DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
161ST NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 28, 2012

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 161st regular meeting on 28 February 2012, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 28 February 2012, from 9:00 a.m. to 2:47 p.m., and closed to the public from 2:47 p.m. to 4:00 p.m. The NCAB Chair, Dr. Bruce A. Chabner, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, presided during both the open and closed sessions.

NCAB Members

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

Alternate *Ex Officio* NCAB Members

Dr. Michael A. Babich, CPSC (absent)
Dr. Patricia Bray, OSHA/DOL
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP
Dr. Marie Sweeney, NIOSH
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. Joseph Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Associate Director for Prevention
Dr. Ed Harlow, Special Assistant for Science Planning
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
Dr. George Komatsoulis, Acting Director, NCI Center for Bioinformatics and Information Technology
Dr. Barry Kramer, Director, Division of Cancer Prevention
Dr. Douglas R. Lowy, Deputy Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Director, Center for Global Health
Mr. Michael Weingarten, Director, Small Business Innovation Research
Dr. Linda Weiss, Director, Office of Cancer Centers
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director
Dr. Barbara Wold, Director, Office of Cancer Genomics
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy

Liaison Representatives

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

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

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TUESDAY, FEBRUARY 28, 2012

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 6 DECEMBER 2011 MINUTES—DR. BRUCE A. CHABNER

Dr. Chabner called to order the 161st NCAB meeting. He welcomed members of the Board, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Chabner reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 6 December 2011 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

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

Dr. Chabner called Board members' attention to future meeting dates. He noted that the June 2012 NCAB meeting date has been changed to 25–26 June 2012 and the June 2013 NCAB meeting date has been changed to 25–26 June 2013 to accommodate joint meetings with the NCI Board of Scientific Advisors (BSA).

Motion. A motion was made to accept the NCAB meeting dates for June 2012 and 2013, as well as fiscal year (FY) 2014. The motion was seconded and approved unanimously.

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

Dr. Harold E. Varmus, Director, NCI, welcomed members and informed the Board that the June 2012 meeting will be a joint meeting with the BSA, Dr. Varmus noted that future June meetings will be jointly held. He also announced that Dr. George Komatsoulis was appointed the Acting Director for the Center for Biological Informatics and Information Technology (CBIIT). The NCI is recruiting for permanent heads of CBIIT, the Center for Cancer Genomics (CCG), and the Office for Science Policy and Analysis (OSPA).

Budget. Dr. Varmus reminded members that the NCI's FY 2012 budget is close to $5 B, slightly higher (0.3%) than the FY 2011 level. Approximately 1,100 research program grants (RPGs) will be supported, and the NCI will issue the complete funding amount for awarded grants following the Office of Management and Budget's (OMB) official apportionment. Dr. Varmus stressed that the NCI does not have a traditional payline, although most applications up to the 7th percentile receive funding. The success rate for FY 2012 is 15 percent and approximates last year's awards. He noted that the National Library of Medicine (NLM) has released information about its applications, percentile scores, and funding rates, which showed similar funding ranges to the NCI. The NCI pays careful attention to priority scores and reviews, but some applications with less favorable scores might be funded for programmatic reasons. The President's Budget (PB) for FY 2013 includes a $3 M increase for the NCI above the FY 2011 budget. The NCI is preparing its Bypass Budget for FY 2013 and will focus on six important types of cancer as well as advances in control of those cancers. Other topics described in the narrative are: cancer genomics, global health, health disparities, Cancer Centers, provocative questions, precision medicine, and the Frederick National Laboratory for Cancer Research (FNLCR).

Congressional Interactions. Drs. Francis Collins, NIH Director, and Varmus visited Mr. Denny Rehburg (R-MT), Chair of the House Labor, Health and Human Services, Education, and Related Agencies Committee, who promised to hold an NIH hearing this year. Topics for the House hearing on 20 March 2012 likely will include the National Center for Advancing Translational Sciences (NCATS) and the pharmaceutical industry. The Senate's hearing on 28 March 2012 will be similar to last year's hearing, with Dr. Collins presenting testimony and Dr. Varmus and several other Institute and Center (IC) Directors present. Dr. Varmus encouraged the cancer

community to attend the hearings and support oncologic research, and he indicated that NCI staff will disseminate information about the hearings to encourage attendance.

The "Research Works Act," proposed by Mr. Darrell Issa (R-CA) and Ms. Carolyn Maloney (D-NY), would dismantle the NIH public access policy and affect the publication of peer-reviewed content. Drs. Collins and Varmus expressed their concerns about the bill to Mr. Issa and Ms. Maloney, and they withdrew their support for the legislation. In related news, Mr. Mike Doyle (D-PA) and Senator John Cornyn (R-TX) reintroduced the "Federal Research Public Access Act." This legislation would extend the NIH public-access policy to all federal agencies that fund more than $100 million worth of scientific research as well as reduce the delay between the acceptance of a federally supported manuscript and its submission to a public digital library from 12 to 6 months.

NCI Activities and News of Interest. Dr. Varmus expressed the NCI's continued interest in the issue of ameliorating the drug shortage. He noted the U.S. Food and Drug Administration's (FDA) efforts in preventing shortages through closer interactions with industry and considering drug importation. In addition, the Director's Consumer Liaison Group (DCLG) will be discussing the topic with Dr. Chabner and other advocates of dealing with drug shortages.

The Center for Global Health (CGH) is holding an NCI planning workshop on global health on 13–14 March 2012 to help refine the CGH's agenda. The meeting will include 150 stakeholders, representing multiple sectors, and discuss opportunities to help countries with national cancer plans, training, issues related to cancer incidence, and implementation science, among other topics. Dr. Olopade will represent the NCAB at the workshop. Other international activities of interest include: Dr. Varmus will attend the opening of the Turkish health agency and cancer institute in April; the NCI's Middle East Cancer Consortium is holding an April meeting in Ankara; and the NCI is assisting the Mexican government with its national cancer planning.

Dr. Varmus informed members that the new name for the NCI-Frederick campus is the Frederick National Laboratory for Cancer Research (FNLCR), and a website that describes the FNLCR's resources is being designed. In addition to input provided to the NCI by the NCI-Frederick Advisory Committee (NFAC), a Frederick National Laboratory Strategic Planning Committee is preparing a FNLCR strategic plan, which will be reported to the NCAB at an upcoming meeting. Dr. Varmus also expressed the NCI's appreciation to Drs. Ed Harlow, Special Assistant to the Director, Tyler Jacks, Director, Koch Institute for Integrative Cancer Research, and David H. Koch Professor of Biology, Massachusetts Institute of Technology, as well as Dr. Douglas Lowy, Deputy Director, and other NCI staff, for their work advancing the Provocative Questions Initiative. Apportionately 750 applications were received, and Dr. Harlow continues to conduct Provocative Questions Initiative workshops. The NCI plans to reissue the request for applications (RFA) annually for the foreseeable future.

NCI's efforts to address an issue at the nexus of cancer genomics, the practice of oncology, and team science were described. Specifically, the NCI's activities in genomics are aggregated in the CCG. Key programs are The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET). TCGA has achieved a level of high productivity, with several papers published or in preparation on squamous-cell lung cancer, gastrointestinal cancer, and other cancers. Pilot projects on 10 less-common tumors currently are underway. The analysis of 300 to 500 tumors comprising 19 major tumor types should be completed by the end of 2014. By that time, TCGA will have completed its mandate. TCGA efforts continue to prosper from a strong collaboration with the National Human Genome Research Institute (NHGRI).

The NCI faces two primary issues in its genomic efforts. The first is informatics, particularly interpreting what sequencing means. To assist with this, the NCI has established the new Center for TCGA Database at the University of California, Santa Cruz, and continues to receive advice from the *ad hoc* Subcommittee on Cancer Bioinformatics Grid (caBIG®), headed by Dr. Daniel Masys. The second issue is precision medicine, which is based on the idea that the accumulation of genomic data about tumors will affect medicine into the future. Dr. Varmus stated that Dr. Charles Sawyer is assisting the NCI in planning a workshop to develop pilot projects to

better understand how to integrate genomics, informatics, and the practice of oncology. The improved integration should accelerate the use of molecular data in all aspects of cancer control and care, prevention, diagnosis, and treatment. An NIH-wide effort at target validation through collaboration with industry also is underway.

Members were told that the NCI held a successful workshop on team science in February 2012. Discussions canvassed ideas on leadership, mentorship, and the utility of goal orientation. Another topic was the difficult issue of sharing credit, acknowledging the conflict between the value of multidisciplinary teams and the need for scientists to receive credit as well as establish themselves as independent investigators. Dr. Varmus is working with Dr. Sally Rockey, NIH Office for Extramural Research, to modify the format of the NIH's biographical sketch to highlight the investigator's five most important contributions to science, similar to the format used by the Howard Hughes Medical Institute. An update on this issue will be given at the joint Board meeting in June 2012.

The NCI leadership is considering changes to the Institute's terms of grantmaking. Dr. Varmus noted that results from less than one-half of all trials supported by the NCI are reported in publications within 30 months after completion of the trial. In addition, there are many scientists aged 40 and older who receive NIH grants, but the lack of senior reviewers on panels is the most significant problem facing the current peer-review system. Requirements being considered are that a paper must be submitted within a specific period of time after completion of a trial and that receipt of a grant includes an obligation to serve as a peer reviewer, which Dr. Varmus proposed could be managed similar to a jury duty system. Members were encouraged to provide feedback about these possible changes to the terms of grantmaking. Dr. Varmus next reviewed the agenda and noted that the President's Cancer Panel (PCP) has been newly constituted with Barbara Rimer, Dr.P.H., Dean and Alumni Distinguished Professor Gillings School of Global Public Health as Chair and Owen Witte, M.D., Director, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research as the second member; a third appointment is pending.

Provocative Questions Initiative (PQ). Dr. Lowy provided an update on the progress of the PQ Initiative. Dr. Lowy informed members that apportionately 750 applications were submitted, with the number of R01 proposals a slight majority over the R21 proposals submitted. All NCI Divisions are actively participating in the oversight process, and recruitment of reviewers is underway. The *en bloc* applications likely will be presented to the NCAB at its closed session in June 2012. The $15 M allocated to the Initiative likely will support 45-60 grants. The NCI leadership is considering reissuance options for FY 2013 and the optimal number of provocative questions. Dr. Ed Harlow is continuing to obtain input for the Initiative from colleagues around the country, and he and Dr. Varmus published an article about the framework and rationale for the Provocative Questions Initiative (*Nature*, January 2012). Dr. Lowy observed that approximately 20 percent of the applications were submitted by M.D./Ph.D. investigators, which is double the number of R01 and R21 applications that are submitted by M.D./Ph.D. investigators in response to the standard RFAs. Dr. Lowy said that the NCI leadership is pleased with the response and expressed optimism for the success of the program.

Interactions With Industry. Dr. James H. Doroshow, Deputy Director, provided an update on an NIH-wide effort to consider the advantages of better interactions with industry to develop precompetitive resources and tools to advance a variety of therapeutic and diagnostic targets. Dr. Doroshow informed members that Dr. Varmus is leading the oncology component to determine which resources would be most helpful for the enhancement of the development of cancer diagnostics and therapeutics, consulting leaders of biotechnology firms, large and small pharmaceutical companies, and diagnostic specialists, among others. Several activities under consideration are the establishment of a working group and planning of a small meeting to survey the precompetitive space to determine utility. Questions include whether the NCI should develop a repository of freely accessible resources and tools, similar to the NCI's provision of commercially available agents, and whether the NCI could validate a very large set of short hairpin RNAs (shRNAs) or monoclonal antibodies. A significant issue is the need to define target validation in light of industry reports of the irreproducibility of some academic target validity claims. Options discussed included the development of consortia around therapeutic or toxicologic targets to help certify that

important novel observations are solid and robust as well as identify which therapeutics or diagnostics development projects to pursue. Dr. Varmus added that contradictory reproducibility results might be due to differing goals of the two communities: academics are geared toward publishing results, and industry wants effective assays for product development. In addition, the exigencies of the particular assays and tests that are conducted in academic laboratories might not be more generally applicable. Being aware of these differences in outlook and techniques will help the NCI vet the panoply of academic activities to provide guidance to industry.

Questions and Answers

Dr. Jacks asked about publishers' responses to the Federal Research Public Access Act's mandate to reduce the time between acceptance of an article for publication and submission to a public digital library. Dr. Varmus indicated that similar public-access policies effected by the Wellcome Trust in Europe and Howard Hughes Medical Institute in the United States provide evidence that the bill will have little or no effect. Dr. Chabner queried about enforcement of the bill and potential penalties to federally funded studies for noncompliance. Dr. Varmus said that investigators are expected to comply and that the current compliance rate at the NIH is approximately 80 percent.

Dr. Chabner encouraged the inclusion of academia in the discussions about interactions with industry to draw on both academics' experience with industry and unique resources in academia. Dr. Doroshow clarified that academia will be involved in the forum, and Dr. Varmus added that the planned workshop will have equal numbers of academic and industry scientists. Dr. Jacks observed that mechanisms are needed to support academic investigators in conducting validation activities in the diagnostic arena.

Dr. Jacks asked about shifts to the FNLCR mission and the NCAB's role in helping to refine the enterprise; he commented that as a centralized national laboratory, FNLCR can perform activities, such as target validation, in a more efficient manner than academic investigators. Dr. Varmus replied that FNLCR is operated through contract programs that are nimble, flexible, and can respond to interest from the extramural community for certain resources or core facilities; although significant changes are not expected, the new oversight could help develop a mechanism to facilitate changes or consider the involvement of Center for Cancer Research (CCR) investigators as part of the FNLCR.

Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research and Scholarship, Indiana University School of Nursing, suggested that Board discussions about team science include how the Specialized Programs of Research Excellence (SPOREs) and Program Project (P01) mechanisms require teams to work together. Dr. Varmus encouraged members to send potential agenda items for future NCAB meetings to Dr. Gray and himself.

Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, asked about the demographics of applicants to the Provocative Questions Initiative. Dr. Lowy replied that applications were submitted by reasonable percentages of early-stage, new, and established investigators. Dr. Gray indicated that additional information about demographics will be available after completion of the peer-review process.

Dr. Olufunmilayo F. Olopade, Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, and Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine, queried about the extramural community's anticipated response to the peer-review process being managed like a jury duty. Dr. Olopade encouraged using incentives for senior colleagues rather than imposing requirements. Dr. Varmus indicated that the idea is being considered and noted that the NCI has the responsibility of forming the terms of grantmaking. Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, and B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, observed that some foundations provide a year of funding to offset a year of peer-review service and have 100 percent

participation in the review cycle. Dr. Chabner said that the greatest incentive to serve on study sections is dissatisfaction with the review received on one's application. Dr. Varmus stated that the makeup of the study sections makes a difference; interacting with a high-level, well-informed group of peers is good. Dr. Jacks suggested that a reduction in the time of service, currently set at 3 years, likely would facilitate recruitment.

Dr. Chabner recommended that the report from the team science workshop provide 5-10 examples of effective team science with a description of how they were supported to illustrate flexible mechanisms. Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, and Director, Institute for Global Health, University of Southern California, asked whether the workshop addressed issues of relevance to the academic sphere, such as promotion of junior faculty based partly on their participation in interdisciplinary team science. Dr. Varmus said that teams represented include those supported by other funding organizations, such as Stand Up to Cancer and the Howard Hughes Medical Institute, and the NCI leadership is considering team composition with respect to precision-medicine pilot projects. He added that some of the most effective teams had leaders with charisma, strong leadership skills, and attention to issues that affect junior investigators; one way to assist junior scientists is to refine biographical sketches to describe roles in the context of a team effort.

Dr. Cruz-Correa asked whether high-scoring but nonfunded applications to the PQ Initiative would be considered in future application cycles. Dr. Lowy clarified that the number of applications funded could be adjusted if many more than 15 were highly meritorious and that there currently is no provision for resubmission.

IV. PRESIDENT'S CANCER PANEL REPORT: A NEW BEGINNING—DR. BARBARA K. RIMER

Dr. Barbara K. Rimer, Dean and Alumni Distinguished Professor, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, provided a report on the goals and plans of the PCP. The PCP currently is comprised of herself and Dr. Owen N. Witte, Professor of Microbiology, Immunology, and Molecular Genetics at the University of California, Los Angeles (UCLA), and Professor of Molecular and Medical Pharmacology at the David Geffen School of Medicine, UCLA; it is anticipated that President Barack Obama will nominate a third member. Dr. Rimer stated that the Panel's role potentially is very broad, but the focus of the PCP is to provide the President with concrete and actionable recommendations rather than establish guidelines.

Dr. Rimer said that the PCP chose *Accelerating Progress in Cancer Prevention: The Human Papilloma Virus (HPV) Vaccine Example* as its topic for 2012 because of the public health burden posed by HPV-related cancers and low HPV vaccination rates in the United States, particularly among males. In the United States, cervical cancer remains the most common form of HPV-related cancer, but the incidence of other HPV-related cancers is increasing. Trends in vaccination rates indicate that compared to other multidose vaccines, progress in HPV vaccination has been slow. Dr. Rimer observed that addressing the topic of HPV vaccination entails a discussion of issues whose diversity, ranging from basic scientific to behavioral, is ideal for the scope of the PCP.

The PCP will explore issues related to the HPV vaccine by sponsoring workshops that will engender interaction and discussion among diverse meeting participants. Workshop goals include developing recommendations to increase HPV vaccination in the United States, identifying lessons to apply to future cancer-related vaccines, addressing issues related to global HPV vaccination, and pinpointing topics for further study. The first workshop will address the state-of-the-science, including fundamental science, potential improvements to the vaccine, and implications for future vaccines. The second workshop will address policy, program, and communication considerations, including assessing vaccine dissemination and recommending strategies to improve vaccine uptake. The third workshop will examine current clinical practice standards for cervical cancer screening and explore the economics of widespread vaccination.

In the spring of 2012, the report *The Future of Cancer Research: Accelerating Scientific Innovation*, drafted by the previous PCP, will be released. Dr. Rimer indicated that potential future topics for the PCP include

accelerating clinical trials, creating a global network of cancer registries, and communicating more effectively about cancer.

Questions and Answers

Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, and Professor of Medicine, University of Maryland, recognized that HPV vaccination is a politically sensitive topic and recommended that the PCP encourage broad participation in the PCP's upcoming workshop by including patient advocates and survivors. Dr. Rimer replied that individuals with a range of perspectives will be invited to participate. In response to Dr. Champion's question about how the NCAB might best assist the PCP, Dr. Rimer answered that recommendations for workshop participants from the NCAB would be helpful. Dr. Meneses asked for more details about selecting participants for the workshop, and Dr. Rimer responded that the PCP plans to consult the literature, solicit advice from NCI staff, and enlist the aid of workshop co-chairs. Dr. Kaur asked how a hearing and workshop differ, and Dr. Rimer indicated that the formats are different, and the PCP might participate in hearings in the future.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, commented that screening measures, including Pap smears, will continue to be important in cancer prevention. Dr. Rimer noted that the PCP was unlikely to recommend a change in preventative care policy.

Dr. H. Kim Lyerly, Vice President/Global Head of Oncology, George Barth Geller Professor of Cancer Research, and Professor of Surgery, Duke University School of Medicine, requested clarification about the PCP's role in global cancer prevention and how it will address related barriers and opportunities in developing countries. Dr. Rimer said that the PCP will have an active global role and will start with the topic of HPV, which is relevant to these efforts. Dr. Olopade inquired about the establishment, direction, and funding of the global cancer registry, as well as how foreign governments and ministries will be approached to enlist support at the cabinet level. Dr. Varmus replied that the NCI's CGH is considering strategies to develop cancer awareness and evaluate the status of cancer research in different countries, and past efforts have included meeting with leaders of other cancer research agencies.

