DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
164th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 10, 2013

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 164th regular meeting on 10 December 2013, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 10 December 2013, from 9:00 a.m. to 3:00 p.m., and closed to the public from 3:00 p.m. to 4:30 p.m. The NCAB Chair, Dr. Tyler E. Jacks, Director, Koch Institute for Integrative Cancer Research, David H. Koch Professor of Biology, Massachusetts Institute of Technology, presided during both the open and closed sessions.

NCAB Members

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

Alternate *Ex Officio* NCAB Members

Dr. Michael A. Babich, CPSC (absent)
Dr. Patricia Bray, OSHA/DOL (absent)
Dr. Vincent J. Cogliano, EPA (absent)
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS (absent)
Dr. Richard Pazdur, FDA (absent)
Dr. Craig D. Shriver, DoD (absent)
Dr. Michael Stebbins, OSTP (absent)
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH (absent)
Dr. Sharlene Weatherwax, DOE (absent)

Members, Scientific Program Leaders, National Cancer Institute, NIH

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

Liaison Representatives

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

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

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I. CALL TO ORDER AND OPENING REMARKS—DR. TYLER E. JACKS

Dr. Tyler E. Jacks called to order the 164th NCAB meeting. Dr. Jacks welcomed members of the Board, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Jacks reviewed the confidentiality and conflict-of-interest required of Board members in their deliberations.

Motion. A motion to approve the minutes of the 10 September 2013 NCAB meeting was seconded, and approved unanimously.

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

Dr. Jacks called Board members' attention to future meeting dates listed on the agenda.

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

Dr. Harold E. Varmus, Director, NCI, welcomed members and informed them of personnel, budgetary, programmatic changes, recent news occurring in the NCI, and activities of interest across the NIH. Dr. Varmus introduced Dr. Warren Kibbe, the new Director of the Center for Biomedical Informatics and Information Technology (CBIIT), and thanked Dr. Lenora Johnson, who accepted a position at the National Heart, Lung, and Blood Institute (NHLBI), for her service to the NCI's communication efforts. Members were informed about the process and effects of the government shutdown and the NCI's start-up efforts. Dr. Varmus informed members that he had discussed the shutdown at recent Town Hall and NCI Board of Scientific Advisors (BSA) meetings, comparing it to the 1995–1996 shutdown, which differed in duration, time of year, causes, and resolution. He remarked on the importance of President Barack Obama's unwavering stance, noted that the shutdown was challenging for both those who stayed home and who came to work, and expressed gratitude to NCI employees and management for their flexibility and perseverance. The experience allowed leadership to see what operational parts worked well, including payroll, the budget office, and contracts, including accelerating peer reviews and rescheduling site visits. Dr. Varmus said that lessons learned include that a better way to communicate with workers and clearer guidance from higher government levels are needed. Additionally, trainees are vulnerable regarding pay and housing, as well as pay issues exist for contract workers.

Budget. Members were reminded that the NCI is operating under a continuing resolution (CR) through January 15, 2014, at the FY 2013 funding level. A bright point is that the NCI has been given more money for these 3 months than it received in the initial 6 months of FY 2012-13. Dr. Varmus reviewed the possible funding options, including a year-long CR or passage of an appropriations bill. The Labor-Department of Health and Human Services (HHS) bill has passed through the Senate and now is with the House Committee. It remains to be determined whether the NIH budget will be included in an omnibus bill or as a single package.

Dr. Varmus described recent changes, including some relaxation of restrictions from the Office of Management and Budget (OMB) regarding the approval of meetings and ability to give some bonuses, but he said that travel restrictions remain onerous and remaining limitations on meetings hamper the scientific process. The NCI continues to award grants despite the CR conditions, paying 90 percent of the non-competing awards. Members were referred to tables comparing fiscal year 2012 and 2013 competing research project grants and to the overall success rate of 14 percent. There were modest declines in the

number of R01 awards but an increase in R21 applications and awards. He noted that the decline in the number of R01 applications from early stage investigators is a concern. The P01 Program project grants (P01s) should experience a success rate of 32 percent. Members were told that the NCI continues to insist on a second-level review of awards that receive intermediate scores.

Major Scientific Findings. Members were referred to several articles, including a report on a trial of combination anti-antigen therapy and docetaxel that shows a dramatic increase in survival of patients with significant, large-lesion, advanced prostate cancer; and the Pan-Cancer papers published in *Nature* last month. Researchers from the University of California, San Francisco, reported that they were able to identify a small molecule inhibitor of RAS that takes advantage of the chemical properties of having cysteine rather than glycine at the 12th position in the RAS protein. Dr. Varmus observed that this allele-specific finding has great potential for NCI's RAS initiative. In addition, members were informed about several online articles from laboratories using large sets of cancer cell lines to examine responses to a large number of drugs. A comparison of results from the two groups involving approximately 470 cell lines found highly correlated, but not perfect, genotype and phenotype expression; the differences were generated by the minor tweaks in the experimental protocol that were carried out with slight differences. Dr. Varmus told members about several upcoming papers, including the NCI's "Annual Report to the Nation," which features comorbidities as the special topic; and a paper coming from the Broad Institute regarding the number of cases of different kinds of cancer that must be analyzed with genomic technologies to discover the driver mutations that occur with at least 2 percent frequency in those cancer types.

News of Interest. Dr. Varmus said that the NCI has contributed to the discussion of failure to replicate scientific findings through publication of guidelines for thinking through certain kinds of studies of clinical trials, and importantly, large-scale -omic studies. Members were encouraged to read a recent article in *The Economist* regarding the topic. He noted that other NIH Institutes and Centers (ICs) are considering more awards that reward past performance, similar to the NCI's proposed Outstanding Investigator Award (OIA). Dr. Larry Tabak, Deputy Director, NIH, is chairing a trans-NIH committee to discuss various modes of grant-making that might be used to serve that purpose: either directed at early stage, experienced, or all-stage investigators. An upcoming IC Directors Retreat will discuss this topic as well as changes to the biosketch that emphasizes the candidate's five most important contributions to science, rather than a bibliometric listing. Dr. Varmus mentioned recent collaborations with the Centers for Medicare and Medicaid Services (CMS), which has become interested in computed tomography (CT) scanning for lung cancer following the United States Preventive Services Task Force (USPSTF) recommendation as well as in molecular diagnostics. These molecular tests will be critical to substantiate precision medicine in the NCI's mission.

Members were told that the President's Cancer Panel's report on the human papillomavirus (HPV) vaccine is nearing publication. He noted that when Mr. Bill Gates gave the David E. Barmes Global Health Lecture at the NIH, he recognized the common missions shared between the NIH and the Bill and Melinda Gates Foundation in many parts of the world, and urged a greater degree of interaction with HPV vaccination, tobacco control, diseases that affect children, and nutrition. Dr. Varmus stated that he had attended the International Cancer Genome Consortium meeting and told members about a joint effort between The Cancer Genome Atlas (TCGA) and the International Consortium to compile 2,000 cancer genomes in unpaired and normal tissue. Potential members of the Alliance to share interoperable matter (i.e., genomic data and clinical data) will meet in England in March 2014. The third international meeting of leaders of cancer research funding agencies from approximately 18 countries will occur in Paris, France, in January. Dr. Varmus referred members to documents in their Board books: a largely supportive analysis of Dr. Varmus' tenure at the NIH and an article in a new journal from the American Academy for the Advancement of Science about the inception of the President's Emergency Plan For AIDS Relief (PEPFAR), which is timely given the interest in science and medicine as tools of diplomacy.

Questions and Answers

Dr. Jacks asked for further details about the launch of the OIA program. Dr. Varmus replied that it will be at least a year before issuance due to permission needed for a 7-year award, publishing requirements, and other tasks. He noted that to build a cadre of high-level cancer researchers, 50–75 awards per year are being considered

Mr. William H. Goodwin, Jr., Chairman and President, CCA Industries, Inc., noted that the U.S. Corps of Engineers was able to continue working through the recent government shutdown because of funds that had been reserved and suggested that the NCI consider a similar approach. Dr. Varmus responded that many parts of the government have multi-year funding and were able to continue work during the shutdown. The NCI, however, must spend down its appropriations on an annual basis but can award multi-year contracts to organizations to ensure that work continues. Work required for safety and to preserve human and animal life and property was allowed to continue.

Dr. David C. Christiani, Elkan Bout Professor of Environmental Genetics, Department of Environmental Health, Department of Epidemiology, Harvard School of Public Health, Professor of Medicine, Harvard Medical School, asked for clarification about PEPFAR. Dr. Varmus said that PEPFAR concerns implementation, not science; it is under the purview of the U.S. State Department and has significant interactions with the Centers for Disease Control and Prevention (CDC).

IV. OVERVIEW OF THE DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS (DCEG)—DR. STEPHEN J. CHANOCK

Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics (DCEG), presented an overview of the DCEG, which has a mission to uncover the causes of cancer and the means of its prevention through broad-based, high-quality, and high-impact research of classical and molecular epidemiology. Dr. Chanock reminded members that the DCEG has two programs covering epidemiology and biostatistics, and human genetics. The Division works closely across NCI to study etiologic questions in the context of preventive or intervention studies, such as with the NCI Clinical Trials Networks (NCTN) with the DCTD, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) with the Division of Cancer Treatment and Diagnosis (DCTD), and HPV vaccine activities with the Center for Cancer Research (CCR) and Division of Cancer Prevention (DCP). Key issues for the DCEG include using emerging technologies to improve exposure assessment and to develop analytic and informatic capacity to match scientific goals, and evaluating the feasibility of new technologies in epigenomics, microbiomics, metabolomics, and proteomics as applied to population sciences.

Dr. Chanock highlighted the Division's strategic initiatives in germline genomics to discover the genetic architecture of the common, uncommon and rare variances as well as familial, highly penetrant mutations. Highly informative cases are studied in familial cancers; pediatric cancers (e.g., the Therapeutically Applicable Research to Generate Effective Treatments [TARGET] germline initiative); and second cancers, such as in the Childhood Cancer Survivor Study. Somatic molecular epidemiology presents an emerging opportunity, in which exposure and susceptibility data from large population studies can be mined to help characterize somatic alterations; interactions between exposures, germline, and somatic profiles are being investigated in high-quality studies, such as lung cancer by the Environment and Genetics in Lung Cancer Etiology (EAGLE) study and radiation-induced thyroid cancer in the

Chernobyl cohort, as well as TCGA-related projects (e.g., PanCan analysis). The DCEG's expertise with risk assessment models is important for both etiologic study and pushing it into clinical implications for risk profiling. In addition, detectable clonal mosaicism found in the germline was an unexpected finding in the Genome-wide Association Study (GWAS) and presents an area for further study. Members were told that the DCEG's special expertise in environmental and occupational exposures is leveraged, such as regarding ultrafine particulates and lung cancer, pesticides and cancer, and the systematic characterization of mechanisms of action of leukemogens and lymphomagens (e.g., benzene, formaldehyde, trichloroethylene, and perchlorethylene). The Division's portfolio also includes environmental and medical/occupational radiation exposures, including Chernobyl and atomic bomb survivors, the effect of CT scans on cancer, and health care workers who provide nuclear medicine technology and angiography. Strategies are being developed in energy balance and obesity, the HPV vaccine, and second cancers, and additional opportunities are long-term, prospective, cohort studies with serial biospecimens that include exposure assessments, with existing infrastructure (e.g., health maintenance organizations [HMOs], military/Veterans Administration [VA], and international partners) leveraged to work within current budget constraints.

Members were informed that Dr. Chanock's management style is ask questions and listen before making decisions, present problems with possible solutions, support the next generation, and learn from past successes and failures. Future directions for DCEG are being informed through a strategic planning process evaluating the scientific goals of senior investigators for the next 1, 3, and 6 years in concert with the state-of-the-science across DCEG, better management of key resources, collaboration and new initiatives. Recruitment is under way or planned for several DCEG leadership positions, including Deputy Director and Chief of the Laboratory of Translational Genomics. The Division's emphasis on education and training includes assessing mentoring and recruiting, deepening the connections across the NCI Divisions, and expanding the DCEG knowledge base through mechanistic insights, modeling, and translating etiologic findings to public health. Lectures from senior cancer experts will highlight their work in a specific discipline, and experts in oncogenes, targeted therapy, immunology, and other related cancer fields will discuss synergies between their respective fields and population sciences and promote collaboration.

Questions and Answers

Dr. H. Kim Lyerly, Vice President/Global Head of Oncology, George Barth Geller Professor of Cancer Research, Professor of Surgery, Duke University School of Medicine, asked about the DCEG's role and coordination with other NIH Institutes and entities in large studies to assess lifestyle risk factors for cancer and other diseases. Dr. Chanock stated that the DCEG has a role in the NIH research community, such as by participating in International Agency for Research on Cancer (IARC) monographs and international committees focused on radiation or occupational exposure. He added that the DCEG engages at specific, larger, and trans-Institute levels including through pilot studies, and meta-analyses of tobacco, body mass index, or other lifestyle topics with other NCI Divisions.

Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, Professor of Medicine, University of Maryland, queried about collaborative efforts to reduce the number of HPV vaccinations. Dr. Chanock expressed the DCEG's strong commitment to this effort, noted that six of DCEG's nine branches are conducting etiologic or biomarker HPV activities, and said that the HPV experience provides a good example of engaging scientists from various activities to consider how to leverage opportunities to conduct the next viral or other study.

Dr. Olufunmilayo F. Olopade, Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine, asked about the ways in which the extramural

program activities interact with the DCEG's direction. Dr. Chanock replied that the DCEG will continue to collaborate as effectively as possible with all areas of the NCI and observed that the fiscally constrained environment has had the benefit of bringing many in the intramural and extramural communities together to leverage infrastructures and studies.

Dr. Christiani reflected on the challenges of studying lung cancer and ultrafine particles. Dr. Chanock said that the DCEG currently is considering feasibility in terms of the technology and measurement accuracy, and he recognized the scientific opportunity presented by controversial molecules.

Dr. Jacks requested further information on the Division's training aspects. Dr. Chanock answered that the DCEG has a stable training structure, with an Office of Education, trainees embedded in program activities, trainees working with and learning from principal investigators (PIs), and Dr. Chanock's practice of meeting trainees and having discussions in informal settings.

V. COLORECTAL CANCER SCREENING—DRS. BARNETT KRAMER, CARRIE KLABUNDE, AND HAROLD P. FREEMAN

Dr. Barnett Kramer, Director, DCP, provided an overview of NCI's studies of colorectal cancer screening and prevention. Dr. Kramer stated that colorectal cancer incidence and mortality have decreased during the past 35 years, based on multiple factors, such as increased screening, reduced smoking, dietary changes, and aspirin use. He introduced his fellow presenters: Drs. Carrie Klabunde, Division of Cancer Control and Population Sciences (DCCPS), and Harold P. Freeman, President and Founder, Ralph Lauren Center for Cancer Care and Prevention.

Colorectal Cancer Screening and Aspirin for Prevention. Dr. Kramer informed members that the USPSTF gave co-equal status to the three most common colon cancer screening tests (fecal tests for blood, sigmoidoscopy, and colonoscopy) for adults aged 50–75 although colonoscopy has the highest sensitivity among them, followed by sigmoidoscopy. Data from NCI's Physician Data Query (PDQ) show different strengths for study designs of the three tests, with mortality risks from colon cancer decreased by approximately 15 to 33 percent for fecal tests and 60 to 70 percent in the left colon for both sigmoidoscopy and colonoscopy. Invasiveness varies by test as well, with colonoscopy having a higher risk of bleeding and perforation. Because medical capacity in the United States cannot accommodate an annual colonoscopy of the full population and subsequent surveillance colonoscopies, fecal tests provide an alternative. In addition, colonoscopies scheduled every 10 years may miss interval cancers whereas annual fecal tests can accumulate sensitivity because of the testing frequency. The USPSTF commissioned a set of statistical models to compare the three commonly used sets and found that in a population per 1,000 people on colonoscopy, significantly more colonoscopies than fecal occult blood tests or sigmoidoscopy would be needed to achieve the same mortality reduction. The Task Force concluded that the most effective colorectal cancer screening test is the one that a patient is willing to take. Preliminary results from a Spanish multi-center randomized controlled trial of 57,000 patients comparing fecal immunochemical testing (FIT) to colonoscopy indicate a statistically significant 34 percent compliance rate for FIT versus 25 percent for colonoscopy. A diagnostic yield showed that colonoscopy was twice as good at picking up advanced adenomas, but more serious complications (0.5%) were seen with colonoscopy (0.5%) than with FIT (0.1%).

Members were told that emerging evidence suggests the benefit of aspirin as a chemoprevention strategy. The NCI has support the National Institute on Aging's (NIA) Aspirin in Reducing Events in the Elderly (ASPREE) trial to study aspirin in people who are 70 years old and older to determine the balance of benefits and harms. The evidence shows that aspirin has positive and consistent results for cardiovascular disease and suggests a benefit in the reduction in incidence and mortality over 5 years that

increases over time, even when harmful events (e.g., vascular events, cancers, fatal extra-cranial hemorrhage) are considered. Data from six randomized trials suggest that aspirin also appears to reduce cancer incidence. Screening may reduce the mortality from one disease, but prevention may reduce the mortality from multiple diseases. Aspirin's mechanism of action of prevention needs further research, but studies that examined the effect of aspirin on 20-year risk of death due to common cancers (e.g., colorectal, esophageal, stomach, lung) in four long-term trials with 20-year followup suggest the utility of aspirin as a prevention strategy.

Dr. Kramer next discussed whether endoscopy and aspirin are complementary. There is emerging evidence that aspirin affects the right side (distal) of the colon, whereas colonoscopy appears most effective on the left side (proximal) of the colon. A population-based case-control study in Ontario compared the history of colonoscopy according to hospital and outpatient records and found that for all cancers a 30 percent reduction was associated with an attempt at colonoscopy, with the benefit restricted to the left side of the colon and the magnitude of effect largest if the colonoscopy simply extended to the cecum. Potential reasons for the difference in proximal versus distal colorectal cancer mortality reduction include technical (e.g., inadequate bowel preparation); levels of expertise and experience; and biological, including faster growing lesions or flat and depressed adenomas in the right side of the colon. Data from four trials of aspirin versus control in primary prevention show that virtually all of the benefit for both incidence and mortality was restricted to the proximal colon as opposed to distal colon and rectum. Dr. Kramer said that areas for further research in colorectal screening and prevention include the comparative effectiveness of the available screening tests, the mechanism of aspirin's action on carcinogenesis, the optimal duration and age range for aspirin use, and whether screening and aspirin intervention are complementary or additive.

