heimbrook agreed that it will be important to bring in non-RAS scientists who might provide new or different perspectives on approaching research problems. Dr. McCormick said that having a junior investigator join the RAS field would be an example of a successful outcome. Dr. Golub said that communication with lay audiences should be prepared with care, as the public generally does not know the level of time, effort, and resources that developing an effective therapy takes. Dr. Varmus said that the RAS Program will need to promote realistic expectations regarding what a reasonable set of milestones might be, and use online communication media effectively to foster meaningful dialogue among RAS and other investigators. He mentioned a general interest at the NIH in encouraging investigators' comments about published work, and he noted that PubMed Central has developed authoring tools and a pilot experiment to allow volunteers to make public commentary on work that is presented in PubMed Central. Dr. Varmus stated that the communication experiment carried out with the RAS project could elucidate the most effective ways to engage the scientific community in important conversations via the Web.

Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, F.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, suggested that positioning the RAS Program as a national priority and as a platform-convening site can help draw other funding resources to support large studies, including foundation support for matching funds. She wondered whether TCGA data have been sorted based on their distinct clinical and biologic properties of allele-specific mutations. Dr. Varmus stated that the CCG is working to capture and present information from all tumor types to allow computation by biologists, and that the issue of interoperability between tumor datasets will be important for a global alliance.

Motion. A motion to concur with the RAS activity was approved unanimously.

VII. NATIONAL LUNG SCREENING TRIAL (NLST) SUBSET ANALYSIS—DRS. PAUL F. PINSKY AND WILLIAM C. BLACK

Dr. Paul F. Pinsky, Acting Chief, Early Detection Research Branch, Division of Cancer Prevention (DCP), provided an analysis of screening efficacy in the NLST. Subjects in the NLST were men and women aged 55-74 who were current smokers or had quit within 15 years; the primary outcome was lung cancer mortality. Subjects were randomized to either a low-dose computerized tomography (LDCT) arm or a chest radiograph (CXR) arm. Histology classifications were obtained from medical records, and there was an endpoint verification process to adjudicate the cause of death. The data from the study were analyzed to determine the dependence of LDCT screening efficacy on demographic factors such as age and sex, smoking status, and lung cancer histology. Analysis of the full data set confirmed initial findings that (LDCT) screening results in an approximately 20 percent reduction in lung cancer mortality compared to CXR screening. The reduced risk associated with LDCT screening was significant for adenocarcinoma but not for small cell lung cancer or squamous cell lung cancer. LDCT efficacy did not vary by age or smoking status. Relative to men, women experienced a borderline significantly greater benefit from LDCT screening. The fact that deaths from small cell and squamous cell lung cancer were greater in the LDCT arm for men but greater in the CXR arm for women, however, might explain the apparent increased screening benefit in women.

Dr. William C. Black, Professor of Radiology, Professor of Community and Family Medicine, and Professor of The Dartmouth Institute, Geisel School of Medicine at Dartmouth, reviewed preliminary results and sources of uncertainty from an analysis of the cost effectiveness of computed tomography (CT) screening in the NLST. The cost-benefit analysis compared the health benefits to individuals with the societal costs associated with different screening programs: LDCT, chest X-ray (CXR), and no screening. Health benefits were quantified as quality-adjusted life years (QALYs). Cost estimates included direct medical costs associated with screening, workup, and treatment, and indirect costs from

travel and lost wages. The preliminary result for the cost-benefit ratio of LDCT was \$72K per QALY. To provide context, Dr. Black stated that a ratio of less than \$100K per QALY generally is considered acceptable in the medical literature. The major sources of uncertainty in the analysis included the assumptions about the lack of benefits conferred by CXR and the number of cases that would have been detected earlier if those who received CXR in the study had instead received LDCT. Dr. Black indicated that the cost effectiveness of implementing an LDCT-based screening program might differ significantly from the estimates determined by data from the NLST, particularly if the screening program were extended to the general population of smokers, who are at much lower risk of lung cancer than the subjects in the NLST.

Questions and Answers

Dr. Roach observed that exposure of older populations to radiation might result in quicker development of cancer and asked about the possible increase of cancer risk to participants in imaging studies. Dr. Black concurred that there may be some radiation-induced lung cancers.

Dr. Champion asked how the benefit described for lung cancer screening compares to mammography or colorectal cancer screening. Dr. Black replied that it depends on patient selection but compares favorably given current guidelines. Dr. Kramer referred members to a one-page NLST fact sheet available on the NCI's website that informs smokers that to avoid death from lung cancer, the best option is to stop smoking, and provides the NCI's Quit Line number. He stated that for approximately 1,000 smokers and former smokers screened after approximately 7 years, there will be 3 fewer deaths from lung cancer, whereas estimates for mammography is 1 death in 1,000 over 10 years.

Dr. LaBaer asked about over-diagnosis, and Dr. Pinsky responded that analysis shows approximately 7 percent over-diagnosis rates that reduce to 5 percent when bronchioloalveolar carcinoma (BAC) is omitted. Dr. Kramer reminded members that the NLST is a comparison of CT and chest X-ray, and that in previous trials, chest X-rays were associated with over-diagnosis.

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, pointed out the healthy person screening bias in the NLST and encouraged incorporating worse cases, such as the higher morbidity, mortality, and costs associated with chronic obstructive pulmonary disease (COPD) patients who meet the 30-pack/year criterion.

Dr. Olopade commented on the effectiveness of screening adenocarcinomas in women and wondered whether biology accounts for this. She said that effectiveness may be due to the cancers having been found early and an effective treatment having been used.

Dr. Frank M. Torti, Executive Vice President for Health Affairs, Dean, School of Medicine, University of Connecticut, expressed enthusiasm for the availability of an effective screening procedure for lung cancer that has long been sought, and stated that an opportunity now exists to see if the NLST results are replicated in real-world settings. Dr. Pinsky agreed and said that an NLST registry is being considered.

Dr. Sellers expressed concern about the challenges in interpreting the graphs, asked whether trends in mortality in lung cancer have been examined to determine the effects of screening over 5-year intervals, and pointed out that the models do not integrate the excess medical care due to incidental findings on CT scans. Dr. Varmus told members that the NCI is working with other organizations to establish a prize competition to develop algorithms to read scans. Both the outcomes data and the original films are available for the competition. In addition, he said that he will invite a representative from the

U.S. Preventive Services Task Force (USPSTF) to discuss the lung screening recommendations and their adoption in general practice.

Dr. Ethan M. Basch, Associate Professor of Medicine, Director, Cancer Outcomes Research Program, University of North Carolina at Chapel Hill, stressed the importance of supporting dissemination and implementation research to help clinicians identify patients who meet the appropriate criteria and also determine how to bring in patients to receive these tests, and he encouraged the NCI to study the harms of screening in real-world populations.

Dr. Daniel C. DiMaio, Waldemar Von Zedtwitz Professor and Vice Chairman of Genetics, Scientific Director, Yale Cancer Center, Yale University School of Medicine, asked how lung and mammography screening compare in terms of cost effectiveness to the Pap smear, a screening test that has worked well. Dr. Kramer said that to determine the efficacy of lung cancer and mammography screening, the largest randomized trials possible are needed but this was not the case for the very effective Pap smear test.

VIII. RFA/COOP AGR./RFP CONCEPTS—NCI STAFF

Division of Cancer Prevention NCI Community Oncology Research Program (NCORP)— Drs. Wortá J. McCaskill-Stevens and Barnett Kramer

Drs. Kramer and Wortá J. McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), described a concept to consolidate the two existing NCI funded community-based programs, the Community Clinical Oncology Program (CCOP)/Minority-Based CCOP (MB-CCOP) and National Cancer Institute Community Cancer Centers Program (NCCCP), to form NCORP, accomplishing the twin goals of increasing efficiency and providing an opportunity to expand the scope of research conducted within these networks to include cancer care delivery and health services research. NCORP will continue NCI's commitment to supporting research in a community setting, with an enhanced focus on issues of disparity in clinical trials and cancer care delivery research (CCDR). Supporting CCDR in a community setting is essential for understanding the effects on patient outcomes and disparities in care in the current rapidly evolving health care environment.

Dr. McCaskill-Stevens highlighted key achievements of NCI's CCOP network. Clinical trials completed within the network have led to practice-changing advances in chemoprevention, symptom management, and health-related quality of life. CCOP, MB-CCOP, and community research bases exhibit a wide range of geographic and organizational diversity, and CCOP and MB-CCOP have been highly successful in enrolling participants in NCI's clinical program, particularly minorities. The clinical trial success of CCOP and MB-CCOP will position NCORP well for its ambitious research agenda in cancer prevention and control trials.

In developing NCORP, the NCI consulted with a broad range of stakeholders—including the Science and Technology Policy Institute, CCOP/MB-CCOP/NCCCP grant awardees, expert investigators in CCDR and cancer disparities, and members of the public—on issues of science, structure, and feasibility, as well as potential challenges. NCORP will expand the diversity, geographic distribution, and number of research sites of NCI's and NIH's CCDR research portfolio while avoiding duplicative efforts. Dr. McCaskill-Stevens depicted NCORP's proposed organizational structure, which includes a steering committee to evaluate and prioritize research; benchmarks will be identified to assess the effectiveness of NCORP in achieving practice change.

Subcommittee Review. Dr. Jeffrey A. Drebin, John Rhea Barton Professor, University of Pennsylvania School of Medicine, and Chairman, Department of Surgery, Hospital of the University of Pennsylvania, voiced the Subcommittee's support for the consolidation of NCI's CCOP and CCDR programs. The Subcommittee expressed reservations about the effects of the reduction in sites on accrual rates but recognized the timeliness of supporting CCDR and encouraged the early development of evaluation metrics.

The first year cost is estimated at \$93 M for 61 U10 awards, with a total cost of \$465 M for 5 years.

Questions and Answers

Dr. Golub asked, independent of accrual, what discoveries or changes in care occurred because of CCOP, MB-CCOP, and CCDR efforts. Dr. McCaskill-Stevens responded that pivotal areas include the symptom management in cancer control trials, chemoprevention trials, and the successful engagement of the cancer care community. Dr. Kramer said that the CCOP structure supported the development of preventive agents and that because CCOP is responsible for approximately 40 percent of all accruals to Cooperative Group clinical trials, therapeutic accomplishments achieved through the Cooperative Groups is partly due to the CCOPs. He added that the CCOPs also have provided the potential energy to expand clinical research beyond the academic centers. Dr. Steven Clauser, NCI, noted that the NCI Community Cancer Centers Program (NCCCP) has shown the ability to accrue patients rapidly and improve adherence to delivering evidence-based therapy.

Dr. Luis Parada, Chairman, Department of Developmental Biology, University of Texas Southwestern Medical Center, asked about critical metrics for the Program. Dr. McCaskill-Stevens replied that the clinical trials system has an established evaluation process. She agreed that benchmarks will be needed for this Program. Early successes are anticipated for cancer care delivery research conducted within existing networks, and evaluations for these may occur sooner than midterm.

Dr. Stillman observed that major cancer centers cover areas of large minority populations, and he asked for clarification about increases in accrual data expected because of the Program. Dr. McCaskill-Stevens responded that the 17 MC-CCOPs contribute significantly to the network, and 60 percent of their accrual is composed of minority and underserved populations; the Affordable Care Act will allow a movement into more urban settings. Dr. Doroshov stated that the CCOPs make it possible for the NCI to conduct early stage, adjuvant, and surgical trials, which involve a type of patient who rarely enters large centers without prior treatment.

Dr. Shannon asked about strategies to reverse the significant declines seen in CCOP patient accruals in the past 3 years and wondered if the Program could reach out to large networks such as Kaiser Permanente to accrue patients in a cost-efficient way. Dr. McCaskill-Stevens answered that CCOP mimics the overall clinical trials network in terms of accrual patterns, and Dr. Doroshov reminded members that the substantial rethinking of the clinical trials system has resulted in uncertainty regarding the amount of reimbursement, a slowdown in the activation of large clinical trials, and the recent closure of some large trials. Dr. Clauser added that 11 integrated health systems have participated in the NCCCP.

Dr. Gerson asked whether oversight would be provided by a steering committee, suggested that Cancer Centers support and help think through how to conduct some of the research, and wondered about the distribution of funds between infrastructure and studies. Dr. McCaskill-Stevens indicated that two steering committees provide oversight and help set milestones. Dr. Kramer stated that the existing CCOPs infrastructure will be used; the Division of Cancer Treatment and Diagnosis (DCTD) mechanisms will assist in the review processes; and that CCDR will comprise approximately 12 percent of all the costs

proposed for the entire NCORP. He expressed the NCI's intention to shift some funding from infrastructure support to studies across the 5-year period.

Dr. LaBaer asked about the \$40 M allocation to research sites. Dr. Lori Minasian, NCI, explained that CCOP's \$81 M is split equally between accrual to the sites and to support the design, development, and conduct of clinical trials. Parallel resources are provided to the research bases and accrual sites. She clarified that more than 45 percent of the \$40 M allocation to research sites funds cancer control studies.

Dr. Olopade advocated for increased resources for the Program to support cancer genomics research in the community. Dr. Garber said that the CCOPs have been remarkably effective, with their greatest success being the large accrual rates to large adjuvant and large prevention trials. She observed that the NCI's greatest challenge with NCORP will be providing adequate funding to support bringing research to the community.

Motion. A motion to concur on the DCP's request for application/Cooperative Agreement (RFA/Coop. Agr.) entitled "NCI Community Oncology Research Program (NCORP)" was approved with 19 ayes, no nays, and 3 abstentions.

Office of the Director

The PROSPR Initiative: Population-based Research Optimizing Screening Through Personalized Regimes—Competitive Revision for the Collection of Cervical Cancer Screening Data—Drs. Robert T. Croyle and V. Paul Doria-Rose

Dr. Robert Croyle, Director, DCCPS, introduced a concept to expand the collection of cervical cancer screening process data in the PROSPR Initiative. Dr. V. Paul Doria-Rose, Health Services and Economics Branch, Applied Research Program, DCCPS, reminded members that PROSPR's objective is to conduct research to evaluate and improve the cervical, breast, and colorectal cancer screening processes through collecting multilevel data, identifying screening process failures and potential remedies, and developing risk-based screening strategies. PROSPR research center activities related to the proposed expansion involve conducting multicenter, collaborative projects, as well as submitting core screening process data to a statistical coordinating center that houses a central data repository. Currently of the nine PROSPR Research Centers, only one collects cervical cancer screening process data. Multiple research centers for each organ site allow comparisons of the screening challenges among different high-risk populations and health care systems to identify improvements that are general as well as those that are tailored to varied environments and populations. Dr. Doria-Rose presented data that demonstrated the broader range of health care systems and high-risk groups that could be sampled by expanding cervical screening process research to candidate PROSPR research centers. The existing centers are uniquely positioned to collect multilevel data to evaluate the entire screening process that are not being gathered by other NIH grants or CDC surveillance efforts. Dr. Doria-Rose asserted that by leveraging the existing infrastructure, the proposed competitive revision would require a relatively modest additional investment of resources yet address important cervical cancer screening questions during a time of rapid change in screening practice.

Subcommittee Review. Dr. Louise Strong, Sue and Radcliff Killam Chair, Department of Genetics, The University of Texas M.D. Anderson Cancer Center, expressed the Subcommittee's enthusiasm for the concept and appreciation for NCI staff's responses to the group's questions. Dr. Strong said that the Subcommittee supported the work of the Centers to address changing cancer prevention and screening studies, noting recently published data on cancer incidence and vaccinations, but had reservations about differences in collecting cervical tumors versus breast or colon cancer specimens. The Subcommittee also raised concerns about adding activities into the last 2 years of the study via a closed competition, but lauded the program's focus on collecting insurance information at the patient level,

better integration with electronic health records to harvest data, and linkages to cancer registries to facilitate the long-term followup with patients.