Dr. Chabner asked about the mechanism by which the PCP will advise the President. Dr. Stebbins, Office of Science and Technology Policy (OSTP), indicated that the President will receive briefings from the PCP primarily in the form of reports.

V. UPDATE: RECENT ACTIONS, RE-ORGANIZATION, AND INITIATIVES—DR. RICHARD PAZDUR

Dr. Richard Pazdur, Director, Office of Hematology and Oncology Drug Products (OHOP), FDA, provided an update on the FDA's reorganized OHOP. The OHOP staff includes oncologists, pediatric oncologists, pharmacologists, toxicologists, regulatory project managers, and support staff. Prior to reorganization, pharmacologist and toxicologist reviewers were interspersed among different clinical divisions, and specialized staff members were located in separate offices, complicating product reviews. Now, there are disease-specific divisions: the Divisions of Oncology Products 1 and 2, Hematology Products, and Hematology Oncology Toxicology. The reorganization ensures more consistent advice to sponsors, a better balance in staff workload, improvements to the quality and efficiency of drug review, and increased recognition of staff expertise by external entities. The FDA's Oncology Program, located in the OHOP, coordinates oncology activities with external entities as well as internal FDA meetings on topics that include approval of treatment devices (Center for Devices and Radiological Health) and tumor vaccines (Center for Biologics Evaluation and Research).

In calendar year 2011, the FDA's Center for Drug Evaluation and Research approved 30 new therapeutics, one-third of which were for use in cancer treatment. These oncology drugs included: agents approved with companion diagnostics to predict whether a patient will respond to the therapy; drugs to treat metastatic melanoma, which had few treatment options; the first new drug in decades to treat Hodgkin's lymphoma; the first drug for myelofibrosis; and therapeutics that had attracted little interest before new treatment endpoints were recognized. The new molecular entity approval process had increased flexibility, including approvals based on single-arm trials and accelerated approvals.

Dr. Pazdur said that accelerated approval is designed to speed access to promising drugs for treating serious or life-threatening diseases. After receiving accelerated approval, applicants are required to carry out post-marketing studies verifying benefit, a process which entails resources equivalent to what is needed to secure regular approval and has taken approximately 4 years on average. If a drug does not meet post-marketing requirements, it must be withdrawn; therefore, Dr. Pazdur suggested that the term "conditional" might describe this approval process more appropriately than "accelerated." The Oncologic Drugs Advisory Committee indicated in December 2011 that of the approximately 50 new indications that have received accelerated approval, one-half have completed post-marketing studies successfully. Only 10 percent failed to demonstrate a benefit, and all but one of these drugs was voluntarily withdrawn. The FDA has initiated involuntary withdrawal proceedings against the sponsor of this product. Dr. Pazdur stated that the FDA is committed to accelerated approval as a way to provide early access to clinically beneficial cancer therapies.

In 2011, the FDA issued a draft guidance document on gaining approval for *in vitro* companion diagnostic devices, which has implications for oncology and other types of disease. The diagnostic tests for approval are regulated by the FDA's Center for Devices and Radiological Health. The draft guidance stipulates that applicants should identify patients who are most likely to benefit from the drug and those at increased risk for adverse reactions as well as monitor treatment response so that it can be adjusted. Use of *in vitro* companion diagnostic devices before approval is permitted in specific cases, including devices that address safety concerns about the administration of previously approved drugs.

The FDA also drafted a guidance document on co-development of drugs to be used in combination. Co-development is appropriate if agents cannot be developed individually and is meant for therapeutically meaningful drugs that justify taking this regulatory risk. Safety profiles, including dose-response evaluations, are developed in clinical trials of individual drugs or nonclinical trials of combinations (if one drug has no activity alone) in Phase 1. Proof-of-concept studies (Phase 2) provide evidence of the combination's effectiveness and data on optimal doses for confirmatory trials (Phase 3). Dr. Pazdur invited comments from NCAB members regarding this document.

Dr. Pazdur said that projects for 2012 include releasing for public comment a draft guidance document on using pathological complete response rates in accelerated approval for drugs intended to treat breast cancer, holding workshops with professional groups, evaluating the practice of independent radiographic review of scans, and exploring ways to reduce regulatory burdens in safety data collection in late-stage clinical trials.

Questions and Answers

To Dr. Cruz-Correa's suggestion that "conditional approval" might be a term that would better describe the accelerated approval process, Dr. Pazdur replied that either term indicates less than full approval, but regardless of the term used, better communication to patients regarding the meaning of this type of approval is needed. Because toxicity is generally the cause of approval being revoked, Dr. Donald S. Coffey, The Catherin Iola and J. Smith Michael Distinguished Professor of Urology, Professor of Urology/Oncology/ Pathology/Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, asked what research on personalized toxicity is being conducted at the FDA. Dr. Pazdur answered that the FDA focuses on responsiveness rather than toxicity, and lack of efficacy is the most common cause for withdrawal of oncology drugs. Dr. Chabner asked how the FDA determines which pharmaceutical agents do not need Phase 3 trials for full

approval. Dr. Pazdur responded that this waiver only is granted to drugs with very impressive response rates in early trials. Dr. Chabner observed that drug shortages exclusively were affecting generic products. Dr. Pazdur replied that the FDA has limited authority to address this issue, and monetary incentives are needed.

Dr. Chabner questioned how the FDA decides whether to continue a trial if the drug arm has a significantly better response. Dr. Pazdur answered that the trial process evolves with the results. Dr. Kaur noted that in the era of precision medicine, participation in trials is very specific, and she asked how this affects the speed with which drugs are brought to market. Dr. Pazdur responded that the FDA has accelerated the process as much as possible, with approval of priority drugs generally being granted within 6 months.

Dr. Lyerly asked whether the FDA plans to continue the workshops for the academic community and the pharmaceutical industry on the drug approval process. Dr. Pazdur responded that the FDA leverages support from professional groups but has a limited budget for regulatory education.

VI. CURRENT AND FUTURE PERSPECTIVES ON CANCER PREVENTION RESEARCH—DR. BARRY KRAMER

Dr. Barry Kramer, Director, Division of Cancer Prevention (DCP), described the NCI's approach to cancer prevention research, which focuses on the development and validation of interventions to reduce the incidence of cancer. Dr. Kramer said that cancer prevention research is distinct from traditional observational epidemiology, which describes patterns rather than tests interventions. Investigators in the cancer prevention field also conduct research on cancer screening to identify lesions as early as possible. Screening can decrease the incidence of cancer, such as through Pap smears and resulting treatment of neoplastic lesions, but it also can appear to increase the incidence, as seen in mammography and PSA testing for prostate cancer. The phases of the cancer prevention research continuum are: hypothesis development; methods development; controlled intervention trials; defined population studies; and implementation projects; in the NCI, the DCP focuses on the first three, and the Division of Cancer Control and Population Sciences (DCCPS) covers population and implementation areas. The DCP's Community Clinical Oncology Program (CCOP), however, does study efficacy in specific populations and minority and underserved populations in Phase 4 and then implementation projects. The DCP's structure incorporates disease-specific and crosscutting research groups, and both research training as well as public and professional education remain important components in the DCP's work. Its activities span multiple phases of the cancer prevention continuum, including a Preclinical Program, an Early Detection Research Network (EDRN), an Early Phase Trial Consortia, and the CCOP.

Dr. Kramer reviewed major trials conducted or supported by the DCP, including the Breast Cancer Prevention Trial, in which an intervention was proved to decrease breast cancer risk, and the Study of Tamoxifen and Raloxifene (STAR), which demonstrated the efficacy of both agents but different spectrums of toxicity. Other major accomplishments include: the Prostate Cancer Prevention Trial, which compared finasteride to placebo and showed a decrease in the overall risk of invasive prostate cancer; the Selenium and Vitamin E for Cancer Prevention Trial (SELECT), which yielded counterintuitive results by showing that vitamin E was associated with increased risk of prostate cancer; the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, in which screening for lung and ovarian cancers showed no benefit but implied a net harm; and the National Lung Screening Trial (NLST), in which a screening test was shown to decrease the mortality risk of lung cancer. All of these studies have biorepositories that are in use for hypothesis testing.

Future scientific directions for cancer prevention research encompass agent development and decision making, overdiagnosis and precancerous lesions, cancer immunoprevention, the role of microbiota, and new approaches to clinical prevention studies. To develop promising agents based on clinical need, the DCP has established the PREVENT Cancer Program, which facilitates a transparent agent review and prioritization process. The PREVENT Cancer Program is modeled after the NCI Experimental Therapeutics (NExT) Program and involves extramural leaders and experts in oversight and review roles as well as NCI staff who handle management

and administrative aspects. Preclinical drug development will be advanced or ceased as needed, and promising agents will be shifted into early-phase clinical development. Better decisions can be made about agents by comparing the success of preclinical models at predicting clinical outcome. Another strategy is to validate successful clinical trials retrospectively using preclinical models, an activity in which the DCP is collaborating with the Division of Cancer Biology (DCB) and the Mouse Models for Human Cancers Consortium (MMHCC).

Overdiagnosis and precancerous lesions uncovered during screening tests raise concerns about harm resulting from unnecessary treatment. As screening tests increase in sensitivity, molecular characterization approaches are needed to distinguish dangerous lesions from those that are not malignant. The EDRN's biometric development laboratories, biomarker reference laboratories, and clinical validation centers are important components in developing, testing, and validating markers. To advance understanding at the molecular level, the EDRN has organized a think-tank conference for March 2012 on overdiagnosis and integral cancers. In addition, the DCP participates in the DCB's Barrett's Esophagus Translational Research Network and might collaborate with TCGA and the DCB to develop a genome atlas for precancers to stratify risk and identify driver mutations.

Cancer immunoprevention offers additional opportunities for prevention research, including infectious causes of cancer, such as the human papilloma virus and hepatitis C virus, and noninfectious tumor agents. The DCP is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID) and other NCI Divisions in these areas. In addition, prevention interventions (e.g., agents, vaccines, diet) theoretically can focus on microbiota to change the balance of microorganisms in the body. Strong evidence suggests that microbiota are involved in cancer through energy exchange, inflammatory pathways and immunity, and dietary choices.

New approaches to clinical prevention studies include repurposing commonly used drugs (e.g., aspirin, other nonsteroidal anti-inflammatory drugs [NSAIDs], statins) for cancer prevention and using noncancer disease trials to detect cancer prevention signals, such as metformin studies at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and a potential lutein and omega-3 fatty acid co-study with the National Eye Institute (NEI). Other approaches involve reciprocal control trials with other NIH ICs, such as the National Heart, Lung, and Blood Institute (NHLBI), as well as work with the National Clinical Trials Network (NCTN) and CCOP network to implement large trials.

Questions and Answers

Dr. Olopade asked about the extent of implementation versus basic discovery in the DCP portfolio. Dr. Kramer answered that the DCP focuses on the earlier trial phases, and the DCCPS mostly addresses the implementation of efficacious interventions; one exception is the CCOPs, which combine efficacy and effectiveness while engaging the community physicians who implement the interventions.

Dr. Olopade noted the common use of several biomarkers, such as Ki67, in the design of studies and suggested that there might be an opportunity to reevaluate biomarker development approaches. Dr. Kramer commented that Ki67 is not a screening test but rather measures a nonspecific process; the use of biomarkers as endpoints in early phase trials to indicate when to move to a larger trial raises the issue of the positive and negative predictive value of preclinical models in early phase studies. He added that one approach might be to develop a biomarker as a true screening tool and analyze its reliability for making decisions about subsequent drug development and preventive agent development. Dr. Jacks cautioned that animal models cannot be applied uniformly to all preclinical studies because of heterogeneity but instead should be identified for their utility as well as where they would never be useful. Dr. Kramer agreed that predicted values should be better understood. Dr. Chabner encouraged prevention screening and trial designs to reflect the many varieties and subsets found within a specific cancer.

Dr. Waun Ki Hong, Professor and Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, observed that preventive agents

that work in animal models frequently do not transfer to human studies, but agents selected such as tamoxifen to prevent primary human breast cancer and lenalidomide that is agent for the treatment of myeloma has been used to delay progression of high risk smoldering multiple myeloma. So question is that can we develop preventive agent through reverse migration approach basically from treatment paradigm to prevention settings? Dr. Kramer acknowledged the issue and expressed the hope that biomarker signals will be identified in humans rather than animals or preclinical models.

VII. ANNUAL DELEGATIONS OF AUTHORITY—DR. PAULETTE S. GRAY

Dr. Gray requested concurrence by the NCAB on two Delegations of Authority to the Director of the NCI. She described the delegations and the provisions in the Statement of Understanding. Delegation A allows the Director to obtain the services of not more than 151 special experts or consultants who have scientific or professional qualifications. Dr. Gray also said that Delegation B specifies that the NCI Director can appoint advisory committees composed of private citizens and officials of Federal, state, and local governments.

The Statement of Understanding with NCI Staff on Operating Principles in Extramural Grants also falls within the Delegations of Authority to the Director, NCI. NCAB operations are conducted in accordance with management and review procedures described in the NIH Manual Issuance 4513. Concurrence of the NCAB with recommendations of initial review groups will be required, except for the following: (1) Training grants and fellowships and other non-research grant applications are not subject to NCAB review and approval, and without other concerns may be awarded without presentation to the NCAB for concurrence, with the exception of Ruth L. Kirschstein National Research Service Awards. (2) Applications over the 50th percentile will not have summary statements presented to the NCAB. (3) For applications assigned raw scores that are not percentiled, the cutoff will be a priority score of 50 for all mechanisms except R41, R42, R43, and R44 awards; for the latter, all scored applications will be included. Expedited Concurrence: (1) for R01 and R21 applications with percentiled or raw scores that fall within the NCI paylines for that mechanism, a process of expedited concurrence will be used; and (2) the Executive Secretary will alert Board members with responsibility for expedited concurrence when review outcomes for eligible applications are available on the Electronic Expedited Concurrence portion of the Electronic Council Book. Administrative Adjustments: (1) Permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards. (2) Administrative requests for increases in direct costs that are the result of marked expansion or significant change in scientific content of a program after formal peer review will be referred to the Board for advice and recommendation. (3) Actions not requiring Board review or advice, such as change of institution, change of principal investigator (PI), phase-out or interim support, or additional support, need not be reported to the Board. (4) NCI staff may restore requested time and support that were deleted by the initial review group when justified by the PI in an appeal letter or when restoration is in the best interest of the NCI and the project is of high NCI programmatic relevance.

Questions and Answers

Mr. William H. Goodwin, Chairman and President, CCA Industries, Inc., asked whether Dr. Varmus accepted this authority, to which Dr. Varmus assented.

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

***Ad hoc* Subcommittee on Global Cancer Research.** Dr. Olopade provided a report of the Subcommittee's meeting, which discussed current work and partnerships that have been formed to promote palliative care globally. The NCI is developing training programs and leveraging resources through the international palliative care consortium. The Middle East Cancer Consortium is striving to overcome barriers to palliative care in Muslim majority countries. The Subcommittee was interested in a successful program in Kerala, India, that educates trainers in palliative care. In addition, Ms. Nelvis Castro, Deputy Director, Office of

Communications and Education, presented an overview on the first in a series of international scientific journalism workshops on *Cancer Research in the Media*, which took place in Mexico. Ms. Kalina Duncan, Behavioral Research Program, Office of the Associate Director, informed the Subcommittee about international activities, many of which are in Africa, China, and India, by NCI-designated cancer centers. Also, the Subcommittee learned about opportunities to build research capacity in Latin America provided by the Latin American Cancer Research Network and resources developed by this collaboration. Dr. Olopade expressed the Subcommittee's interest in establishing metrics to monitor success of training programs administered by the CGH. The CGH's first stakeholder meeting is scheduled for March 13–14, 2012.

Questions and Answers

Dr. Kaur suggested that given the variety and significance of the programs presented to the Subcommittee, it will be important to use the workshop as an opportunity to prioritize global cancer research activities.

Motion. A motion to accept the summary report of the 27 February 2012 *Ad hoc* Subcommittee on Global Cancer Research meeting was approved unanimously.

Clinical Investigations Subcommittee Report. Dr. Hong provided a report of the Subcommittee's meeting. Dr. James Zwiebel, Branch Chief, Investigational Drug Branch (IDB), presented an overview of the Cancer Therapy Evaluation Program's (CTEP) NExT. The Experimental Therapeutics Program has met its goals of decreasing the time from concept development to trial activation and terminating trials that have insufficient patient accrual. Dr. Percy Ivy, Associate Branch Chief, IDB, then outlined plans to redesign the Experimental Therapeutics Program to emphasize understanding mechanisms behind drug action and resistance. Challenges include patient accrual, access to certified biomarker laboratories and imaging facilities, and expense. The Subcommittee discussed approaches to redesigning the Program successfully.

The Subcommittee made the following recommendations for redesigning the Experimental Therapeutic Program: (1) focus on "Team Science" and collaborations, which should include translational scientists and clinicians; embrace the concept that the patients are "our patients;" (2) reduce the number of trials but focus on high quality, especially in quality-based, biomarker-driven studies; (3) consider keeping trials in the network open continuously so that enough patients can be accrued; (4) include adaptive design in future trials to partially address the issue of statistical power for outcomes; (5) focus on molecular characterization studies; U01-funded facilities must have molecular profiling capabilities to target patients to do what the CTEP is planning for future trials; and (6) integrate with the SPOREs whenever possible as they can provide translational expertise.

Motion. A motion to accept the summary report and recommendations of the 27 February 2012 Clinical Investigations Subcommittee meeting was approved unanimously.

Establish NCI *Ad hoc* Information Technology (formerly caBIG®) Working Group. Dr. Gray explained that the *Ad hoc* Subcommittee on Cancer Bioinformatics Grid (caBIG®) was formerly a BSA subcommittee but was being reformed as an NCAB working group, chaired by Dr. Daniel Masys. It will report to the NCAB *Ad hoc* Subcommittee on Biomedical Technology and thereby to the Director of the NCI. Dr. Varmus indicated that the NCI is restructuring its informatics activities and recruiting a new leader who will coordinate information technology activities within NCI Divisions and Offices.

Questions and Answers

In response to questions by Drs. Olopade and Chabner about how the working group will function and the issues it will address, Dr. Varmus said that the working group will advise the NCI on organizing its informatics efforts—ranging from genomics recordkeeping to ensuring interoperability to grants administration—and

recruiting an information technology leader. It will meet independently of the NCAB, mostly by teleconference, and at least two NCAB members will serve as working group members.

Dr. Olopade suggested that the working group might want to broaden its discussions to how bioinformatics issues affect the cancer centers. Dr. Varmus agreed and added that several members of the working group are affiliated with cancer centers.

Dr. Chabner encouraged strategic planning to ensure that funding is directed toward those informatics projects that are most needed by the research and clinical community.

Motion. A motion to form an *Ad hoc* Information Technology Working Group on was approved unanimously.

Future Agenda Items. Dr. Chabner reviewed several potential agenda items raised during the meeting, including bioinformatics at the NCI, the NCI-Frederick Strategic Plan, the NCI's approach to team science, results and a cost-benefit analysis of the NLST, and the results of and future plans for the Provocative Questions Initiative. He invited members to send additional items to him and Dr. Gray.