Colorectal Cancer Screening Rates in the United States. Dr. Klabunde said that colorectal cancer screening data from the National Health Interview Survey (NHIS) for U.S. adult population aged 50 to 75 years, shows a significant increase in the use of colonoscopy during the past 10 years compared to the fecal occult blood test (FOBT) and sigmoidoscopy, as well as a 20 percent increase (36–60%) from 2000 to 2010 for up-to-date for colorectal screening (i.e., had one of the three strategies within the recommended time intervals) but lower than the Healthy People 2020 target of 70 percent for up-to-date. Additional NHIS data show screening use by major racial/ethnic groups in the United States, with similar increases in uptake of colonoscopy and the up-to-date rates, both of which are higher for whites and black than for Hispanics and Asians. Asians and Hispanics have up-to-date rates that are approximately 10 to 12 percentage points lower than for non-Hispanic whites.

Large disparities exist in colorectal cancer screening uptake for various population subgroups in the United States, such as by education and annual family income. Screening rates are in the 40 percent range for those who have less than a high school education or a family income of less than $35,000 a year, and 20 percent for those who have no health insurance, no usual source of care, or do not visit the doctor. Recent immigrants have screening rates of approximately 25 percent compared with people born in the United States (55–60%). Data from the Behavioral Risk Factor Surveillance System (BRFSS), a CDC-sponsored data source based on a telephone survey, show that up-to-date rates for the 50 to 75 age group in 2012 were at 65 percent and higher than the younger 50 to 64 age group. In addition, the never-screened group is larger than those who had a screening test at some point in time but are not up-to-date. The BRFSS provides state-level estimates of being up-to-date, with a 20 percentage point difference between Massachusetts, which has the highest rate and only 4 percent of its population uninsured, and Arkansas, with the lowest up-to-date rate at 56 percent. California has 22 percent of its age-eligible population up-to-date by FOBT within the past year, compared with 3 percent in Utah; this may be partly attributable to Kaiser Permanente's FIT-based colorectal cancer screening program, implemented in 2007.

Colorectal cancer screening in the United States is dominated by colonoscopy. A number of studies, however, have shown that patients have distinct preferences for tests. One study of 1,200 patients who were overdue for screening found that preferences for FOBT and colonoscopy were split equally. Preferences vary by racial/ethnic group, with Hispanics generally preferring FOBT. The study also showed that only 35 percent of these patients were screened and only one-half of these received their preferred test. Test attributes (e.g., what it involves, accuracy, frequency, discomfort, preparation) are important to patients. Direct observation studies of clinic encounters indicate that primary care physicians infrequently discuss patient preferences or choice of test type, and most of the discussions are colonoscopy-centric.

Factors contributing to rates and patterns include the decentralized nature of health care delivery in the United States. National guidelines are provided by the USPSTF, but most people rely on their primary care physicians for guidance. An effective practice-based approach to achieving high colorectal cancer screening requires physician recommendations and an office system to identify patients, present options and track results. Surveys of primary care physicians showed a substitution effect of colonoscopy for sigmoidoscopy over a short time period of 7 years. Many physicians discuss colonoscopy first but mention FOBT or FIT as an alternate but inferior screening test.

Physician recommendation is a key facilitator of and can be a barrier to colorectal cancer screening. The second reason given by age-eligible adults in NHIS who are not up-to-date with screening is that the doctor did not recommend or order it. In 2010, less than 10 percent of age-eligible adults who were not up-to-date, including Medicare beneficiaries, indicated that they had received a recent provider recommendation for colorectal cancer screening.

In a 2007 NCI-sponsored primary care physicians' survey, less than 50 percent of physicians indicated that they usually presented more than one test option when they discussed colorectal cancer screening with their patients, with colonoscopy (88%) presented most frequently. In addition, 61 percent of physicians indicated that their practice had guidelines in place and use of full or partial electronic medical records (EMRs); less than one-third used reminder systems in their practices.

Opportunities to reduce barriers to colorectal cancer screening exist at the policy, system, and practice levels. The Affordable Care Act (ACA) is designed to substantially reduce the number of uninsured in the United States and requires insurers to cover colorectal cancer screening, with prohibitions against copayments and deductibles for colorectal cancer screening tests. Provisions in the ACA aim to improve access to and strengthen primary care, including new care delivery models to better track preventive services. At the system level, the CDC has implemented a colorectal cancer control program in 26 states and territories in the United States. The program targets low-resource individuals and is based on the CDC's highly successful National Breast and Cervical Cancer Early Detection Program. New funding and reporting requirements for Health Resources and Services Administration (HRSA)-sponsored community health centers also should improve colorectal cancer screening uptake. In 2007, Kaiser Permanente established a centralized screening program that mailed FIT kits directly to patients and achieved a dramatic increase in screening rates between 2007 and 2012. Strategies at the practice level that are effective in increasing screening uptake include: offering home FIT kits during influenza vaccination clinics; mailed outreach invitations for FIT or colonoscopy sent to unscreened, low-income individuals; and stepped interventions, such as nurse navigation.

NCI collaborations to support programs and research include the Population-based Research Optimizing Screening through Personalized Regimens (PROSPR), which is studying the screening process from recruitment through initial treatment for breast, cervical, and colorectal cancers. PROSPR identifies ways to improve cancer screening and where breakdowns occur in the process, and whether there is potential for less intensive screening in low-risk groups; it also is examining some of the patient,

provider, facility, and system factors that optimize screening. Breakdowns would be the failure to detect, follow up, or treat. The project also can conduct comparative effectiveness analyses looking at colorectal cancer screening tests as practiced in the community. In addition, the NCI is an institutional member of the National Colorectal Cancer Roundtable and has partnered with sister agencies in the HHS, including projects with the CMS, Agency for Healthcare Research and Quality (AHRQ), CDC, and HRSA.

Poverty, Culture, and Social Injustice: Determinants of Cancer Disparities. Dr. Freeman discussed the issues of poverty, culture, and social injustice as they apply to cancer and specifically colon cancer. Screening is important but is only a first part of a larger continuum. The most meaningful measure of disparities is premature death. Three fundamental drivers of disparities—whether people have resources (e.g., lack of insurance and poverty); how people behave (i.e., culture and lifestyle); and whether people have been treated fairly—encompass prevention, early detection, diagnosis, treatment, and survivorship, and possibly influence gene-environment interactions. The Health Care Continuum includes screening, abnormal finding, diagnosis, and treatment. Key issues for cancer disparities include which populations have the heaviest cancer burden, the disconnection between discovery and delivery, the principal determinants of cancer disparities, who the poor and uninsured are, the meaning of race, patient navigation, and how best to reduce or eliminate cancer disparities.

Diseases occur under human circumstances, including economic, social, cultural, and environmental. To understand a disease in total, the human circumstances in which diseases develop must be understood. Race and sex are determinants of how long people live: white females live to be about 80 years, black males about 67 years, and black females and white males are in between. Surveillance, Epidemiology, and End Results (SEER) incidence and death rates show that African Americans have the highest incidence over time and the highest mortality for all cancers, including colon. Dr. Freeman asked what it is about black Americans that drives high disparities. The war on cancer was declared in December of 1971 by President Richard Nixon, but cancer is a complex problem and the war was not over in 8 years, as he had projected. Cancer is not simply one disease, and the delivery system to share discoveries with the public is broken; this disconnect between what is known and done is the major driver of disparities.

There is a need to distinguish between the meanings of class (i.e., economic status), culture, race, and social injustice. Poverty involves substandard housing, lack of knowledge, a tendency to risk-promoting lifestyles, and diminished access to health care. A shared communication system, similar physical and social environments, common beliefs and world view, and similar lifestyles and attitude comprise culture. Poverty drives certain negative events, such as diminished access to health care and a risk-promoting lifestyle; culture may serve as a prism through which poverty operates, with the power to either diminish or accentuate poverty's negative effects. Poverty drives disparities: poor Americans have a 10–15 percent lower 5-year cancer survival rate compared to other Americans. Currently, there are 43 million poor Americans and 50 million uninsured Americans.

According to U.S. Census Bureau data, approximately 10 percent of white Americans are poor, as are 27 percent each of black Americans and Hispanics. The uninsured include 30 percent of Hispanics and 14 percent of white Americans, with black Americans in between. The terms "black" and "white" are used often in science, but it is not always clear who is "black." The "One Drop Rule" is that anyone with one black ancestor is consider black. Findings from a 2003 Institute of Medicine (IOM) report on unequal treatment stated that bias, stereotyping, prejudice, and clinical uncertainty on the part of health care providers may contribute to racial and ethnic disparities in health care. An analysis (Bach, 1999) examined national data and found that white patients and black patients with early lung cancer are treated differently, with the rate of surgery being less in black Americans than white Americans, resulting in differences in survival. The American Cancer Society's *Report to the Nation on Cancer and the Poor* found that poor people encounter barriers when they attempt to seek diagnosis and treatment of cancer,

often do not seek cancer care if they cannot pay for it, and experience more pain and suffering. There is a critical window of opportunity to save lives between the point of an initial suspicious finding and a resolution of the finding by diagnosis and treatment.

Dr. Freeman said that the slow movement from finding to resolution is a critical issue for cancer screening. A patient navigation intervention began in Harlem, NY, in 1990, picking up at the point of abnormal finding and navigating a person through to resolution; that is, diagnosis and treatment. This model was expanded to encompass patient navigation across the entire health care continuum—from prevention, detection, diagnosis and treatment, and survivorship—as well as outreach to stimulate communities to come in for a test. Navigation issues include transporting people from where they live to a facility where tests can be conducted, ensuring that those with abnormal findings get to diagnosis in a timely manner, and ensuring that those diagnosed with cancer move rapidly through complex treatment, followed by survivorship issues. One of the solutions to the problem of disparities in colon and other cancers is the point that people need special, personal assistance in getting through a complex care system, particularly those who are uninsured, poor, and belong to disconnected racial groups.

The Patient Navigation Act was signed by President George W. Bush in 2005, giving attention to patient navigation. Significant efforts by the government, foundations, and private organizations, including demonstration sites supported by the NCI and CMS, have been made to understand the value of patient navigation. In addition, the American College of Surgeons Commission on Cancer determined that patient navigation is a standard of care that must be applied in every cancer facility to pass inspection, beginning in 2015. Likewise, the ACA requires that states that use patient navigators provide access support to health insurance.

To eliminate health disparities, what is known should be applied at any given time to all people, regardless of their ability to pay: universal access to health care must be provided. Geographic areas with excess cancer mortality should be delineated and targeted with an intense approach to providing culturally relevant education; appropriate access to screening, diagnosis, and treatment; and improved social support. In addition a high level of awareness should be developed among medical trainees and professionals regarding their role in eliminating bias in medical care delivery. Personal assistance also should be provided to eliminate barriers to timely care across the entire health care continuum in underserved communities.

Disparities in cancer are caused by the complex interplay of low economic class, culture, and social injustice, with poverty playing the dominant role. There is evidence that race, in and of itself, is a determinant of the level of health care received, according to the IOM. There is a need to disentangle the social and political meaning of race from assumptions about its biological meaning. Health disparities exact an extraordinarily high human cost and a significant economic cost to this Nation. Dr. Freeman quoted Goethe: “Knowing is not enough; we must apply. Willing is not enough; we must do.” and commented that the unequal burden of disease in society is a challenge to science and a moral dilemma for the Nation. He proposed a new paradigm—of biomedical sciences, civil and human rights, and social sciences and history—to reduce health disparities.

Questions and Answers

Dr. Victoria L. Champion, Associate Dean for Research, Mary Margaret Walther Distinguished Professor of Nursing, Center for Research & Scholarship, Indiana University School of Nursing, asked about the advantages of the FOBT versus FIT. Dr. Kramer replied that FOBT is guaiac based and yields higher positive and false-positive rates, whereas FIT is specific for human globin, has fewer dietary restrictions, and is easier to administer.

In response to a query by Dr. Olopade about strategies for a personalized approach to prevention, Dr. Kramer indicated that most screening trials to date have been conducted in broader populations, and said that emerging evidence suggests that the efficacy of aspirin may depend on the mutation itself. He added that population-based strategies are refined based on family history, background mutations, and other factors.

Dr. Marcia R. Cruz-Correa, Associate Professor of Medicine and Biochemistry, University of Puerto Rico, Basic and Translational Science Director, University of Puerto Rico Comprehensive Cancer Center, noted that many organizations recommend only one type of test and suggested that colon cancer screening choices be reduced as evidence demonstrates the levels of efficacy among tests. Dr. Klabunde agreed that the colorectal cancer screening message often is complicated and presents challenges to patients who often only have a short encounter with the physician.

Dr. Champion reflected on the barriers, including physician recommendations and time limitations during patient visits, and encouraged a cost-effectiveness strategy to identify the best approaches and reposition screening efforts as a prevention system rather than a physician services model.

Dr. Elizabeth M. Jaffe, The Dana and Albert "Cubby" Broccoli Professor of Oncology, Co-Director of the Gastrointestinal Cancers Program, Associate Director for Translational Research, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, noted the efficacy of mini-clinics in national pharmaceutical chain stores and recommended that the NCI consider collaboration opportunities to conduct FIT studies in those clinics.

Dr. Michael Kelley, VA, encouraged the NCI to include the VA in the models of how to deliver this care. He added that the VA has high rates of colorectal cancer screening, which are captured in its EMR system.

Dr. Olopade applauded the comprehensive focus of the cancer continuum, from screening through treatment, and appreciated the lessons from the Kaiser Permanente experience.

Dr. Judy E. Garber, Director, Center for Cancer Genetics and Prevention, Dana Farber Cancer Institute, Professor of Medicine, Harvard Medical School, commented that follow-up poses a significant challenge and encouraged the NCI to develop a campaign to educate physicians on the benefits of FIT screening and patient follow-up.

Dr. Champion expressed appreciation for Dr. Freeman's thoughts about navigation and observed that, with low-income African Americans in the Midwest, navigators who lived within the community doubled the screening rate above recommendations. Dr. Freeman shared the "mile relay analogy." In a mile relay, the forerunners pass the baton to the next runner, with passing continuing until the fourth runner takes the baton across the finish line. The patient is the baton, and a team of people might include lay (e.g., a community person) and professional (e.g., a nurse) people together passing a baton under the guidance of a coach. The race is not over for the patient until the race is over. Navigation should involve all of the people who can help in a given phase, and these will be connected as a team.

Dr. Olopade commented on economic development and the role of doctors in Africa and in Chicago, wondering who speaks for the poor and pointing out an opportunity for the NCI and broader cancer community to speak with one voice about equity issues to solve health problems. Dr. Freeman recognized Dr. Olopade's commitment to personalized medicine and distinguished between ancestry, race, and racism. He noted that Dr. Olopade stresses scientific and genetic components, and that he emphasizes the social and economic parts of the disparities problem.

Dr. Cruz-Correa suggested that because the biological basis of disease might be explained by ancestry, more weight should be given to biological bases (i.e., genetics) rather than race in health disparities screening. Dr. Freeman differentiated between skin color and race and observed that everyone is of African origin.

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

***Ad hoc* Subcommittee on Global Cancer Research.** Dr. Olopade reported that the Subcommittee met on 9 December 2013, and heard NCI's strategy for global health and the Center for Global Health's (CGH) direction. She said that the Subcommittee appreciated the discussions between Bill Gates and the NIH and felt strongly that the NCI should participate in collaborative efforts to advance global health. The Subcommittee also discussed the non-communicable disease (NCD) landscape following the United Nations' declaration on non-communicable conditions and agreed that the NCI should take a leadership role in cancer as an NCD. In addition, the issue of global disparities arose regarding access to cancer drugs and the ethics of cancer screening if not accompanied by access to treatment. Dr. Olopade said that the Subcommittee next will consider metrics for CGH resources and how the NCI's impact in the world should be measured. She indicated that the Subcommittee heard a presentation on the NCI Ambassador's Program, encouraged a dedicated campaign as diplomacy is an important part of global health, and recommended PEPFAR as a successful model for metrics.

***Ad hoc* Subcommittee on Planning and Budget.** Mr. William Goodwin, Chairman and President, CCA Industries, Inc., informed members that the Subcommittee on Planning and Budget held its inaugural meeting on 9 December 2013, and included presentations by Adrianne Hallett, Staff Director, Subcommittee on Labor, Health and Human Services, and Education of the U.S. Senate Appropriations Committee, and Mr. Patrick McGarey, NCI, Executive Secretary. Mr. Goodwin said the increase in the National debt, which has nearly doubled in the past 10 years, is a driving issue in Washington. He recalled the expansion of the NCI budget from the 1990s into the mid-2000s, from approximately $2.5 billion (B) up to $4.8 B, followed by a flattening from 2004 to 2010, a small increase for 3 years to $5.1 B, and a decrease last year to $4.8 B. In real dollars, the period of flatness was a decrease of purchasing power by approximately 25 percent. Mr. Goodwin commended Dr. Varmus for finding more efficient ways to support cancer research activities during the past several years. He said that Ms. Hallett discussed possible budget outcomes in Congress and strongly encouraged the Subcommittee and the NCI to market Congress for increased funding as the NCI has an economic and health impact for U.S. citizens and on people worldwide. She noted that biomedical research funding was increased in the United Kingdom although all other funding was decreased. The Subcommittee requested clarity about NCI's budgetary data in an effort to become better educated, and also invited Dr. Varmus to attend the next Subcommittee meeting to discuss how he has handled budgetary reductions and his future plans.