The first year cost is estimated at \$1.37 M for two U54 awards, including a statistical coordinating center, with a total cost of \$2.74 M for 5 years.

Questions and Answers

Dr. Maria Martinez, Professor, Department of Family & Preventive Medicine, UCSD Moores Cancer Center, pointed out that two of the current PROSPR Centers focus explicitly on minority groups and asked about the composition of the other Centers in terms of underserved populations. Dr. Doria-Rose said that the Centers working in integrated care communities struggle with the same issues in screening patients as those in large minority areas. Dr. Rachel Ballard-Barbash, DCCPS, added that some Centers have a significant community clinical presence in underserved areas in their locales.

Dr. Chanita Hughes-Halbert, Professor and Endowed Chair, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Hollings Cancer Center, asked whether dissemination of the funds to all the PROSPR sites to allow each to conduct some of this work would be possible. Dr. Doria-Rose said that the NCI's intention is to fund the sites that are best able to collect the data and have the most relevant expertise within the site. Dr. Croyle added that the NCI is adopting the most cost-effective approach now, with a future reissuance being openly competitive and expanding into other areas of screening data collection, such as lung cancer.

Motion. A motion to concur on the Office of the Director's request for application/Cooperative Agreement (RFA/Coop. Agr.) entitled "The PROSPR Initiative: Population-based Research Optimizing Screening Through Personalized Regimes—Competitive Revision for the Collection of Cervical Cancer Screening Data" was approved with 21 ayes, no nays, and 1 abstention.

Sub-Saharan African Collaborative HIV and Cancer Research Consortia— Dr. Geraldina Dominguez

Dr. Geraldina Dominguez, Program Director, AIDS Malignancy Program, Office of HIV and AIDS Malignancy (OHAM) described a concept to build on assistance provided by NCI's collaborative research training program through a D43 mechanism to address the double disease burden of HIV and oncogenic viruses in sub-Saharan Africa. The training initiative aimed to strengthen the capacity for research for HIV-associated malignancies in Africa by supporting nine partnerships between U.S. and African institutions that provided long-, medium-, and short-term training opportunities in diverse aspects of cancer research, ranging from basic laboratory research to clinical trials. The goal of the concept is to accelerate basic, translational, population, and implementation research in sub-Saharan Africa by soliciting research projects that address high-priority research questions and enhancing the ability of African institutions to train and provide career development opportunities for leaders in scientific cancer research. This concept was developed in consultation with the NCI CGH, Office of Cancer Centers, Center for Cancer Training, and the Fogarty International Center, which will provide co-funding. The Specialized Center—Cooperative Agreements (U54) grant mechanisms that this concept will support must demonstrate equal and shared partnership between a U.S. and a sub-Saharan African institution. The RFA will be open to all qualified applicants, and D43 trainees will be encouraged to apply. Possible research topics include epidemiological, population, social behavioral, basic, translational, and clinical studies, although the program is not intended to support clinical trials. Dr. Dominguez outlined possible research areas, including studies of HIV-associated cancers; prevention, diagnosis, and treatment of cancer in HIV-positive people; strategies to improve integration of HIV and cancer care; and regional strategies to reduce cancer burden.

Subcommittee Review. Dr. Torti expressed the Subcommittee’s enthusiasm for this concept. Dr. Torti noted the topic’s importance and timeliness, asked about the management of the D43 grants, expressed concerns about a compressed timeframe for new investigative units, and encouraged expansion to other regions outside sub-Saharan Africa with similar issues, such as Haiti. The Subcommittee applauded the ongoing focus on mentoring and translational impact, which will lead to sustainability, and encouraged the NCI to promote career paths for the investigators as a way to increase retention. Members were told that investigators with a D43 award have an advantage, and that their D43 performance should be evaluated in the application.

The first year cost is estimated at \$5 M for 6–7 U54 awards, with a total cost of \$25 M for 5 years.

Questions and Answers

In response to the Subcommittee’s and others’ concerns, Dr. Dominguez confirmed that the NCI will release the RFA as soon as possible, that the research will be conducted in Africa with the U.S. investigator providing leadership, and that protected time is required for the African investigator.

Dr. Golub asked about the proportion of the Office of AIDS Research’s (OAR) AIDS spending that this concept represents. The response was only a sliver. Dr. Varmus said that several models are being considered, including that of the collaboration between the Uganda Cancer Institute and Fred Hutchinson Cancer Center. Other examples also exist that are focused on problems arising in the African setting.

Dr. Califano asked whether the collaborations must focus on epidemiologic research versus genomic. Dr. Dominguez answered that there is no limitation regarding this. Dr. Betty Ferrell, Professor, Nursing Research and Education, City of Hope National Medical Center, applauded efforts to address symptom, pain, and wound management as well as epidemiological and clinical research, given the overall comorbidities and mortality in Africa, and she encouraged opportunities for supportive care and collaboration to advance clinical care for all those suffering.

Dr. Champion expressed that applicants who have not had the D43 are significantly disadvantaged, and that the mentoring component is essential. Dr. Yarchoan explained that originally the concept was to be restricted to D43 recipients, but it has been expanded to take advantage of those who have established presence and collaboration in the countries. Dr. Olopade observed that many cancer centers have been funded and trained through other vehicles, including through PEPFAR. She added that this concept provides an opportunity for those with training to collaborate in research with the NCI.

Motion. A motion to concur on the Office of the Director’s request for application/Cooperative Agreement (RFA/Coop. Agr.) entitled “Sub-Saharan African Collaborative HIV and Cancer Research Consortia” was approved unanimously.

Cancer Detection and Diagnostic Technologies for Global Health— Dr. Edward L. Trimble

Dr. Trimble provided a brief overview of the proposed program to support the development of technologies for cancer detection, diagnosis, and treatment in low-resource settings. Two-thirds of cancer deaths occur in LMICs where the lack of low-cost, portable, easy-to-use, minimally invasive technologies for detection, diagnosis, and treatment of cancer contribute to poor prognosis and outcomes. Examples of technologies that are adaptable to low-resource settings include the “lab-on-chip” technology careHPV;

DermLite, which has an iPhone interface for remote diagnosis and data transmittal; smart phone technologies and applications for remote retinoblastoma diagnosis and fluorescence detection; cryotherapy for cervical cancer treatment; and hand-held ultrasound, currently marketed worldwide for obstetrics but applicable to breast mass triage. Point-of-care and close to point-of-care tests have attracted increasing attention, and the technologies have evolved. Many promising technologies developed under NCI's sponsorship have failed to be deployed in global health settings because of a lack of a mechanism for multisite validation and interest by the private sector in commercialization. The proposed approach in Phase I will be to establish strategic partnerships among engineers, oncologist, experts in global health delivery, and business interests to develop a prototype adapted to low-resource settings and demonstrate the clinical potential of the technology in a global health setting. If the program's evaluation criteria are met, the device will undergo validation in a global setting in Phase II. The goal of successful Phase II projects will be to secure regulatory approval for deployment and use, demonstrate adequate accrual for the validation study, develop a commercialization plan if the validation is successful, secure commercial partners for production and marketing, and develop an education plan for use of the device in health care delivery.

Subcommittee Review. Dr. Sangeeta N. Bhatia, John H. and Dorothy Wilson Professor, Institute for Medical Engineering and Science, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, expressed the Subcommittee's enthusiasm for the concept and encouraged the NCI to consider platform standardization as an incentive in the UH3 phase and to require connections with companies at the outset to spur technology commercialization. The Subcommittee also observed that this mechanism could help in resource-poor areas and health costs in the United States as well as in developing countries. Members were told that this type of research would not be supported by traditional mechanisms, such as NIH R01s or typical foundation support, and that the Subcommittee appreciated the focus on team science.

The first year cost is estimated at \$3 M for 18 UH2/UH3 awards, with a total cost of \$45 M for 5 years.

Questions and Answers

Dr. Sellers encouraged the NCI to provide specific applications, as building a detection device without knowing the measurement in existence would pose challenges. Dr. Trimble replied that cancers that are relatively easy to detect or treat in high-resource settings or if found early are high priorities; the concept suggests cervical, breast, skin, and oropharyngeal cancers. For example, a device that provided timely evaluation of breast masses, such as benign versus malignant mass or lactating women presenting with mastitis, would be useful.

Dr. Stillman asked whether technology developed under this concept could be transitioned into the Small Business Innovation Research (SBIR) mechanism. Dr. Trimble responded that the SBIR vehicle does not provide funding outside the United States. Dr. Arul M. Chinnaiyan, Director, Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, asked about the types of companies targeted, and Dr. Stillman observed that engineers are adept at starting companies. Dr. Lowy indicated that the NCI leadership is considering IMAT as a way to advance applications, but further upstream. Dr. Graham A. Colditz, Neiss-Gain Professor of Surgery, Department of Surgery, Washington University School of Medicine, suggested that applicants should involve the low-income end user from the beginning of the work.

Dr. Califano asked in what part of the process awardees would need to consider the need for regulatory approval. Dr. Trimble stated that this concept involves conducting a trial and marketing the device, and that during this process, the grantees would develop a business plan.

Motion. A motion to concur on the Office of the Director’s request for application/Cooperative Agreement (RFA/Coop. Agr.) entitled “Cancer Detection and Diagnostic Technologies for Global Health” was approved unanimously.

NCI Cancer Genomics Cloud Pilots—Dr. George Komatsoulis

Dr. George Komatsoulis, Acting Director, CBIIT, briefed the boards on the concepts involved in cloud storage of NCI genomics data. Dr. Komatsoulis asserted that the standard model of computational analysis, which combines network access to public data repositories and analytical software with local storage and computational resources, has become obsolete because the rapid growth of information produced using next-generation sequencing technologies has resulted in high storage costs and practical barriers to data access, such as inadequate data downloading rates. He provided an example of the amount of data generated by TCGA, which currently is 0.5 petabytes (PB) but is expected to reach 2.5 PB at its completion in 2014. Integrating genomic data with other large data sets—including gene expression data, imaging data, and clinical data—has increased the complexity and added additional dimensions to the problem. Extramural and intramural NCI research scientists have reported that IT limitations currently are presenting barriers to performing high-level genomics research and slowing the pace of discovery. The alternative that the NCI is proposing is the creation of a biomedical cloud that would be a secure computational environment providing two distinct services to users: access to NCI genomic data and analytical capabilities within the cloud environment. In addition, users will be able to upload local data and conduct computational analyses using compatible local computational applications. As a first step in developing a biomedical cloud, the cloud pilot project would fund a cloud consortium comprised of three independent cloud prototypes, each with the capacity to store all of the data that will be produced by TCGA. After they are designed and implemented, the prototypes would be made available to researchers for evaluation by users within the NCI and the community. An advantage of fostering multiple design architectures is that they are anticipated to be compatible to varying degrees with different applications. Allowable prototype designs will permit inclusion of specialized and commercial products but must be open-source; focus on core data types but be capable of extension to additional data types; be interoperable to the maximum degree possible; support future expansion in data size and usage; and be financially sustainable. Initially, prototype designs would be selected using a peer-review process, and the genomics cloud development program would be re-evaluated upon completion of the pilot project. Dr. Komatsoulis indicated that possible long-term models for the NCI genomics cloud include exclusive NCI funding, institutional funding, commercial fee-for-service, or a hybrid of these three.

Subcommittee Review. Dr. Califano expressed the Subcommittee’s strong support for the concept and recommended a cost-recovery approach by extending the pilot projects to 3 years, with the final year serving as a bridge between the implementation and evaluation phases; this allows a “staggered” model. The Subcommittee weighed the merits of providing scientific questions or use of cases in the concept, recognizing that this approach applies lessons learned from the caBIG experience, with suggestions that the science cases not be limited to the ones collected thus far and that each pilot center could demonstrate several scientific projects from collaborating institutions that could not be answered without the cloud infrastructure. Other members noted that the informatics problem is daunting and suggested that the platform might be designed to facilitate analysis rather than start solving scientific problems. In addition, the Subcommittee debated the proposed Application Programming Interface (API) model, with recommendations that the three pilots have one committee that develops a common API as a group application; an alternative approach would be for groups to bid a proposal and implement the solution. The Subcommittee acknowledged the importance of making full datasets accessible and useful to noncomputational biologists as seen in the example of the Group on Earth Observations (GEO) experience, appreciated the concept’s technology and architecture agnostic characteristics, and noted that its aggressive timing ties in with the global alliance activities. The Subcommittee also wondered about the

NCI's capabilities to conduct the work itself, whether the exercise is a sorting among three clouds, the sustainability of the effort by academia or industry following the pilot phase, and whether the cloud will be limited to NCI's data or encompass cancer data from the International Genomic Consortia and other organizations and even leverage co-funding by including data from other diseases.

The first year cost is estimated at \$15 M for three awards, with a total cost of \$18 M for 2 years.

Questions and Answers

Dr. Varmus informed the members that the NCI leadership will discuss the NIH's Big Data to Knowledge (BD2K) program at its senior retreat. He said that the NCI is concerned about the sustainability of the pilots and recognized many uncertainties exist regarding the outcome of building a successful cloud. He added that the NCI was clear that it wanted those who were competing to have a sense of the kinds of questions for which users sought answers, and Dr. Komatsoulis clarified that the three pilots are seen as being complementary, not competitive. Dr. Roach suggested that the funding level be significantly enhanced to properly support the effort.

Dr. Sellers asked about the possibility of funding the pilot projects in perpetuity and expressed concern that potential players are not involved in this discussion. Dr. Komatsoulis responded that a single cloud likely is not sufficient to meet the total needs of the cancer research community. Dr. Lincoln Stein, Director, Informatics and BioComputing Platform, Ontario Institute for Cancer Research, noted that a number of institutions already are building genomic clouds and are in a position to build pilots. Dr. Pietenpol appreciated the open competition approach but encouraged discussions with organizations that already have built clouds. Dr. Sawyers supported efforts to time the pilots with the ongoing discussions of the Global Alliance Organizing Committee. Dr. Basch commended the concept as a strong proposal and observed that the population research community is facing similar issues with enormous datasets.

Dr. Drebin asked whether the pilots could be staggered so that lessons learned from the first pilot could be applied to the second pilot. Dr. Komatsoulis replied that the NCI's intent is to have the groups interact. Dr. Califano commented that limiting the pilots to one solution at a time would be challenging as the pilots will build three different tools to respond to the needs of different parts of the community.

Dr. Sellers noted that pilot projects will need to have the robust network capability to support user access of up to 10,000 users a month. Dr. Komatsoulis said that the concept has several mandatory requirements, including that the ability to make the cloud available to people external to the builder's institution must be demonstrated during the pilot.

Motion. A motion to concur on the Office of the Director's request for proposal/Broad Agency Agreement (RFP/BAA) entitled "NCI Cancer Genomics Cloud Pilots" was approved unanimously.

IX. CANCER CENTERS WORKING GROUP REPORT—DRS. KEVIN J. CULLEN AND STANTON L. GERSON

Dr. Varmus informed the members that currently 67 NCI-designated Cancer Centers receive an aggregate \$275 M in funding from the NCI. The Institute has been striving to manage budgetary reductions across its portfolio, including the funding of Cancer Centers. The wide range of Centers—by type, size, structure, portfolio, recruitment strategy, and focus—makes this challenging. He said that the NCAB *Ad Hoc* Cancer Centers Working Group was convened and met several times under the leadership of Dr. William Hait, Chair. Drs. Gerson and Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, University of Maryland, presented the Working Group's report.