IX. UPDATE: COOPERATIVE GROUPS REORGANIZATION—DR. JEFF ABRAMS

Dr. Jeff Abrams, Acting Director for Clinical Research and Associate Director, CTEP, Division of Cancer Treatment and Diagnosis (DCTD), provided an update on the reorganization of the NCI cooperative groups. Dr. Abrams informed members that the concept, which was presented to and approved by the BSA in late 2011, aims to make the development and conduct of trials more efficient, incorporate innovative science, advance science and patient care, orient trials toward disease management in lieu of an agent-specific approach, and better engage the broad oncologic community in trial development and conduct.

Major accomplishments during the past 6 years include more than 30 practice-changing clinical trials, with findings such as: sentinel lymph node dissection is not inferior to axillaries dissection even when the sentinel lymph node was positive; regional nodal radiation therapy reduces local recurrences and improves disease-free survival in node-positive breast cancer; a higher dosage of methotrexate can improve event-free survival in pediatric acute lymphoblastic leukemia (ALL); and short-term androgen deprivation combined with radiation improves overall survival in prostate cancer. The NCI's work with agents that have received FDA approval include nelarabine for T-cell ALL and lymphoma and anti-GD1 antibody (ch14, 18) in neuroblastoma. New indications for generic agents include daunorubicin in acute myeloid leukemia (AML) and dexamethasone in multiple myeloma.

Dr. Abrams described the NCI clinical trials system, which encompasses 3,000 U.S. institutions and 14,000 investigators across every state, including Alaska and Hawaii, with a primary focus on Phase 3 trials (80%). Based on extensive review by NCI staff and clinical trial stakeholders, the clinical trials system has been reorganized to: meet aggressive timelines for trial activation and accrual; ensure better incorporation of critical correlative science into Phase 2 and 3 studies through the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP); facilitate trial prioritization by Disease-Specific Steering Committees; and engage physicians and their patients more fully in the system. Dr. Abrams informed members that trial activation and accrual rates have been improved already by approximately 50 percent over the historical medians. The program structure has changed to an integrated clinical trials network with one pediatric group and up to four adult groups. In addition, review criteria emphasize integration and collaboration, increase per-case reimbursement, integrate translation science awards, and revitalize the role of Cancer Centers in the network.

The infrastructure consolidation will allow much efficiency in information technology as well as regulatory and tissue-resource management. The consolidation of the imaging and radiation therapy core services also will benefit the entire network by adding value to research questions. These core services are services performed for NCI-sponsored Cooperative Group trials by organizations both inside and outside the Cooperative Groups to

provide quality assurance for imaging and radiotherapy studies. These organizations include: ACRIN, RTOG, QARC, RPC, and ATC. They primarily do quality control on both the machines and the dosimetry in RT trials and help with quality control for the machines/software/measurement parameters on imaging studies. In addition, new agents (e.g., erlotinib, crizotinib, ipilimumab) will be integrated into trials during earlier stages and be evaluated in molecularly defined disease subsets. The Canadian network will continue to participate in the clinical trials system, and operations and statistical centers will provide scientific strategies and goals across a broad range of diseases along with statistical leadership for effective trial design and data quality monitoring, management, and analyses. Dr. Abrams said that peer review of the clinical trial system has been reconfigured to ensure that all groups are compared every 5 years at the same time. In addition, scientific evaluation will shift to evaluating the group role in the national network, including collaborative management as well as operational efficiency. Multiple-PI grants from leading academic centers are encouraged; awards made midway through each grant period will ensure that new lead academic participating sites join the program.

Dr. Abrams described the network funding, which will provide increased research reimbursement from the NCI's previous level of $2K per patient. Cost analyses indicate that real research costs per patient in 2006 ranged from $5K to $8.5K for Phase 3 and Phase 2 trials, respectively. High-performance sites will be rewarded with $4K per patient reimbursement. The overall budget, which was approved by the BSA, totals $178 M per year, with $900 M for 5 years. This includes $152 M for 20,000 treatment trial enrollments as well as increased capitation to high-performance sites and support for the CCOPs and BIQSFP. New review criteria will abet the NCI and the clinical trials steering committee in developing strategic consensus about scientific opportunities and facilitating more trials in underrepresented disease areas, including rare and uncommon tumors. Dr. Abrams said that the RFA is expected to be released in the summer of 2012, with applications due in late 2012 or early 2013, reviews completed by late 2013, and awards made in March 2014.

Questions and Answers

Dr. Chabner observed that the NCTN proposed budget includes a substantial increase and asked whether, given the economic conditions, the NCI has considered reducing clinical trial accrual rates and operating under the previous budget. He noted significant shifts in how trials are conducted and wondered if such a large system is needed for Phase 3 studies, which pharmaceutical companies focus on, or if the NCI's resources might be better spent on understanding the disease or basic science grants. Dr. Chabner also cautioned that the emphasis on team work should not be allowed to impede innovation and progress. Dr. Abrams responded that NCTN funding will be approved based on the NCI's resources each year. He added that the NCTN has reduced trial accrual rates from 25,000 to approximately 19,000 patients in consideration of the fiscal situation. Dr. Varmus said that the proposed budget reflects reasonable estimates, but funding will be determined with each year's actual budget. He noted that funding increases for the program are expected to come from the attrition of other programs.

Dr. Lyerly queried about the role of the cooperative group system and the effect of improved operational efficiency in the trial system on obtaining support for patient-centered research and enticing the pharmaceutical industry to collaborate more closely with the Institute regarding newly approved molecular entities. Dr. Abrams replied that the cooperative groups are the only mechanism that has included radiation, surgery, and many types of adaptive immunotherapy strongly in its approach along with system treatment; pharmaceutical companies have interacted with the cooperative groups, such as in studies of bevacizumab. He also confirmed that the NCI is emphasizing greater efficiency to attract industry partners and provide answers to the American public; effectiveness analyses have helped in comparing hormonal therapy alternatives in the adjuvant as well as various surgical approaches versus radiation. The new system should facilitate trial starts and rapid accruals, with steering committees and advisors selecting the trials that benefit the most from the available resources.

Dr. Kaur asked about funding for rare-tumor trials. Dr. Abrams responded that steering committees for melanoma and sarcoma are being established. In response to a query by Dr. Champion, Dr. Abrams indicated that the cooperative groups have not yet conducted behavioral trials.

X. CLOSED SESSION—DR. BRUCE A. CHABNER

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 552b(c)(6), Title 5 U.S. code, and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

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

The en bloc vote for concurrence with the IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 3,970 applications were reviewed requesting support of $1,136,486,865 and 25 FDA applications were reviewed.

XI. ADJOURNMENTCDR. BRUCE A. CHABNER

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

There being no further business, the 161st regular meeting of the NCAB was adjourned at 2:47 p.m. on Tuesday, 28 February 2012.

_____ _____

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

_____ _____

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

President's Cancer Panel: A new beginning

2/28/2012

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.**

Topics today

- New appointments to President's Cancer Panel
- How we will function
- Meeting approach
- First topic
- Potential topics for other years
- Report in process

The White House

Office of the Press Secretary

For Immediate Release November 29, 2011

President Obama Announces More Key Administration Posts

WASHINGTON, DC – Today, President Barack Obama announced his intent to nominate the following individuals to key Administration posts:

- **Frederick "Rick" Barton** – Assistant Secretary for Conflict and Stabilization Operations and Coordinator for Reconstruction and Stabilization, Department of State
- **Arun Majumdar** – Under Secretary of Energy, Department of Energy
- **Marie F. Smith** – Member, Social Security Advisory Board

The President also announced his intent to appoint the following individuals to key administration posts:

- **Barbara K. Rimer** – Chairman, President's Cancer Panel
- **Owen N. Witte** – Member, President's Cancer Panel

President Obama said, "These men and women have demonstrated knowledge and dedication throughout their careers. I am grateful they have chosen to take on these important roles, and I look forward to working with them in the months and years to come."

BLOG

ama: Changing the
onversation on Healthy Eating

In an op-ed published today, the First Lady talks about the progress Let's Move has made in its first two years

Our approach

- **Focus on actionable recommendations**
- **Track recommendations over time**
- **Meeting format based on topic goals**
- **Interaction & discussion among participants**
- **Participants from different sectors and perspectives**

Criteria for topic selection

- **Related to FUNCTIONAL OUTCOMES that influence resource allocation, organizations, industry practices and, potentially, cancer prevention, detection and therapeutic interventions**
- **SIGNIFICANT: AFFECTS CRITICAL ASPECTS of cancer-related discovery, prevention, early detection, treatment, delivery, control and policy**
- **MANAGEABLE AND FOCUSED**
- **CAN LEAD TO ACTIONABLE RECOMMENDATIONS**
- **ADDRESSED within timeframes and resource constraints of PCP**

Criteria for topic selection

- **NOT EXCLUSIVELY FOCUSED ON NCI issues**
- **SALIENT, RELEVANT AND TIMELY**
- **NOT EXAMINED RECENTLY by other credible leadership organizations *(except where deeper/broader exploration is needed)***
- **Based on SOUND SCIENCE and policy**
- **NOT CREATING GUIDELINES**

2012 Topic

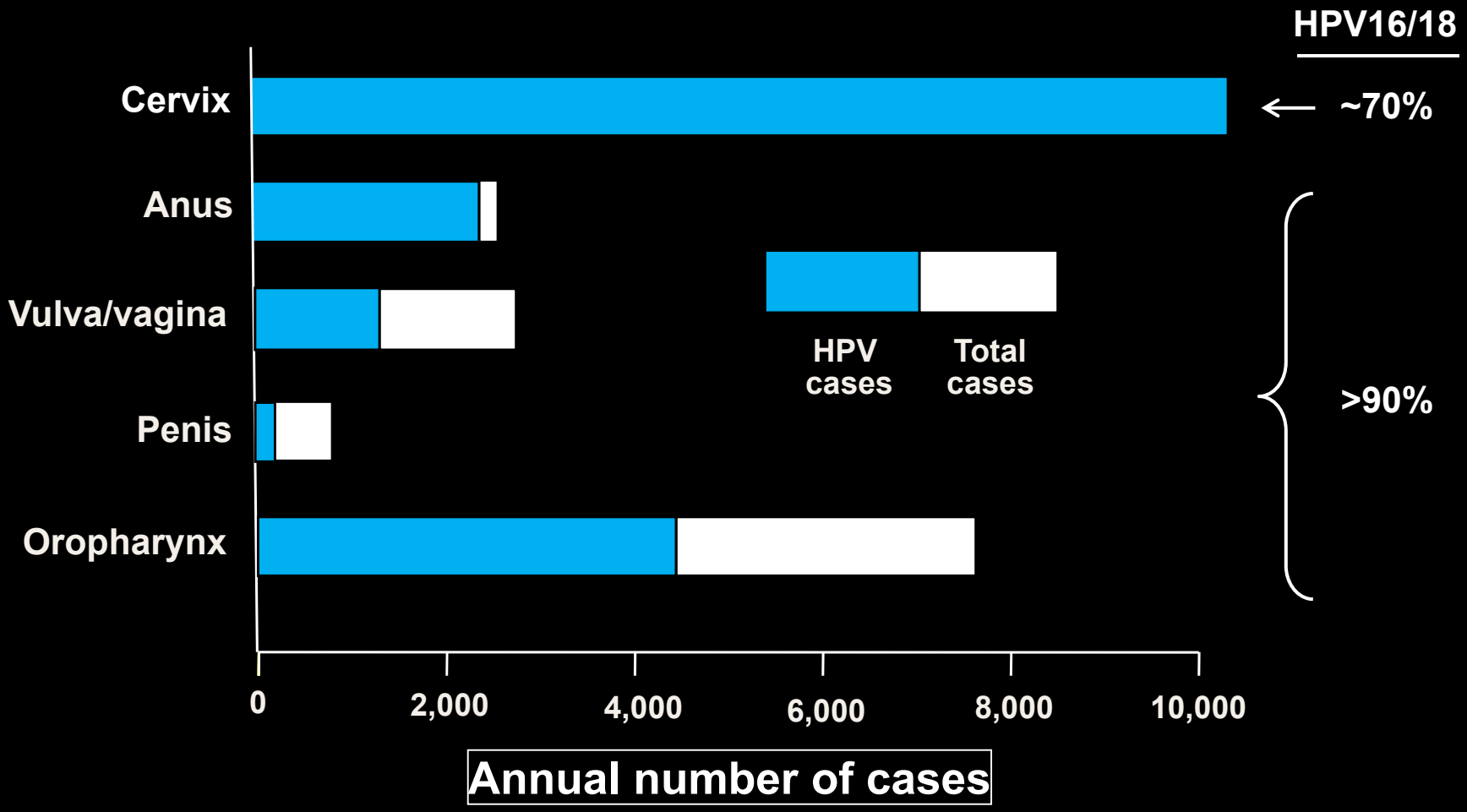
Accelerating Progress in Cancer Prevention:

The HPV vaccine example

Rationale

- **Globally, HPV infections cause most cervical cancers: over 560,000 new HPV-related cases/year (cervical and other cancers).**
- **Vaccines protect against most common forms of oncogenic HPV infections (e.g. HPV 16, 18).**
- **Only 1.4% of US males and 32% of US females ages 13-17 have received 3 vaccine doses.**
- **US rates are too low to achieve population potential of HPV vaccines to reduce cancer incidence.**
- **Increasing HPV vaccination could effect a major reduction in HPV-related cancers.**

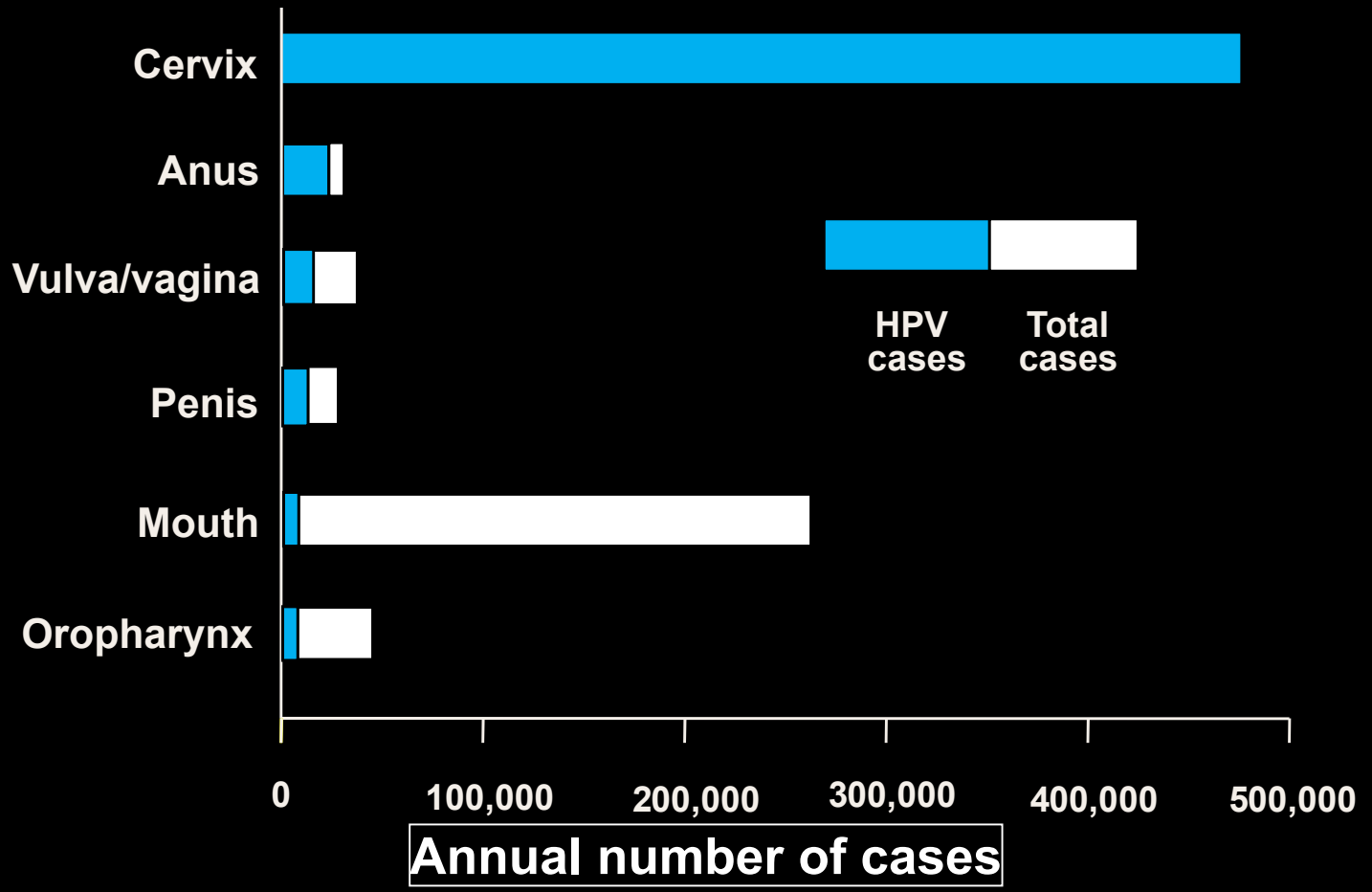
United States: Incidence and Distribution of Cancers Attributable to HPV



- *Pap screening has reduced the incidence of cervical cancer by ~80%*

Gillison, Chaturvedi, and Lowy. Cancer 113: S3036-46, 2008 ** From D. Lowy presentation to NCAB, 12/11*

*Worldwide Incidence and Distribution of Cancers Attributable to HPV**



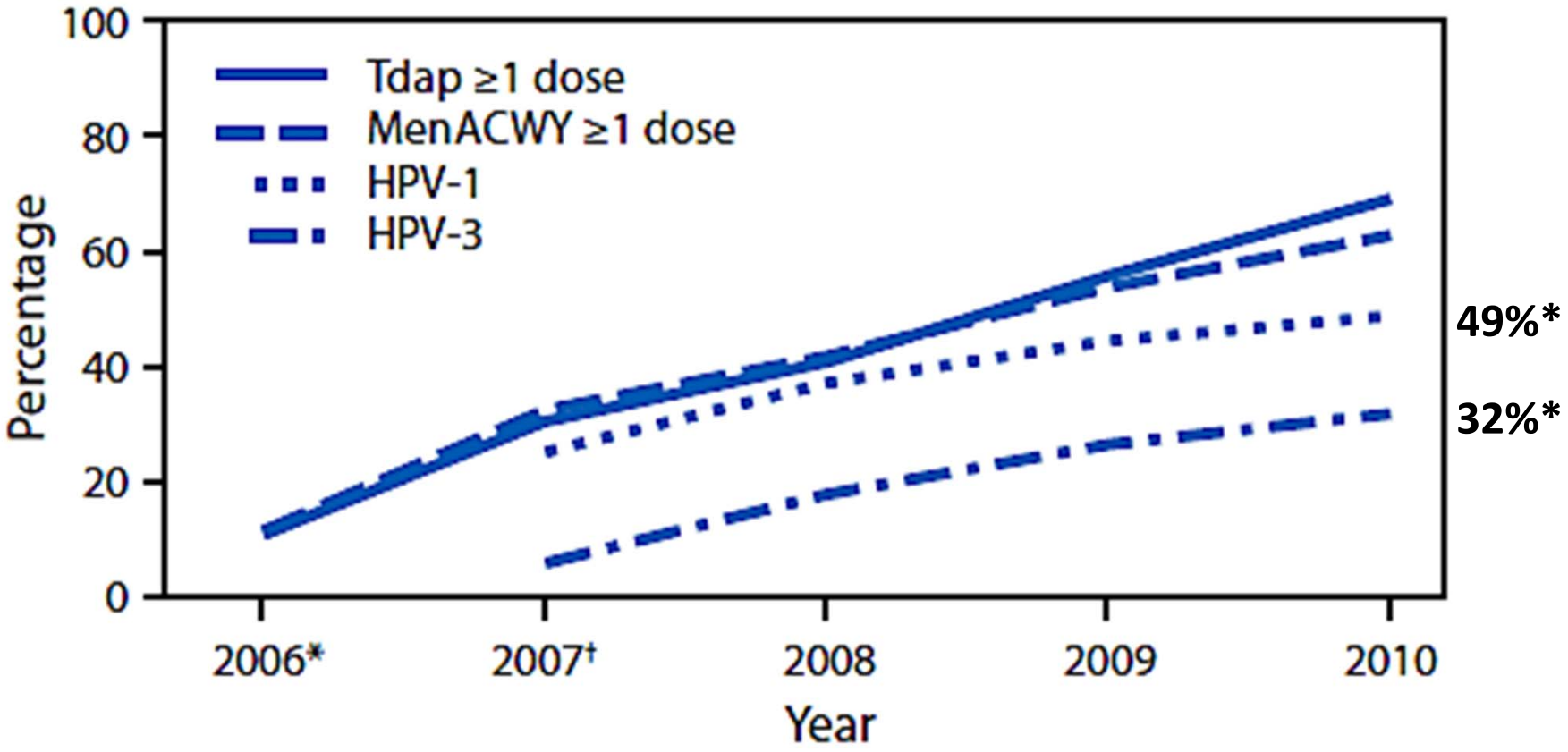
- *Cervical cancer = ~10% of all female cancers worldwide*
- *~80% of cervical cancers occur in developing world*

Adapted from Parkin, Int J Cancer 118:3030, 2006

** From D. Lowy presentation to NCAB, 12/11*

Trends in U.S. Vaccination Rates: Ages 13-17 Yrs**

MMWR Vol 60, #33, August 26, 2011



*** Females; adolescent male vaccination 1.4%**

Abbreviations: Tdap = tetanus, diphtheria, acellular pertussis vaccine; MenACWY = meningococcal conjugate vaccine; HPV-1 = human papillomavirus vaccine, ≥1 dose; HPV-3 = human papillomavirus, ≥3 doses.