Motion. A motion was made to accept the reports of the 9 December 2013, NCAB Subcommittee on Planning and Budget and *Ad Hoc* Subcommittee on Global Cancer Research meetings. The motion was seconded, and the Board unanimously approved the reports.

Future Agenda Items. Dr. Jacks asked members of the committee for potential agenda topics. No topics were suggested.

VII. MATCHING THERAPY TO DIAGNOSTICS—DRS. JAMES H. DOROSHOW, BARBARA CONLEY, AND ELIZABETH MANSFIELD

Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, provided an overview of NCI-supported genomic clinical trials. Dr. Doroshow informed members that the NCI's

initiatives on precision medicine aimed to help advance molecular profiling from research use into the clinic; move from genotype to phenotype across disease spectrums to identify molecular features to predict response to a drug with a specific mechanism of action, and analyze tumor specimens at relapse to define mechanisms of resistance; and develop a public database that links clinical outcomes with molecular tumor characteristics. Dr. Doroshow introduced the other speakers: Drs. Barbara Conley, NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Program, and Elizabeth Mansfield, Division of Devices, U.S. Food and Drug Administration (FDA).

NCI-supported Genomic Clinical Trials Overview. Dr. Doroshow described three studies: ALCHEMIST; Biomarker-driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer (SWOG1400); and Molecular Profiling Based Assignment of Cancer Therapeutics (M-PACT). There is a need for therapy studies as approximately 40 percent of lung cancer patients in the United States are adenocarcinoma patients, and one-half of those diagnosed with Stage 1A and B disease will relapse and die within 5 years.

The goal of ALCHEMIST is to determine whether adding crizotinib or erlotinib to adjuvant standard therapy for patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) abnormalities will improve long-term outcome. The trial requires significant efforts in tissue acquisition and DNA sequencing, and 7,000–8,000 patients will be screened for ALK fusion or EGFR mutation to get to about 800 total patients who will be randomized either to standard chemotherapy or chemotherapy plus the compound of interest to determine survival benefit. ALCHEMIST presents a unique opportunity as one of the largest natural history studies of molecular endpoints ever undertaken. Tissue biopsies will come from Stage 1A, 1B, and 2A patients with lung cancer at trial onset, with many patients followed for 5 years and biopsied at each recurrence.

SWOG1400, focused on second-line squamous cell cancer therapies, was developed with the input of the FDA and in collaboration with the Foundation for the NIH (FNIH). The focus starts with a series of Phase II studies that have progression-free survival that might progress to Phase III and potentially a registration indication. Patients will be registered and tumors assessed in a short period of time by a mutation panel that has specific actionable mutations. Trials resources will come from the pharmaceutical industry through the FNIH, and the NCI will handle the trial conduct and data collection through its Thoracic Malignancy Steering Committee and the Friends of Cancer Research. The study should open in 2014 and provide a forum for screening 500–1,000 patients through separate randomized arms. SWOG1400 involves many partners and provides a state-of-the-art approach to advanced squamous cell lung cancer.

M-PACT is a histology-independent study to understand in a randomized, prospective way the endpoints of response to progression-free survival. It is a response rate and progression-free survival umbrella study, with a series of nested Phase II investigations that can be expanded or dropped. All of these patients give fresh tumor biopsies at enrollment and progression. The study will help the NCI better understand particular therapies and mutations, and the year and a half process has allowed the NCI to understand how to work with the FDA and develop an investigational device exemption (IDE) for the lock down algorithms for the mutational analyses. Approximately 1,000 biopsies gathered from patients to acquire 250 with mutations of interest will bring 1,000 fresh biopsies to the NCI. This may be used to establish patient-derived xenograft (PDX) models and be characterized genomically, and approximately 100–200 of these will be matched to biopsies at the time of progression. This will represent an important repository of metastatically biopsied patients with clinical histories.

NCI-MATCH. Dr. Conley told members that the premise for NCI-MATCH, an umbrella protocol for multiple, single-arm Phase II trials, is that molecularly targeted therapy benefits patients with defined molecular features, both within individual tumor types and across tumor types. The trial will

identify mutations, amplifications, and translocations in patient tumor samples, assign eligible patients to the relevant regimen, sequence large numbers of tumors, use many targeted treatments, and study tumor biopsies and sequencing at progression to illuminate resistance mechanisms. Genetic sequencing of an estimated 3,000 patients will occur early in the process, with a study agent assigned if an actionable mutation is detected. A patient with stable disease, partial response, or complete response continues until progression, with another biopsy for additional mutations. The Cancer Therapy Evaluation Program (CTEP)-Investigational New Drug (IND) Application (IND) will be used as the protocol template, with arms added or deleted as needed. The initial focus is on single agents, and the studies will be reviewed by the Central Institutional Review Board (CIRB). Eligible subjects will have solid tumors or lymphomas that have progressed following at least one line of standard therapy, a tumor(s) accessible for biopsy, and adequate organ function. The intent is to target 25 percent of the enrollment for rare tumors, with common tumors defined as breast, non-small cell lung cancer, colon, and prostate. Dual primary endpoints include that a response rate of 5 percent or less would not be interesting to pursue in a molecularly defined population, and progression-free survival at 6 months of 15 percent versus 35 percent. A Simon two-stage design will enroll 30 patients per arm. The Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) will lead the effort with the cooperation of the NCTN, national access is through the Cancer Trials Support Unit (CTSU), and community participation will be garnered through the community oncology groups.

Dr. Conley described four levels of drug evidence. Level 1 is a drug that the FDA approved for some disease with particular tumor characteristics. Level 2 is an agent that met a clinical endpoint, although it may not have received FDA approval yet, and evidence of target is inhibition as well as plausible evidence of a predictive or selection assay or analyte. Level 3 involves agents that have demonstrated some evidence of clinical activity and evidence of target inhibition. Level 4 is a preclinical area and is not planned for NCI-MATCH. Members were informed that the level of evidence for genes is under discussion but may include a variant: credentialed for selection of an approved treatment agent in a particular malignancy (e.g., ERBB2 amplification and trastuzumab); credentialed for selection of an approved treatment target in any malignancy but without clinical data in other malignancies that might have that variant; or is an eligibility criteria for an ongoing clinical trial. In addition, preclinical data would show response in at least two xenografts (or cell lines) that have the mutation, and no response in xenografts without the mutation.

Members were informed that an Agent and Gene Selection Committee will vet the actionable genetic alterations and the most robust agents. In addition, essential targets and pathways include the major cancer-related abnormal pathways. The genetic platform will be validated and developed at NCI-Frederick with a group of assay development laboratories in the extramural area. More than 40 drugs have been pledged by pharmaceutical companies, and 20 arms are being considered. A next-generation sequencing assay that includes a custom panel of 200–300 actionable genes (e.g., single nucleotide variants, amplifications, and selected translocations) will serve the primary assay. Validation will occur through a network of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories, and immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) will be used as needed. In addition, a central pre-analytic pathology laboratory will receive and process biopsies and specimens as needed and handle shipment to the MATCH Clinical Laboratory Network for the sequencing assay. The assay report will be sent to the patients and their doctors during the trial. Dr. Conley reviewed the workflow for the assay system and pointed out that the tumor content will be more than 50 percent, an appropriate yield of DNA will be needed, standard operating procedures will be used for the library preparation, and sequencing will be in the data analysis, with the pathology report or the assay report being issued. The expected timeframe for the assay process is 10 days.

Dr. Conley said that current activities include the nomination of investigators, who will become authors of the protocol and PIs of the study arm, to guide target/agent selection; continued engagement

with patient advocates to ensure that the design is responsive to patients' needs and concerns; and development of a master protocol that includes elements pertinent to all of the arms and considers tissue submission results reporting, response criteria, and quality of life.

On the Horizon: Next Generation Sequencing as Companion Diagnostics. Dr. Mansfield provided a report on companion diagnostics in the FDA. Prior to a formal policy, the FDA used estrogen receptors (ER) and progesterone receptor (PR) to direct therapy. The first matching was seen in 1998 with HER-2/Herceptin, and moved forward with other matches, which were not spectacular. There was a dawning recognition that tests can be drivers of therapy as more information about the genome becomes known. The FDA developed a policy in 2008 that addressed patient safety, predictability for the device element, and support for therapeutic approvals. The policy effected a change in drug development strategies to account for genetic information through numerous public discussions. The landscape of companion diagnostics has changed dramatically since 2008, partly because of new technologies and studies involving genomics. Dr. Mansfield said that the FDA is now seeing multiple drugs with the same or similar indication, multiple drugs within a disease area, and the potential for molecular diagnosis where drugs may target a particular alteration rather than disease. These are leading to multiple tests for single diseases, limited tissue, and reimbursement concerns. Challenges include minimizing the number of different tests needed, the amount of tissue required, and incremental regulatory requirements, as well as maximizing the information content per test. To handle next-generation sequencing and other high-content, multiplexing technologies for companion diagnostics, the FDA has developed a model that uses a validated platform to identify appropriate patients for clinical trials, is used in an investigational mode, allows regulatory submission of the data, and builds a panel over time as new markers are identified. Outstanding issues include that a sponsor must choose to come to the FDA and submit to the process; the number of platforms that could meet FDA Quality System requirements is not known; and approved test systems tend to be static, whereas technologies change and grow rapidly. Additional challenges include the possibility of validating next-generation sequencing systems against already approved tests and that the platform cannot substitute for IHC or other non-nucleic acid tests; there is a need to determine how to bring protein information into genomics or to develop a second, multiplex platform to address this.

Questions and Answers

Dr. Jacks asked whether companies cover the costs of ALCHEMIST, given their interest in knowing if their drug(s) can be used in the adjuvant setting. Dr. Doroshow said that the drugs are not approved in the adjuvant setting, and Dr. Jeff Abrams, Co-Director, DCTD, added that all of the ALCHEMIST studies involve collaboration with pharmaceutical partners: in such a partnership, the NCI might cover the costs of the testing, and the collaborator might pay for the scans.

Dr. Waun Ki Hong, Professor, Head, Division of Cancer Medicine, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, asked how the treatment of patients with variable core or other mutations will be managed in M-PACT's master protocol with drugs obtained from different companies. Dr. Doroshow answered that the initial approach is to use a target agent plus chemotherapy but mentioned that the oversight group for the SWOG1400 Master Protocol is considering the feasibility of combination trials.

Dr. Cullen wondered how NCI-MATCH is designed to allow more than one drug for a given target. Dr. Conley indicated that the process is limited to one drug for a given target, with other drugs brought in for new arms.

Dr. Mack Roach III, Professor of Radiation Oncology and Urology, Chair, Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, commented on the complexity of the trial and asked how an agent's value to treatment will be

shown and how the next actionable portion will be determined. Dr. Conley clarified that NCI-MATCH is a signal-finding trial looking across tumor characteristics to ascertain whether treating by that characteristic is effective. She agreed that the process will not be straightforward and reminded members that the arms are defined by their molecular abnormality rather than type of cancer.

Dr. Beth Y. Karlan, Director, Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Director of Gynecologic Oncology, Department of Obstetrics & Gynecology, Cedars-Sinai Medical Center, Professor, Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, queried about the advantages of collecting samples from screened patients for use in a simple actionable test and then confirming whether circulating tumor cells are found in the peripheral blood. Dr. Conley confirmed that NCI-MATCH will collect blood from patients with the hope that the circulating cell-free DNA might replace the biopsy.

Dr. Jacks remarked on the inherent challenges in the eligibility criteria for pre-clinical validation, that is, whether the mutation predicts response in a xenograft study, given that mutation versus pathway alteration can be highly confusing. Dr. Conley agreed, said that discussions are ongoing about this, and welcomed further input from members.

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, Director, Institute for Global Health, University of Southern California, encouraged the NCI-MATCH program to establish a formal protocol to classify evidence in terms of both strategies for literature searches and criteria for classification. Dr. Roach commented that a pilot project could help determine the number of specimens that will need to be reviewed to identify specimens with actionable findings before beginning a full study.

Dr. Hong stated that the number of mutations rises when metastatic patients are tested. In response to comments by Dr. Olopade regarding statistical analysis for NCI-MATCH, Dr. Conley clarified that the trial is focused on finding either a progression-free survival of interest or an overall response rate of interest through Phase II studies; Bayesian statistics and powering applications are not needed for these.

Dr. Varmus asked Dr. Mansfield about the number of manufacturers beyond the NCI coming to the FDA since approval of the next-generation sequencing platform. Dr. Mansfield responded that there are many users but few manufacturers in this space and expressed hope for a lung panel, given that at least three actionable mutations have been identified. Dr. Jacks wondered about the progression from panel to test. Dr. Mansfield said that the FDA has focused on providing a stable platform that manufactures well and has known sequencing performance and suggested that laboratories eventually may be able to buy kits or panels rather than building distinct tests.

Dr. Kelley wondered whether tests must provide results that are comparable to an existing approved diagnostic or show a clinical outcome. Dr. Mansfield stated that the FDA looks for measurement performance, such as accuracy, precision, and reproducibility. She added that for companion diagnostics, the test usually is used in a clinical trial and is considered valid if the trial reads out successfully.

VIII. CLOSED SESSION— DR. TYLER E. JACKS

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

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

IX. ADJOURNMENT— DR. TYLER E. JACKS

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

There being no further business, the 164th regular meeting of the NCAB was adjourned at 4:30 p.m. on Tuesday, 10 December 2013.

_____ _____

Date Tyler E. Jacks, M.D., Chair

_____ _____

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

National Cancer Institute

National Cancer Advisory Board

Division of Cancer Epidemiology and Genetics

Overview

Stephen J. Chanock, M.D.

December 10, 2013

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Background

Drs. Chanock and Purcell

- Came to NIH in 1958
  - Building 7
- Undergraduate degree in music
  - Composition
- Studied conducting/composition in UK
- Harvard Medical School
- Two pediatric subspecialties
  - Infectious Diseases
  - Hematology/Oncology
- Laboratory Fellowship in Molecular Hematology
  - Dr. Stuart H. Orkin (HHMI / Boston Children's Hospital)

Mozart

Career at NCI

- **1991 - Joined Pediatric Oncology Branch**
  - **Infectious complications of pediatric cancer and HIV infections**
  - **Molecular biology of immunosuppression**
- **1996 - First DCEG collaborations**
- **1991-2007 CCR PI**
- **2001-Today Director of CGR**
- **2007-2013 Chief of LTG**
- **2012-2013 Acting Co-Director of CCG**

DCEG Mission

- **To uncover the causes of cancer and the means of its prevention through broad-based, high-quality, high-impact research**
  - **Classical epidemiology**
  - **Molecular epidemiology**

NATIONAL CANCER INSTITUTE
Division of Cancer Epidemiology and Genetics

Office of the Director
Stephen J. Chanock, M.D.
Director

Joseph F. Fraumeni, Jr., M.D.
Senior Investigator and Advisor

Epidemiology and Biostatistics Program
Robert N. Hoover, M.D., Sc.D.
Director

Biostatistics Branch
Nilanjan Chatterjee, Ph.D.
Chief

Hormonal and Reproductive Epidemiology Branch
Louise A. Brinton, Ph.D.
Chief

Infections and Immunoepidemiology Branch
Allan Hildesheim, Ph.D.
Chief

Nutritional Epidemiology Branch
Robert N. Hoover, M.D., Sc.D.
Acting Chief

Occupational and Environmental Epidemiology Branch
Debra T. Silverman, Sc.D.
Chief

Radiation Epidemiology Branch
Martha S. Linet, M.D.
Chief

Human Genetics Program
Margaret A. Tucker, M.D.
Director

Genetic Epidemiology Branch
Neil E. Caporaso, M.D.
Chief

Clinical Genetics Branch
Mark H. Greene, M.D.
Chief

Cancer Genomics Research Laboratory
Stephen J. Chanock, M.D.
Director

Laboratory of Translational Genomics
Margaret A. Tucker, M.D.
Acting Chief

DCEG Today

- **Intellect**
  - Re
  -
  -
  -
  -
  -
  - **Immi** c decisions f

Key Issues

- **Use emerging technologies** to improve exposure assessment
- **Develop analytic/informatic capacity** to match scientific goals

Exploring New Technologies

- **Evaluate feasibility of new technologies as applied to population sciences**
  - **Epigenomics**
  - **Microbiomics**
  - **Metabolomics**
  - **Proteomics**

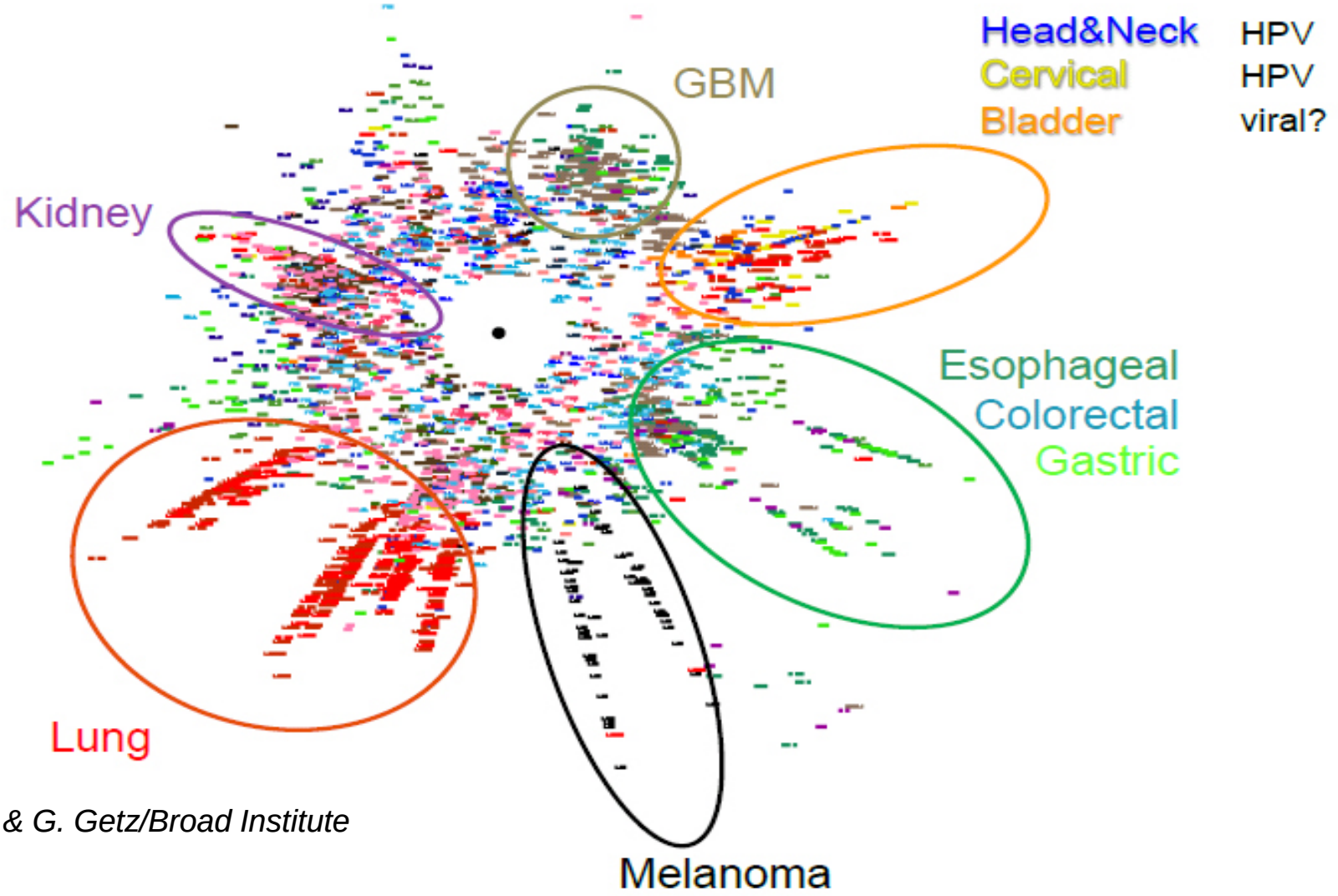
Strategic Initiatives in Germline Genomics

- **Susceptibility**
  - Discovery
  - Comprehensive maps of cancer-specific genetic architecture
- **Focus on highly informative cases**
  - Familial Cancers
  - Pediatric cancers
    - TARGET germline initiative
  - Second Cancers
    - Childhood Cancer Survivor Study
- **Laboratory investigation of mechanistic insights**
  - How does the germline inform somatic alterations?