Dr. Gerson told members that the Working Group met to discuss a new award cost structure that alleviates real and perceived disparities in the funding of the Cancer Center Support Grants (CCSGs). The Working Group was charged with reviewing the NCI's CCSG funding policies under the current fiscal stringency and identifying the best metrics for the NCI to use in CCSG funding allocations. The Working Group is composed of 10 Cancer Center Directors who met in person in February 2013, followed by three teleconference calls. The discussions covered the new CCSG guidelines, funding elements, and the limits on CCSG budget growth, with special consideration to issues about support for timely initiatives, the funding of new Centers, and the best ways to ensure fairness in funding. Dr. Gerson reminded members that the NCI Cancer Centers Program is perceived as highly successful, as it is a focal point for a large percentage of NCI grants and for coordinating big science, outreach, and translational efforts in cancer research. The CCSG provides a framework to align the efforts of cancer centers with the NCI's mission, promotes the leveraging of funds from other sources through the prestige of the NCI designation, and provides essential support for clinical research infrastructure and shared resources. Factors other than merit, such as longevity, size of the NCI budget and competitors, in transition bridge awards, and the entry of new centers, however, have skewed the distribution of CCSG funds. Another challenge has been that the review process did not account for the complexity and differences among centers, such as whether they are a basic, clinical, or comprehensive center, or have a university matrix, free-standing, or consortium structure.

The Working Group identified several problems, including that the disparities in the size of CCSG awards are not fully explained by either the merit scores or the size of the research base, and that the awards often are based on the size of previously funded grants. In addition, the CCSG budget process has posed challenges to the NCI at a time of fiscal constraint, and the 2013 award guidelines limit the evolution of smaller centers and impact larger ones. The amendment to the CCSG guidelines, which was implemented in January 2013, cap awards of more than \$6 M at current direct costs, allow awards of less than \$6 M to request a maximum increase of 10 percent or \$1 M, and allow new centers to request awards up to \$1 M. The amended guidelines in effect have fixed NCI funds for Centers at current levels, making increases in awards difficult over time regardless of the Centers' quality or scientific contributions.

Dr. Cullen described the Working Group's consensus recommendation that the CCSG award should be comprised of base, multiplier, and innovative supplements. The award should be implemented as a point-in-time adjustment starting around 2016 for new awards and phased in for renewal contracts. The base supplement should support standard components of centers based on the type of center. The Working Group is proposing a model using a direct-cost base of \$1 M for basic science centers, \$1.2 M for clinical centers, and \$1.4 M for comprehensive centers. A center's history should not be a factor in the base supplement, but flexibility would be used in distributing the base funding. Dr. Cullen stated that the merit score and cancer center size would be used for standard multipliers, with the merit score drawn from the peer review priority score. The merit score reflects how well the Center preformed in its last grant period, including science, translation, and impact, and takes into consideration the complexity of the Center's structure. The Working Group also discussed other multipliers, such as accrual rates to clinical trials. Dr. Cullen provided a hypothetical funding example of a comprehensive cancer center with a \$35 M direct-cost base and a favorable merit score of 23; a base award of \$1.4 M, with \$1.4 M and \$0.42 M for merit and size multipliers, respectively, yields a total direct cost award of \$3.22 M. Proposed models showed a significant correlation between the size of award and merit score, suggesting that this approach may decrease the variability in "arbitrary" CCSG funding effectively.

Dr. Cullen said that, based on where the multipliers were placed, a pool for supplements could be available to support highly innovative and impactful programs that address priority topics, such as precision medicine and global health. In addition, the Working Group agreed that the current percentage of CCSG funding to the total NCI budget should be retained. Members were told that the Working

Group's overall goal is to increase the fairness of the award process, not to arbitrarily "level the playing field." Some Centers will have greater merit, size, and complexity and will deserve greater funding than others. Additional issues to consider include adapting the model to future changes in the NCI budget, termination of poorly performing centers, budgetary feasibility and the impact of the award adjustment on centers, and support and credit for clinical investigations and accruals.

Questions and Answers

Dr. Varmus reminded members that political will is an important factor. Congress members, mayors, and others are focused on the success of the Cancer Centers in their regions and are not reticent to call the NCI Director when they perceive Centers to be losing money unfairly or to not be receiving the funding amount that they should. He reminded members that the NCI has struggled with allocating its budget, noting that nearly 80 percent of NCI's research occurs through the Cancer Center Program, and he reflected on where the Cancer Centers stand within the NCI's \$4.8 B budget. Dr. Sellers commented that the Cancer Centers have transformed the way science is conducted around care, been highly influential in the translation of basic science to the clinic, and advanced the concept of multimodality of care. He suggested that the NCI frame the issue in terms of a return on its investment.

In response to several questions about a chart depicting CCSG funding variability for the Centers in aggregate, Dr. Cullen clarified that supplemental funding is not included, reducing the base multiplier will allow more funds for supplements, separate analyses for each type of Center does not provide a more helpful picture, and no geographic adjustments are made for direct costs.

Dr. Pietenpol said that the Cancer Centers' value lies in the huge amount of resources provided to cancer research, including for institutions' philanthropic endeavors and the marketing benefit to the NCI throughout all regions of the United States. She encouraged the inclusion of a forward-looking vision as a component of the merit score or multiplier. Dr. Linda Weiss, Director, NCI Cancer Center Program, mentioned that future visions and activities of a Cancer Center are taken into account during the review process in both the past performance section and the question about future plans. Dr. Gerson indicated that a Center's vision is reflected in its merit score and stated that innovative supplements could be part of the renewal application.

Dr. H. Kim Lyerly, Vice President/Global Head of Oncology, George Barth Geller Professor of Cancer Research, Duke University School of Medicine, asked whether the CCSG could include a formal commitment from the Cancer Center institutions to monetize the benefits an institution receives by having the NCI designation for its Cancer Center, to achieve similar success as experienced by the Specialized Programs of Research Excellence (SPORes). Dr. Cullen said that institutional commitment is one of the six essential characteristics for NCI designation and that a key value of the CCSG is for Directors to leverage that importance at their home institutions. Dr. Gerson suggested that the NCI could help its designated Cancer Centers in this leverage process by helping the Cancer Center be recognized by its institution and city.

Dr. Stillman encouraged inclusion of a future vision but was wary of subjective approaches. The vision in a Cancer Center is reflected over time, and he encouraged the NCI to consider adopting the Howard Hughes Medical Institute's peer review system, which invests in great science and in people. He also requested clarification about the supplements. Dr. Cullen said that supplements are decided at the NCI leadership level to support a specific activity and could be requested by the Cancer Center or provided by the NCI. Dr. Varmus explained that the supplement allows the NCI flexibility to use the Cancer Centers in a productive way.

Dr. Roach cited three points from the presentation as very important: (1) the goal is not to arbitrarily level the playing field; (2) the goal is to increase the fairness of awards; and (3) terminating poorly performing Centers. He particularly encouraged making tough decisions regarding poorly performing centers and redistributing the funds. Dr. Gerson said that performance should be reflected in the priority score. In response to a query by Dr. Varmus, Dr. Weiss said that approximately 5 centers have been terminated from the NCI Program. She added that the Program works with struggling centers, with remediation as the first step. Dr. Varmus added that it is not uncommon to have a 50 percent reduction until the situation is ameliorated, and the multiplier allows a gentler downward reduction.

Dr. Shannon said that the Cancer Center infrastructure provides uniformity around conducting clinical trials, including monitoring, data safety, and closing out the trial, and that the Centers' investments benefit the patients as well as core research.

Dr. Olopade asked whether the Cancer Centers' interactions with the community and translation of their science to improve outcomes could be measured, and queried about the assistance that new Centers receive from the NCI to develop and maintain their relationship with the community. Dr. Gerson said that for existing Centers, community interactions likely would fall under innovation, and that the NCI Centers Office helps new Centers significantly, including identifying a catchment focus for the Center.

Dr. Califano voiced appreciation for the data-driven aspect of the model but was surprised at the small difference in the designation between basic, clinical, and comprehensive Centers. He agreed that past performance serves as a strong correlation metric and suggested that greater accountability for performance would simplify the evaluation process.

Dr. Stillman cautioned that large centers could take advantage of the size multiplier by hiring additional staff. Dr. Cullen replied that good Cancer Center Directors would be accountable for NCI grants on their campus.

Dr. Basch asked if how Centers spend their funds has been examined and whether each Center must excel in every area to perform well on the priority score. Dr. Gerson replied that the Working Group reviewed the amount of dollars spent across Centers for essential components, and he agreed that Centers should showcase their unique characteristics.

Dr. Golub told members that this is an interim report, and the Boards will receive a final report later. Dr. Varmus expressed appreciation to the Working Group for its efforts.

X. ESTABLISHING AN OUTSTANDING INVESTIGATOR AWARD—DR. DINAH S. SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology, presented information about a proposed NCI Outstanding Investigator Award (OIA). Dr. Singer stated that the NCI previously had supported an outstanding investigator grant from 1984 through 1993, but that the program was discontinued when the grants represented a substantial fraction of NCI's commitment to the research project grant pool. Members were informed that the NCI is proposing the OIA to provide long-term support to experienced investigators with outstanding records of research productivity who are likely to continue to conduct seminal cancer research. The goal is to encourage investigators to embark on innovative cancer research that breaks new ground or extends previous discoveries in new directions or applications.

Awards would be for 7 years and could include a 3-year extension, require a 50 percent time commitment for research effort, and a total up to \$600,000 in direct costs. In addition, the program would aggregate only NCI awards, and institutions would provide 20 percent salary support for the duration of

the award. Eligible candidates would have demonstrated outstanding research productivity with the potential for continued high-quality research and have been funded by the NCI for the last 5 years or more. Dr. Singer said that applicants would be nominated by their institution, provide a research strategy for the award, and include a detailed description of five of the PI's significant scientific accomplishments. Review criteria are that the PI is a leader in the field with evidence of innovation and significance in cancer research and the potential to continue at a high caliber level, relevance of the proposed scientific field to the NCI's mission, and the nominating institution's selection process for the OIA. The review process will include a three-stage editorial board review and a final level review by the NCAB. The 3-year extension would be based on the awardee's innovation and productivity, continued leadership in the field, and cutting-edge research, and also would be subject to reviews by an editorial board and the NCAB. Oversight would involve annual progress reports and an annual meeting of recipients to present their progress. Members were informed that the yearly cost is estimated at \$90–\$181 M for 20–40 awards, with a cost of \$906 K for each award, and up to 200 awards in 5 years. These awards will represent approximately 4.5 to 9 percent of NCI's research project grants.

Questions and Answers

Dr. Golub requested clarification about the types of NCI grants that will be aggregated in this vehicle. Dr. Singer replied that the grant types are R01s, and that the aggregation could be staged for OIA recipients who have 1-year grant award remaining. Dr. Varmus added that some details will be further refined, such as in instances where OIA nominees already have more than one-half of their time allocated to research through a different contract vehicle than an R01.

Dr. Califano commented that the best way to evaluate performance is through past performance, and he asked why an awardee can apply for the 3-year extension but not for a reissuance of the award. Dr. Varmus responded that a renewal is not excluded and that nominees can be at the professor level and do not have to be National Academies of Science (NAS) members. Dr. Singer added that the 3-year extension provides the ability to ramp down the research, if necessary. Dr. Sellers observed that a 3-year extension likely would ensure that the OIA is perceived as a *de facto* 10-year award; he recommended that it be a 7-year award, with a reapplication mechanism effective in the fifth year.

Dr. Califano suggested that the NCI consider reducing the burden of time for OIA recipients who hold large center or collaborative grants that require a one-third or more time allocation to the center; if the center's RFA requires 30 percent of an investigator's dedicated time, one-half of that time would be in support of the OIA. Dr. Champion agreed that the 50 percent time commitment may be challenging for OIA recipients to meet due to heavy workloads. Dr. Shannon countered that allocating 50 percent of one's time to the research effort is appropriate for the OIA, which has the aim of funding the best science; an administrator should not be eligible for this award.

Dr. Sawyers voiced strong support for this award, encouraged the NCI to discourse with the Howard Hughes Medical Institute (HHMI) about their awards, and asked whether the NCI has calculated the number of R01 investigators who have multiple awards. Dr. Varmus indicated that most individual investigators have one R01, some have two R01s, and far fewer have up to four. Dr. Sawyers recommended that a stipulation for this prize could be to serve once a year on a study section. Dr. Singer stated that the NCI is considering this issue broadly, and Dr. Varmus pointed out that not all outstanding investigators are good peer reviewers.

Dr. Cruz-Correa suggested that the NCI consider reducing the OIA from 9 percent to 5 percent of the total budget and reserving 45 percent for the Cancer Centers or other research mechanisms. Dr. Singer said that, if the peer review system has been used properly, OIA recipients would be funded through the R01 mechanism anyhow.

Dr. Ferrell expressed concerns about the potential detracting of awards from new investigators and encouraged the NCI to obligate some of an OIA recipient's time as a mentor for young investigators. Drs. Cullen and Roach also indicated concerns about the real and perceived impact on new investigators. Dr. Shannon referred to the American Cancer Society (ACS) professorship program as a possible model for a mentoring criterion. Dr. Singer professed the NCI's commitment to support new investigators but pointed out that this award is intended to serve the mid-career group. Dr. Varmus stated that the OIA will not take funds from young investigators and that most of NCI's funding supports more established investigators who continue to conduct excellent science.

Dr. Lysterly asked about the advantages and differences of the OIA compared with the MERIT program. Dr. Singer said that the OIA is not comparable with MERIT and has a different goal of providing long-term, stable funding for outstanding investigators. Dr. Varmus reminded the members that MERIT awards are not applied for but rather advanced by the Program Officer for select awards with high-priority scores. In addition, the MERIT program is not a systematic process like the OIA.

Dr. Hughes-Halbert encouraged the NCI to ensure that the OIA encompasses a broad representation of disciplines, including health sciences and population sciences research. Dr. Varmus agreed and noted that institutions making nominations should be cognizant of this.

Dr. Olopade stated that this mechanism is to improve efficiencies in the system of peer review and relieve scientists of incessant grant writing so that they can focus on conducting science.

Motion. A motion to concur on the direction of the Outstanding Investigator Award (OIA) was approved unanimously.

XI. ONGOING AND NEW BUSINESS—DR. TODD R. GOLUB

Ad Hoc Subcommittee on Global Cancer Research. Dr. Olopade, Subcommittee Chair, provided a brief report of the Subcommittee's meeting. Members were informed that the Subcommittee met and heard about the activities of the CGH during the past 6 months. A Global Cancer Research Day, held in conjunction with the Consortium for Universities in Global Health, was over-subscribed, and the CGH received positive feedback from Cancer Center participants. Dr. Olopade said that a \$200,000 pilot RFA for Cancer Center collaboration with organizations in LMICs received 43 applications. In addition, the NCI is compiling a report about international activities of NCI-designated Cancer Centers, including 69 projects in China; 10 or more each in Brazil, India, and Uganda; and nine each in Nigeria, Mexico, South Africa, and Tanzania. The Subcommittee also was informed about the Short-term Scientist Exchange Program (STSEP), a popular program that brings scientists from LMICs to the NIH for short-term training; many are from the Middle East and Africa, and there are plans to expand to Eastern Europe and Latin America. The Subcommittee discussed global health career track and training, including the Fulbright and Fogarty fellowship programs, as well as whether decisions about research priorities are based on United States or LMIC needs. Brief consideration was given to the idea of extending the NCI-designation to cancer centers who conduct international research; the Subcommittee's consensus was that the conduct of global cancer research is sufficient. The PEPFAR reauthorization may present additional ways to fund global cancer research, drawing on the activities of the Pink Ribbon/Red Ribbon Alliance and the efforts concerning HPV vaccination, including the enthusiasm engendered by the PCP's workshops.

Discussion

Dr. Lyerly commended NCI's efforts to enhance and leverage global efforts through connections among activities; he said that the convening power of the NCI is creating substantial opportunities.

Dr. Francis Ali-Osman, Margaret Harris & David Silverman Distinguished Professor of Neuro-Oncology Research, Duke University School of Medicine, encouraged the NCI to develop effective metrics of success, particularly with STSEP.