* Tdap and MenACWY vaccination recommendations published March and October 2006

† HPV vaccination recommendations published March 2007

**** * from presentation at NCI 2011 by Noel Brewer***

2012 Topic

Accelerating Progress in Cancer Prevention:

The HPV vaccine example

Approach

- Workshop model: encourage interaction and discussion
- Invite two co-chairs for each of 3 workshops.
- Identify provocative questions.
- Assess scientific basis for, current status of, and continuing efforts for effective HPV vaccination.

2012 Topic

Accelerating Progress in Cancer Prevention:

The HPV vaccine example

Approach

- Examine epidemiologic, behavioral, sociopolitical, communication, and policy issues that influence effectiveness of HPV vaccines in reducing population cancer risks.
- Also: clinical and economic issues
- Consider global impact and strategy.

2012 Topic

Accelerating Progress in Cancer Prevention:

The HPV vaccine example

Workshop goals

- Develop actionable recommendations that focus on ways to increase uptake of HPV vaccines in US.
- Identify lessons learned from vaccination programs that may be applied to future cancer-related vaccines.
- Address issues related to global HPV vaccination strategy.
- Identify topics and issues that require further study.

HPV Vaccination as a Model Cancer Prevention Method:

State-of-the-science and evidence

July 24, 2012
San Francisco, CA
(Workshop 1)

- **Preventive vaccine for HPV serotypes most commonly associated with cervical, vulvar, vaginal, anal, penile, oral cavity and oropharyngeal cancers is a major advance in preventive oncology.**
- **Potential impact of HPV vaccine on cancer incidence and mortality has not been realized.**

HPV Vaccination as a Model Cancer Prevention Method:

State-of-the-science and evidence

- **Fundamental science that laid foundation for development of HPV vaccine, specifically, basic, translational, and clinical research that brought the vaccine from discovery to approval**
- **Surveillance and epidemiology to determine:**
  - ✓ **durability of immunity**
  - ✓ **safety**
  - ✓ **cross-protection among multiple oncogenic HPV strains**
  - ✓ **high risk groups**
  - ✓ **incidence of CIN, HPV infections, and cervical, vaginal, vulvar, anal, penile, oral cavity and oropharyngeal cancers among vaccinated populations**

HPV Vaccination as a Model Cancer Prevention Method:

State-of-the-science and evidence

- Implications for future vaccines
- Financing development and dissemination of HPV vaccines; implications for other vaccine development
- Improvements in formulation and delivery of HPV vaccines that will inform development of future vaccines

Achieving Widespread HPV Vaccine Dissemination:

Policy, program, and communication considerations

September 13, 2012
Washington, DC
(Workshop 2)

- **US HPV vaccination rates should be increased.**
- **Assess vaccine dissemination, communication/education, sociopolitical issues, barriers to greater use, and current policy environment.**
- **Recommend strategies to improve communication, other critical factors, decision making, and vaccine uptake.**

Achieving Widespread HPV Vaccine Dissemination:

Policy, program, and communication considerations

- Policies that determine where and by whom vaccines are administered, and who is eligible to receive them, under what conditions, affect use.
- What, if any, policy changes are needed to increase use of HPV vaccines?
- Issues related to messaging strategies, campaigns and use of social and other internet media
- Vaccine characteristics that are barriers to uptake
- Choice of vaccines (Gardasil vs. Cervarix)

HPV Vaccination :

Clinical practice issues, standards and economic implications

Date & Location TBD
(Workshop 3)

- **Impact of HPV vaccination on cervical cancer rates is uncharacterized.**
- **Cervical cancer screening still is needed to minimize cancer incidence and mortality.**
- **Examine current clinical practice standards for cervical cancer screening—and related economic implications of widespread vaccination.**

HPV Vaccination :

Clinical practice issues, standards and economic implications

- Definition of potential changes in risk evaluation and clinical practice standards that effective HPV vaccination may catalyze
- Cost-effectiveness of widespread vaccination
- Economic approaches (e.g., tiered pricing, innovative financing mechanisms, interdisciplinary partnerships) that may increase access to vaccines
- Potential economic effects of increased vaccination rates on federal, state, and private health care and insurance costs

Potential future topics

- Accelerating clinical trials through new discovery pathways and agents, trial designs, statistical methodologies, trial processes and policies
- Creating a global network of cancer registries as foundation for global health efforts
- Communicating more effectively about cancer—changing the paradigm

Report in process

The Future of Cancer Research: Accelerating scientific innovation

Tentatively scheduled for release late Spring, 2012

FDA Office of Hematology and Oncology Products (OHOP)—2011 Review

OHOP

- 130 total employees
- 55 oncologists including 9 pediatric oncologists
- 25 PhDs in Pharmacology/Toxicology
- 24 Regulatory Project Managers
- Support staff

Prior Organization Structure

- Division of Drug Oncology Products
- Division of Biologic Oncology
- Division of Hematology Products
- Pharm/Tox reviewers located in clinical divisions
- Matrix organization—statisticians, clinical pharmacology, chemistry/manufacturing located in separate offices

New Divisions and Therapeutic Areas

- **Division of Oncology Products 1 (DOP 1):** Breast, Gynecologic & Supportive care, Genitourinary
- **Division of Oncology Products 2 (DOP 2)**: Lung/H&N; Gastrointestinal; Melanoma/Sarcoma; Neuro-oncology, Rare cancers, Pediatric Solid Tumors
- **Division of Hematology Products (DHP):** Benign Heme, Heme Malignancy, Heme Support
- **Division of Hematology Oncology Toxicology (DHOT)**

Principles Behind Re-organization

- Consistency of advice to sponsors
- Workload more efficient and balanced
- Coordinated understanding of specific diseases and all protocols within disease → efficient review of drug applications
- Staff expertise recognized by external entities
- Formation of Division of Hematology Oncology Toxicology (DHOT) → increased opportunities for review of broader classes of molecules and development of specialized expertise

Oncology Program—located in OHOP

- Coordinates external oncology activities—monthly teleconference with EMA, Health Canada, professional groups, advocacy groups
- Coordinates internal FDA activities—meetings with CDRH and CBER to discuss applications, guidances, programs

2011 New Molecular Entity (NME) Approvals

CDER 2011 NMEs

Datscan (ioflupane I-123)	Zytiga (abiraterone)	Brilinta (ticagrelor)
Natroba (spinosad)	Tradjenta (linagliptin)	Zelboraf (vemurafenib)
Viibryd (vilazodone HCl)	Victrelis (boceprevir)	Adcetris (brentuximab)
Edarbi (azilsartan)	Edurant (rilpivirine)	Firazyr (icatibant)
Daliresp (roflumilast)	Incivek (telaprevir)	Xalkori (crizotinib)
Benlysta (belimumab)	Dificid (fidaxomicin)	Ferriprox (deferiprone)
Gadavist (gadobutrol)	Potiga (ezogabine)	Onfi (clobazam)
Yervoy (ipilimumab)	Nulojix (belatacept)	Jakafi (ruxolitinib)
Horizant (gabapentin enacarbil)	Arcapta (indacaterol)	Erwinaze (asparaginase *Erwinia chrysanthemi*)
Caprelsa (vandetanib)	Xarelto (rivaroxaban)	Eylea (aflibercept)

OHOP 2011 NMEs/Original BLAs

Drug	Indication	Study	Endpoint
Yervoy (ipilimumab)	Unresect/met. melanoma	Randomized, double-blind; 676 pts	OS
Zelboraf (vemurafenib) *-Diagnostic*	Unresect/met. melanoma BRAFV600E mutation	Randomized, open-label; 675 pts	OS & PFS
Xalkori (crizotinib) *-Diagnostic* *-Accelerated*	Local adv/met. ALK+ NSCLC	2 multicenter, single-arm trials; 255 pts	ORR
Zytiga (abiraterone)	Met. castration-resistant prostate cancer	Randomized, plac-controlled; 1,195 pts	OS
Xarelto (rivaroxaban)	DVT prophylaxis, which may lead to PE in knee/hip replacement surgery	3 randomized, double-blind; over 6000 pts	Occurrence of VTE

OHOP 2011 NMEs/Original BLAs (con't)

Drug	Indication	Study	Endpoint
Adcetris (brentuximab) *-Accelerated*	HL & ALCL	• HL: open-label, single-arm; 102 pts • ALCL: open-label, single-arm; 58 pts	ORR
Jakafi (ruxolitinib)	Intermediate or high-risk myelofibrosis	2 randomized, Phase 3; 528 pts	% Pts w/ 35% or greater ↓ in spleen vol
Ferriprox (deferiprone)	Transfusional iron overload due to thalassemia	Prospective, planned, pooled analysis of studies; 236 pts	20% ↓ serum ferritin
Caprelsa (vandetanib)	Symp./prog. Medullary Thyroid Cancer	Randomized, double-blind; 331 pts	PFS
Erwinaze (asparaginase *Erwinia chrysanthemi*)	ALL in pts hypersensitive to *E.coli*-derived asparaginase	Single-arm, open-label, safety & clinpharm study; 58 pts	Sustained Asparaginase Activity

2011 OHOP Approval Highlights

- Two drugs (Zelboraf, Crizotinib) approved concurrently with companion diagnostics
- Two drugs (Zelboraf, Yervoy) for melanoma
- First drug (Adcetris) in decades for Hodgkins
- First drug (Jakafi) for myelofibrosis—use of patient reported outcome

2011 OHOP Approval Highlights (con't)

- Flexibility with 3 NME approvals based on single-arm trials and 1 NME approval based on prospectively pooled analysis
- Two NME approvals were accelerated approval and 8 were regular approval
- Continued drug development in prostate cancer with approval of Zytiga (abiraterone)
- Pediatric drug approval (Erwinase)
- Rare diseases—Vandetanib for medullary thyroid cancer
- Variety of endpoints-OS, PFS, PROs, decreased serum ferritin level, spleen size, asparaginase activity

Accelerated Approval ODAC

Types of Approval

- Regular approval
  - Direct evidence of clinical benefit (e.g., improved survival or reduction in symptoms)
  - Improvement in established surrogate for clinical benefit (e.g., durable CR's in acute leukemia)
- Accelerated approval
  - Surrogate endpoint reasonably likely to predict clinical benefit (e.g., ORR)

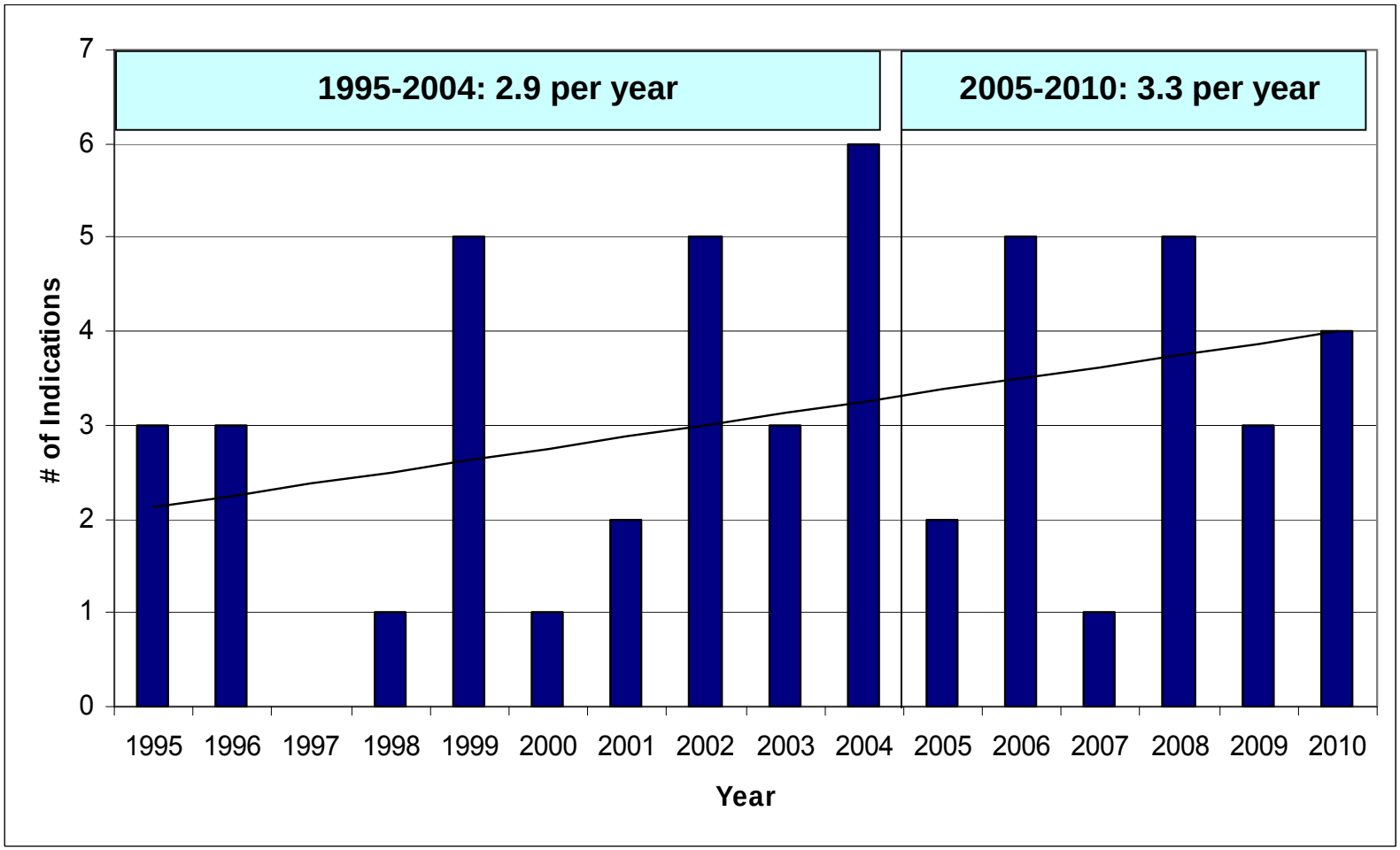
Accelerated Approval

- For serious or life-threatening diseases
- Drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
- Applicant must verify and describe benefit
- Post-marketing studies usually underway
- The applicant must carry out such studies with due diligence

2011 ODAC on Accelerated Approval

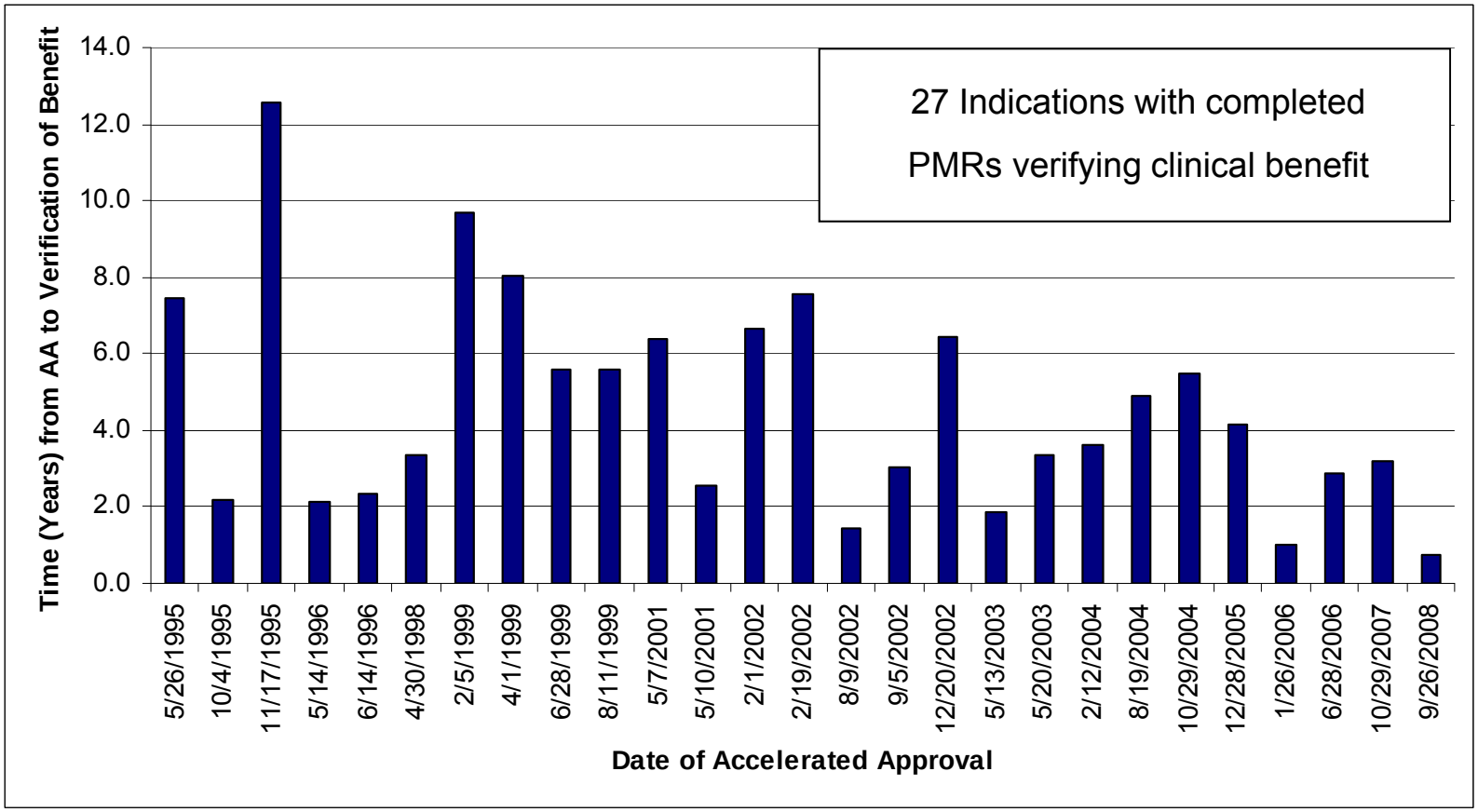
- 49 new indications, 37 oncology products
  - 55% (27/49) completed PMRs verifying benefit
  - 14.3% (7/49) AA < 24 months
  - 10.2% (5/49) have failed to confirm a benefit
    - Amifostine, celecoxib, gemtuzumab, gefitinib, bevacizumab

Accelerated Approvals over Time



Time from AA to completed trials confirming clinical benefit

Median 3.6 years (0.8 – 12.6)



Due Diligence

- AA indications that **have not completed confirmatory trials:**
  - The 5 longest times since AA: 11.0, 6.9, 6.0, 6.0 and 5.2 years
  - Celecoxib, Cetuximab, Tositumumab 131, Clofarabine and Nelarabine respectively
- AA indications with **completed trials verifying clinical benefit:**
  - 5 longest times since AA: 12.6, 9.7, 8.1, 7.5 and 7.4 years
  - Liposomal Doxorubicin, Denileukin, Lipo-cytarabine, Ibritumomab and Dexrazoxane respectively
- This represents a suboptimal period of time for a drug to be marketed prior to verification of clinical benefit.