Strategic Initiatives in Genomics

- **Somatic Molecular Epidemiology**
  - Investigate interaction between exposures, germline and somatic profiles in high-quality studies
    - EAGLE- lung cancer
    - Chernobyl radiation-induced thyroid cancer
  - Close partnership with Center for Cancer Genomics
  - TCGA-related projects
    - PanCan analysis

TCGA: Lessons Learned from the Data



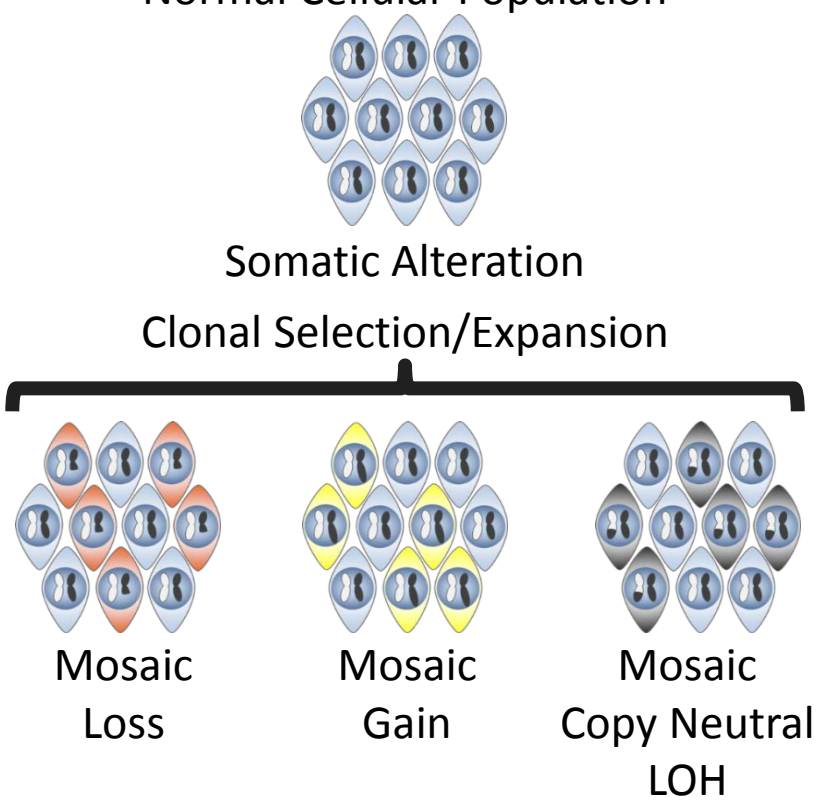
M. Lawrence & G. Getz/Broad Institute

Atlas

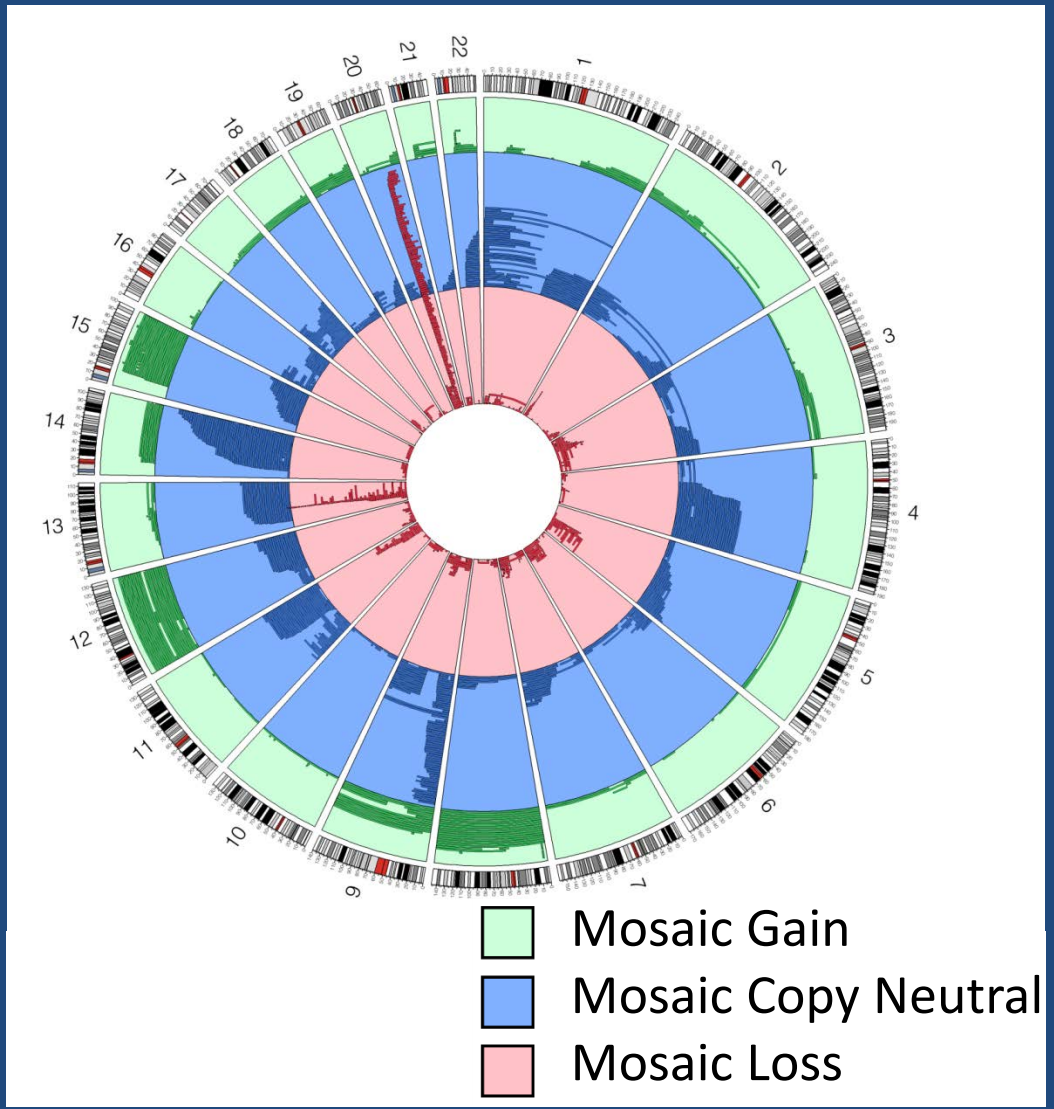
Strategic Initiatives in Genomics

- **Somatic Molecular Epidemiology**
  - Investigate interaction between exposures, germline and somatic profiles in high-quality studies
    - EAGLE- lung cancer
    - Chernobyl radiation-induced thyroid cancer
  - Close partnership with Center for Cancer Genomics
  - TCGA-related projects
    - PanCan analysis
- **Risk Assessment and Modeling**

Detectable Clonal Mosaicism in 'Germline' Unexpected Finding in GWAS



- **Breadth of mosaicism**
- **Risk factor for cancer?**
- **Insights into 'genomic stability'**



Leverage Areas of Special Expertise

- **Environmental and Occupational Exposures**
  - **Ultrafine particulates and lung cancer**
  - **Pesticides and cancer**
  - **Systematically characterize mechanisms of action of leukemogens and lymphomagens**
    - **Benzene**
    - **Formaldehyde**
    - **Trichloroethylene**
    - **Perchlorethylene**

Leverage Areas of Special Expertise

- **Radiation Exposure**
  - **Environmental**
    - Risk assessment in Chernobyl and atomic bomb survivors
    - Genomic characterization of radiation-induced thyroid cancer
  - **Medical and Occupational**
    - CT scans
    - Healthcare workers
      - Nuclear medicine
      - Angiography

Emerging Opportunities

- **Develop New Strategic Studies**
  - **Energy balance and obesity**
    - Physical activity
  - **HPV vaccine**
    - Optimal dose efficacy (< 3)
  - **Second cancers**
    - Childhood Cancer Survivors Study

Emerging Opportunities

- **Launch new long-term prospective cohort study**
  - **Serial biospecimens**
  - **Exposure assessments**
- **Leveraging existing infrastructure**
  - **HMOs**
  - **Military/VA**
  - **International partners**

Management Style

- **Gather information before making decisions**
  - **Ask many questions**
  - **Seek wise counsels**
  - **Listen to many perspectives**
- **Present problems with possible solutions**
  - **Consider alternative perspectives**
- **Support the next generation**
  - **Feature young investigators (TT/Fellows) in team science**
- **Consider the past, but not be wedded to it**

"When you call me that, smile……."

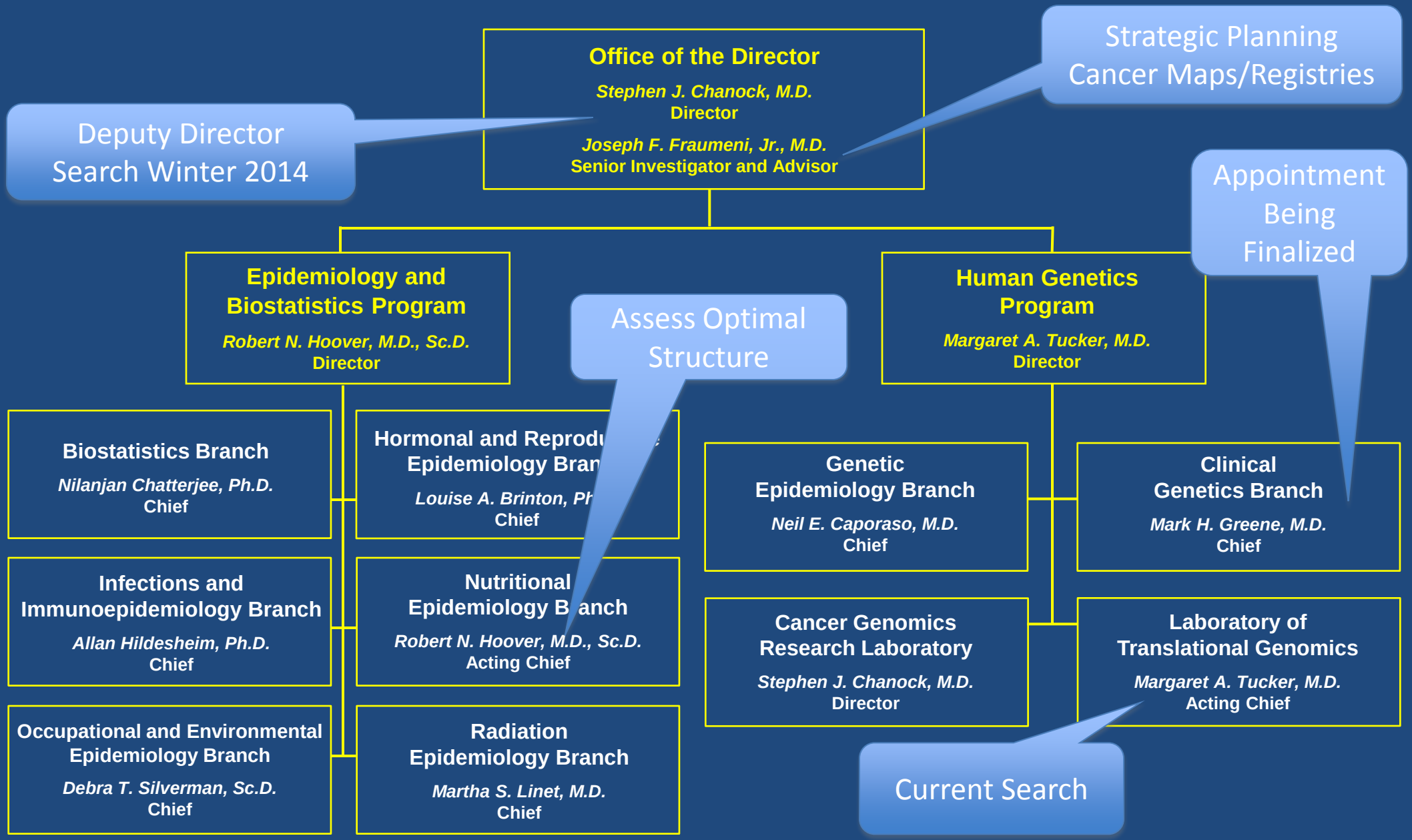
Mae West

Strategic Planning

- **Concise statements of**
  - **Principal Investigators' scientific goals over 1, 3, 6 years**
  - **Staff Scientists/Clinicians' accomplishments and future directions**
- **Value in assessing**
  - **State of science across DCEG**
  - **Improvements for managing key resources**
  - **Promote new initiatives**
  - **Enhance collaboration**

NATIONAL CANCER INSTITUTE

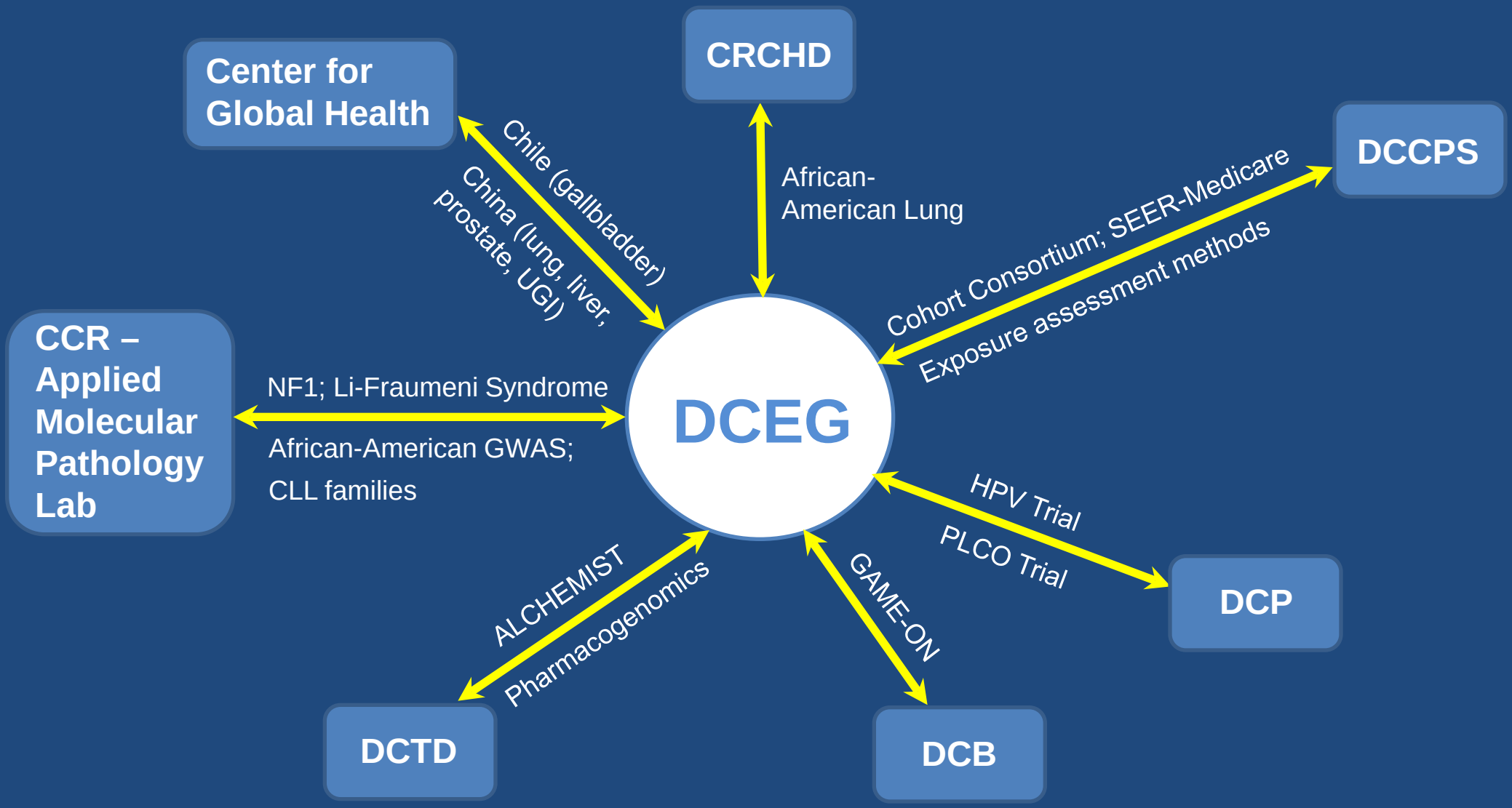
Division of Cancer Epidemiology and Genetics