Ad Hoc Subcommittee on Communications. Dr. Champion, Subcommittee Chair, provided a brief report of the Subcommittee's meeting. She reported that the Subcommittee is working under a revised charge to evaluate and prepare a report on how the NCI's Web presence aligns with or diverges from industry best practices, as well as how NCI's online efforts might be better coordinated, resourced, managed, and made more efficient. Current challenges include costs associated with the production and magnitude of website activities, the lack of a cohesive NCI identity, the difficulty in ensuring standards, the lack of interconnectivity, and the varied audiences. The Subcommittee was provided with information about NCI's current website configurations and determined that its first task would be to prioritize the audiences and then identify the types of information that the NCI publishes online.

Ad Hoc Subcommittee on Human Immuno-deficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancy. Dr. Yarchoan presented preliminary recommendations from the BSA *Ad Hoc* Subcommittee on HIV and AIDS Malignancy's meeting on February 14, 2013. Members were informed that approximately \$255 M of NCI's budget are designated as "AIDS dollars," which are by the NIH Office of AIDS Research (OAR). The NCI is congressionally mandated to spend these on AIDS-related research. NCI's AIDS research is coordinated by the Office of HIV and AIDS Malignancy (OHAM), but the activities take place in nearly all of the Divisions, Offices, and Centers. OHAM also directly manages some of the NCI AIDS research. Extramural research is focused on AIDS malignancy, whereas intramural research also includes HIV. Notable epidemiologic changes in AIDS malignancies have occurred, particularly since the development of highly active anti-retroviral therapy (HAART). These include a decrease and then leveling of AIDS-related malignancies, as well as a substantial increase in non-AIDS defining cancers among AIDS patients as the AIDS population in the United States has aged and lived longer with HIV infection. A significant problem of AIDS-related malignancy exists internationally.

The Subcommittee was formed in 2012 to advise the BSA and NCI leadership; advance knowledge in this area; and provide advice on research opportunities, priorities, and needs on HIV/AIDS malignancies associated with cancer research. In its discussions, the Subcommittee identified the underlying theme that HIV malignancies represent a unique experiment of nature because of the high incidence and speed at which certain cancers develop. The NCI was encouraged to integrate this research into general cancer research to promote cross-fertilization, and to focus on seven HIV-associated cancers: Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin disease, anal cancer, liver cancer, lung cancer, and HPV-related tumors. The Subcommittee encouraged the study of HIV tumors as experiments of nature as well as a Provocative Question initiative focused on AIDS malignancies. In addition, the Subcommittee endorsed the HSIL Outcome Study (HOST), a trial to determine if treating anal high grade anal intraepithelial lesion (HSIL) can prevent anal cancer, articulated a need for epidemiologic studies, and encouraged capacity building and research in resource-limited regions where AIDS malignancies abound.

Dr. Yarchoan stated that the Subcommittee also supported an increase in efforts to improve epidemiologic data on malignancies in resource-limited areas, such as sub-Saharan Africa, Latin America, and Asia, because data is so incomplete and unreliable. Additional recommendations were to conduct genetic typing of HIV-associated malignancies, including the inclusion of tumors from HIV in sequencing efforts beyond the Center for Genomics' current focus on lymphoma, cervical cancer, and lung cancer from HIV patients. Expertise within the NCI and Cancer Centers might assist in efforts to "cure" HIV infection

because of the techniques used. In addition, the Subcommittee noted that studies of cancer in HIV patients might provide synergies for other cancer research. It advocated for NCI's continued efforts to identify novel infectious agents and understand those tumors where there are not causative agents; study the tumor microenvironment, including how HIV proteins may affect tumor development; and investigate changes in tumor incidence. Dr. Yarchoan indicated that the NCI has begun work already on some of the Subcommittee's recommendations, including planning a Provocative Questions workshop on the topic.

Motion. A motion to accept the summary reports of the 7 February 2013, and 23 June 2013 NCAB *Ad Hoc* Subcommittee on Global Cancer Research meeting, and the 23 June 2013 NCAB *Ad Hoc* Subcommittee on Communications meeting were approved unanimously.

Motion. A motion to accept the summary report of the 14 February 2013 BSA *Ad Hoc* Subcommittee on Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancy meeting was approved unanimously

XII. CLOSED SESSION— DR. TODD R. GOLUB

“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.

The NCAB *en bloc* vote for concurrence with IRG recommendations was unanimous. During the closed session, a total of 2,234 NCI applications requesting support of \$629,708,468 and 4 FDA applications were reviewed.

XIII. ADJOURNMENT—DR. TODD R. GOLUB

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

There being no further business, the 2nd joint meeting of the BSA/NCAB was adjourned at 12:00 p.m. on Tuesday, 25 June 2013.

Date

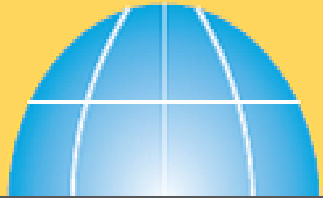
Todd R. Golub, M.D., Chair, BSA

Date

William R. Sellers, M.D., Interim Chair, NCAB

Date

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



THE HPV
VACCINE
EXAMPLE

2012-13

THE PRESIDENT'S
CANCER PANEL

PRESIDENT'S CANCER PANEL UPDATE

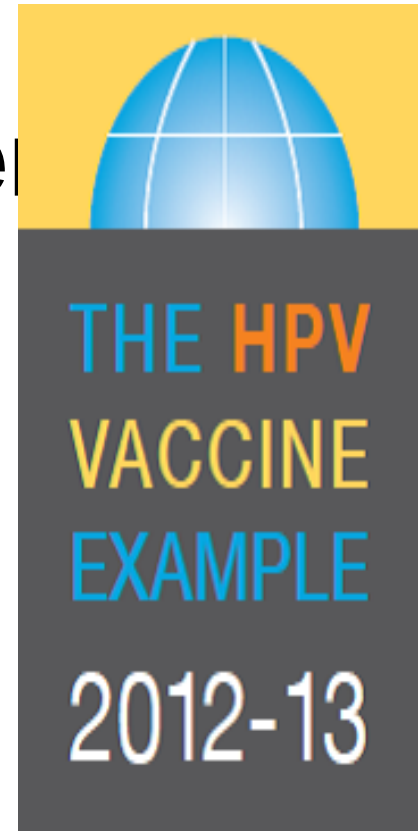
NATIONAL CANCER ADVISORY BOARD
MEETING

6/24/2013

Barbara K. Rimer, DrPH

Overview

- **Update: HPV Vaccine Series**
- **2013-2014 Series**



THE PRESIDENT'S
CANCER PANEL

PCP Mission

- ❑ **The Panel shall monitor the development and execution of the activities of the National Cancer Program, and shall report directly to the President.**
- ❑ **Any delays or blockages in rapid execution of the Program shall immediately be brought to the attention of the President.**

PCP Members

- **Barbara K. Rimer, DrPH,**
Univ. of North Carolina at Chapel Hill (Chair)
- **Owen N. Witte, MD,**
Univ. of California Los Angeles (Member)
- **Hill Harper, JD,**
*Cancer Survivor, Actor and Best-Selling
Author, Los Angeles, CA (Member)*

Accelerating Progress in Cancer Prevention: The HPV Vaccine Example

Four Workshops *(completed)*

1. **HPV Vaccination as a Model for Cancer Prevention**
2. **Achieving Widespread HPV Vaccine Uptake**
3. **Creating an Integrated HPV Vaccination and Screening Program**
4. **Challenges of Global HPV Vaccination**

Early HPV Vaccine Impact in the US

MAJOR ARTICLE

Reduction in Human Papillomavirus (HPV) Prevalence Among Young Women Following HPV Vaccine Introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010

Lauri E. Markowitz,¹ Susan Hariri,¹ Carol Lin,¹ Eileen F. Dunne,¹ Martin Steinau,² Geraldine McQuillan,³ and Elizabeth R. Unger²

¹Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, and ²Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; and ³National Center for Health Statistics, CDC, Hyattsville, Maryland

Background. Human papillomavirus (HPV) vaccination was introduced into the routine immunization schedule in the United States in late 2006 for females aged 11 or 12 years, with catch-up vaccination recommended for those aged 13–26 years. In 2010, 3-dose vaccine coverage was only 32% among 13–17 year-olds. Reduction in the prevalence of HPV types targeted by the quadrivalent vaccine (HPV-6, -11, -16, and -18) will be one of the first measures of vaccine impact.

Methods. We analyzed HPV prevalence data from the vaccine era (2007–2010) and the prevaccine era (2003–2006) that were collected during National Health and Nutrition Examination Surveys. HPV prevalence was determined by the Linear Array HPV Assay in cervicovaginal swab samples from females aged 14–59 years; 4150 provided samples in 2003–2006, and 4253 provided samples in 2007–2010.

Results. Among females aged 14–19 years, the vaccine-type HPV prevalence (HPV-6, -11, -16, or -18) decreased from 11.5% (95% confidence interval [CI], 9.2–14.4) in 2003–2006 to 5.1% (95% CI, 3.8–6.6) in 2007–2010, a decline of 56% (95% CI, 38–69). Among other age groups, the prevalence did not differ significantly between the 2 time periods ($P > .05$). The vaccine effectiveness of at least 1 dose was 82% (95% CI, 53–93).

Conclusions. Within 4 years of vaccine introduction, the vaccine-type HPV prevalence decreased among females aged 14–19 years despite low vaccine uptake. The estimated vaccine effectiveness was high.

Keywords. human papillomavirus; vaccine effectiveness; HPV vaccine; vaccine impact; prevalence.

“We found a [56%] decrease in vaccine type HPV prevalence among females 14–19 y.o. in the vaccine era (2007–2010) compared with the pre-vaccine era (2003–2006).”

Markowitz et al, J Infect Dis. (2013) doi: 10.1093/infdis/jit192
First published online: June 19, 2013

Early HPV Vaccine Impact in the US

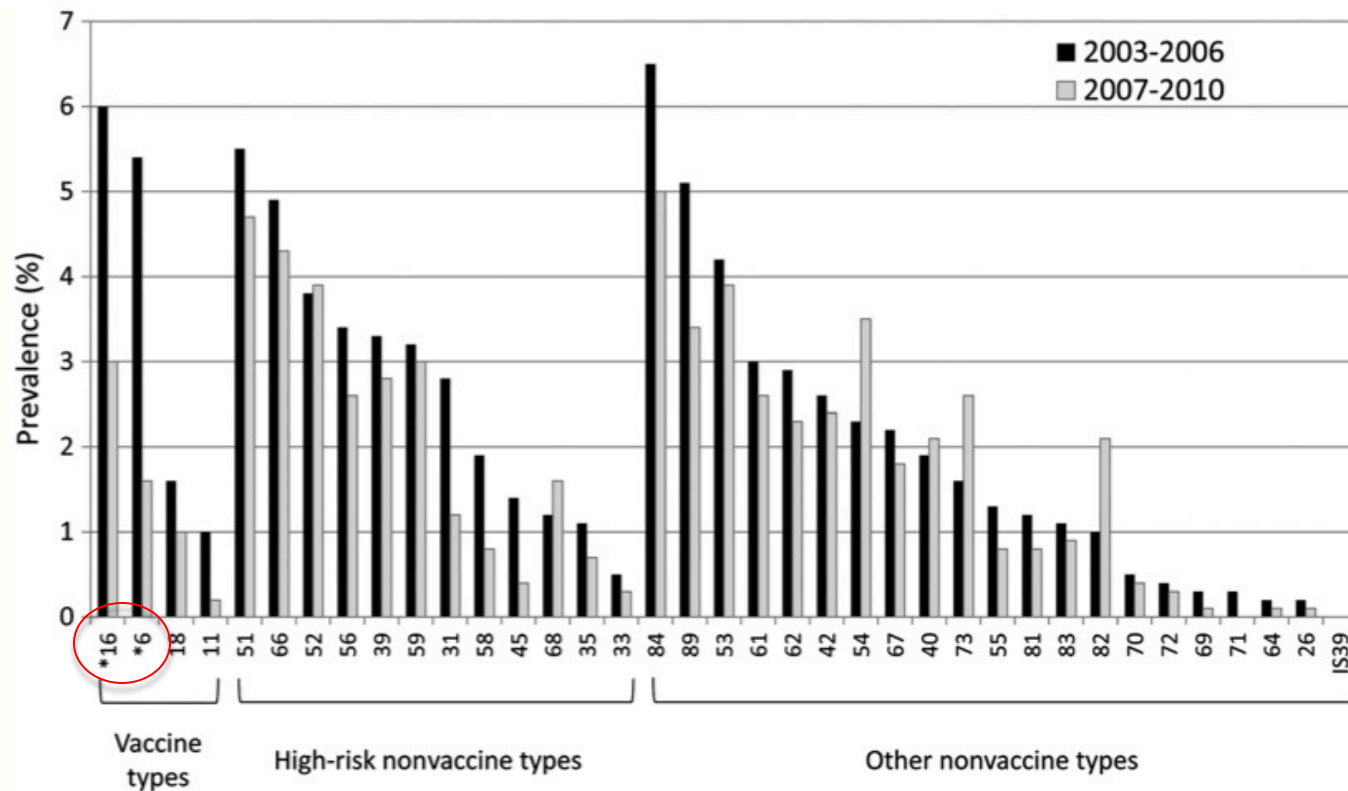


Figure 1. Prevalence of individual human papillomavirus (HPV) types among females aged 14–19 years, 2003–2006 and 2007–2010. Data are for all females aged 14–19 years, including those who did not report having had sex. HPV types ordered from highest to lowest prevalence in the prevaccine era within each HPV type category. Estimates with a relative standard error (RSE) of >30% or <10 observations: 2003–2006, HPV-11, -26, -33, -64, -69, -71, -72, -82 and -IS30; 2007–2010, HPV-11, -18, -21, -26, -31, -33, -35, -45, -55, -56, -58, -64, -69 -70, -72, and -81 (Supplementary Table 1 provides further detail). * $P < .05$.