Indications failing to demonstrate a benefit

AA Date	Drug	Abbreviated Indication	Outcome	Years on Market
3/15/1996	Amifostine	Cisplatin-Induced renal toxicity in NSCLC	Voluntarily Withdrawn 3/28/2006	10.0
12/23/1999	Celecoxib	Reduction in colonic polyps FAP	Voluntarily Withdrawn	11.0
5/17/2000	Gemtuzumab	2nd line AML in patients >60	Voluntarily Withdrawn 6/21/2010	10.1
5/5/2003	Gefitinib	3rd line NSCLC	Voluntarily Withdrawn 7/1/2011	2.1
2/22/2008	Bevacizumab	1st line metastatic HER-2 neg Breast Ca	Withdrawal	2.9

Withdrawal Procedures

CFR 21 314.53 and 601.43

- AA indications may be withdrawn by FDA if:
  - Postmarketing study(s) fails to confirm a benefit
  - Failure to perform PMR with due diligence
- Until recently, products that failed to confirm benefit were withdrawn voluntarily by sponsor
- 12/16/2010 FDA initiated withdrawal proceedings for bevacizumab for treatment of HER-2 negative metastatic breast cancer.
  - The first FDA-initiated withdrawal for an accelerated approval oncologic drug indication

Accelerated Approval ODAC Conclusions

- **FDA remains committed to the accelerated approval pathway**
  - 49 new oncology indications since 1995
  - 3.3 oncology indications per year since 2005
- **AA has provided early access to clinically beneficial cancer therapies**
  - 27 oncology indications have confirmed benefit in post-marketing trials
  - Made available a median of 3.6 years prior to the verification of their clinical benefit

Draft Guidance: *In Vitro* Companion Diagnostic Devices

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

Diagnostic Tests

- Drugs approved for a target-selected sub-population need an assay that is
  - linked to assay used in clinical trials
  - reliable
  - widely available
- Assays are regulated by CDRH
- Involving CDRH:
  - by sponsor and/or diagnostic partner directly
  - by CDER during Pre-IND and EOP2 meetings

Draft Guidance

- Identify patients who are most likely to benefit from drug
- Identify patients likely to be at increased risk for serious adverse reactions
- Monitor response to treatment for purpose of adjusting treatment (schedule, dose, discontinuation) to achieve improved safety or effectiveness

IVD Guidance

- Novel Drug—If IVD is *essential* to safety and efficacy, then FDA does not believe drug can be approved without approval (clearance) of IVD
- Exceptions: *Life-threatening diseases*—if benefits from drug outweigh risks of not having IVD approved. *Already approved drugs*--safety issues

Guidance: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

Codevelopment is Appropriate?

- Intention is to treat serious disease
- Compelling biological rationale (e.g., drugs inhibit distinct targets)
- Preclinical model (*in vivo or in vitro*) or short term clinical study suggests that combination has substantial activity and provides greater than additive activity or more durable response
- Compelling reason why agent cannot be developed individually—i.e. drugs have limited activity when used as monotherapy
  - Example: two investigational drugs target different pathways

Phase 1

- Safety profile for individual drugs should be characterized in phase 1 studies, including DLT, PK parameters, effect on biomarker
- If not possible to characterize safety of individual drugs, nonclinical studies of combination should support initial dosing of combination
- Safety/dosing of combination could use sequential testing in same patient—subjects receive A, then B, then AB

Clinical Pharmacology

- Same pharmacology studies for each drug in combination as if drugs developed separately
- Drug interaction potential follows same sequence as in other development program—results of *in vitro* metabolism studies inform need for *in vivo* drug interaction studies
- Dose response should be evaluated for each drug of the combination. If one drug has no activity alone, dose response should be assessed when the drugs are administered in combination

Proof of Concept Studies

- Demonstrate the contribution of each component of the combination to extent possible and needed (given nonclinical/pharmacological data)
- Provide evidence of effectiveness of combination
- Optimize dose/doses of combination for phase 3 trials

Confirmatory Trials: Phase 3

- If findings from preclinical models and/or phase 2 trials adequately demonstrate contribution of each drug, phase 3 trials comparing the combination to SOC will be sufficient to establish efficacy
- Unexpected toxicity attributed to one drug combination may use lower dose of drug

2012 Projects

- Draft Guidance: Path CR in the neoadjuvant treatment of breast cancer
- Joint workshops with professional groups: Minimal Residual Disease as a registration endpoint in pediatric ALL, adult CLL, AML
- PFS: Role of Independent Radiographic Review of scans
- Draft Guidance: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations: public comment February 2012

National Cancer Institute

Current and Future Perspectives on Cancer Prevention Research

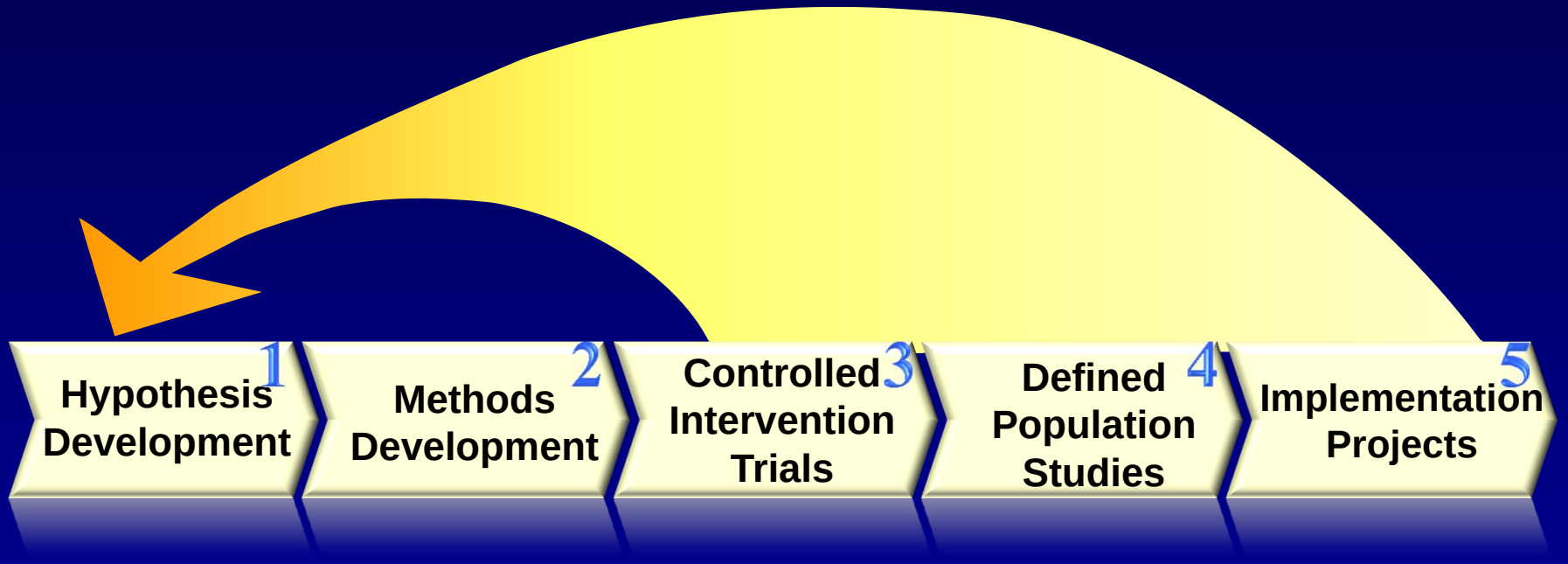
National Cancer Advisory Board
February 2012

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Phases of the Cancer Prevention Research Continuum



Research Training

Public and Professional Education

NCI Division of Cancer Prevention

Office of the Director
Barry Kramer, MD, MPH
Director

***Acting* Deputy Director**
Lori Minasian, MD, FACP

Associate Director for Clinical Research
Leslie Ford, MD

Community Oncology & Prevention Trials
W. McCaskill-Stevens, MD
***Acting* Chief**

Early Detection
Christine Berg, MD
Chief

Cancer Biomarkers
Sudhir Srivastava, PhD, MPH
Chief

Chemopreventive Agent Development
Vernon Steele, PhD
***Acting* Chief**

Nutritional Sciences
John Milner, PhD
Chief

Biometry
Philip Prorok, PhD
Chief

Breast & Gynecologic Cancer
Terri Cornelison, MD, PhD
***Acting* Chief**

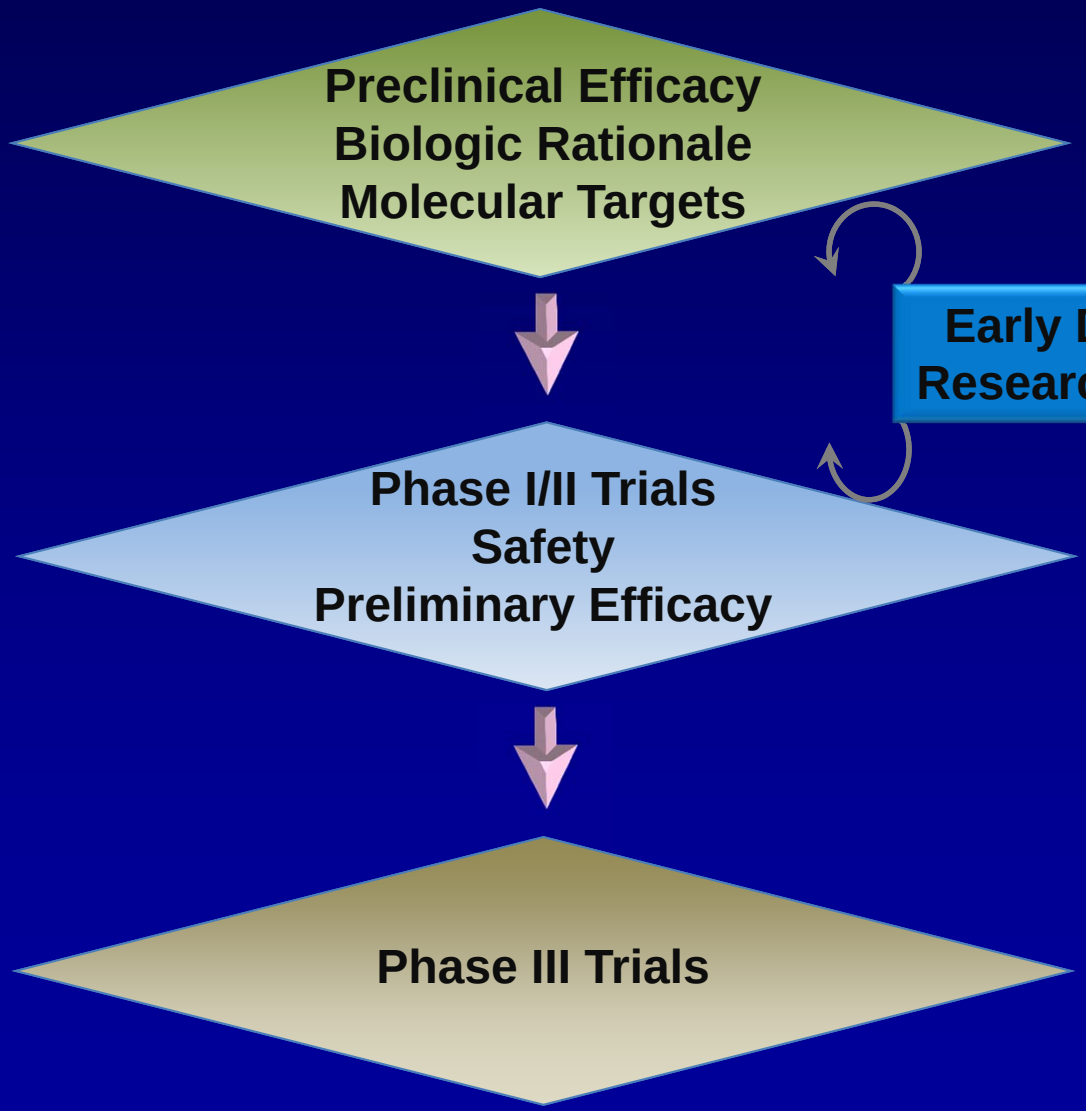
Gastrointestinal & Other Cancer
Asad Umar, DVM, PhD
Chief

Cancer Prevention Fellowship Program
David Nelson, MD
Chief

Lung & Upper Aerodigestive Cancer
Eva Szabo, MD
Chief

Prostate & Urologic Cancer
Howard Parnes, MD
Chief

Example of the Cancer Prevention Continuum



Preclinical Program

Early Phase Trial Consortia

CCOP Network

NCI Division of Cancer Prevention 2012

Major Accomplishments

- **Breast Cancer Prevention**
  - **Breast Cancer Prevention Trial (tamoxifen) (BCPT)**
  - **Study of Tamoxifen and Raloxifene (STAR)**
- **Prostate Cancer Prevention**
  - **Prostate Cancer Prevention Trial (finasteride) (PCPT)**
  - **Selenium and Vitamin E Cancer Prevention Trial (SELECT)**
- **Cancer Screening Trials**
  - **Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)**
  - **National Lung Screening Trial (NLST)**

All have biorepositories in use for hypothesis testing.

Future Scientific Directions

- Agent Development and Decision Making
- Overdiagnosis and Precancerous Lesions
- Cancer Immunoprevention
- Role of Microbiota
- New Approaches to Clinical Prevention Studies

Future Scientific Directions

- **Agent Development and Decision Making**
- **Overdiagnosis and Precancerous Lesions**
- **Cancer Immunoprevention**
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Agent Development and Decision-Making (1)

- **Development of Promising Agents Based on Clinical Need**
- **Transparent Agent Review & Prioritization Process**
  PREVENT Cancer Program, modeled after DCTD's NExT Program
  - **External Steering Panel (Leaders from Academia and Pharma)**
  - **External Special Emphasis Panel (Review)**
  - **Management & Administration Committee (DCP & DCTD experts)**
- **Preclinical Drug Development**
  - **Predetermined Decision Gates (Go/No-Go)**
  - **Hand-off to Early Phase Clinical Development**

Agent Development and Decision-Making (2): Making Better Decisions About Agents

- **Determine Which Preclinical Models Predict Clinical Outcome** (Positive & Negative Predictive Values)
  - **Evaluate Efficacy of Cancer Preventive Agent Development in Preclinical Models in Relation to Clinical Data**

- **Back Validate Successful Clinical Trials in Collaboration with DCB's Mouse Models for Human Cancers Consortium (MMHCC)**
  - **DCP participates in MMHCC Prevention Subcommittee (DCB)**

Future Scientific Directions

- Agent Development and Decision Making
- **Overdiagnosis and Precancerous Lesions**
- Cancer Immunoprevention
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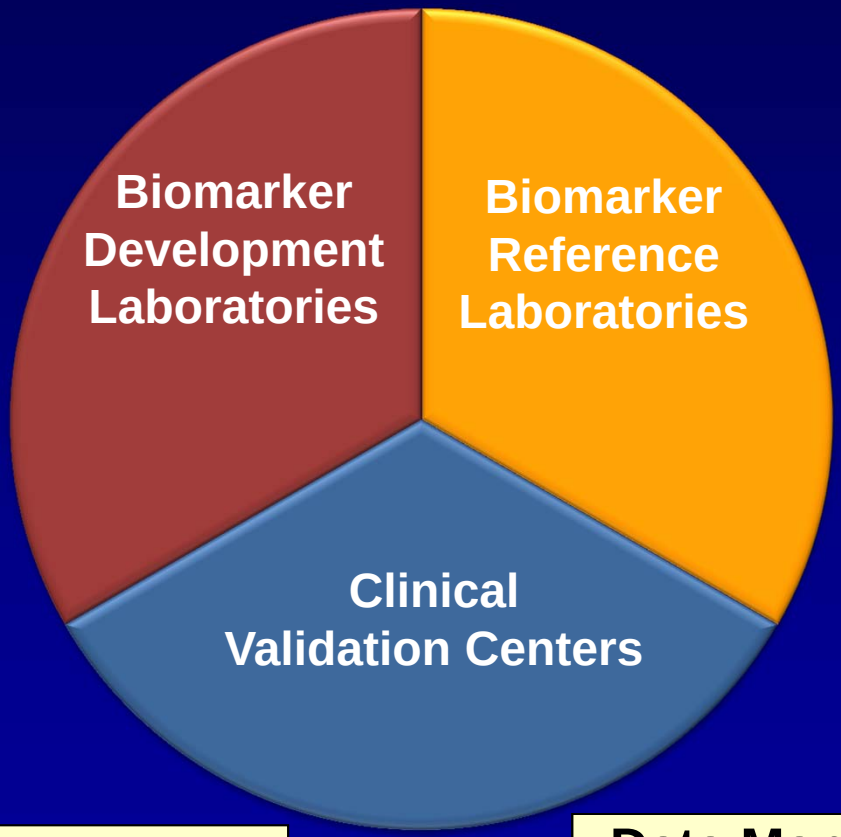
- New Approaches to Clinical Prevention Studies

Overdiagnosis and Precancerous Lesions (1): Early Detection Research Network

Network Consulting Team



Steering Committee

Data Management & Coordinating Center

- Biomarkers developed & tested for pancreatic, lung, prostate, ovary & liver cancers (>300)
- 8 Validation studies in progress; 4 FDA-approved markers
- Standard Reference Samples (serum & plasma) to test emerging biomarkers
- Collaborations
- Biomarker Database
- Biomarker plus Imaging Studies (DCTD)

Overdiagnosis and Precancerous Lesions (2): Molecular Characterization of Preclinical Lesions

- Molecular Characterization of Overdiagnosis & True Interval Cancers from Existing Screening Programs
- Overdiagnosis & Interval Cancers Think Tank
- Barrett's Esophagus Translational Research Network (BETRNet) (DCB)
- Proposed: The Genome Atlas for preCancers (TGAC) (DCB)
  - Risk Stratification
  - Driver Mutations

Future Scientific Directions

- Agent Development and Decision Making
- Overdiagnosis and Precancerous Lesions
- **Cancer Immunoprevention**
- Role of Microbiota
- New Approaches to Clinical Prevention Studies