Education & Training

- Assess mentoring and recruiting
- Deepen connections across NCI Divisions
- Expand DCEG knowledge base
  - Furthering exposure to mechanistic insights
  - Modeling
  - Translating etiologic findings to public health

Collaborations Across NCI



Senior Expert Lectures

- **‘State-of-the Art’ presentation of a discipline**
  - **Feature *some* of their work**
- **Experts in related cancer fields**
  - **Oncogenes**
  - **Targeted Therapy**
  - **Immunology**
- **Discuss synergies between their field and population sciences**
- ***Important Metric: New Collaborations***

The Challenges Ahead

- **Retain academic excellence** in fiscally restricted times
- **Strengthen connections across DCEG**
  - Enhance collaborative network
  - Promote new initiatives
    - Translational Epidemiology
    - Unattended Opportunities
- **Upgrade informatic infrastructure**
- **Sunset studies past their prime**

National Cancer Institute

Colorectal Cancer Screening and Aspirin for Prevention

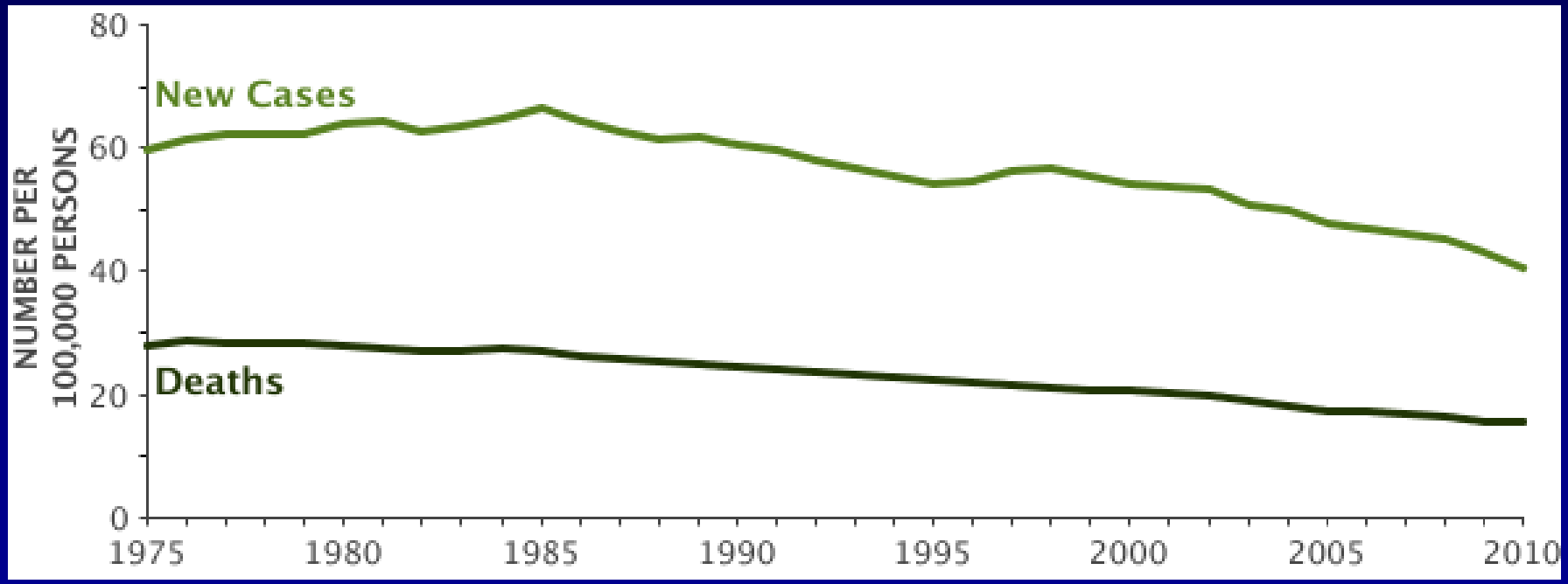
December 2013

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

Trends in Incidence and Mortality For Colorectal Cancer



http://seer.cancer.gov/statfacts/html/colorect.html

Outline

- What's the best colorectal cancer screening test?
- Aspirin chemoprevention
- Are endoscopy and aspirin complementary?

Outline

- **What's the best colorectal cancer screening test?**
- **Aspirin chemoprevention**
- **Are endoscopy and aspirin complementary?**

U.S. Preventive Services Task Force Recommendations for CRC Screening

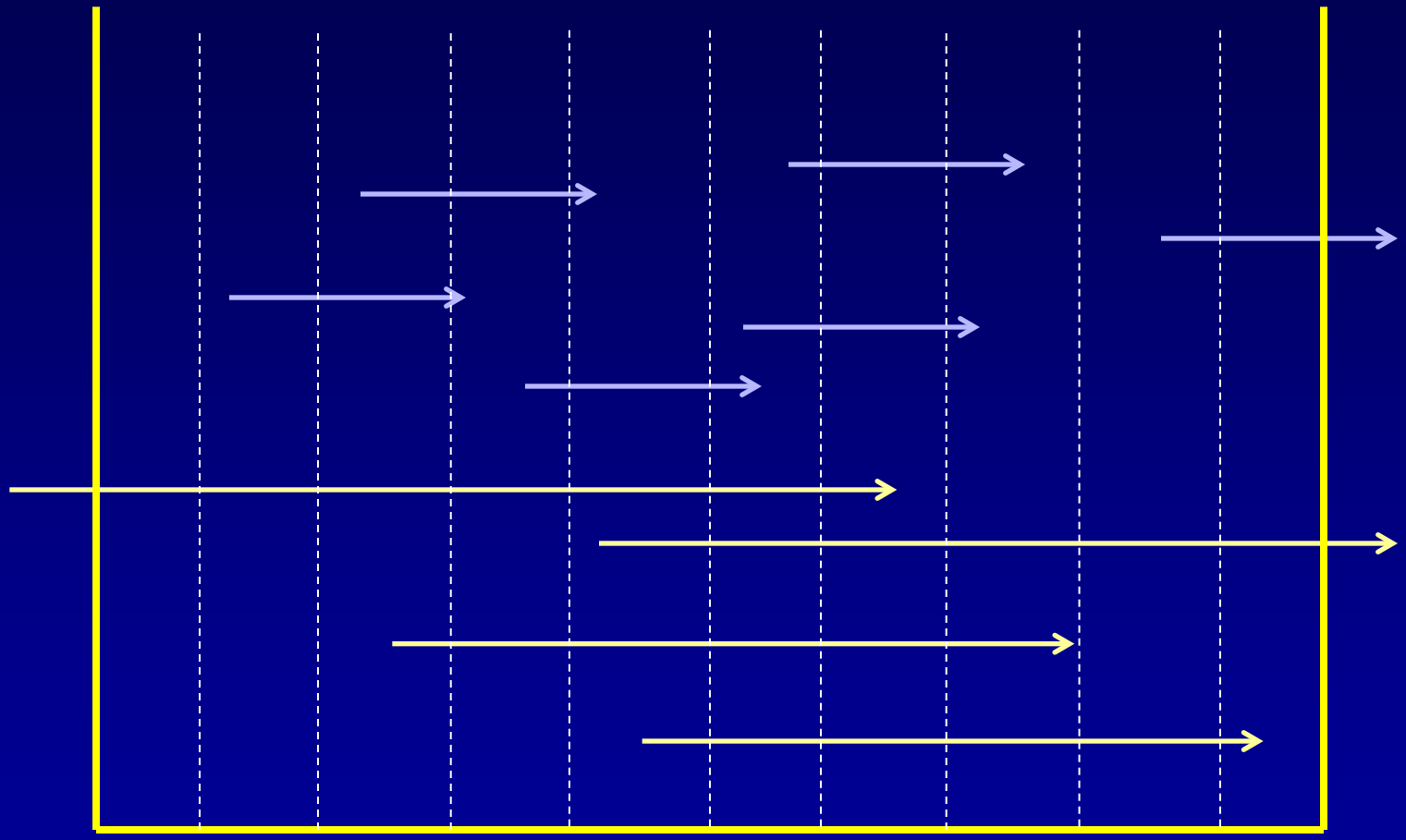
Adults Age 50-75 Years	Adults Age 76-85 Years	Adults Older than 85 Years
Screen with high-sensitivity FOBT (annual), Sigmoidoscopy (5 years) + HS-FOBT (3 years), or Colonoscopy (10 years) Grade: A	Do not screen routinely Grade: C	Do not screen Grade: D
For all populations, evidence is insufficient to assess the benefits/harms of screening with CT colonography and fecal DNA testing Grade: I (Insufficient evidence)		

Effect of Screening Intervention on Reducing Mortality from Colorectal Cancer

	Fecal Occult Blood Test	Sigmoidoscopy	Colonoscopy
Study Design	RCTs	Case-control studies; RCTs	Case-control studies, RCTs in progress
Magnitude of Effects	15%-33%	About 60%-70% for left colon	About 60%-70% for left colon; uncertain for right colon
Invasiveness	+	++	+++

http://www.cancer.gov/cancertopics/pdq/screening/colorectal/HealthProfessional

The Effect of Screening Intervals on Cancer Detection



Outcomes for the Recommendable Set of Screening Strategies/MISCAN

Beginning tests at age 50, ending tests at age 75, per 1,000 people

	No. of Colon--oscopies	Life Years Gained per 1,000 people	Incidence Reduction	Mortality Reduction
Colonoscopy	4136	230	51.9%	64.6%
Hemoccult SENSA	3350	230	49.7%	66.0%
FIT	2949	227	47.2%	64.6%
Hemoccult II	1982	194	37.1%	55.3%
Flexible Sigmoidoscopy	1911	203	46.8%	58.5%
Flexible Sig + SENSA	2870	230	51.2%	65.7%

Zauber, *Annals of Internal Medicine*
4 Nov 2008

The most effective colorectal cancer screening test is the one you are willing to take.

Compliance to FIT vs. Colonoscopy: First Round of a Spanish Randomized Trial

- Households randomly assigned to either biennial FIT or 1-time colonoscopy
- Randomization performed before invitation
- Invitation letters sent with reminders at baseline, 3 months, and 6 months
- 57,404 Randomized, 1st Round Compliance/Acceptance Rates
  - FIT 34.2 %
  - Colonoscopy 24.6%
  - OR=0.63 p <.001

Quintero, *N Eng J Med*, 23 Feb 2012

Colonoscopy vs. FIT: First Round Detection in the Spanish Randomized Controlled Trial

Table 1. Diagnostic Yield of Colonoscopy and Fecal Immunochemical Testing (FIT), According to the Intention-to-Screen Analysis.*

Colorectal Lesion	Colonoscopy (N=26,703)		FIT (N=26,599)		Odds Ratio (95% CI)†	P Value
	Subjects	Rate	Subjects	Rate		
	no.	%	*no.*	%		
Cancer	30	0.1	33	0.1	0.99 (0.61–1.64)	0.99
Advanced adenoma‡	514	1.9	231	0.9	2.30 (1.97–2.69)	<0.001
Advanced neoplasia§	544	2.0	264	1.0	2.14 (1.85–2.49)	<0.001
Nonadvanced adenoma	1109	4.2	119	0.4	9.80 (8.10–11.85)	<0.001
Any neoplasia	1653	6.2	383	1.4	4.67 (4.17–5.24)	<0.001

* The diagnostic yield was calculated as the number of subjects with true positive results divided by the number of subjects who were eligible to undergo testing. Subjects were classified according to the most advanced lesion.
† Odds ratios were adjusted for age, sex, and participating center. CI denotes confidence interval.
‡ Advanced adenoma was defined as an adenoma measuring 10 mm or more in diameter, with villous architecture (>25%), high-grade dysplasia, or intramucosal carcinoma.
§ Advanced neoplasia was defined as advanced adenoma or cancer.

Quintero, *N Eng J Med*, 23 Feb 2012

Harms/Complications in the First Round of the Spanish Randomized Trial of Colonoscopy vs. FIT

- 24 of 4,953 patients in colonoscopy group had complications (0.5%)
  - Bleeding (12)
  - Hypotension or bradycardia (10)
  - Perforation (1)
  - Desaturation (1)

- 10 of 8,983 patients in FIT group had complications (0.1%)
  - Bleeding (8)
  - Hypotension or bradycardia (2)

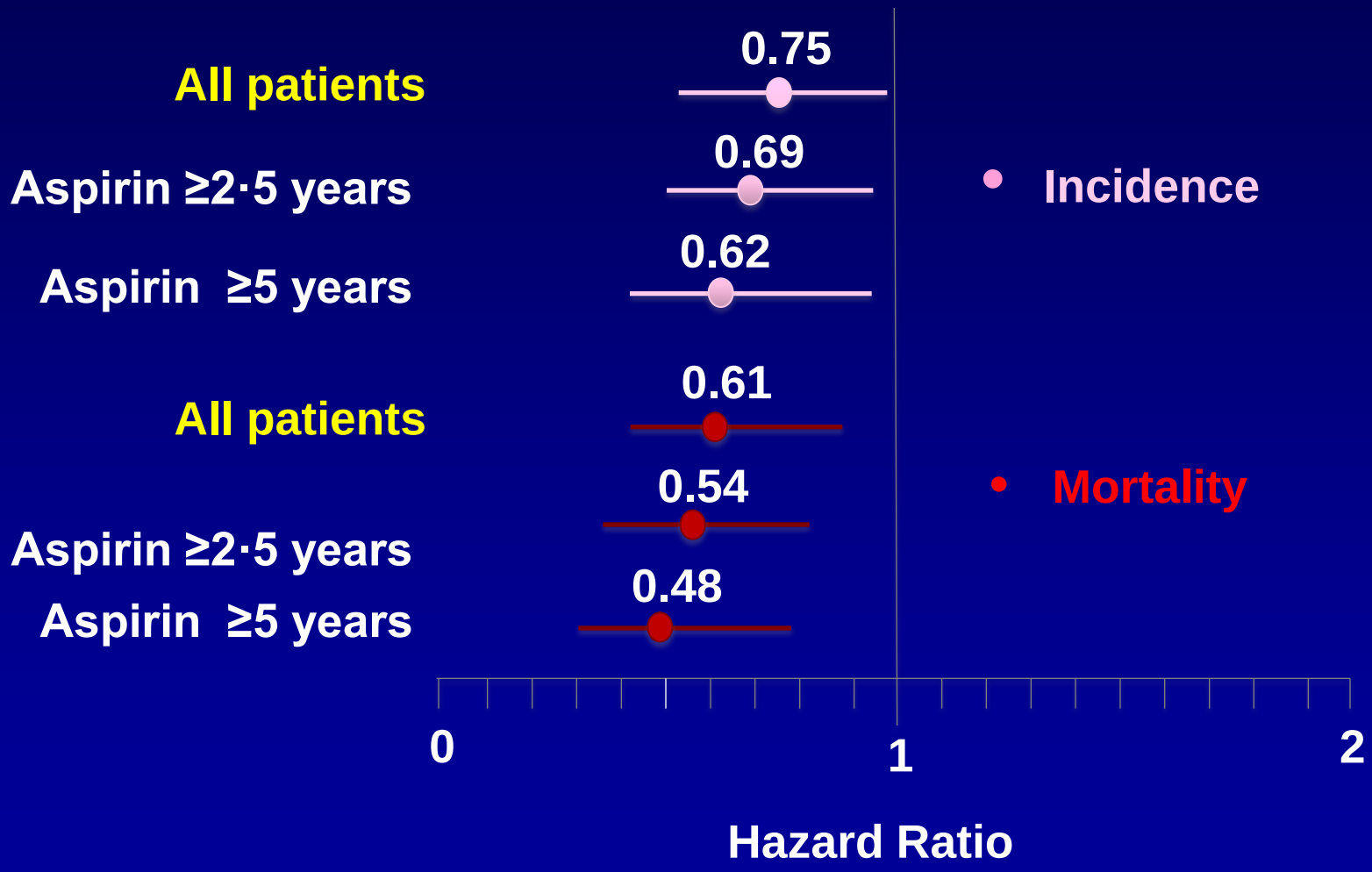
  (all 10 had positive FIT and received a colonoscopy)

Quintero, *N Eng J Med*, 23 Feb 2012

Outline

- What's the best colorectal cancer screening test?
- **Aspirin chemoprevention**
- Are endoscopy and aspirin complementary?