Challenges of Global HPV Vaccination

(Miami, 4/23 - 24, 2013)

Workshop Co-Chairs

- Rima Khabbaz, MD (CDC)
- Ted Trimble, MD, MPH (NCI)
- Funmi Olopade, MD, FACP
(University of Chicago), NCAB

Challenges of Global HPV Vaccination

Workshop Foci

- **Global epidemiology of HPV infection and HPV vaccination coverage**
- **Global HPV vaccine policy and financing**
- **Global vaccine program development, implementation, monitoring and evaluation**

22 participants from various global regions and organizations

Argentina

Australia

Canada

Mexico

Rwanda

Spain

**Bill & Melinda Gates
Foundation**

GAVI Alliance

PATH

**GlaxoSmithKline
Biologicals**

Merck Vaccines

IARC

PAHO

University of Chicago

**University of North
Carolina**

**US Centers for Disease
Control and Prevention**

US DHHS

**US National Cancer
Institute**

WHO

Challenges of Global HPV Vaccination

Key Points

- **Effective communications are a critical component of all HPV vaccine programs, in high- and low-resource settings.**
- **Clear, concise messages from credible sources increase vaccine uptake.**

Challenges of Global HPV Vaccination

Key Points

- ❑ **Financial resources and infrastructure (e.g., cost of purchasing and delivering vaccines) are implementation barriers for low and middle-income countries.**
- ❑ **US should continue to support programs like GAVI that make HPV vaccines available in low-resource areas.**



SAVING LIVES AND PROTECTING
HEALTH THROUGH IMMUNISATION
IN DEVELOPING COUNTRIES

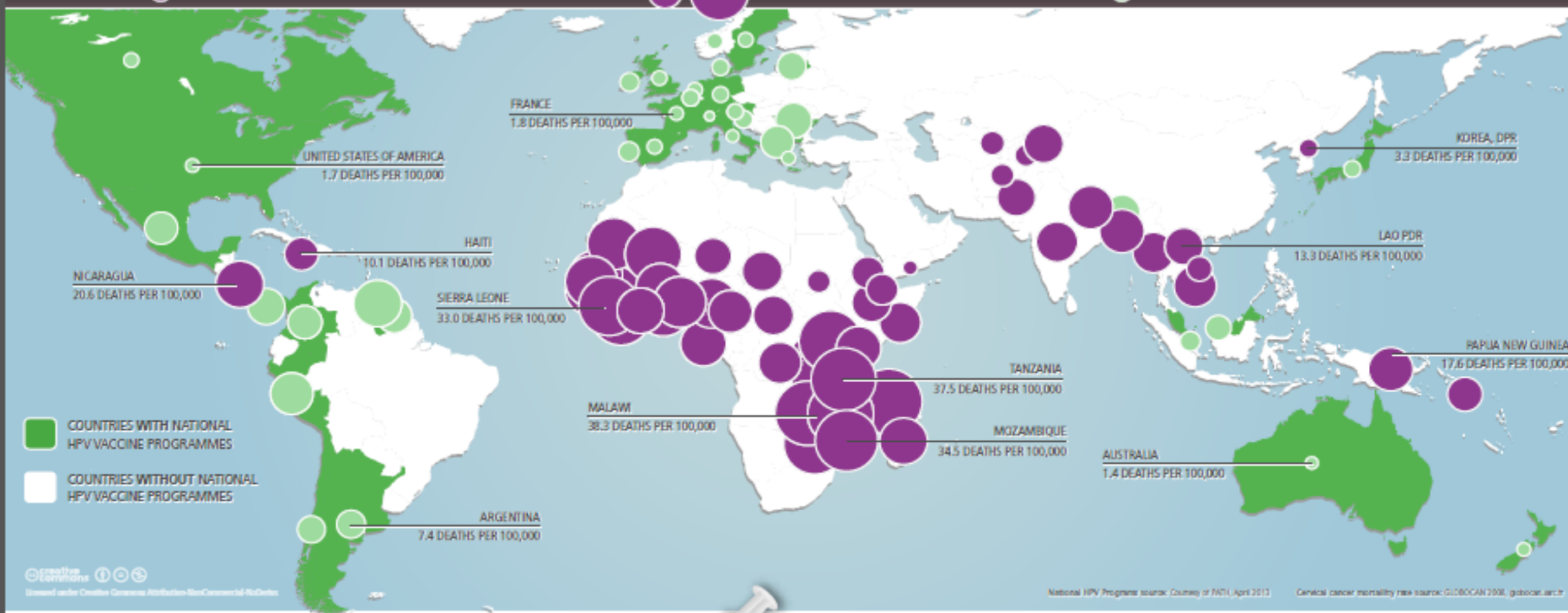
GAVI ALLIANCE TACKLES CERVICAL CANCER

EVERY YEAR, 275,000 WOMEN DIE OF CERVICAL CANCER. OVER 85% OF THOSE DEATHS ARE IN DEVELOPING COUNTRIES

○ COUNTRIES ELIGIBLE FOR GAVI'S HPV VACCINE FUNDING

○ 1 ○ 10 ○ 30 SCALE: CERVICAL CANCER DEATHS PER 100,000

● COUNTRIES WITH NATIONAL HPV VACCINE PROGRAMMES



CHANGING THE BALANCE



GAVI's support for HPV vaccines will help redress the inequity, delivering vaccines to countries with the highest burden.

ABOUT HPV VACCINE



Safe and effective, human papillomavirus (HPV) vaccines protect against 70% of cervical cancer.

LOWERING THE PRICE



The new low price of US \$4.50 per dose marks a two-thirds reduction on the current lowest public sector price.

DRAMATIC ACCELERATION

By 2020, over **30** million girls in more than **40** countries will be vaccinated against HPV

The first GAVI-supported HPV vaccines will be delivered in May 2013.

What can the US learn from the rest of the world?

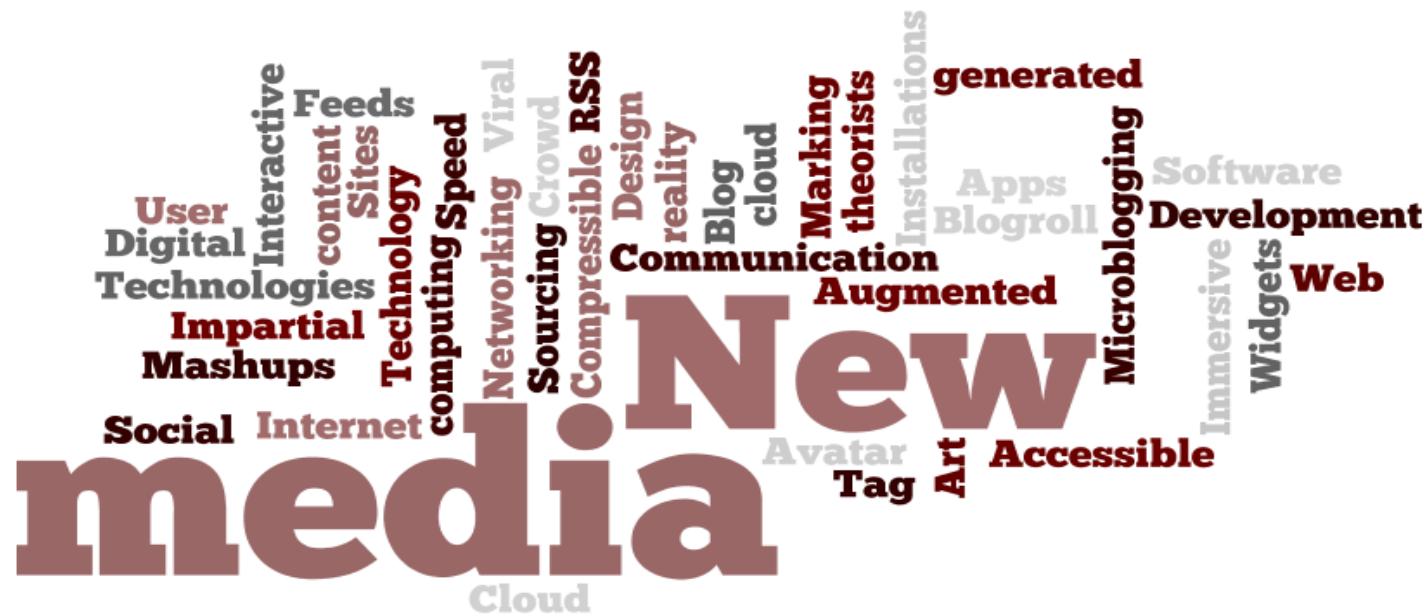
- ❑ **Champions should be recruited to promote HPV vaccination within US.**
- ❑ **US should develop stronger public health messages to encourage HPV vaccination and use multiple channels.**
- ❑ **US should support research to make vaccine delivery affordable and sustainable.**
 - **Vaccine research (e.g., reduced dosage)**
 - **Health delivery systems research**

Next Steps...

Coming
Soon

- ❑ **Cross-walks to show how our recommendations complement those of others**
- ❑ **Designs for online and mobile versions**
- ❑ **Report completed late summer**
- ❑ **Examine ways to assess**

EMERGING MEDIA AND CANCER PREVENTION



Prospects, Perspectives &
Partnerships

Emerging Media and Cancer Prevention

- ❑ **Massive shifts in how people get information**
 - **85% of US adults use the Internet.**
 - **72% of them looked for health information online.**
 - **56% of US adults use smartphones.**
- ❑ **Emerging media enable access to the vast universe of information about how to prevent, detect, diagnose, and treat cancer.**



Fox S., Health Online, Pew Internet & American Life Project, Jan 15, 2013,
<http://www.pewinternet.org/Reports/2013/Health-online.aspx>, June 12, 2013.

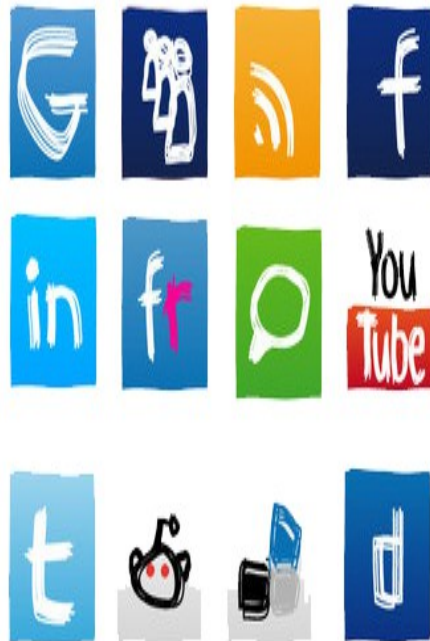
Emerging Media and Cancer Prevention



- ❑ The Internet has altered boundaries between communicators and the public.
- ❑ Older technologies, such as print, television and radio, co-exist with new technologies.
- ❑ Online sources and communities are vital communication portals.
- ❑ Government and NGO communicators

Emerging Media and Cancer Prevention

Social Media Landscape



New Media



Emerging Media and Cancer Prevention

- ❑ **More information, more ways to access it, and more communicators than ever before**
- ❑ **Content can be created by anyone.**
- ❑ **Established organizations (incl government) are no longer the only respected or sought after communicators.**
- ❑ **Rapid pace of technological innovation creates a growing gap between public**

Emerging Media and Cancer Prevention



- **How can we accelerate use of emerging media for cancer control, especially, prevention?**
 - **Today, no major cancer organization has a free or low-cost E-book on how to prevent or cope with cancer. (Google search 6/17=0)**
 - **Could we have known, even before Twitter, that we would need to highlight the benefits of quitting smoking in 140 characters?**
 - **On 6/18, 6-10 tweets/minute mentioned HPV vaccines.**
 - **Mobile health applications are proliferating, but**

Emerging Media and Cancer Prevention

- ❑ Still, millions of people in the US lack access to credible health information.
- ❑ Inequities in communication may widen knowledge gaps instead of bridging them.
- ❑ May also exacerbate health c
- ❑ Emerging media could improve reach of communication about cancer prevention to diverse audiences



Emerging Media and Cancer Prevention: **Planning**

Workshop

- ❑ **Invitees--people who can anticipate the future**
- ❑ **Leaders and innovators from communication, technology (including EHR, mHealth, and HIT developers), policy, academic, health, government and advocacy sectors**
- ❑ **Shape series on use of emerging media to accelerate cancer prevention and reduce cancer communication inequities**

Emerging Media and Cancer Prevention:

Planning Workshop

- Identify who should participate to discuss:
 - ▣ Strategies to overcome barriers to health organizations' use of emerging media to improve health and reduce communication inequities;
 - ▣ How to increase individuals' access to emerging media; and
 - ▣ Opportunities to link EHRs w/ individualized health messages.

Contact Information:

President's Cancer Panel

9000 Rockville Pike

Bld. 31/B2B37

Bethesda, MD 20892

(301) 451-9399

pcp-r@mail.nih.gov

<http://pcp.cancer.gov>



Implementation of the RAS Program

David C. Heimbrook, Ph.D.
CEO, SAIC-Frederick

Presentation to Joint BSA / NCAB Meeting

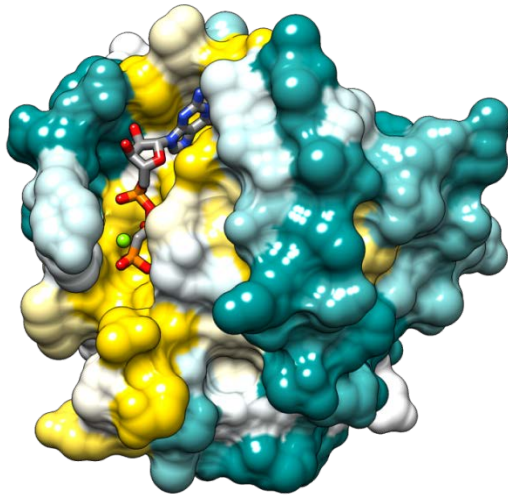
June 24, 2013

Frederick National Laboratory Missions

What is RAS, and why is it so important?

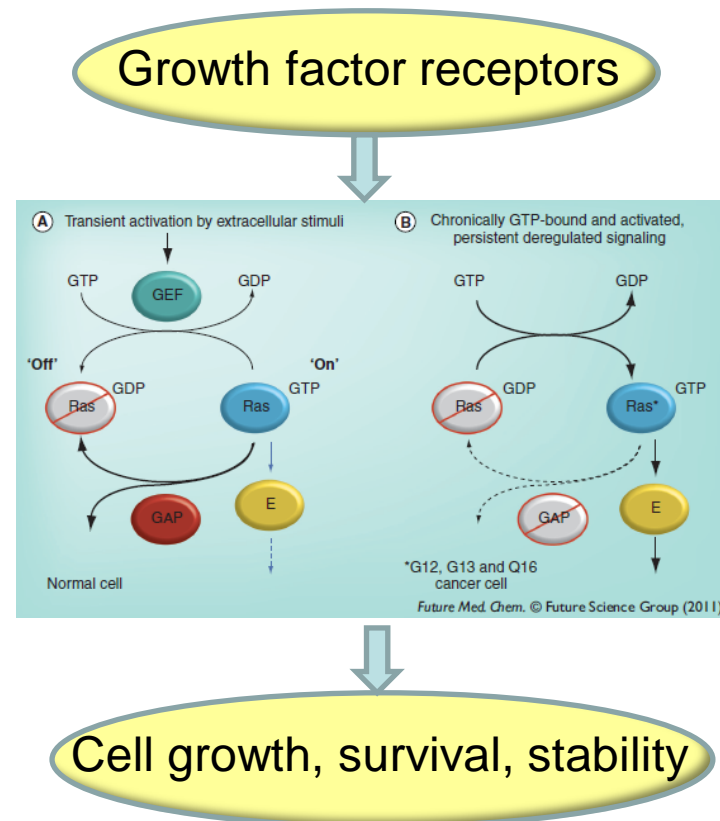
RAS stands for **R**at **S**arcoma viral oncogene homolog, and is a protein which is a key regulator of signal transduction in normal and cancerous cells

- Four flavors : **H**arvey, **K**irsten (A & B), and **N**euroblastoma



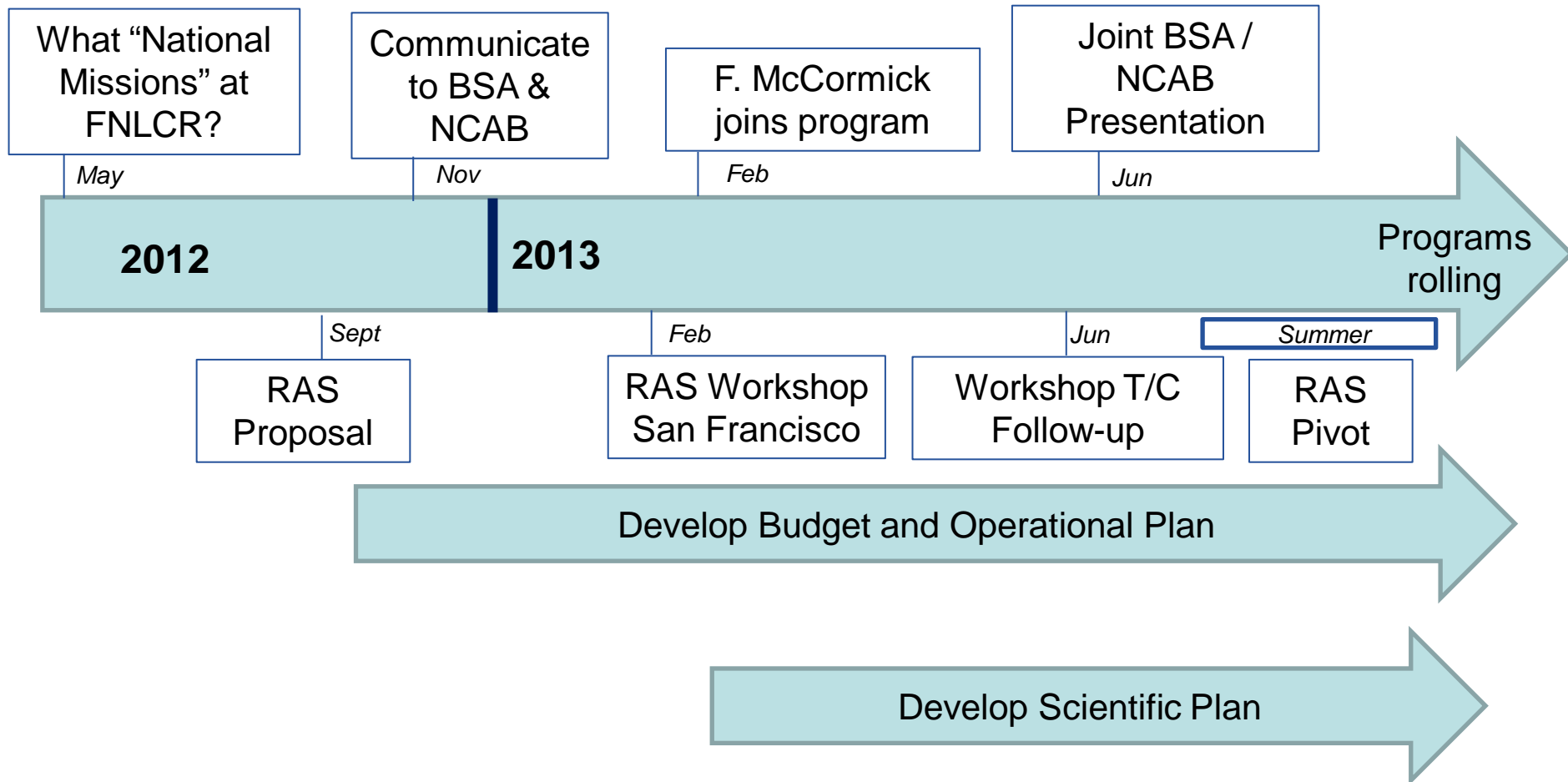
HRAS

(Wikimedia commons)