Cancer Immunoprevention

- **Infectious Causes of Cancer**
  - **Human Papilloma Virus, Hepatitis C Virus, etc.**

    (NCI Center for Global Health, DCB, DCEG and NIAID)
- **Non-Infectious Tumor Antigens**
  - **Carcinoembryonic Antigen (CEA), Mucin 1 (Muc1), Human Epidermal Growth Factor Receptor 2 (Her2/neu) etc.**

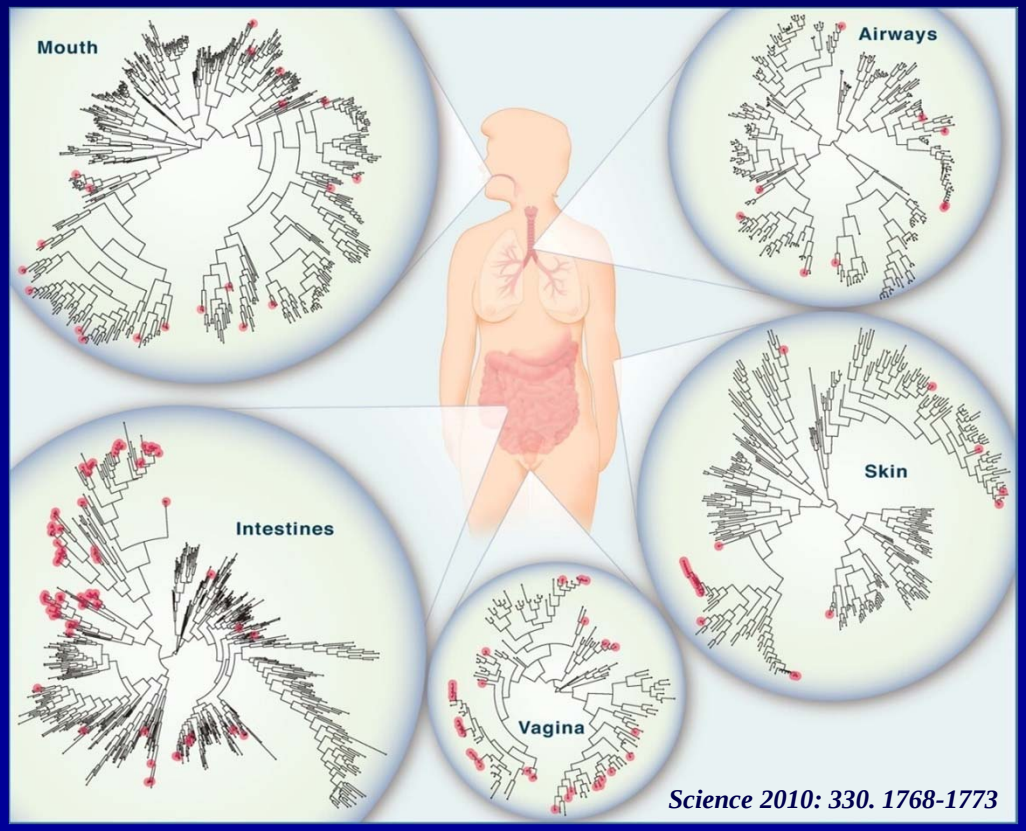
    (CCR, DCB)

Future Scientific Directions

- Agent Development and Decision Making
- Overdiagnosis and Precancerous Lesions
- Cancer Immunoprevention
- **Role of Microbiota**
- New Approaches to Clinical Prevention Studies

Role of Microbiota

- **Study prevention interventions (agents, vaccines, diet) as modifiers of the balance of microorganisms in the body**
  - Energy Exchange
  - Inflammation & Immunity
  - Dietary Choices



Future Scientific Directions

- Agent Development and Decision Making
- Overdiagnosis and Precancerous Lesions
- Cancer Immunoprevention
- Role of Microbiota
- **New Approaches to Clinical Prevention Studies**

New Approaches to Clinical Prevention Studies

- Repurposing Commonly Used Drugs For Cancer Prevention
  - NSAIDs (including aspirin), statins
- Using Non-cancer Disease Trials To Detect Cancer Prevention Signals
  - Metformin studies at NIDDK
  - Lutein/omega-3 fatty acid study at NEI
- Reciprocal Control Trials With Other Institutes/Centers
  - NHLBI

New Approaches to Clinical Prevention Studies

- Repurposing Commonly Used Drugs For Cancer Prevention
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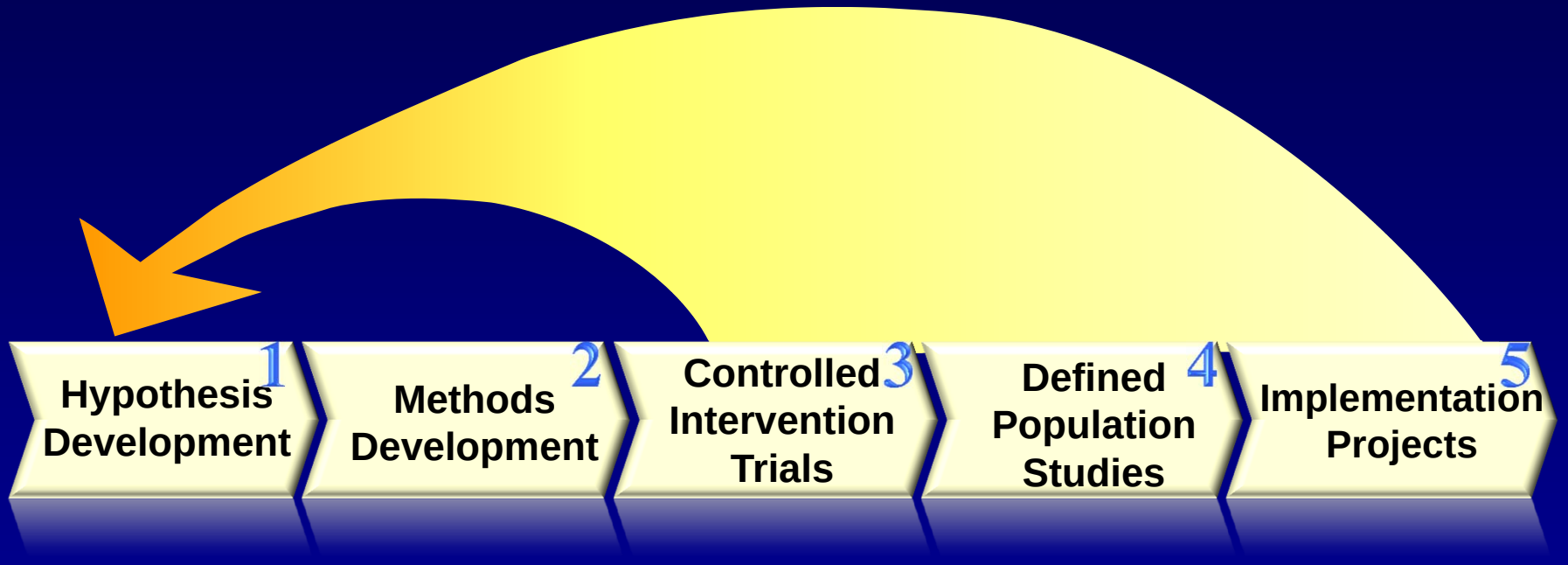
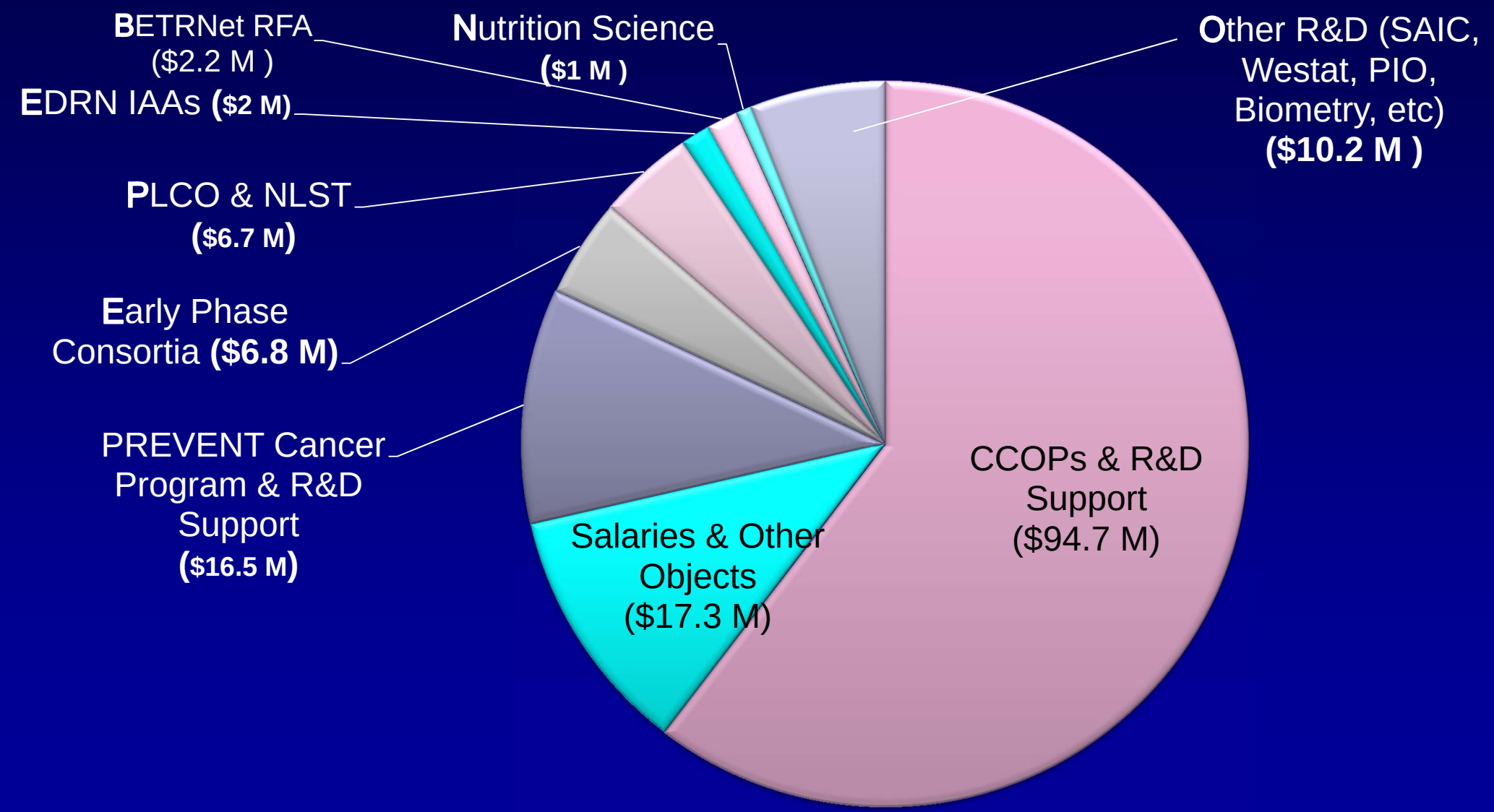
- Reciprocal Control Trials With Other Institutes/Centers
  - NHLBI
- National Clinical Trials Network and CCOP Network Continue as Effector Arm for Implementing Large Trials

Phases of the Cancer Prevention Research Continuum



DCP Controlled Funding FY 2011



NCI Division of Cancer Prevention 2012

National Cancer Institute

Request for Application (RFA)

U10 Cooperative Agreement for NCI Clinical Trials Network

Jeff Abrams, MD
Acting Director for Clinical Research, DCTD
Associate Director, CTEP

Meg Mooney, MD
Chief, Clinical Investigations Branch, CTEP

on behalf of the

Division of Cancer Treatment & Diagnosis:
Biometric Research Branch, Cancer Diagnosis Program, Cancer Imaging Program, Cancer Therapy Evaluation Program, and Radiation Research Program

Division of Cancer Prevention:
Community Clinical Oncology Program (CCOP) & Minority-Based CCOP

Presentation to NCAB
February 28, 2012

National Cancer Institute

BSA Presentation of New RFA for NCI National Clinical Trials Network (NCTN)

New RFA Concept for NCI National Clinical Trials Network (NCTN) presented to BSA on Nov. 7, 2011

BSA voted unanimously to approve the Concept

URL to NCI Presentation to the BSA:
http://deainfo.nci.nih.gov/advisory/bsa/bsa1111/130%20Mooney%20Abrams.pdf

National Cancer Institute

Re-thinking the Clinical Trials Systems at NCI

Improve speed & efficiency of development & conduct of trials

- ✓Cancer Trials Support Unit - provide 24/7central registration & collection regulatory documents
- ✓Provide NCI Central IRBs – Adult and Pediatric
- ✓Qualify sites for advanced imaging

Incorporate innovative science and trial design

- ✓NExT – multiple agents under development, with external peer review
- ✓Clinical Assay Development Program (CADP)
- ✓Develop support & funding for non-Group investigators with novel ideas
- ✓ Increase randomized phase 2 studies, use common control arms, stratify/randomize by genotype, early stopping rules

National Cancer Institute

Why Support a Standing, Publicly Funded Clinical Trials Network?

- **Advance science & patient care, especially on important research questions that are not priorities for industry, including evaluating:**
  - **Integration of new agents into standard regimens**
  - **Combinations of novel agents developed by different sponsors**
  - **Multi-modality regimens (e.g., Surgery, Radiotherapy, IP therapy)**
  - **Therapies for pediatric cancers, rare cancers, and uncommon presentations of more common cancers**
  - **Screening, diagnostic, & prevention strategies**
  - **Optimal duration and dose of drugs & radiotherapy**
  - **Different treatment approaches already approved for clinical care**

National Cancer Institute

Why Support a Standing, Publicly Funded Clinical Trials Network?

- **Trials oriented toward disease-management, not agent-specific or limited by marketing constraints, with inclusion of research questions related to:**
  - Correlative science
  - Imaging
  - Quality of Life
  - Symptom Management
  - Special Populations (e.g., analyis by sex, age, race/ethnicity)
- **Extensive, direct involvement of entire oncology community in the design, development, & conduct of trials:**
  - Academic center investigators
  - Community & private practice investigators
  - Patient advocates
  - Young investigators in training
  - International collaborators
  - Data-sharing of clinical data & banked biospecimens

National Cancer Institute

Selected Major Accomplishments of Program: 2005 - 2011

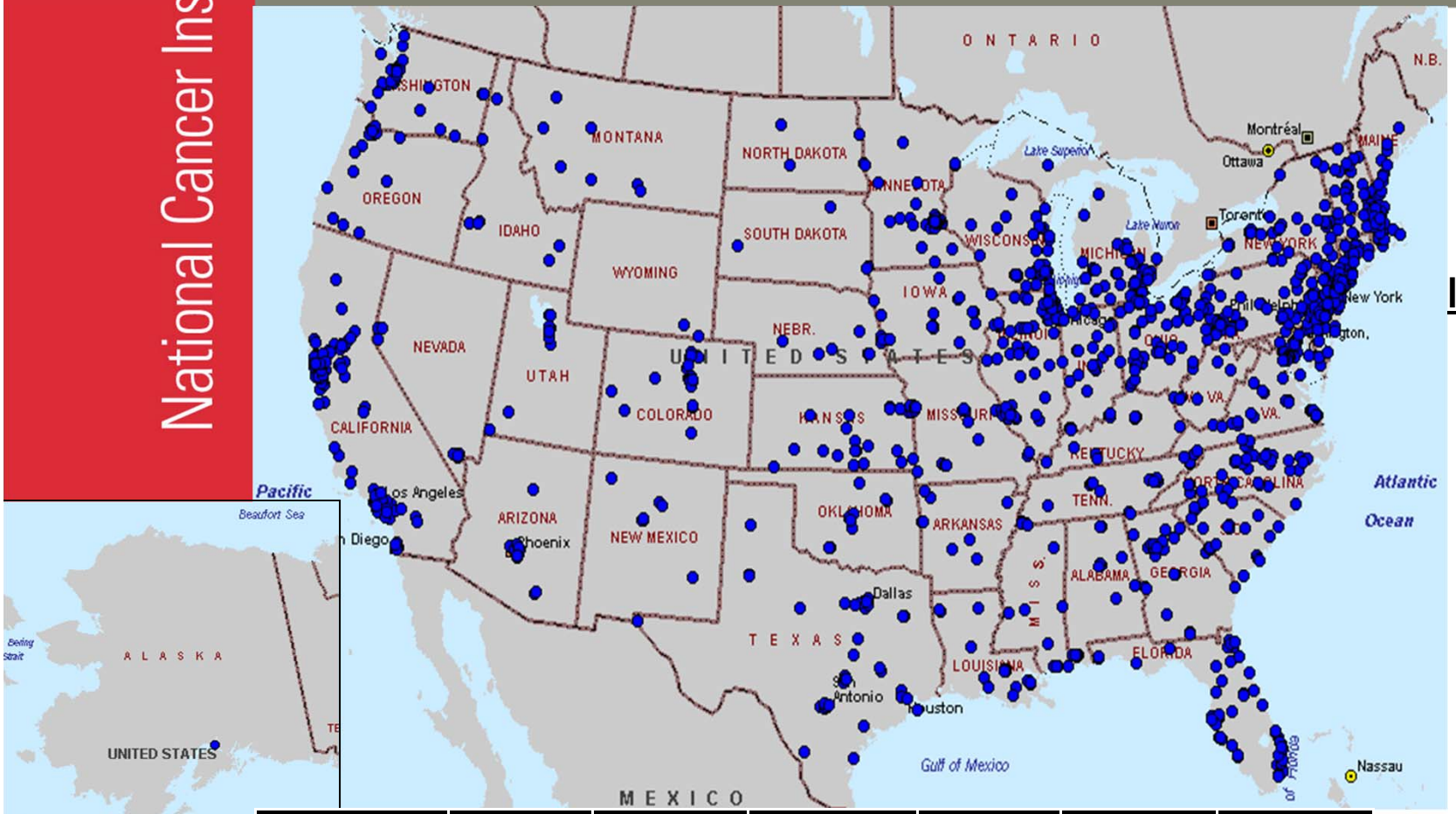
- **Over 30 Practice-Changing Clinical Trials** including therapeutic agents and other modalities, with 4 announced in first 6 months of 2011
  - ACOSOG-Z0011 – **Surgery:** SLND not inferior to Axillary Dissection in SLN+ BC
  - NCIC-CTG MA.20 – **RT:** Regional Nodal RT reduces LR & improves DFS in Node+ BC
  - COG-AALL0232 – **Pediatrics:** High Dose MTX improves EFS in pediatric ALL
  - RTOG-94-08 – **Multimodality:** Short-term ADT with RT improves OS in prostate cancer

- **Over 10 FDA Indications - New Oncology Agents** (Yr FDA Approval)
  - Bevacizumab – CRC (2006); NSCLC (2006); Renal Cell Cancer (2009)
  - Imatinib mesylate – Pediatric CML (2006); Adjuvant GIST (2008)
  - Nelarabine – T-ALL and T-LBL (2005)
  - Rituximab – Diffuse Large B-cell Lymphoma (2006); Follicular NHL (2006)
  - Trastuzumab - Adjuvant Therapy for Early-stage Her2+ Breast Cancer (2006)
  - Thalidomide – Newly Diagnosed Multiple Myeloma (2006)
  - Anti-GD2 Antibody (ch14.18) in Neuroblastoma (BLA Currently in Preparation)

- **Examples: New Indications Generic Agents** (Yr Publication/Press Release)
  - Daunorubicin in AML (2009); Dexamethasone in Multiple Myeloma (2007)