Effect of Low-dose (75-300mg) Aspirin Versus Control on Colorectal Cancer Incidence & Mortality

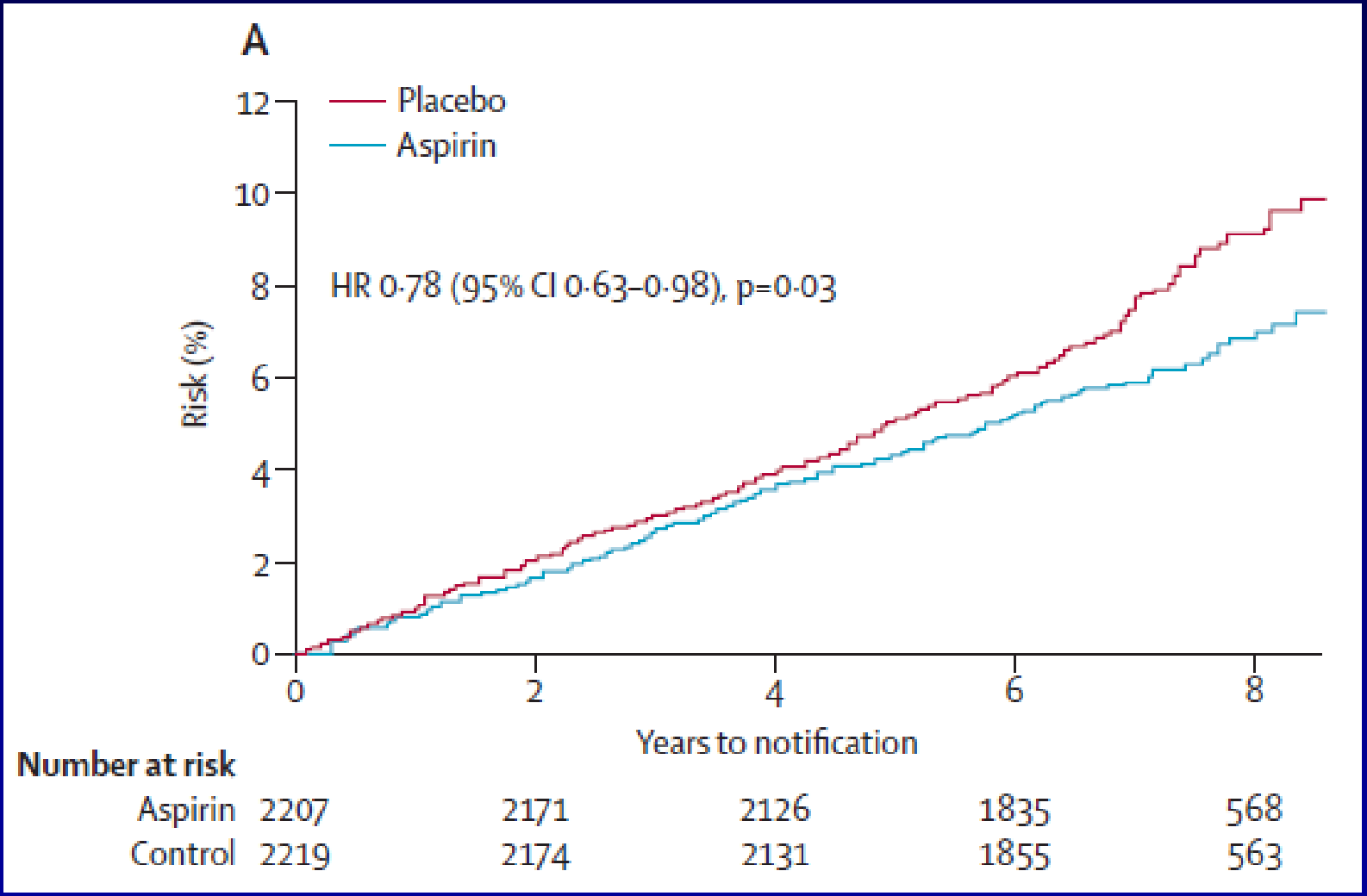


Rothwell, *Lancet,* 20 November 2010

Data from 4 randomized trials of aspirin vs. control

Effect of Aspirin on Incidence of Cancer

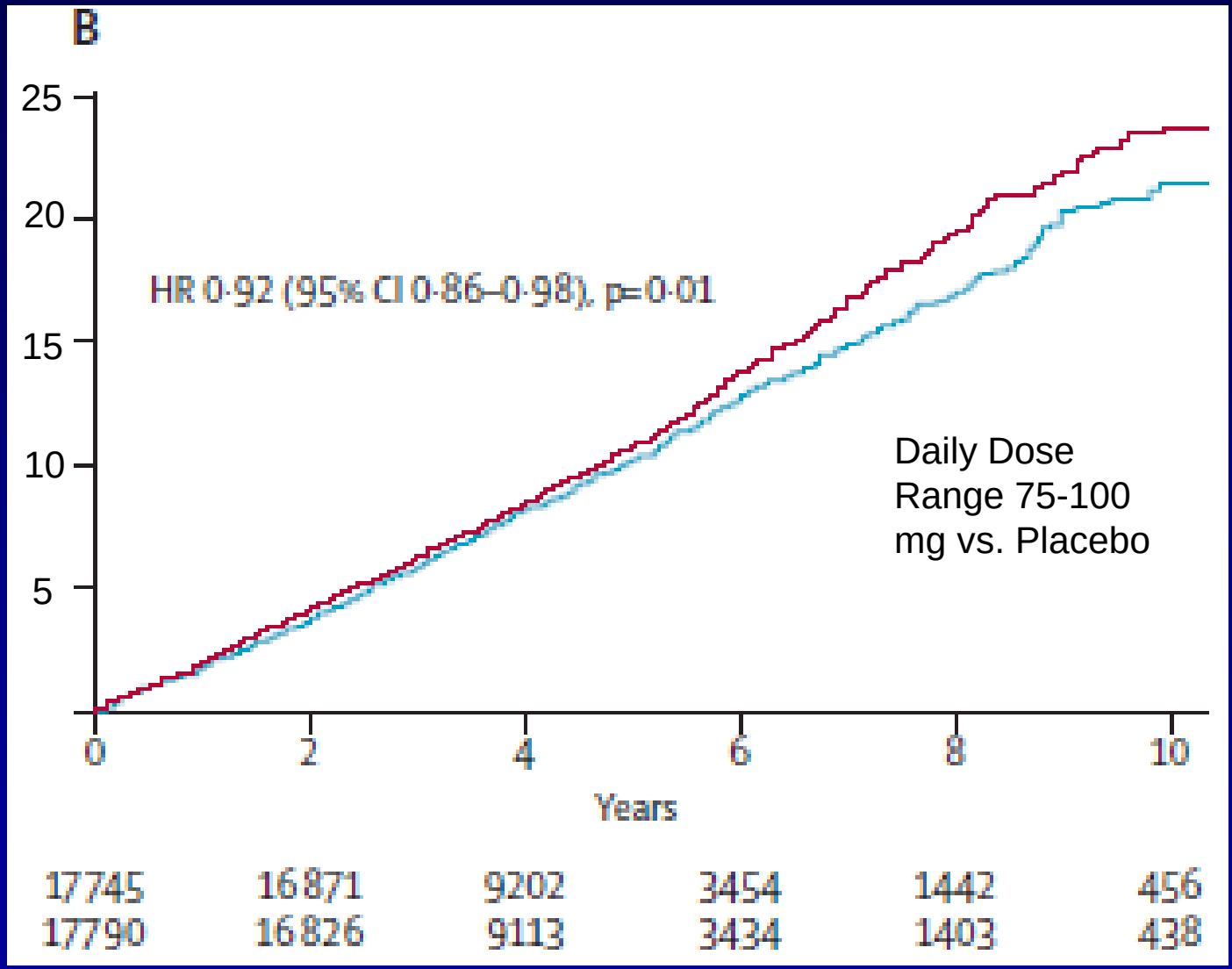
Daily Dose Range 75-100 mg, vs. Placebo



Rothwell, *Lancet,* 28 April 2012

Data from 6 randomized trials of aspirin vs. control

Effect of Aspirin on Vascular Events, Cancers, or Fatal Extra-cranial Hemorrhage



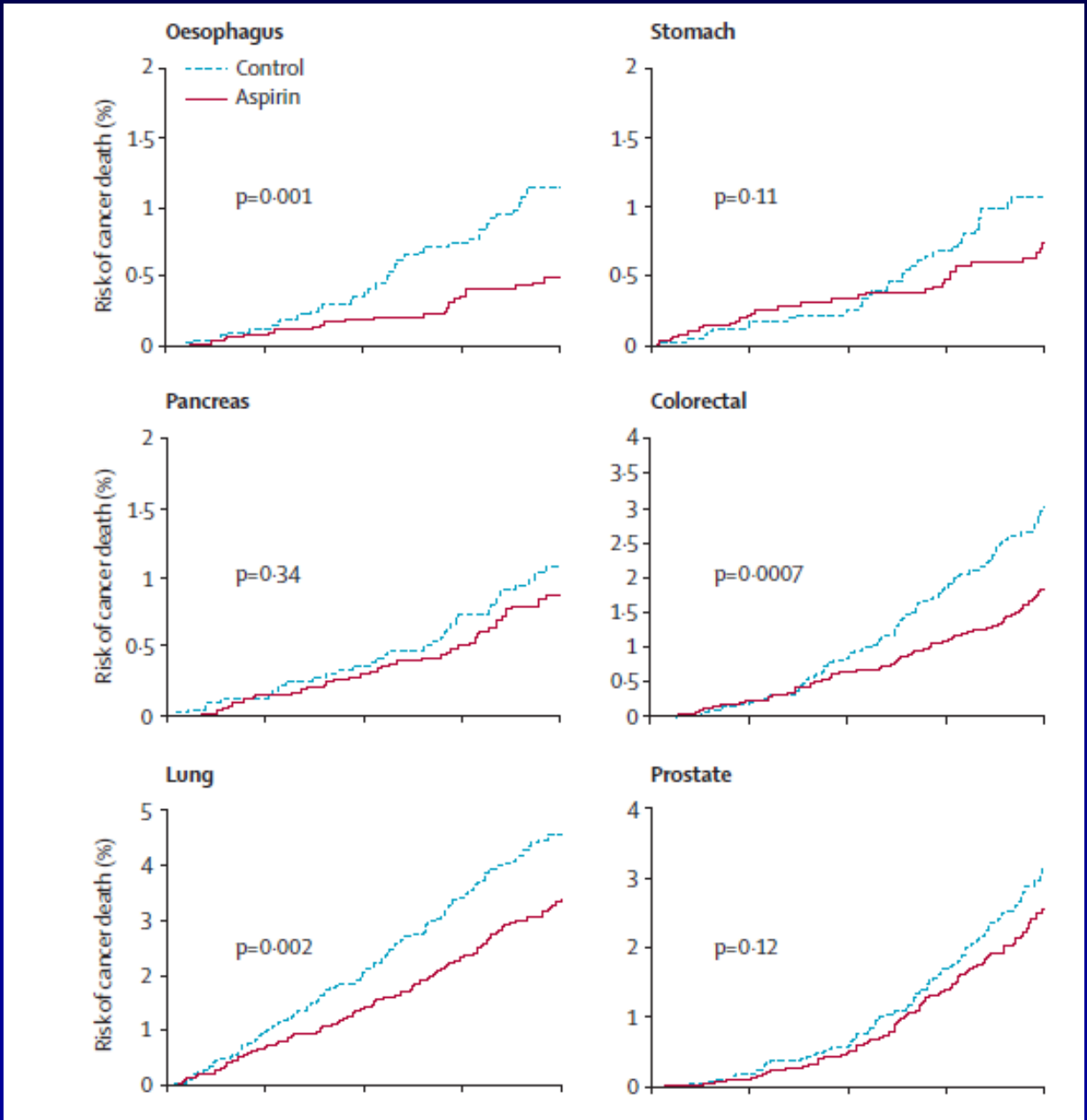
Rothwell, *Lancet,* 28 April 2012

Data from 6 randomized trials of aspirin vs. control

Screening vs. Prevention

- Screening may reduce the mortality from one disease.
- Prevention may be able to reduce the mortality from multiple diseases.

Effect of Aspirin on 20-Year Risk of Death Due to Common Cancers in 4 Long-Term Trials



Rothwell, *Lancet*,
1 Jan 2011

Outline

- What's the best colorectal cancer screening test?
- Aspirin chemoprevention
- **Are endoscopy and aspirin complementary?**

Colonoscopy and Right- versus Left-sided Colorectal Cancer Death

	Odds Ratio (95% CI)		
	All Cancer	Right-Sided Cancer	Left-Sided Cancer
Attempted Colonoscopy			
None	1.00	1.00	1.00
Any	0.69 (0.63-0.74)	1.07 (0.94-1.21)	0.39 (0.34-0.45)
Completeness of Colonoscopy			
None	1.00	1.00	1.00
Complete	0.63 (0.57-0.69)	0.99 (0.86-1.14)	0.33 (0.28-0.39)
Incomplete	0.91 (0.78-1.07)	1.35 (1.07-1.69)	0.63 (0.49-0.81)

Baxter, *Ann Intern Med*, 6 Jan 2009

Differential Efficacy of Colonoscopy

Potential reasons for difference in proximal vs. distal colorectal cancer mortality reduction

- **Technical: Inadequate bowel prep**
- **Expertise/ Experience**
- **Biological**
  - **Faster growing lesions on the right**
  - **Flat and depressed adenomas on the right**

Effect of Aspirin (75-1200 mg) on Right- versus Left-sided Colorectal Cancer Incidence

	All Patients		
	Events	Hazard Ratios (95% CI)	P
All Cancers	397	0.76 (0.63-0.94)	0.01
Proximal Colon	69	0.45 (0.28-0.74)	0.001
Distal Colon	100	1.10 (0.73-1.64)	0.66
Rectum	119	0.90 (0.63-1.30)	0.58

Rothwell, *Lancet,* 20 November 2010

Data from 4 trials
of aspirin vs. control

Effect of Aspirin (75-1200 mg) on Right- versus Left-sided Colorectal Cancer Death

	All Patients		
	Events	Hazard Ratios (95% CI)	P
Fatal Cancers	240	0.66 (0.52-0.86)	0.002
Proximal Colon	41	0.34 (0.18-0.66)	0.001
Distal Colon	44	1.21 (0.66-2.24)	0.54
Rectum	70	0.80 (0.50-1.28)	0.35

Data from 4 trials of aspirin vs. control

Rothwell, *Lancet,* 20 November 2010

Remaining Uncertainties in Colorectal Screening and Prevention

- Comparative effectiveness of the available screening tests?
- Mechanism(s) of aspirin action on carcinogenesis?
- Optimal duration & age range for aspirin use
  - Aspirin in Reducing Events in Elderly (ASPREE) is examining composite disability-free survival in ≥ 70 years
- Are screening and aspirin complementary, additive?

National Cancer Institute

Colorectal Cancer Screening Rates in the United States

Carrie Klabunde, Ph.D.

Health Services & Economics Branch

Division of Cancer Control and Population Sciences

KlabundC@mail.nih.gov

http://healthservices.cancer.gov

National Cancer Advisory Board Meeting
December 10, 2013

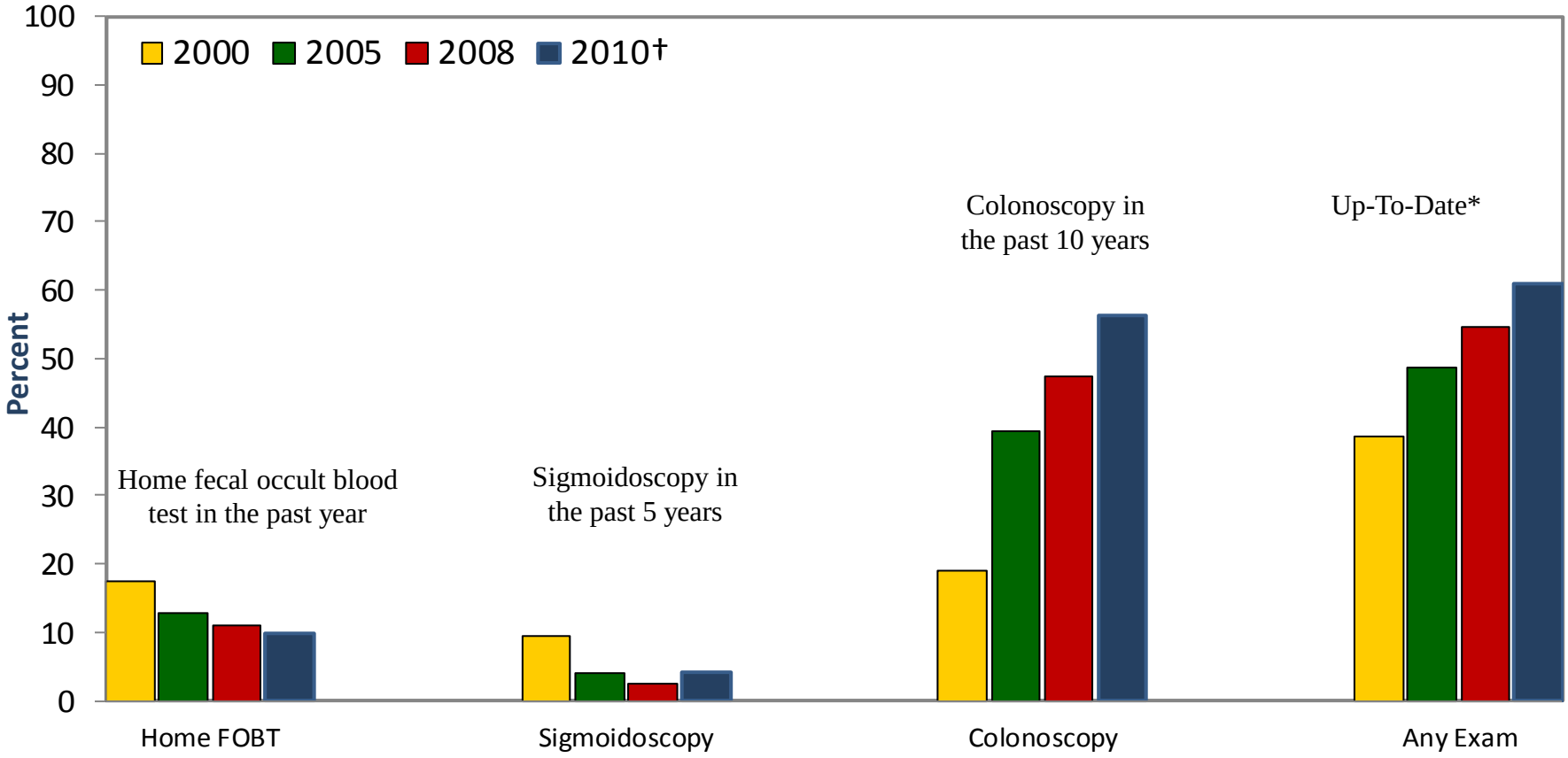
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Presentation Topics