Mutated RAS is found in ~33% of human cancers, is currently undruggable, and enables resistance to many existing cancer therapies

Etiology of the RAS Program at FNLCR



Full-Spectrum Research & Development at FNLCR

Frederick
National
Laboratory
for Cancer Research

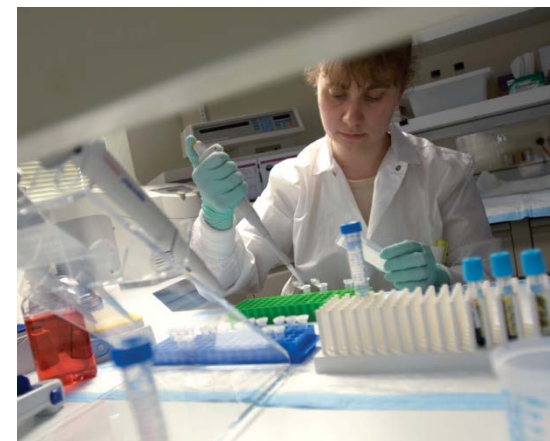
Research & Development

- **Basic Research:** New knowledge about AIDS and cancer
- **Applied R&D:** New diagnostics and therapeutics
- **Clinical Research:** Clinical trials and laboratory analysis
- **cGMP manufacturing:** Biologicals and vaccine production



Specialties

- Genomics, proteomics, and metabolomics
- Bioinformatics and imaging
- Nanotechnology
- Animal models
- Tumor cell biology and virology
- Immunology and inflammation



Customers

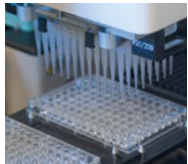
- NCI, NIH, and external academic and commercial biomedical scientists

All FNLCR assets and expertise are available to the RAS program

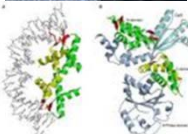
Implementing “National Missions” at FNLCR *The RAS Hub*

Frederick
National
Laboratory
for Cancer Research

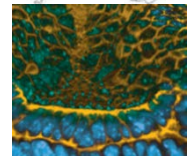
Essential capabilities....



Genetics and Genomics



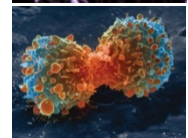
Proteins and Proteomics



Imaging and Nanotechnology



Advanced Biomedical Computing



Cell Biology

...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

Operationalizing the RAS Program

Hub and Spoke model

Intramural Labs



Extramural NCI-Supported Labs



FNLCR – The Hub



Biotechs



Pharma



Contract Research

Hub Partnerships Facilitated through NCI and **Contractor** Mechanisms

Material Transfer Agreement (MTA)

- Research materials transferred (in or out); research plan
- No fees; No joint IP

Technical Services Agreement

- Purchase of contractor-developed assays or reagents
- Minimal paperwork; Assay list online
- Cost recovery only

Collaboration Agreement

- Research materials transferred (in or out);
- Research plan developed
- Both contribute intellectually; no \$\$ to NCI

Cooperative Research & Development Agreement (CRADA)

- R&D collaboration both partners contribute intellectually
- Both contribute resources; can include \$\$ to NCI
- Both NCI and **Contractor** mechanisms

The RAS Program

Funding Model

- **Funding for FNLCR RAS Hub**

- Approximately \$10 M / yr from NCI-directed re-prioritization of ongoing activities within the existing FFRDC contract - No new money
 - The Advanced Technology Program “Pivot” re-orientes a predominantly intramural effort towards driving the RAS Hub
 - Additional “one-time” funds from within the existing contract facilitate start-up activities
- This funding supports ongoing research activities within the Hub, as well as initial phase of subcontracts between the Hub and external laboratories

- **Funding for RAS Spokes**

- Contract Research Organization – subcontracts from FNLCR RAS Hub
- Pharma, Biotech – Self-funded
- Academic : Some subcontracts from FNLCR RAS Hub;
 - Existing and future grantees working on RAS will have the opportunity to participate in RAS program

The RAS Program

Oversight and Governance

- **Oversight**

- An NCI-Frederick Advisory Committee (NFAC) subgroup will be formed
 - Will include NFAC members and representatives from academia and industry (TBD)

- **Research Program Prioritization**

- Joint recommendations by RAS Program leadership (Frank McCormick and SAIC-F leadership) and RAS Program oversight group, with concurrence by NCI Leadership (Drs. Varmus and Lowy)

The Ras Project: Overview



The clinical need

- High incidence of RAS mutations in cancer
- No drugs that target RAS proteins directly or indirectly
- No therapies effective for RAS-driven cancers
- RAS cancers excluded from treatment with targeted therapies

The approach

- Focus on alleles of RAS that cause human cancer (G12D, G12C, G12V, G13D)
- Hub and Spoke model
- Solve critical structures, coordinate drug discovery efforts
- Optimize novel assays for disrupting RAS signaling
- Map surfaces of KRAS cancer cells to facilitate drug delivery, immune attack
- Optimize MABs, proteins, cell lines, mice, etc for research community

The opportunities

- New ways of targeting un-druggable proteins
- Better, faster ways of structural analysis
- New ways of interrogating signaling networks
- Power of RNAi for target identification and therapy
- Harnessing the immune system
- Better mouse models

RAS mutations in human cancer

Pancreatic	95%	KRAS
Colorectal	45%	KRAS
Lung adenoCA	35%	KRAS
AML	30%	NRAS
Melanoma	15%	NRAS
Bladder	5%	HRAS

Major knowledge gaps

- No structures of mutant KRAS proteins with regulators or effectors
- Different alleles have different clinical outcomes, don't know why
- Don't know which effectors are important in established cancers
- Don't know which cancers remain RAS-dependent
- Signaling complexes un-characterized
- Don't know how to target KRAS cancers for drug delivery or immune therapy

Project One: Allele specific compounds.

Focus on the alleles that are most prevalent in human cancer, G12D, G12C, G12V and G13D. G12V and G12C

- Determine which effectors each of these engages
- Solve structures of mutant protein complexed with relevant effectors and regulator
- Identify new opportunities for small molecule intervention

KRAS mutations in 3 diseases

	G12C	G12D	G12V	G13D
Colorectal	6,300	22,000	12,600	11,250
Lung	22,000	9,520	11,900	1,190
Pancreas	1,200	19,000	12,000	1,000
Total	29,500	50,520	36,500	13,440

Distinct biological and clinical properties of KRAS alleles

KRAS G12V, G12C worse clinical outcome than G12D

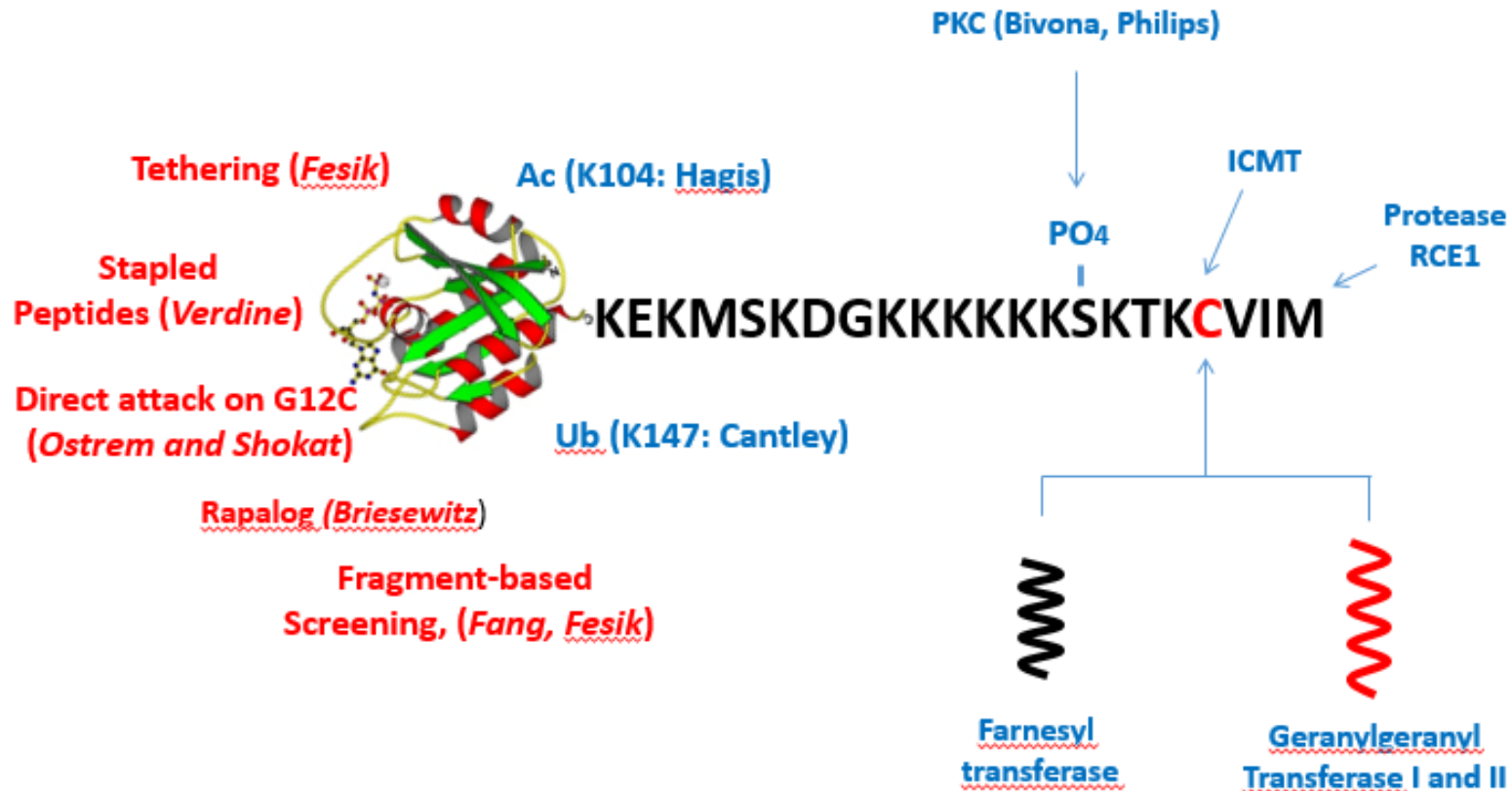
KRAS G12D: elevated PI 3' kinase, MAPK signaling

KRAS G12C, G12V: elevated RalGDS signaling

KRAS G13D: responds to Cetuximab: G12 mutants do not....

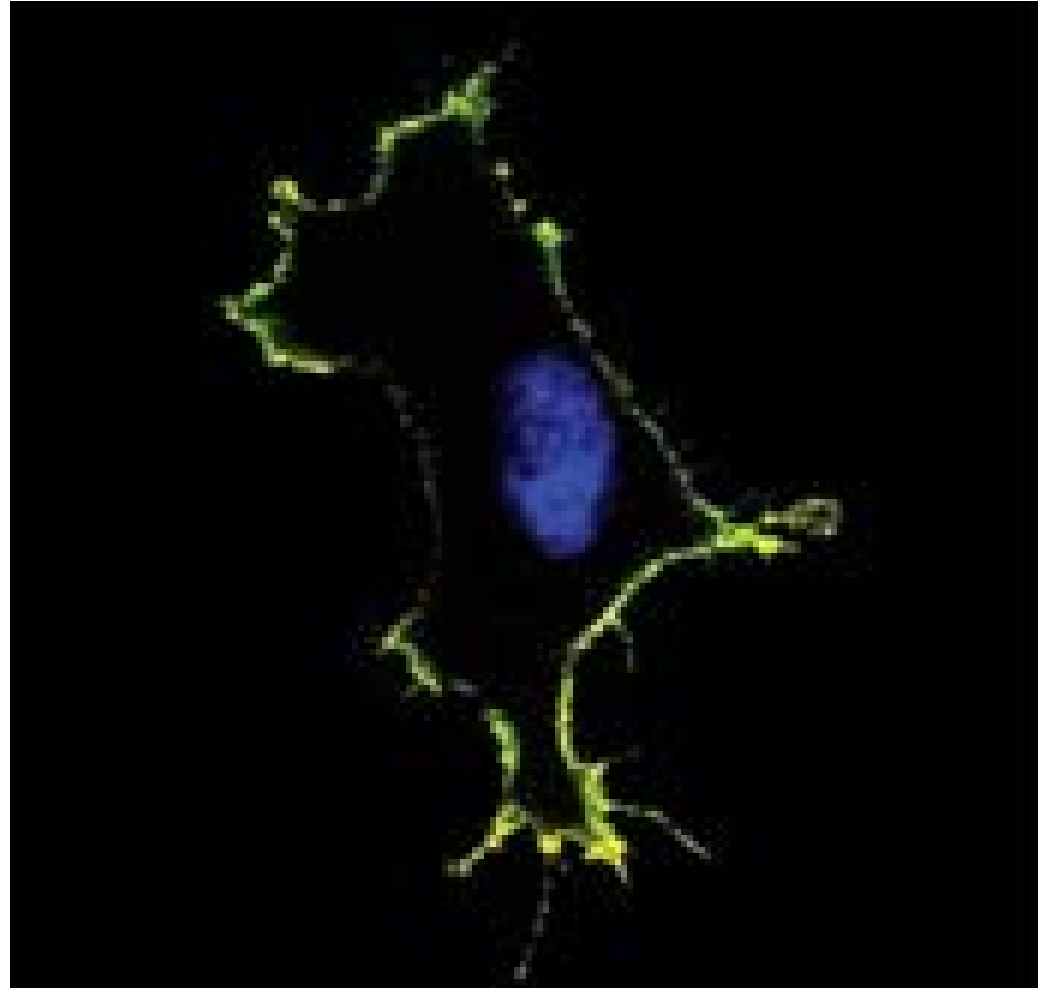
Project Two: KRAS selective compounds.