National Cancer Institute

Overview of the Program



3,100 Institutions

14,000 Investigators

About 25,000 pts enrolled on tx trials annually

Trials	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011
All Phases: Treatment Trials	27,263	24,289	25,540	29,063	23,299	19,462

Accrual Distribution:

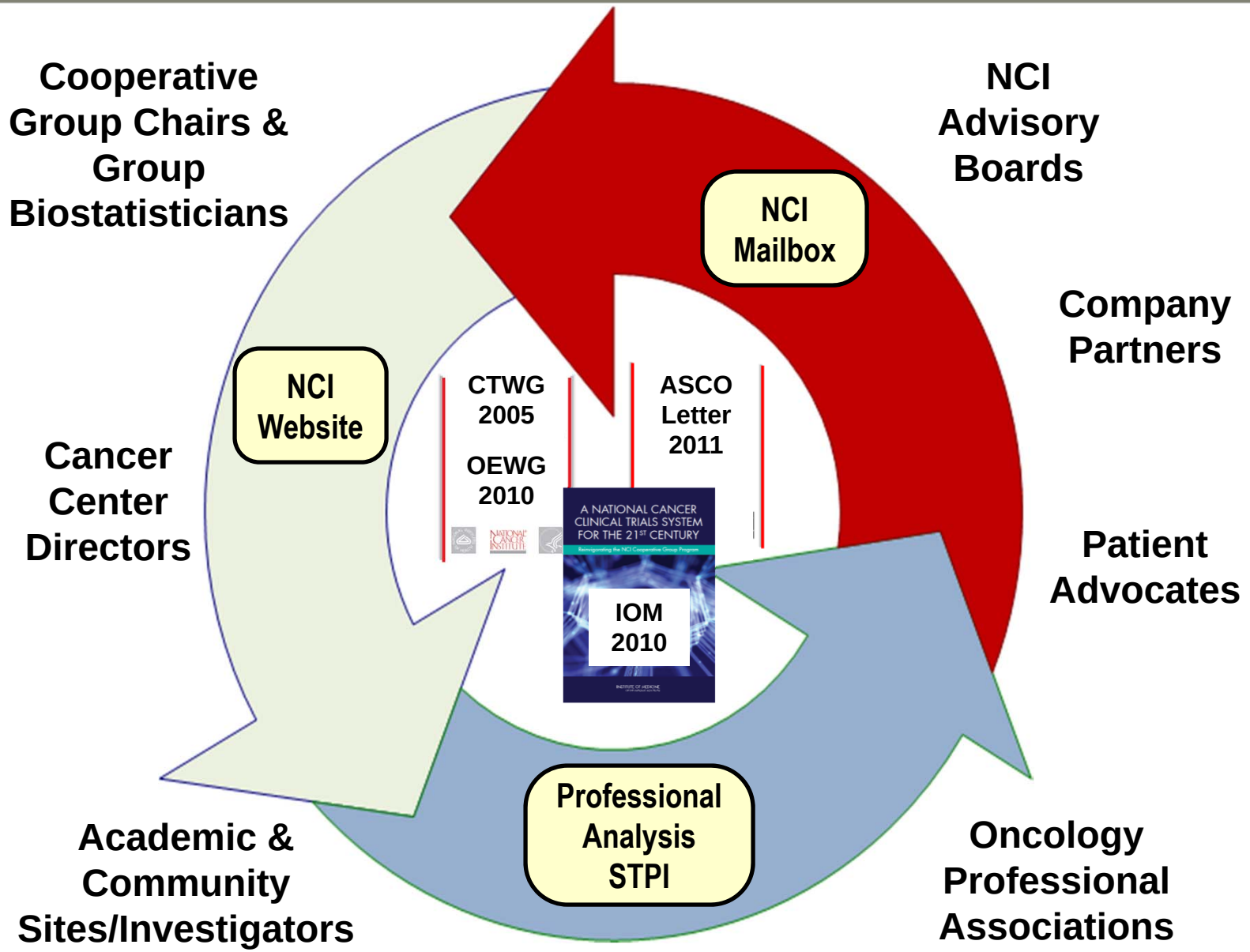
Phase 3: 82.0%

Phase 2: 15.3%

Phase 1/Pilot: 2.6%

National Cancer Institute

Extensive Review & Stakeholder Input Revised NCI's Clinical Trials System



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Progress Toward Consensus Goals for a Transformed System

Improve speed & efficiency of development & conduct of trials

- ✓ Implementation of operational efficiency timelines
- ✓ Implementation of Common Data Mgt System for all trials

Incorporate innovative science and trial design

- ✓ Implementation of BIQSFP program for integral & integrated biomarkers, imaging, and quality of life studies in trials
- ✓ Encourage randomized phase 2 trials

Improve trial prioritization, selection, support, & completion

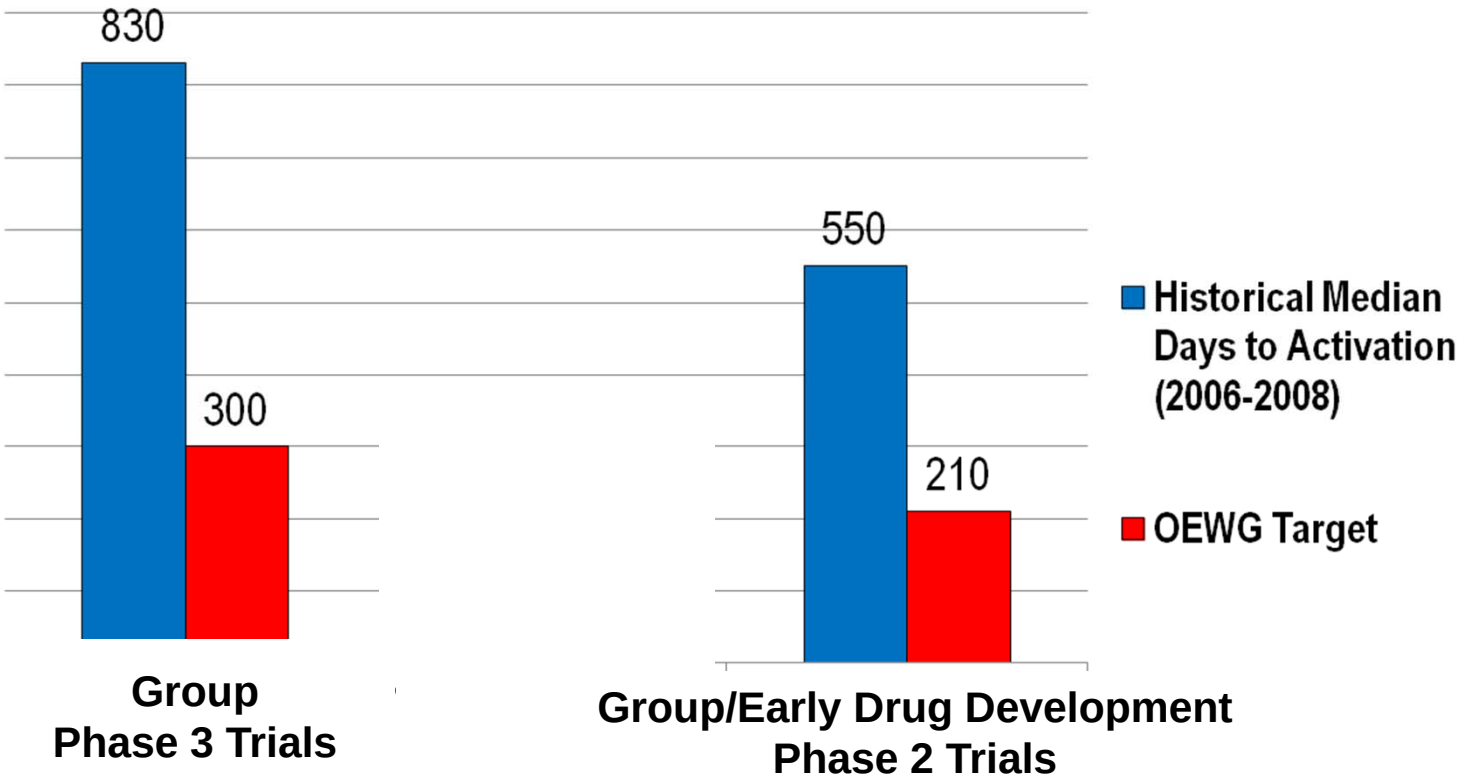
- ✓ Disease-specific and specialty Steering Committees prioritize trials
- ✓ Implementation of slow accrual guidelines

Ensure participation of patients & physicians in system

- ✓ Pilot initiatives for increased reimbursement for phase 2 and 3 trials
- ✓ Pilot initiatives to assess physician & patient feedback on trials to enhance accrual

National Cancer Institute

Operational Efficiency: Aggressive But Necessary New Targets



Timelines include IRB approval, industry negotiations, & FDA approval

Phase 3 trial development stopped if not open in 2 years
Phase 2 trial development stopped if not open in 18 months

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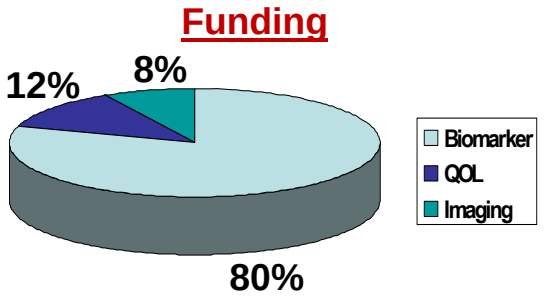
Incorporating Innovative Science and Trial Design Into Late Phase Cancer Clinical Trials

Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) ensures critical correlative science incorporated into phase 3 and large phase 2 trials

From 2008-2011, 13 phase 3 trials received support totaling over $22 Million

Phase 3 Trial Examples:

- **COG: AAML0531**: Evaluation of Bortezomib and Sorafenib for patients with de novo AML & FLT3 ITD (high allelic ratio)



- **RTOG-1010**: Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma

- **S1007**: Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer According to Gene Profile/Recurrence Score

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Disease-Specific Steering Committees : Prioritizing Clinical Trials

Steering Committee	Year Established	Co-Chairs as of 10-7-2011 Disease-Specific Steering Committees (SCs)
GI	2006	Dan Haller, MD & Joel Tepper, MD (Incoming Co-Chair Neal Meropol, MD)
Gyne	2006	David M. Gershenson, MD, Gillian Thomas, MD, & Michael Birrer, MD
Head & Neck	2007	David Adelstein, MD, David Brizel, MD, & David Schuller, MD
GU	2008	Eric Klein, MD, George Wilding, MD*, & Anthony Zietman, MD
Breast	2008	Charles Geyer, MD & Nancy Davidson, MD*
Thoracic	2008	David Harpole,MD, William Sause, MD, & Mark Socinski, MD
Leukemia	2009	Wendy Stock, MD & Jerry Radich, MD
Lymphoma	2009	Oliver Press, MD & Julie Vose, MD
Myeloma	2009	Morie Gertz, MD & Nikhil Munshi, MD
Brain	2010	Ian Pollack, MD & Al Yung, MD
Pediatrics (Heme & Solid Tumors)	2011	David Poplack, MD & Robert Arceci, MD, PhD (Hematology) Mark Bernstein, MD & Katherine Matthay, MD (Solid Tumors)

*Cancer Center Directors

Over 170 Concepts evaluated since inception of SCs

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Related Steering Committees as of 10-7-2011: (Non-disease Focus)

- **Investigational Drug Steering Committee**
  - **Co-Chairs: Pat LoRusso, DO, & Dan Sullivan, MD**
- **Clinical Imaging Steering Committee**
  - **Co-Chairs: Steven Larson, MD & Etta Pisano, MD**
- **Symptom Management & Health-Related Quality of Life Steering Committee**
  - **Co-Chairs: Deborah Bruner, RN, PhD & Michael J. Fisch, MD, MPH**
- **Patient Advocate Steering Committee**
  - **Co-Chairs: Regina Vidaver & Nancy Roach**

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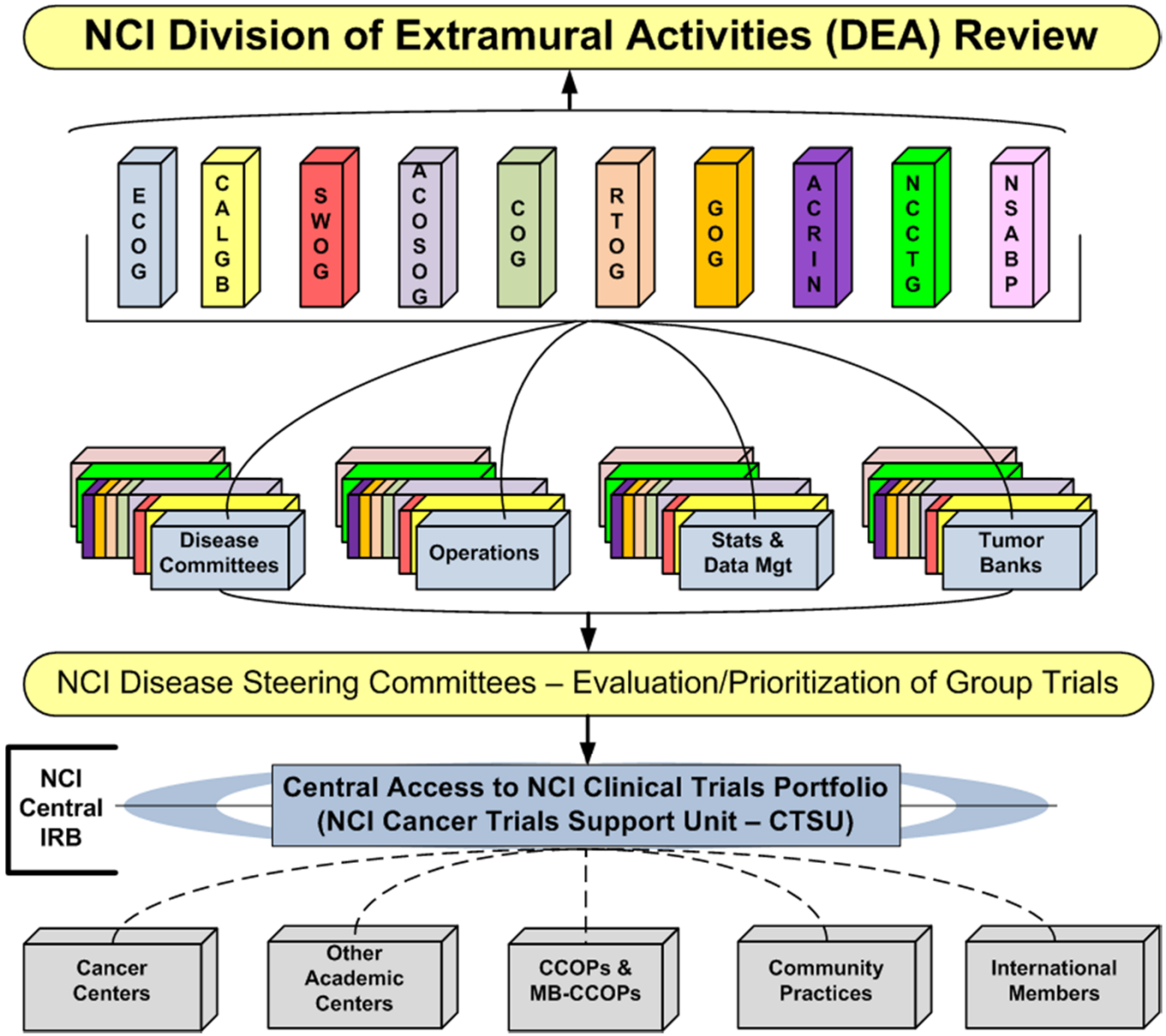
Structure of Program: As of January 2011



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Next Steps in Transforming the System

- New RFA for an Integrated National Clinical Trials Network
- Consolidated Organizational Structure with Funding for 1 Pediatric Group and up to 4 Adult Groups
- Review Criteria with Emphasis on Integration & Collaboration for Overall Scientific Achievement and Operational Efficiency
- Funding Model with Increased Per-Case Reimbursement for "High-Performance" Academic & Community Sites
- Competitive Integrated Translational Science Awards
- Revitalize Cancer Center Role in the Network (U10 awards)

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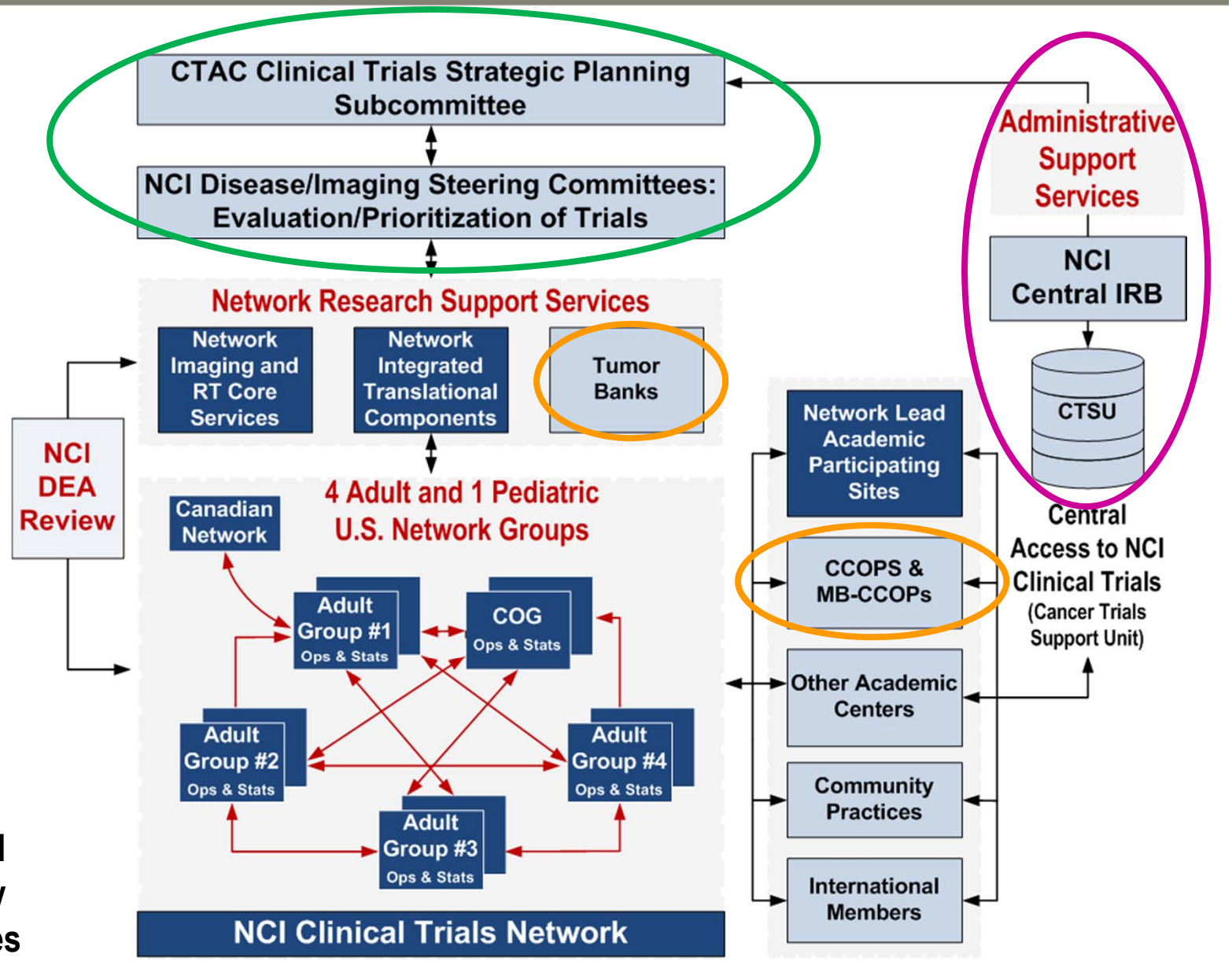
Introducing A New Organizational Structure
NCI Clinical Trials Network



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Rationale for Transforming Current Program: How Will Consolidated Network System Help?