- U.S. colorectal cancer (CRC) screening rates and patterns
- Factors contributing to rates and patterns
- Reducing barriers to CRC screening
  - Patient, provider, system, policy
- NCI collaborations to support programs and research

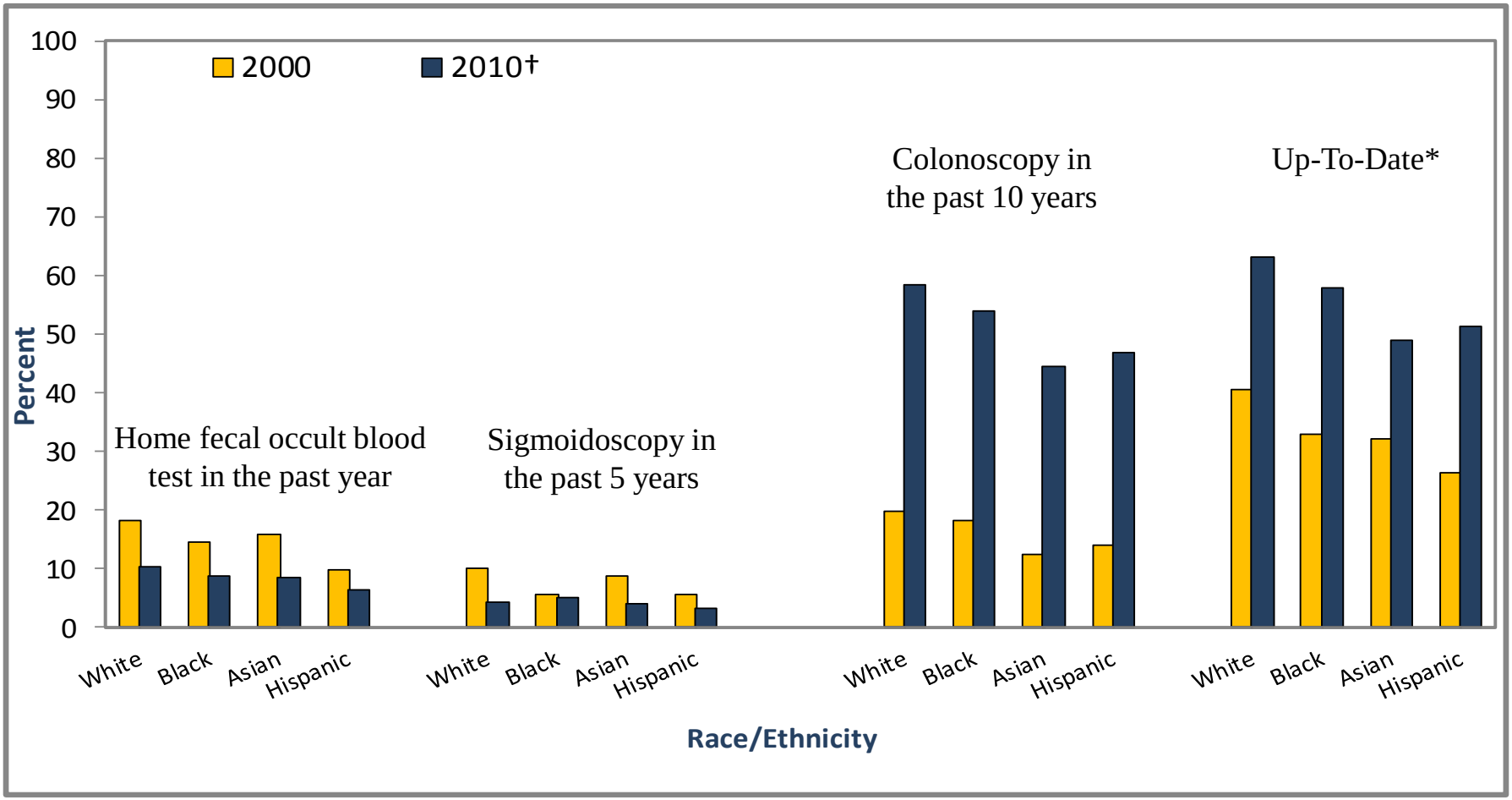
Colorectal Cancer Tests Within Recommended Time Intervals in Adults Ages 50-75, U.S. 2000-2010



*Either FOBT within the past year or sigmoidoscopy within the past 5 years or colonoscopy within the past 10 years.
†Due to a survey modification, an individual may appear in both sigmoidoscopy past 5 yr and colonoscopy past 10 yr groupings, beginning with 2010 data.
Rates are age-adjusted to the 2000 US standard population; excludes respondents that reported history of CRC.

Source: National Health Interview Survey Public Use Data File 2000, 2005, 2008 and 2010. NCHS/CDC

Colorectal Cancer Tests in Adults 50-75, U.S. 2000-2010, by Race/Ethnicity



*Either a home FOBT within the past year or a sigmoidoscopy within the past 5 years or a colonoscopy within the past 10 years.
†Due to a survey modification, an individual may appear in both sigmoidoscopy past 5 yr and colonoscopy past 10 yr groupings, beginning with 2010 data.
Rates are age-adjusted to the 2000 US standard population; excludes respondents that reported history of colon or rectal cancer.

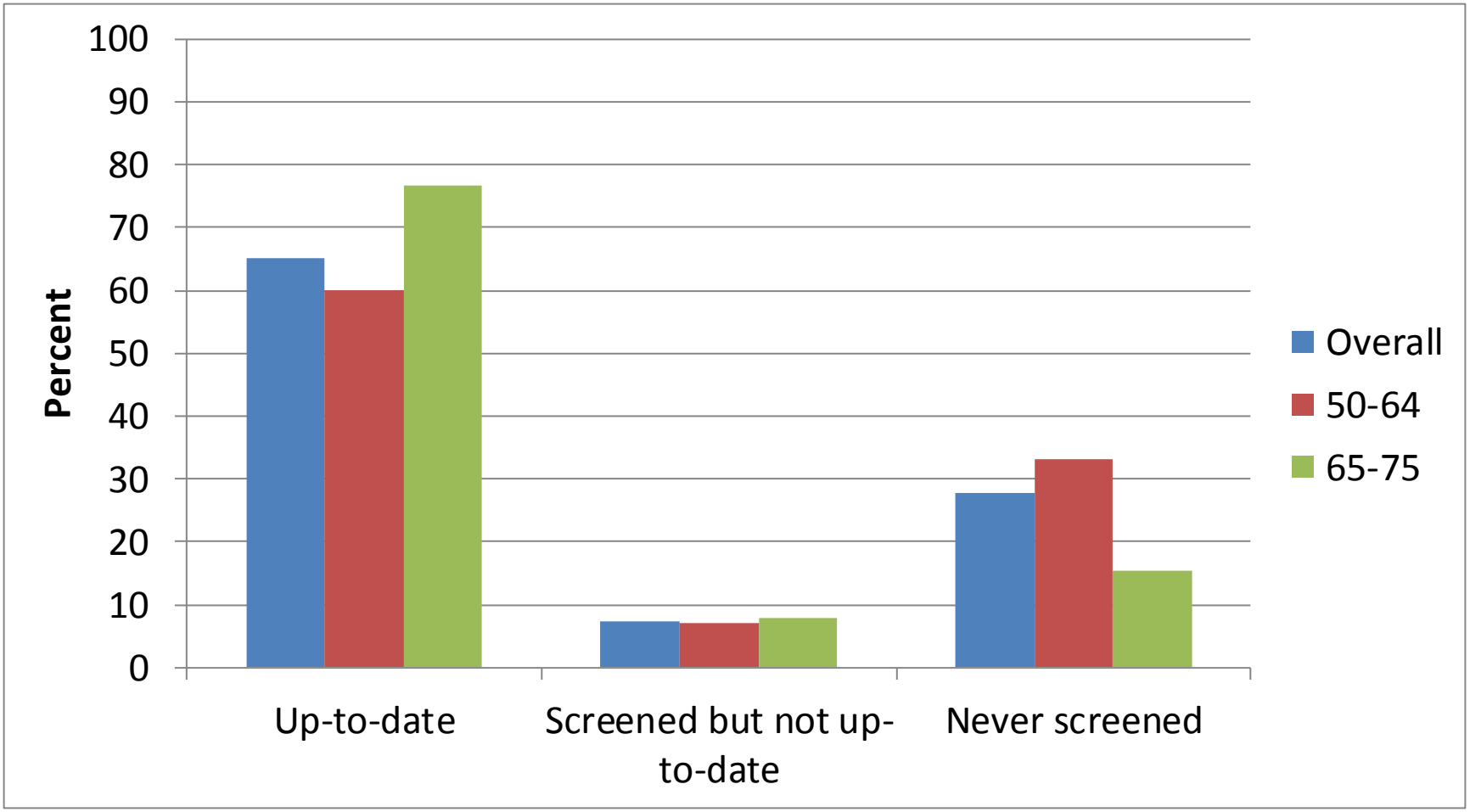
Source: National Health Interview Survey Public Use Data File 2000, 2005, 2008 and 2010. NCHS/CDC

Large Disparities in CRC Screening Uptake (≥20 Percentage Point Differences)

- Education (< High School vs. College Graduate)
- Annual Family Income (<$35,000 vs. ≥$100,000)
- Health Insurance (None vs. Any)
- Usual Source of Care (No vs. Yes)
- No MD Visits in past year vs. 2+ Visits
- Recent Immigrant vs. Born in the U.S.

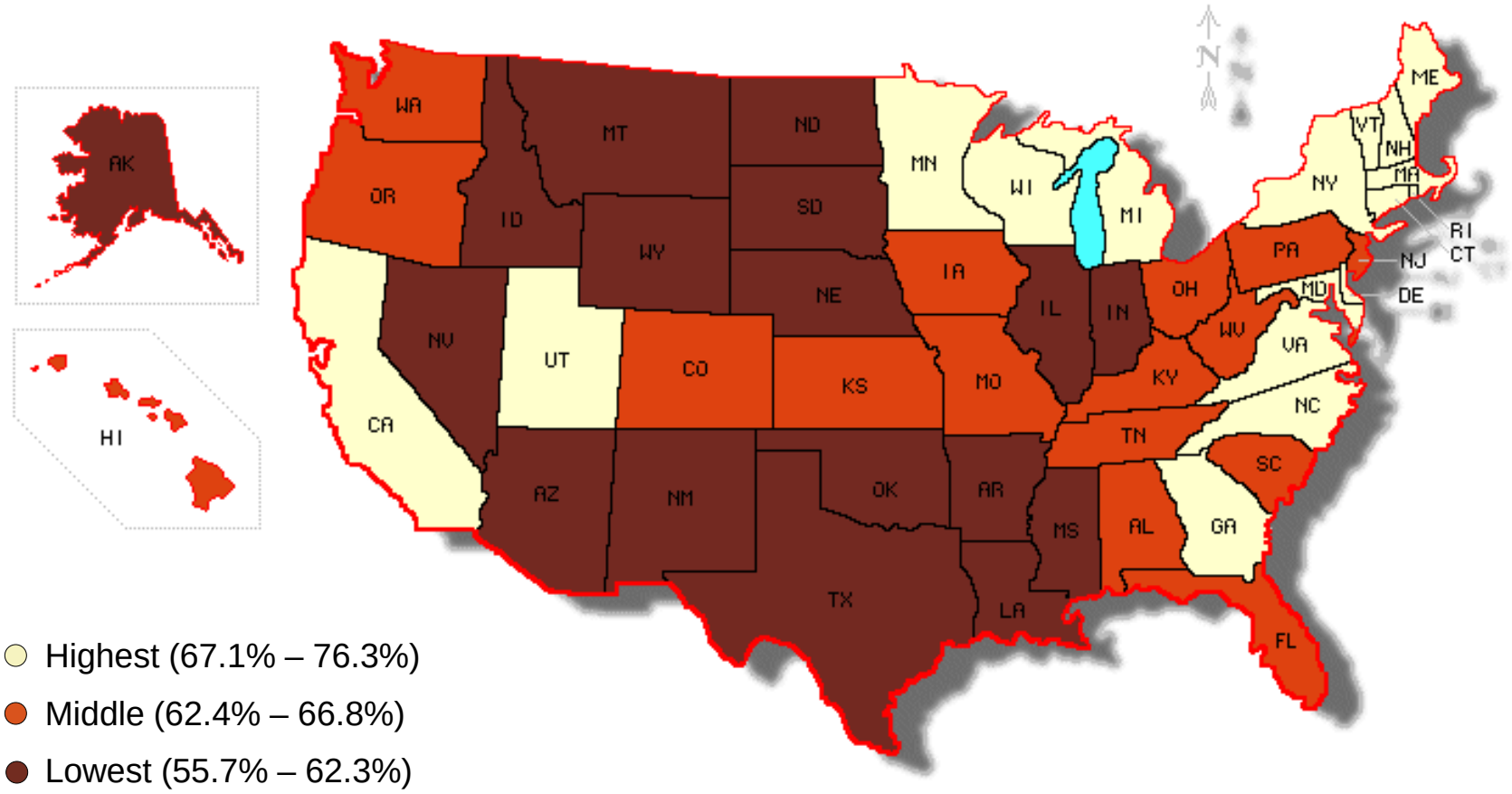
Source: 1) Shapiro JA et al., *CEBP*, 2012; 2) Klabunde CN et al., *CEBP*, 2011.

Percentage of U.S. Adults by CRC Screening Status and Age Group, 2012



Source: Behavioral Risk Factor Surveillance System; Joseph DA, Klabunde CN, et al., *MMWR*, Nov 2013.

U.S. Adults Ages 50-75 Up-to-Date with CRC Screening, by State (in Tertiles)



Source: Behavioral Risk Factor Surveillance System; Joseph DA, Klabunde CN, et al., *MMWR*, Nov 2013.

Percentage of Adults ages 50-75 Up-to-Date with CRC Screening, by Test Type and Highest, Median, and Lowest States, U.S., 2012

	Up-to-Date	Colonoscopy within 10 years	FOBT within 1 year
Overall (U.S.)	**65.1%**	**61.7%**	**10.4%**
Highest State	76.3% Massachusetts	73.7% Massachusetts	20.2% California
Median State	64.3% Tennessee	61.4% Kansas	10.1% Colorado
Lowest State	55.7% Arkansas	53.4% Arkansas	3.4% Utah

Source: Behavioral Risk Factor Surveillance System; Joseph DA, Klabunde CN, et al., *MMWR*, 2013

Patients have Distinct Preferences for CRC Screening Tests

- Among 1224 patients overdue for CRC screening:
  - 35% preferred FOBT, 41% COL, 13% SIG, 6% BE
  - Preferences varied by racial/ethnic group
  - Of those screened (35%), only 50% received their preferred test
- Test attributes important to patients:
  - What the test involves
  - Accuracy; Frequency; Discomfort; Preparation
- Primary care physicians (PCPs):
  - Infrequently discuss patient preferences or choice of test type
  - Focus on colonoscopy

Sources: 1) Hawley ST et al., *Cancer*, 2012; 2) Hawley ST et al., *Med Care*, 2008; Lafata JE et al., *Patient Educ Couns*, 2013; McQueen A et al., *JGIM*, 2009

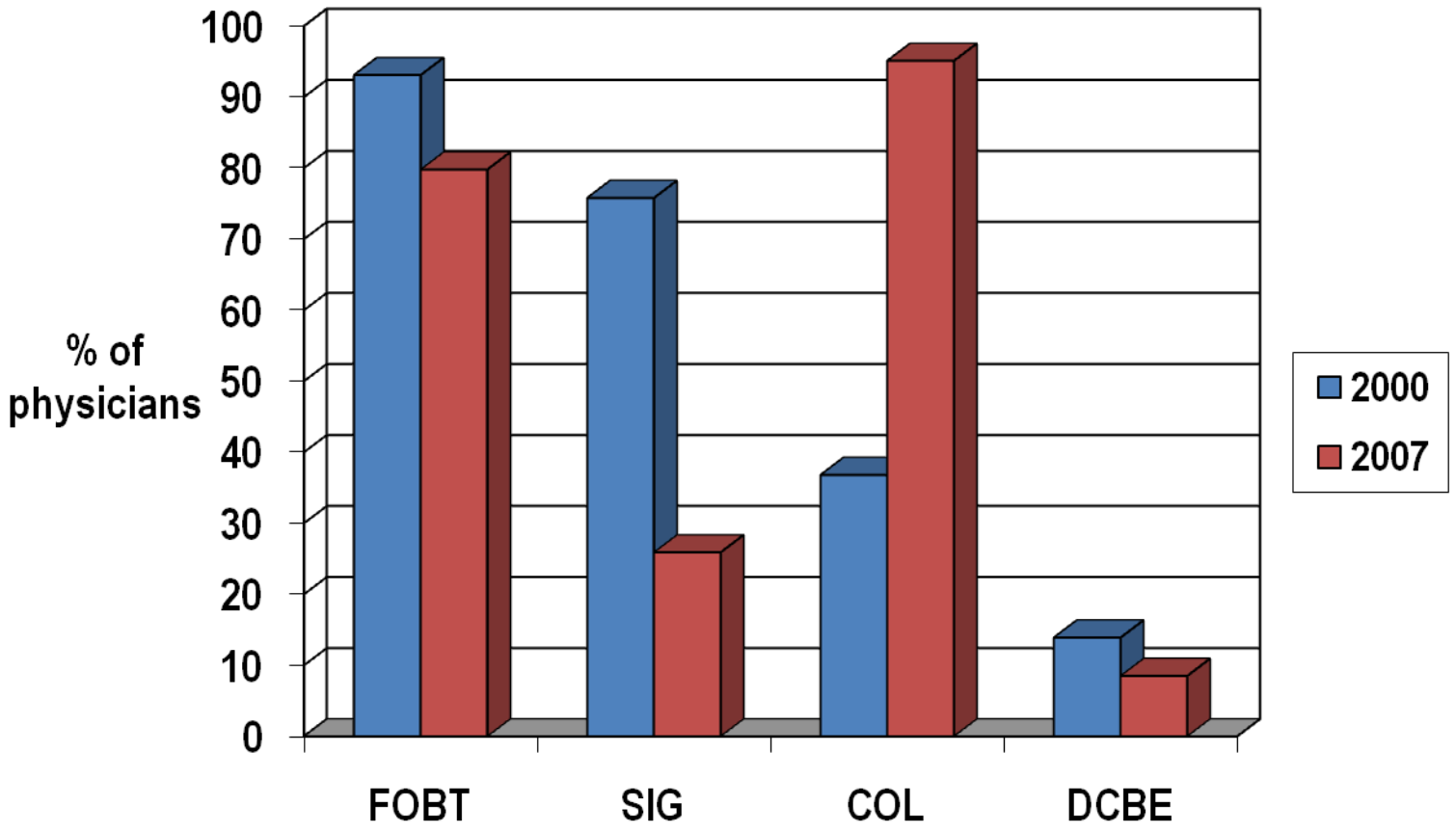
Framework for Improving CRC Screening Delivery

Health care delivery in the U.S. is largely decentralized ("medical" vs. "public health" model):

- Focus on activities within individual primary care practices
- Effective practice-based approach to achieving high CRC screening rates requires*:
  - Physician recommendation
  - Office system(s) for:
    - Identifying/activating eligible patients
    - Presenting options/determining preferences
    - Tracking screening process/results

*Source: Sarfaty M, Wender R. *CA Cancer J Clin* (2007).