Ablation of KRAS may be effective, without being allele specific



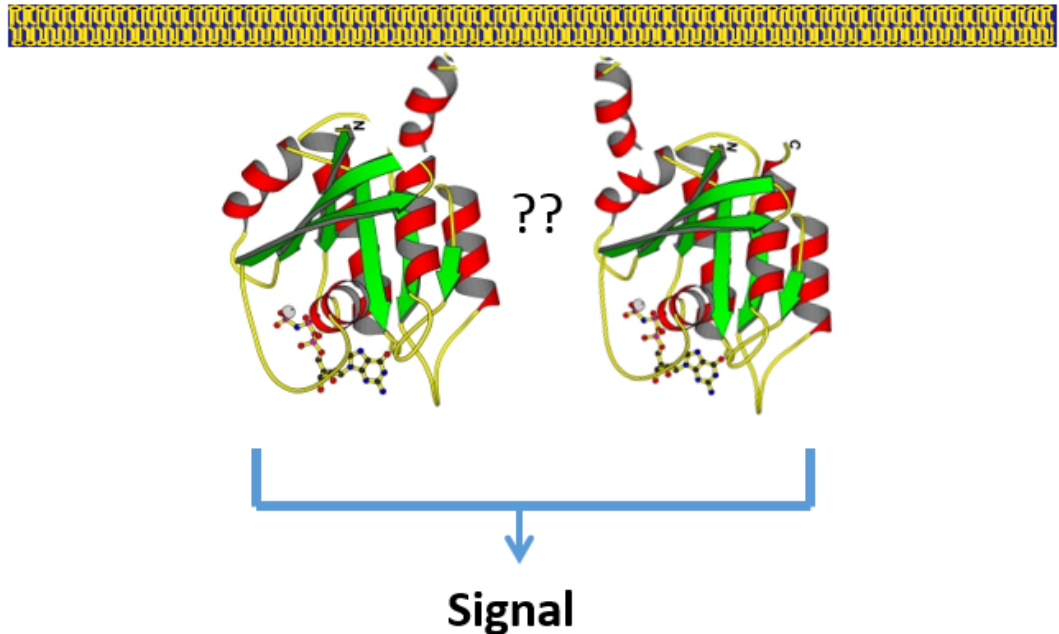
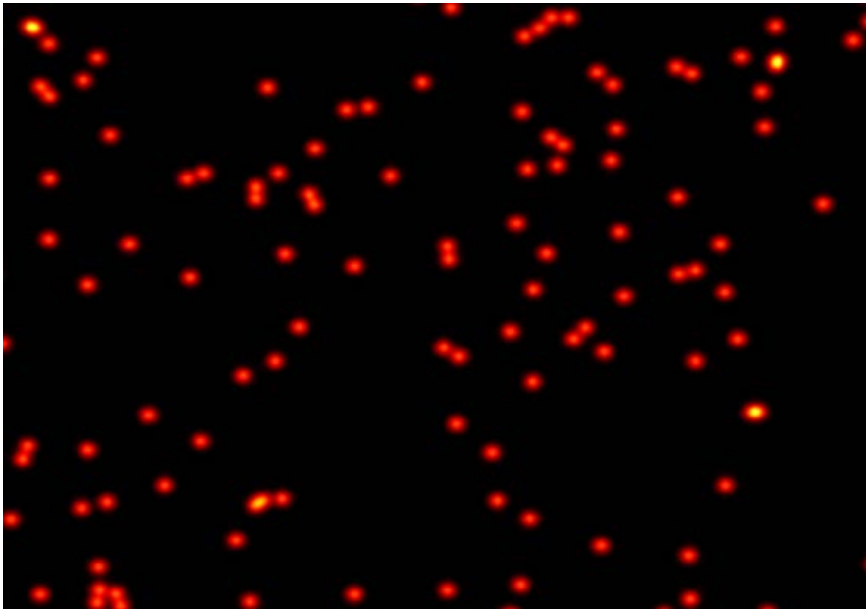
Project Two: KRAS selective compounds.

Preventing KRAS signaling from the plasma membrane (eg from Mark Philips)



Project Three: Disrupting KRAS complexes

- Develop imaging methods to identify KRAS complexes in cells
- Develop screens for disrupting complexes



Project Four: Mapping the surface of KRAS cancer cells

- analyze the protein composition of K-RAS cancer cell membranes
- identify peptides that could be targeted by immunotherapy
- Identify proteins that could target nanoparticles for drug delivery
- Use mass spec, phage display, bioinformatics, etc

Subset and Histological Analysis of Screening Efficacy in NLST

NCAB/BSA June 24th, 2013

NLST Design

- ~54,000 subjects randomized to low-dose CT (LDCT) or chest radiograph (CXR)
- Eligibility: age 55-74, 30+ pack years, current smoker or quit within 15 years
- 33 screening centers across U.S.
- 3 annual rounds of screening
- 6-7 years of total follow-up
- Primary Outcome: lung cancer mortality

NLST Design, cont.

- Deaths ascertained by Annual Study Update forms and NDI searches
- Endpoint verification process – adjudicated cause of death
- Histology – classifications derived from medical records, as in main paper (NEJM 2011); note diagnosis occurred outside of trial auspices
- Limited centralized pathology available (some tumor specimens collected retrospectively)

Secondary Hypotheses in NLST

- Does LDCT screening efficacy vary by major demographic factors (e.g., age, sex)?
- Does LDCT screening efficacy vary by smoking status (current vs. former)?
- Is LDCT screening efficacy differential across lung cancer histologies?
- If screening varies by demographics/smoking status, can this be explained by histology?

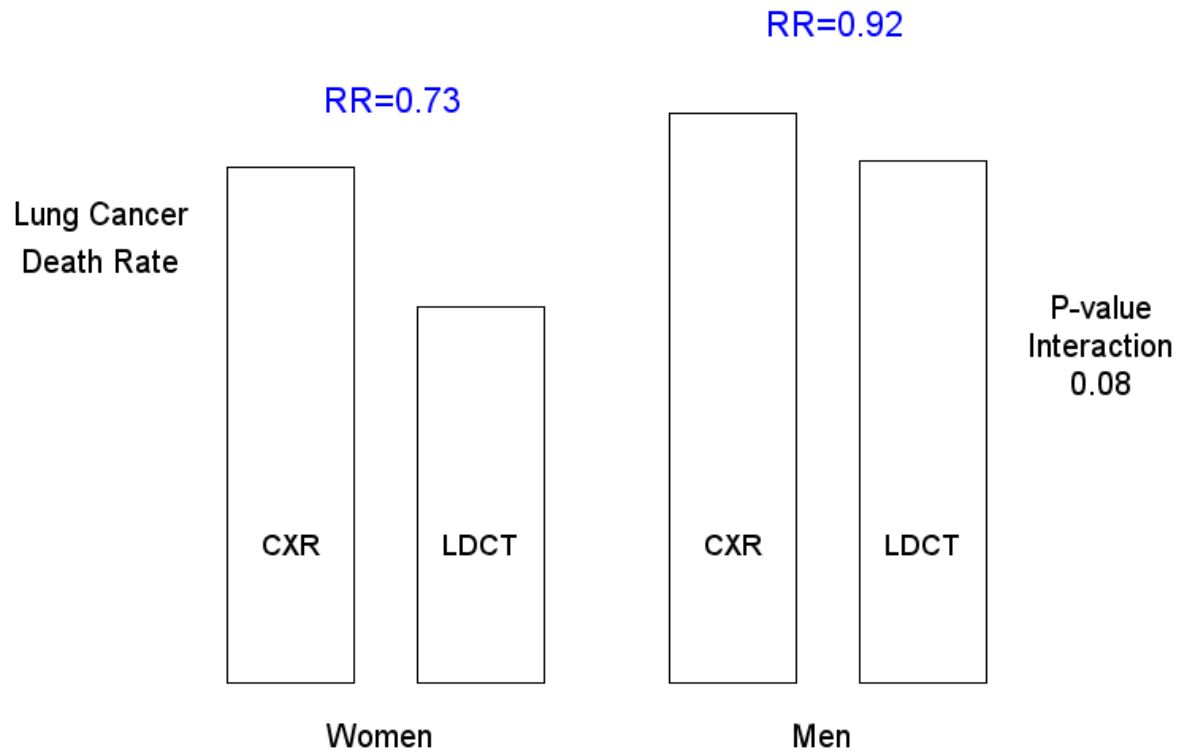
Lung Cancer Screening Mortality Effect by Cutoff Date

	Lung Cancer Deaths (#)		Relative Risk (95% CI)	Number Needed to Screen (95% CI)
	LDCT Arm	CXR Arm		
Jan 15, 2009 Cutoff (NEJM, 2011)	356	443	0.80 (0.73-0.93)	307
Dec 31, 2009 Cutoff (all available data)	469	552	0.84 (0.75-0.95)	322

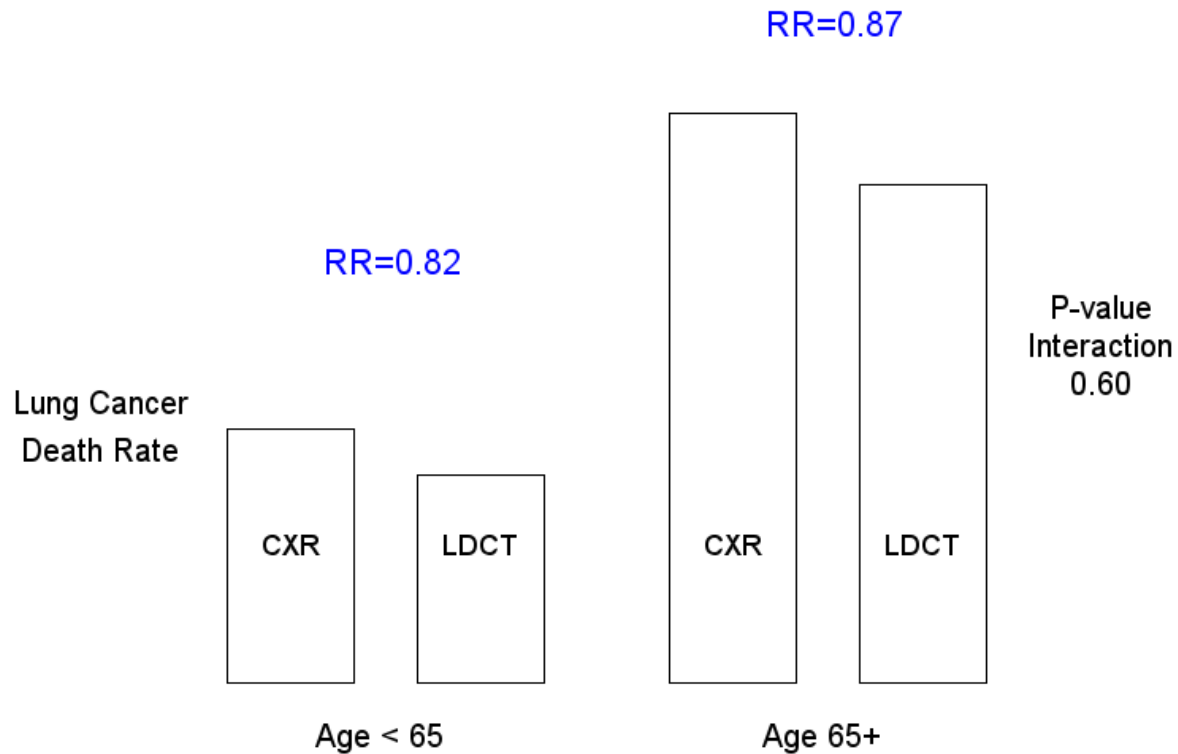
NLST Demographics

	LDCT Arm	CXR Arm
Male	59.0%	59.0%
Age 65+	26.6%	26.6%
Current Smoking	48.1%	48.3%

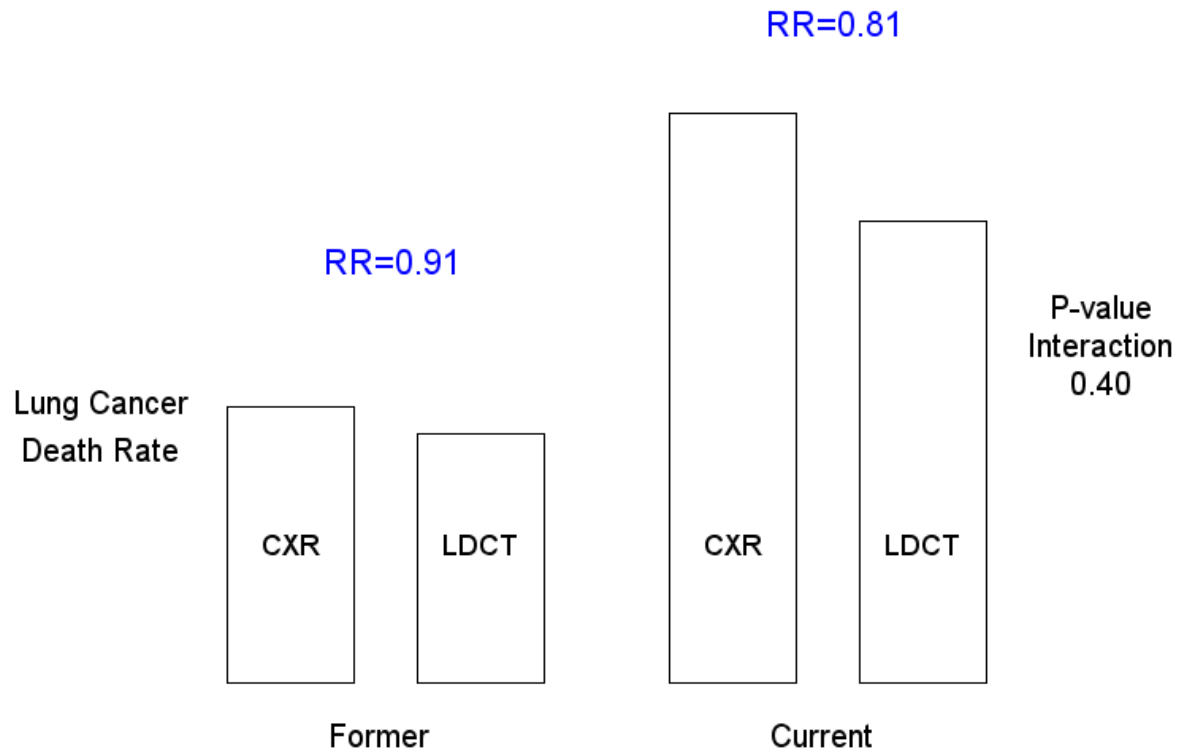
Screening Mortality Benefit by Sex



Screening Mortality Benefit by Age



Screening Mortality Benefit by Smoking Status



Lung Cancer Deaths by Histology

	LDCT Arm	CXR Arm	
	Lung Cancer Deaths	Lung Cancer Deaths	Relative Risk
Adenocarcinoma	136	181	0.75 (0.60-0.94)
Squamous Cell	102	83	1.23 (0.92-1.64)
Other NSCLC	100	144	0.69 (0.54-0.90)
Small Cell	102	113	0.90 (0.69-1.18)
Other/Unk	29	31	0.94 (0.6-1.6)

Global Test for RRs differing
by histology: $p < 0.01$

Survival by Histology

	Start Time of Follow-up	6 Year Survival	6 Year Survival	
Histology		LDCT Arm	CXR Arm	P-value
Adenocarcinoma	Diagnosis	59.1	33.2	<0.0001
	Randomization	71.6	54.5	<0.0001
Squamous Cell	Diagnosis	50.7	48.5	0.82
	Randomization	66.6	65.7	0.68
Small Cell	Diagnosis	14.4	11.5	0.72
	Randomization	39.1	37.8	0.80

LDCT Mortality Benefit by Histology and Sex

Histology	Sex	RR (LDCT vs. CXR)
Adenocarcinoma	Men	0.77 (0.6-1.02)
	Women	0.73 (0.5-1.05)
Squamous Cell	Men	1.31
	Women	1.04
Small Cell	Men	1.10 (0.8-1.6)
	Women	0.67 (0.4-1.03)
All except Small Cell	Men	0.88
	Women	0.76
All except Squamous & Small Cell	Men	0.77 (0.6-0.9)
	Women	0.71 (0.5-0.9)