- **Consolidate infrastructure to gain efficiencies (e.g., IT, Regulatory, Administrative, Tissue Resource Management)**
- **Consolidate Imaging & RT core services to benefit entire Network**
- **Integrate new components into trials to provide value-added research questions (e.g., advanced imaging, translational science)**
- **Integrate new agents into trials**
  - **Ex: Erlotinib, crizotinib, & ipilimumab are being integrated into trials in earlier stages of lung cancer & melanoma treatment requiring screening large populations & combining the agents optimally with surgery, RT, and immunotherapy**
- **Evaluate new agents in molecularly-defined disease subsets**
  - **Ex: Even for common diseases such as breast cancer, # of molecularly-defined patient subsets is increasing & there is a need for trial prioritization evaluating multiple new agents with standard regimens across subsets to avoid duplication & optimize accrual**

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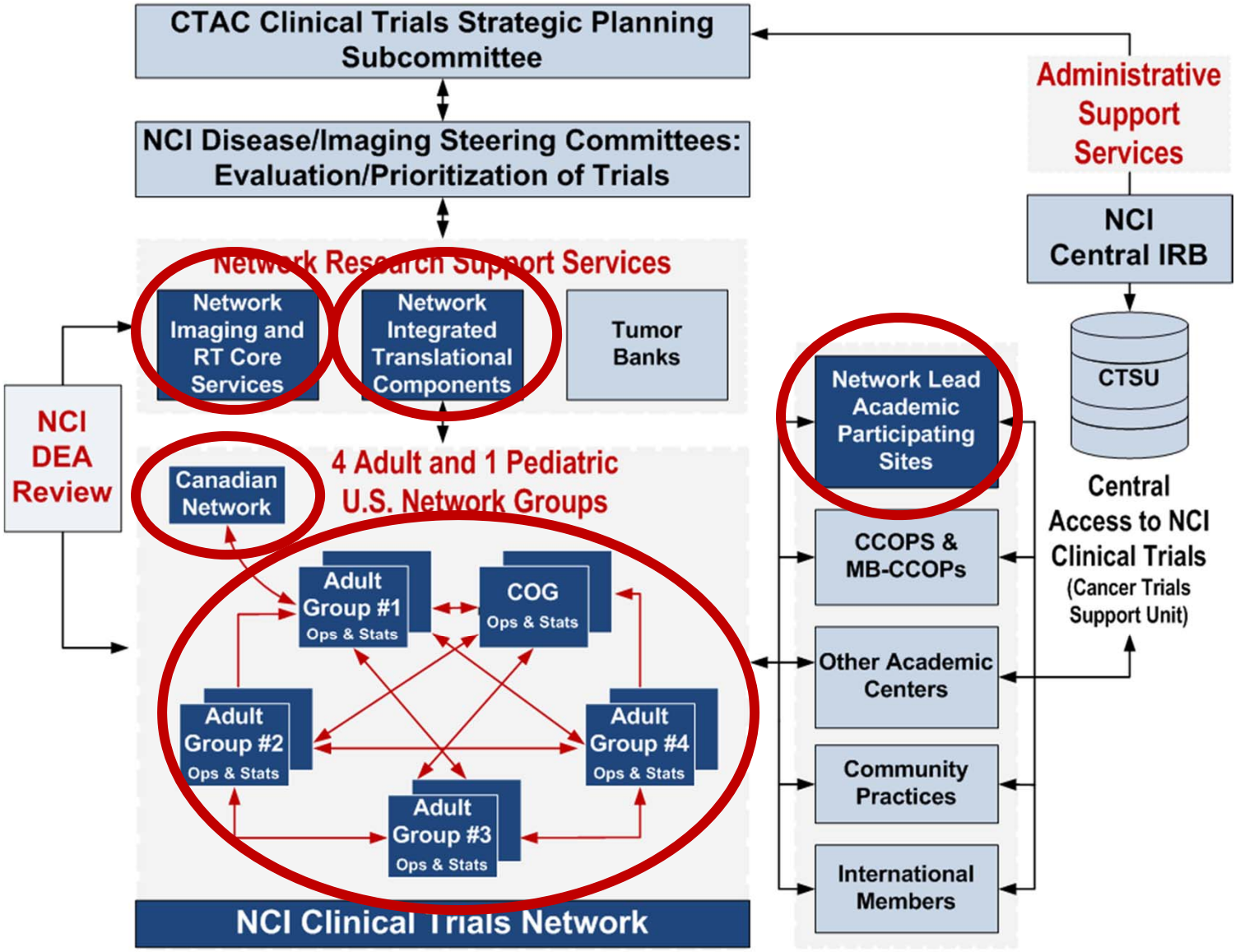
Introducing A New Organizational Structure
NCI Clinical Trials Network



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Network Component Description
Group Operations Ctrs & Group Stats Ctrs

- Provide scientific strategy & goals across broad range of diseases
- Responsible for Network Group administration including
  - Study conception, protocol development, and accrual to trials
  - Adherence to "Operational Efficiency" timelines
  - Audits and QA/QC of protocol therapy
  - Coordinating biospecimen collection from patients on trials
  - Compliance with FDA, OHRP, NCI/NIH regulations
- Statistical leadership for effective design & trial conduct
- Monitors data quality for primary analysis & correlative science
- Supports data mgt & analyses for studies outside the Network Groups as appropriate (e.g., Steering Committee-approved studies)

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Network Components Review Criteria
Group Operations & Statistical Centers

- **Reconfigure NCI/NIH external peer-review of System**
  - **Emphasis on incentives for a national system with trials open to all qualified sites & sites able to credit any Group to which they belong**
  - **Review of all Network Groups/components at same time (specific review panels for particular Network components)**
  - **Scientific evaluation will shift to evaluating Group role in national network, overall scientific strategy, innovation and quality (~50%)**
  - **Review criteria for operational efficiency & collaborative management of Network (~50%)**
    - ✓ **Coordination with other Network Groups, NCI programs, NCI investigators outside Groups (e.g., CCOPs, MB-CCOPs, Tumor Banks, Cancer Centers, SPORES, N01s/U01s, P01s, etc.)**

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Network Description & Review Criteria
Lead Academic Participating Sites

- **Description**
  - Multiple-PI grants for academic institutions with demonstrated scientific leadership in ≥ 1 adult Network Groups, substantial accrual, & excellent data quality ("high-performance" sites)
  - Targeted at NCI Comprehensive and Clinical Cancer Centers and other leading academic centers

- **Review Criteria**
  - Meets accrual threshold set from trials across entire Network
  - Expertise & leadership role in Group(s)
  - Data quality
  - Contributions to translational science within Group trials
  - Scientific collaborations across Cancer Center/Institution & Network

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Network Description & Review Criteria
Integrated Translational Science Awards

- **Description**
  - Multiple-PI grants to support prominent researchers for their expertise and efforts in incorporating molecular studies into Network trials & enabling acquisition of preliminary data for further research
  - Laboratory-based researchers will also facilitate hand-off of early phase clinical trial findings into later phase, definitive trials
- **Review Criteria**
  - Peer-review of quality of scientific approach & plans for integration of translational science into clinical trials
  - Leverages independently funded laboratory resources with Group clinical specimens & data to benefit Group research aims
  - Research area likely to benefit trial efforts across Network

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Network Description & Review Criteria
Core Services & Canadian Partner Network

- **RT and Imaging Core Services**
  - Provides scientific leadership for incorporating appropriate QA & image data management for research trials involving RT & imaging
  - Review Criteria for scientific leadership & expertise as Network-wide resource, integrated IT platforms for capturing and storing images, & efficient procedures for accessing site data for RT & image-related trial questions

- **Canadian Collaborating Trials Network**
  - NCI Program has had long history of collaboration with Canadian sites and non-profit Canadian clinical trial organizations
  - Review Criteria for ability to provide appropriate regulatory oversight for US Networks trials conducted in Canada, irrespective of which Group leads trial and to be full partners in accruing patients to US Network trials

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Overview of RFA: Cooperative Agreement 6 FOAs and Estimated # Grants

Network Component	Mechanism (Duration)	Est. Max. # Grants	Frequency New Application Accepted?	Multiple PI Option?
Group Operations Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Group Statistical & Data Mgt Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Canadian Collaborating Network	U10 (5 Yrs)	1	Every 5 Years	Yes
Integrated Translational Science Awards	U10 (5 Yrs)	1 to 5	Every 5 Years	Yes
RT and Imaging Core Services	U24 (5 Yrs)	1 to 2	Every 5 Years	Yes
Lead Academic Participating Sites	U10 (5 Yrs)	30 to 40	Any Year	Yes

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Principles of Network Funding Plan

- All external reviews of the NCI clinical trials system emphasized need to provide increased research reimbursement to ensure continued participation of sites in the public program

- Base "per-case" reimbursement for patient enrollment in the program has remained fixed at $2,000 per patient in treatment trials for over a decade
  - 2006 estimate for average per patient cost in industry trials was $4,700 for phase 3 & $8,450 for phase 2 Trials (& some industry trials at ≥ $15,000)
  - Survey in 2009 of Group sites found that of those planning to limit participation in the program (32% of respondents), 75% cited inadequate reimbursement for the decline in their level of participation

- "High-Performance" sites incur additional infrastructure costs due to the number of patients they accrue & additional funding is especially needed to compensate these sites for their large patient follow-up burden - (propose additional $2,000 /pt for these sites for total of ~$4,000/pt)

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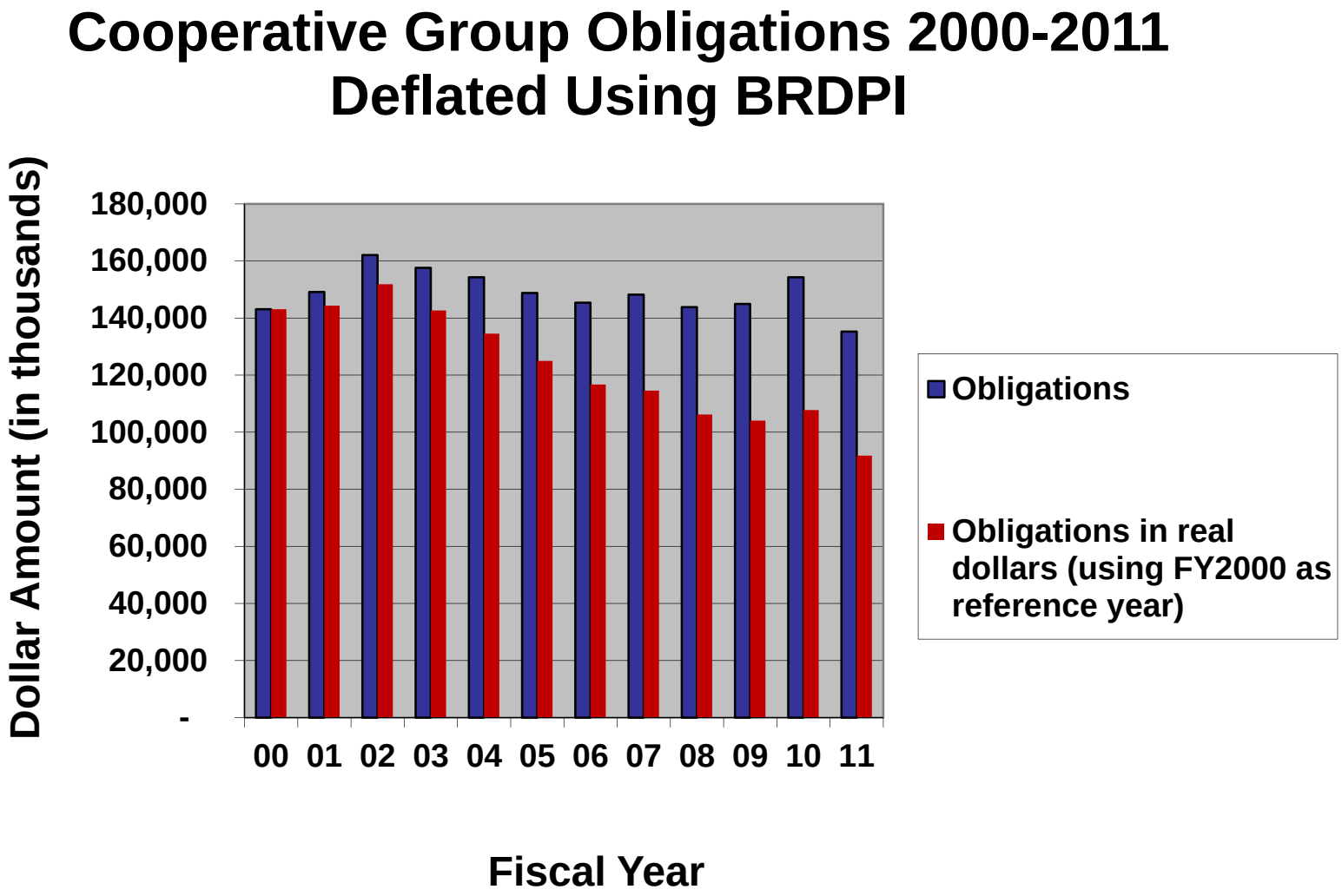
Trials Program Funding 2000 to 2011: Real $



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5-Year Annual Funding Request for NCI Clinical Trials Network

Category for Base Division Set-Aside for Network Program	Annual Total Cost for FY14 to FY18 Based on 20% Reduction in Accrual Compared to Average Accrual Over Last 6 Years (Approx. 20,000 Treatment Trial Enrollments)
Funding Based on FY2011 Levels:	
Group Operations & Statistical Centers (includes Capitation), Lead Academic Participating Sites, and Core Services	$ 152,644,335
Funding Request Based on New Funding Model & BIQSFP:	
Increase Capitation to "High-Performance" DCTD-funded Sites	$ 11,520,000
Increase Capitation to "High-Performance" DCP-funded CCOPs & MB-CCOPs	$ 10,080,000
Increase Funding for Integral and Integrated Markers (BIQSPF)	$ 4,000,000
Subtotal:	$ 25,600,000
Grand Total:	$ 178,244,335 *

* The 5-Year Total Cost Funding Request for FY2014 to FY2018 for the NCTN is $891,221,675

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Strategic Planning for the New NCTN Program

- Treatment trial accrual has been dominated by Breast and GI Cancer trials, especially large adjuvant trials, over past decade
- The new funding model will require Network organizations and Steering Committees to monitor the balance of trials prioritized for development and help develop a strategic consensus about the diseases in which to encourage more trials as scientific opportunities arise
- New review criteria should facilitate more trials in disease areas which have been typically underrepresented, relative to their incidence, and portfolio balance will be monitored closely by CTAC's NCTN Strategic Planning Subcommittee to ensure that scientific opportunities in less common tumors are not missed

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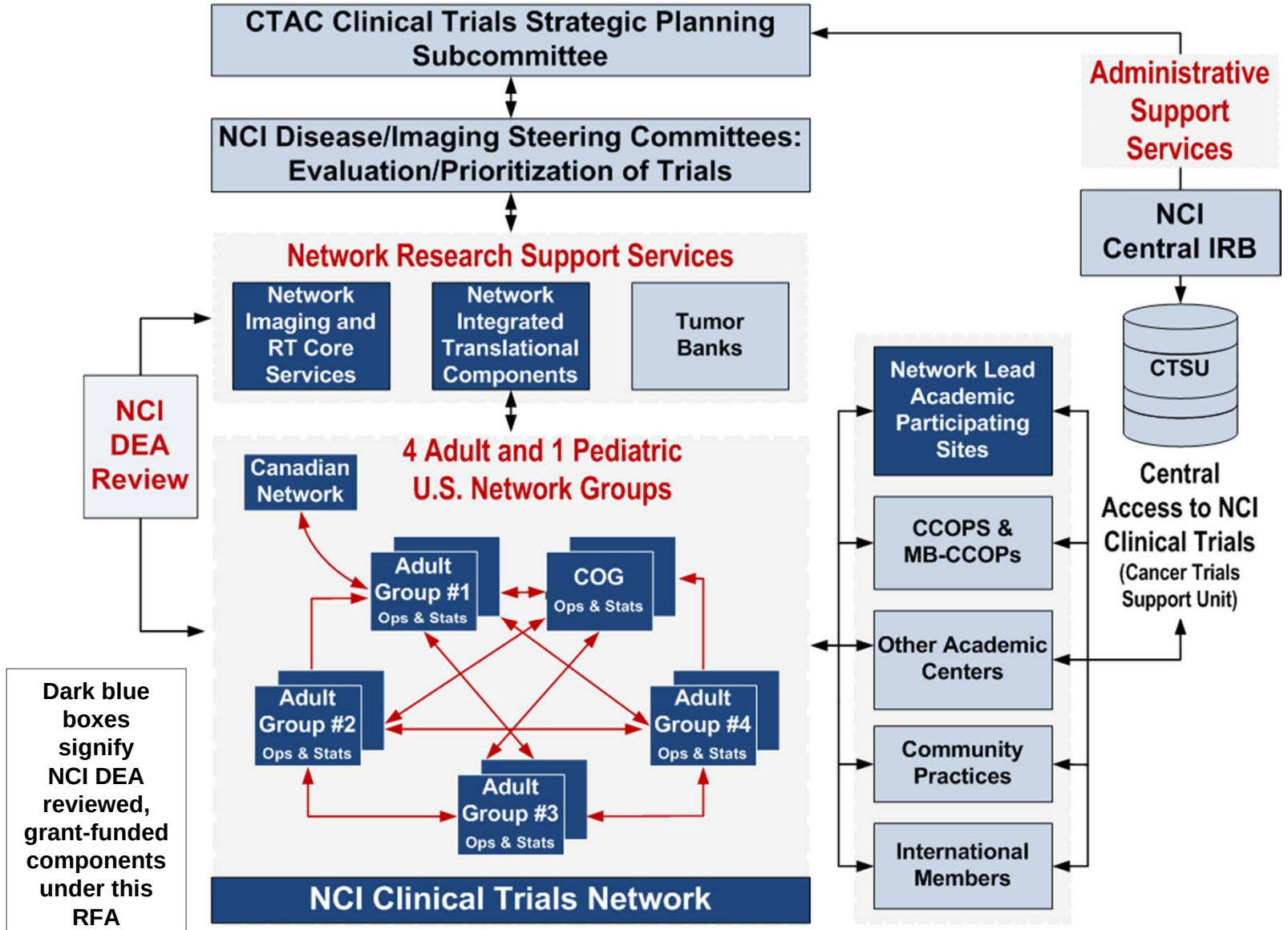
Introducing A New Organizational Structure
NCI Clinical Trials Network



Dark blue boxes signify NCI DEA reviewed, grant-funded components under this RFA

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Tentative Timeline for Potential Implementation

BSA Concept Review	**Nov 2011**
NCI DEA & NIH Review FOA/Guidelines	**Nov 2011 – July 2012**
New FOA Released/Published	**July 2012**
Receipt Competing Applications	**Winter 2012** **[Nov 2012- Feb 2013]**
Review Competing Applications	**Summer 2013** **[May 2013 - Aug 2013]**
NCAB Review	**Dec 2013**
Rollout of Awards in FY2014	**March 2014**