Conclusions

- LDCT screening efficacy did not vary by age or smoking status in NLST
- LDCT screening efficacy showed borderline significant interaction with sex in NLST, with women having increased benefit
- LDCT screening efficacy appears to vary with lung cancer histology
- Histology may help explain the apparent differential in screening efficacy by sex



Extra Slides

Lung Cancer Histology Distribution by Sex and Trial Arm

	LDCT	LDCT	CXR	CXR
	Men	Women	Men	Women
	# (%)	# (%)	# (%)	# (%)
BAC	47 (7)	64 (15)	18 (3)	18 (5)
Adenocarcinoma	220 (34)	169 (39)	194 (34)	143 (36)
Squamous Cell	182 (28)	67 (15)	147 (26)	67 (17)
Small Cell	92 (14)	51 (12)	89 (16)	74 (19)
All	665 (100)	434 (100)	574 (100)	395 (100)

Screen Detection by Histology and Trial Arm

	LDCT Arm	CXR Arm
Histology	Screen detected cases #, % of total cases	Screen detected cases #, % of total cases
Adenocarcinoma	258 (68%)	112 (34%)
Squamous Cell	136 (56%)	70 (34%)
Small Cell	49 (36%)	28 (18%)
All Lung Cancer	649 (61%)	279 (30%)

Centralized Pathology Results

Original Histology	# with Centralized Pathology	% Concordant
Squamous Cell	108	88%
Adenocarcinoma	185	81%

Project Five: Next-generation synthetic lethal screens

- Develop synthetic lethal screens in 3D models, and in vivo
- Engineer mice to facilitate screens
- Test combinations of siRNAs, shRNAs and/or small molecules

Report of the NCAB Cancer Centers Working Group

Kevin Cullen, MD

Stan Gerson, MD

June 25, 2013

Purpose

- To propose a new award cost structure that alleviates real and perceived disparities in the size of Cancer Center Support Grants (CCSGs)

Working Group Charge

To advise on how to allocate funds to NCI-designated cancer centers in a time of fiscal stringency, focusing on

1. Whether current funding policies, as outlined in the 2012 guidelines, are appropriate
2. If not, whether there are better metrics to use, e.g., based on size, merit, complexity, type of center, ways in which funds are used

Working Group members

- Dr. William N. Hait, Janssen Research & Development, Chair
- Dr. Fred Appelbaum, University of Washington School of Medicine
- Dr. Mary Beckerle, University of Utah
- Dr. Kevin J. Cullen, University of Maryland
- Dr. Chi V. Dang, University of Pennsylvania
- Dr. Stanton L. Gerson, Case Western University
- Dr. Michelle M. Le Beau, The University of Chicago Comprehensive Cancer Center
- Dr. Kristiina Vuori, Cancer Center at Sanford-Burnham
- Dr. George J. Weiner, Holden Comprehensive Cancer Center
- Dr. Craig B. Thompson, Memorial Sloan-Kettering Cancer Center

Working Group Meetings

- 2/6/13 Bethesda Retreat
 - 2/13/13 Preliminary report presented at Cancer Center Directors Retreat
- 3/13/13 Conference Call
- 4/12/12 Conference Call
- 5/20/13 Conference Call

Topics Covered

- New CCSG guidelines including funding caps
- Funding elements and correlations
 - Core Center activities
 - Metrics *e.g.* priority scores, center size and complexity, funded research base, special attributes,
 - Importance/consideration of Center-specific initiatives
- Limits on CCSG budget growth

Special Considerations in a Flat Budget Environment

- How can NCI encourage timely initiatives in centers, *e.g.* disparities, precision medicine, global health, shared information technology, etc
 - supplements, cooperative agreement, other arrangements?
- Funding new Cancer Centers
- Ensuring fairness within and across funding years

CCSG Value

- NCI Cancer Centers Program is viewed as highly successful
- Focal point for a large percentage of NCI grants
- Coordination of big science and outreach
- Demonstrated progress through translational science in eliminating the nation's burden of cancer

Value Creation

- CCSG is essential for providing framework for structuring centers and for rigorous review
 - results in prestigious and coveted NCI designation
- NCI designation is the imprimatur that allows cancer research to be leveraged
 - institutional support, space, fundraising, authority, and the motivation of cancer advocacy groups, etc.
- CCSG provides essential support for clinical research infrastructure and shared resources

Challenges

- Factors other than merit have skewed the distribution of CCSG funds
 - Longevity
 - Size of NCI budget and competitors in year of application, historical effect of previous NIH budget growth
 - In transition bridge awards
 - Entry of new centers
- Different types of centers have different microenvironments not reflected in funding review
 - Basic, clinical, comprehensive
 - Matrix, free-standing, consortia

Problem(s) to be Solved

- Disparities in size of CCSG awards not fully explained by merit scores or size of the research base
- CCSG awards often based on size of previously funded grant
- Given fiscal constraints, by 2011, CCSG budget process posed serious challenges to NCI including y/y award range
- 2013 award guidelines limit evolution of smaller centers and impact larger ones

2013 Guideline Amendments

- CCSG awards \geq \$6 million capped at current direct costs
- CCSG awards of $<$ \$6 million can request increase of 10% or \$1,000,000, whichever is greater
- New centers can request awards \leq \$1 million

Problems for Centers

- 2012 guidelines would have practical effect of largely fixing funds for centers at current levels
- Very difficult for centers to increase awards over time no matter their quality/contributions/growth

Consensus Recommendation

- The CCSG award should be comprised of three components
 - **base**
 - **multiplier**
 - **innovative supplements**
- **Implemented as a point in time adjustment**
 - **2016 +/- vs phased in with renewal cycles**

Base

- Funds **standard components** of center
 - Senior Leadership, program leaders, cores, and developmental funds, clinical elements
- Award based on **type of center**: basic vs clinical vs comprehensive
- Performance history of center, before most recent grant period, **will not be a factor**
- **flexibility** in distributing base funding

Base Funding Hypothetical Model (annual direct cost)

- Basic Science Center \$1.0M
- Clinical Center \$1.2M
- Comprehensive Center \$1.4M

Standard Multipliers

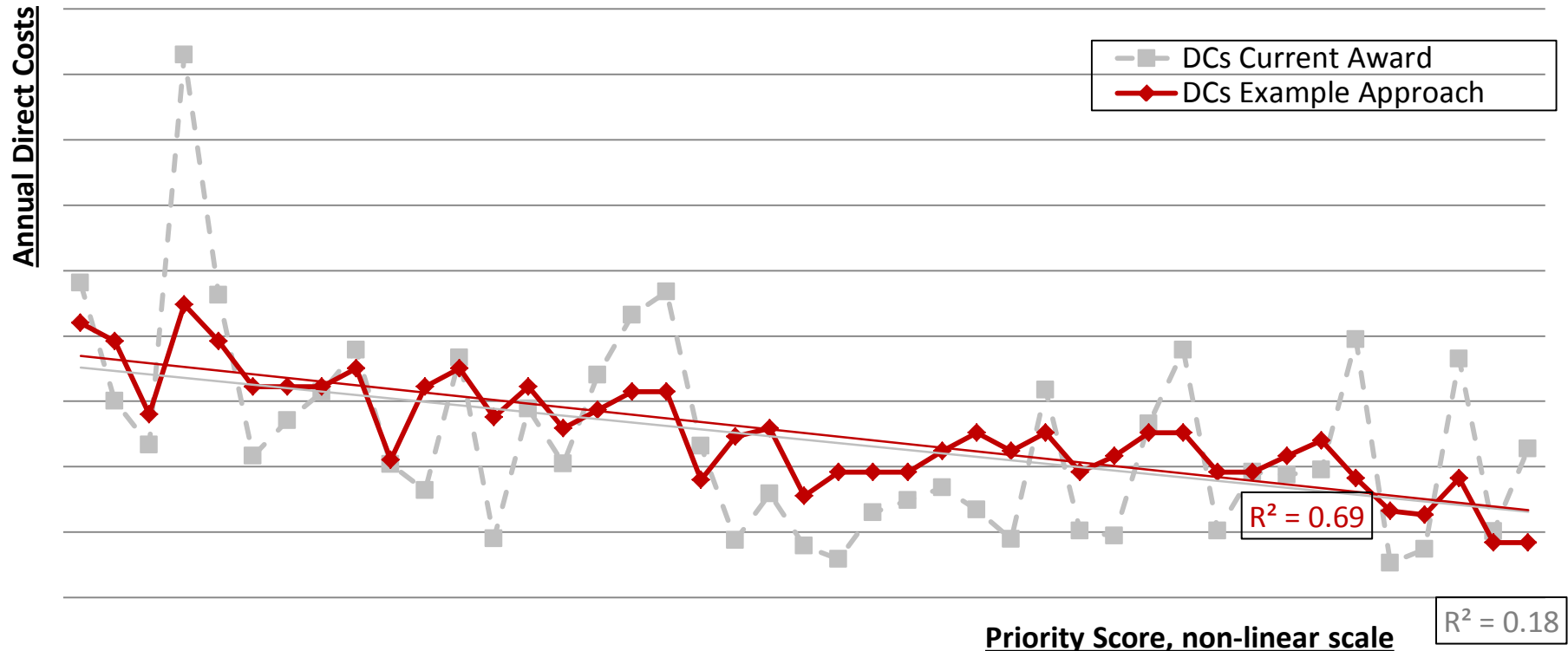
(about 50% of total CCSG budget)

- **Merit score – based on peer review priority score**
 - how well the center performed in its last grant period
 - science, translation, impact
 - complexity of the center's structure
 - multiplier can be below one (1) for underperforming centers
- **Cancer Center Size**
 - NCI funding base or other size metric
- **Other?**

Funding Formula Example

- Comprehensive Cancer Center with a \$35M direct NCI grant base and a merit score of 23
- Base Award = \$1.4M DC
- Merit multiplier (@ 100% of base) = \$1.4 DC
- Size multiplier (@ 30% of base) = \$0.42 DC
- Award calculation: $\$1.4 + \$1.4 + \$0.42 = \3.22 DC

Proposed Models May Decrease 'Arbitrary' CCSG Funding Variability



Notes:

1. Data include the 47 Cancer Centers that have competed under the new scoring system
2. Direct Cost base awards of \$1.0M, \$1.2M, \$1.4M were used to calculate the CCSG Award amount for Basic, Clinical, and Comprehensive Centers
3. Standardized multipliers for priority score and size were used to calculate the CCSG Award amount

Innovative Supplements

- Based on review of Center's proposal for highly **innovative and impactful** programs, cores, new initiatives, and consistency with **NCI priorities** such as precision medicine and global health
- Distributed based on available funds

Additional Points

- Current percentage of Centers Branch/CCSG funding to total NCI budget should be retained
- The goal is not to arbitrarily “level the playing field”
 - Some centers will have greater merit, size, complexity and deserve greater funding than others
- The goal is to increase **fairness** of the award process

Remaining issues (partial list)

- Refine modeling and evaluate impact on overall NCI budget
- How will model adapt to future changes in NCI budget?
- Maintaining the unique value of NCI-designation locally and nationally?
- Termination of poor performing centers
- Budgetary feasibility and center impact of award adjustment at single time point, v phase in at scheduled renewals
- Do potential models reflect other CCSG issues- i.e. support and credit for clinical investigation & accruals
 - How should clinical trial metrics be defined? NCI, third party, CMS, other? Are they adequately reflected in current review guidelines?

The NCI Outstanding Investigator Award

Dinah Singer, Ph.D.

Director

Division of Cancer Biology

National Cancer Institute

The Outstanding Investigator Grant (OIG)

1984-1993

OIG Characteristics:

- **Provided long-term support to experienced investigators with outstanding records of research productivity**
- **Emphasis placed on evidence of recent substantive contributions, i.e., seminal ideas and innovative approaches to difficult problems**
- **Awarded for 7 years and renewable**
- **PI was required to commit at least 75% time and effort**
- **Institution was required to provide 25% salary support**

The Outstanding Investigator Grant (OIG)

Why was the OIG Discontinued?

- **To reduce the burden of submitting multiple grants, the OIG aggregated all of the PI's grants, including those from other IC's.**
- **The NCI's commitment to the OIG eventually represented a substantial fraction of the RPG**

Proposed Outstanding Investigator Award (OIA)

Goals of the Proposed OIA:

- **Provide long-term support to experienced investigators with outstanding records of research productivity who are likely to continue to conduct seminal cancer research**
- **Encourage investigators to embark on innovative cancer research that breaks new ground or extends previous discoveries in new directions or applications**

Proposed Outstanding Investigator Award (OIA)

Features of Award:

- **Project period of 7 years, with the possibility of a 3 year extension following NCI review**
- **Requires a commitment of at least 50% of research effort**
- **Budget of up to \$600,000 in direct costs**
- **Would aggregate only NCI awards**
- **Institutions would provide 20% salary support for the duration of the award**

Eligibility:

- **Demonstrated outstanding research productivity and the potential for continued high quality research.**
- **Funded by NCI for the last five or more years**

Proposed Outstanding Investigator Award (OIA)

Application Characteristics:

- **Nomination by the grantee Institution**
- **Research Strategy should provide a description of the broad scientific questions to be addressed over the project period**
- **Detailed description of five of the PI's significant scientific accomplishments**

Proposed Outstanding Investigator Award (OIA)

Review Criteria:

- **Evidence that the PI is a leader in the field**
- **Evidence of innovation and significance in cancer research**
- **Potential for the PI's research productivity and impact to continue at the same high caliber level**
- **The proposed scientific field is of high priority and long-term relevance to the mission of the NCI**
- **The selection process used by the Institution to nominate the Principal Investigator (PI) for the OIA.**
- **An Institutional commitment of at least 20% salary support to the PI for the duration of the award.**

Proposed Outstanding Investigator Award (OIA)

Editorial Board review:

- **Stage 1:** Applications are assigned to 4 Editors with broad scientific expertise and are reviewed for past productivity, innovation and potential. Those applications with the best average scores proceed to Stage 2 review.
- **Stage 2:** Mail review by subject matter experts mail - 3 distinguished cancer researchers specializing in the field review each application and focus on its scientific merit; full written critiques with criterion scores are provided to the Editors. Those applications with the best average scores proceed to Stage 3 review
- **Stage 3:** Editors' face to face review—Editors focus their review on impact and significance, taking into consideration the critiques from Stage 2, write the overall impact paragraph and assign an overall impact and priority score

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Proposed Outstanding Investigator Award (OIA)

Review (cont.)

- **The National Cancer Advisory Board (NCAB) will conduct the final level of review.**
- **Optional: Those investigators whose submissions are judged to be the highest priority will be invited to NCI for interviews conducted by a panel of distinguished outside cancer researchers.**

Proposed Outstanding Investigator Award (OIA)

Criteria for 3 year Extension:

- **Awardee's continued scientific innovation, originality, and productivity**
- **Progress made by the awardee during the award period, which must demonstrate continued leadership in the field**
- **The research must continue to be at the cutting edge of the discipline in an area of continued importance to the NCI mission and goals**

Review:

- **Editorial Board review.**
- **NCAB will conduct the final level of review**

Proposed Outstanding Investigator Award (OIA)

Oversight:

- **Annual progress reports submitted by the PI and evaluated by NCI Program staff**
- **Annual meeting of OIG recipients to present their progress**

Proposed Outstanding Investigator Award (OIA)

Budgetary Impact of OIA:

- **Expected Awards: 20-40/year; 100-200 total**
- **Cost of each Award: \$600K DC + \$306 F&A = \$906K/year**
- **Total Cost: \$90-181M/year**

- **RPG (FY12): \$1.997 B**
- **% of RPG: 4.5 – 9%**

Questions?

Thank You

- Dr. Harold Varmus
- Working Group Members
- Linda Weiss and NCI Staff