U.S. Primary Care Physicians' Recommendations for CRC Screening in Asymptomatic, Average-Risk Patients; 2000 & 2007



Source: Klabunde CN et al., *Am J Prev Med* (2009)

SIG=Sigmoidoscopy; COL=Colonoscopy
DCBE=Double-contrast barium enema

Provider Recommendation is a Key Facilitator of / Barrier to CRC Screening

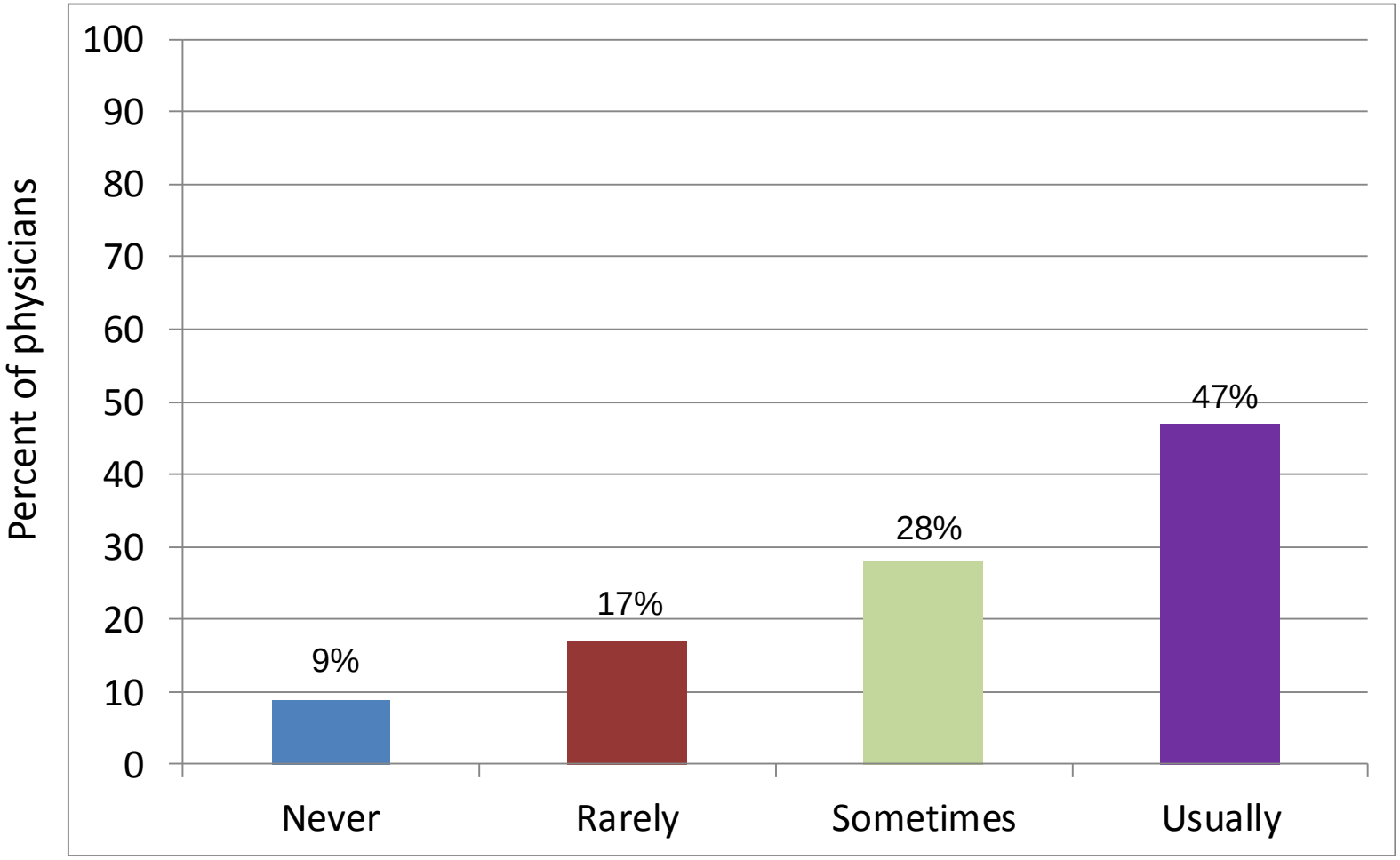
- In the NHIS (2000, 2005, 2010), “doctor didn’t recommend or order it” is the #2 reason given by age-eligible adults who are not up-to-date with CRC screening (Seeff LC et al., 2004; Shapiro JA et al., 2008; Shapiro JA et al., 2012).
- <10% of age-eligible adults who were not up-to-date reported receiving a recent provider recommendation (2010 NHIS; Klabunde CN et al., submitted)
- Among Medicare beneficiaries who are not up-to-date , the majority had at least one physician visit in the past year; mean number of visits: 4.7 (Schenck AP et al., *Prev Chron Dis*, 2011)

Types of Tests Recommended to Respondents Ages 50-84 Not Up-to-Date with CRC Screening Who Received a Provider Recommendation

	%	95% CI
Health care provider recommended particular tests ("Yes")	73.2	67.4-78.3
Test or test combination recommended:		
Colonoscopy only	88.8	83.8-92.4
FOBT only	5.7	3.3-9.6
Sigmoidoscopy only	0.5	0.1-3.8
FOBT and Colonoscopy	1.8	0.6-5.1
Other combinations	2.4	1.0-5.7

Source: 2010 NHIS; Klabunde et al., submitted.

How Often PCPs Present > 1 Test Option when Discussing CRC Screening with Patients (N=1266)



Source: Zapka JG et al., *Cancer Epidemiol Biomarkers Prev* (2011)

Office Systems to Support CRC Screening Reported by PCPs, 2007

Office System		% Physicians
Practice has implemented CRC screening guidelines:		
	Yes	61
	No	38
Medical record system used:	Full or partial EMR	28
	Moving from paper to EMR	16
	Paper charts	56
Practice uses reminder systems for CRC screening:		
	Physician reminders	31
	Patient reminders	18
Practice provides CRC screening rate reports to physician:		12

Source: Klabunde CN et al., *Am J Prev Med* (2009)

Reducing Barriers to CRC Screening

Policy level: Affordable Care Act (ACA)

- Designed to substantially reduce the number of uninsured in the U.S.
- Requires insurers to cover CRC screening
- Prohibits copays & deductibles for CRC screening
- Has provisions for:
  - Improving access to and strengthening primary care
  - New care delivery models—medical homes; accountable care organizations

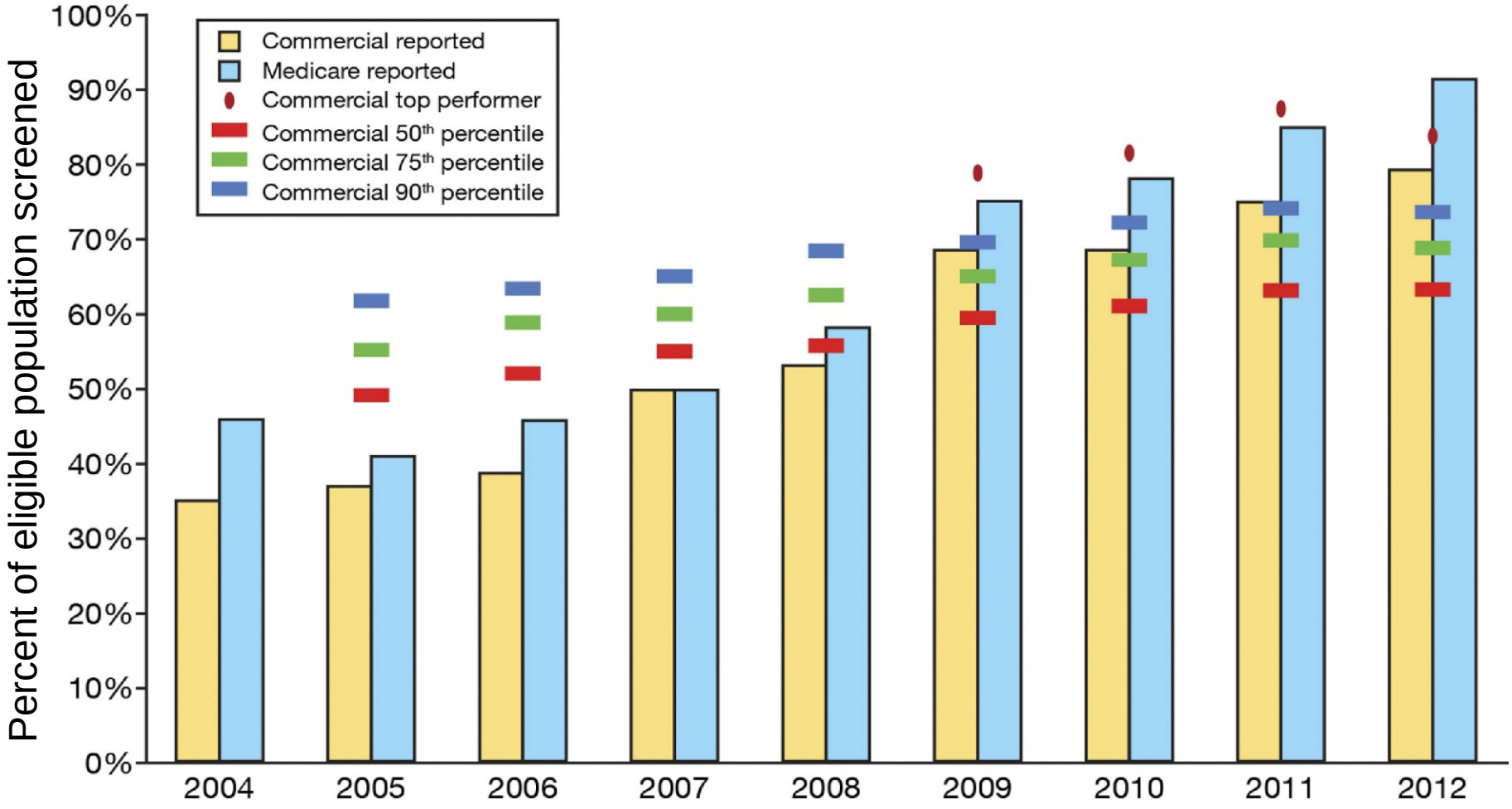
Reducing Barriers to CRC Screening

System level:

- CDC's Colorectal Cancer Control Program in 26 states and territories (www.cdc.gov/cancer/crccp/)
- New funding and reporting requirements to engage HRSA-sponsored community health centers in improving CRC screening uptake
- Direct mailing of FIT kits; centralized, organized, "public health" approach to CRC screening (Kaiser Permanente)

Sources: 1) Seeff LC et al., *Cancer*, 2013; 2) Sarfaty M et al., *CA Cancer J Clin*, 2013; 3) Levin TR, *Am J Gastroenterol*, 2012.

Colorectal Cancer Screening: HEDIS Performance, KPNC



Source: Kaiser Permanente Northern California: T.R. Levin
HEDIS = Healthcare Effectiveness Data and Information Set

Reducing Barriers to CRC Screening

Practice level: strategies that are effective in increasing CRC screening uptake

- Offering home FIT kits during influenza vaccination clinics (FLU-FIT trial).
- Mailed outreach invitations for FIT or colonoscopy sent to unscreened, low-income individuals.
- Stepped interventions vs. usual care: EHR-generated mailings, telephone assistance, & nurse navigation; uptake greatest with highest level of support.

Sources: 1) Potter MB et al. *Am J Public Health*, 2013; 2) Gupta S et al. *JAMA Intern Med*, 2013; 3) Green BB et al. *Ann Intern Med*, 2013.

NCI-sponsored PROSPR Consortium Aims to Improve Cancer Screening

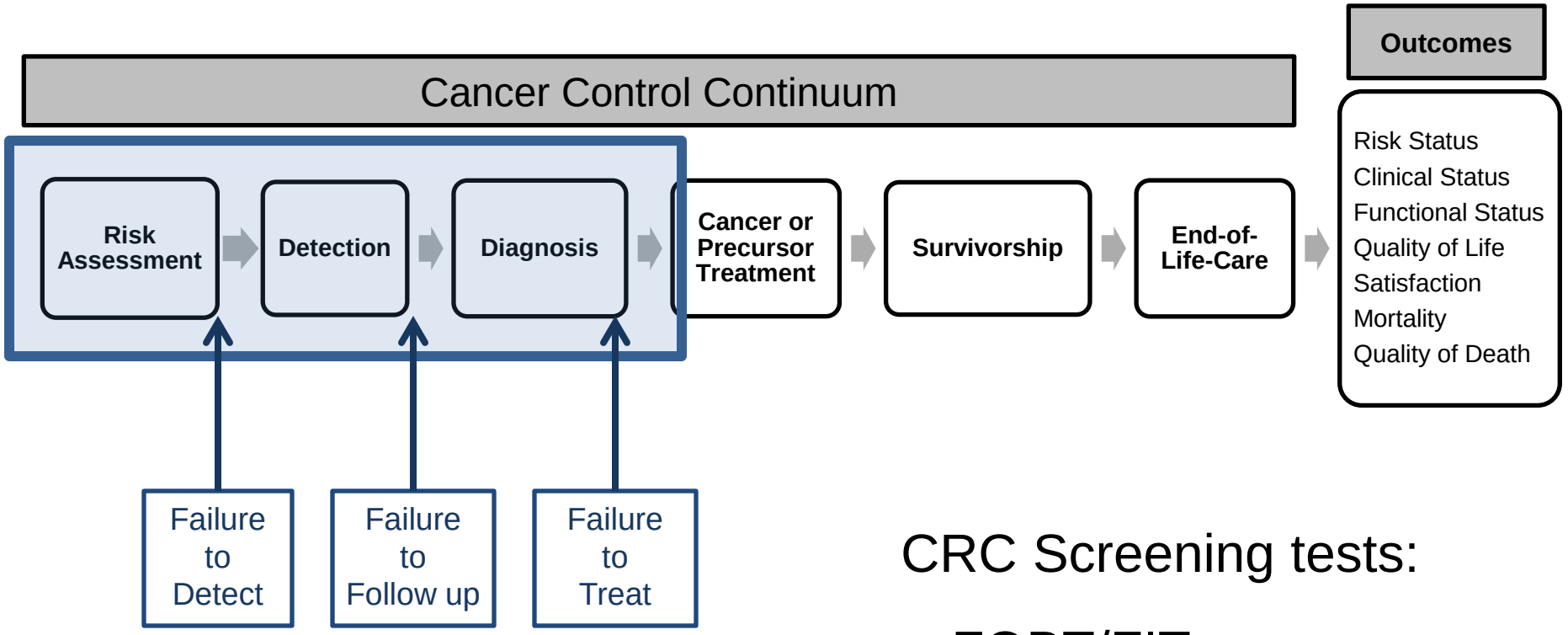
Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) is studying the screening process from recruitment through initial treatment for breast, cervical, and CRC–

- Where breakdowns occur; possible corrective strategies
- Potential for less intensive screening in low-risk groups
- Multilevel factors that optimize screening
- For CRC, comparative effectiveness of screening tests in community practice: colonoscopy, FIT, FOBT, sigmoidoscopy

www.appliedresearch.cancer.gov/networks/prospr

PROSPR
Population-based Research Optimizing Screening through Personalized Regimens

Breakdowns Can Occur at Multiple Points in the CRC Screening Process



CRC Screening tests:

- FOBT/FIT
- Colonoscopy
- Sigmoidoscopy

NCI Collaborations to Support CRC Screening Programs and Research

- National Colorectal Cancer Roundtable (est. 1996)
  - Institutional member
- Centers for Medicare and Medicaid Services (CMS)
  - Pilot project to increase CRC screening rates in the Medicare population
- Agency for Healthcare Research and Quality (AHRQ)
  - Joint FOA: Improving CRC screening in primary care practice
- Centers for Disease Control and Prevention (CDC)
  - National survey data sources
  - Evaluation of the Colorectal Cancer Control Program
- Health Resources & Services Administration (HRSA)
  - Cancer Collaborative
  - Workshop for community health center managers/leaders

Summary: CRC Screening Progress and Opportunities

U.S. CRC screening rates are increasing, but public health targets are not met:

- Colonoscopy is driving the increase
  - Cost, access, capacity issues
- Disparities: Asians and Hispanics; patients with no insurance, no usual source of care, no physician visits; geographic region
- Need to offer HS-FOBT/FIT as a reasonable, evidence-based alternative to colonoscopy
  - Patients have distinct preferences for CRC screening tests
  - Will require changing provider and public perceptions
- Need for improved implementation of EHRs and office systems to support CRC screening in primary care

Poverty, Culture and Social Injustice

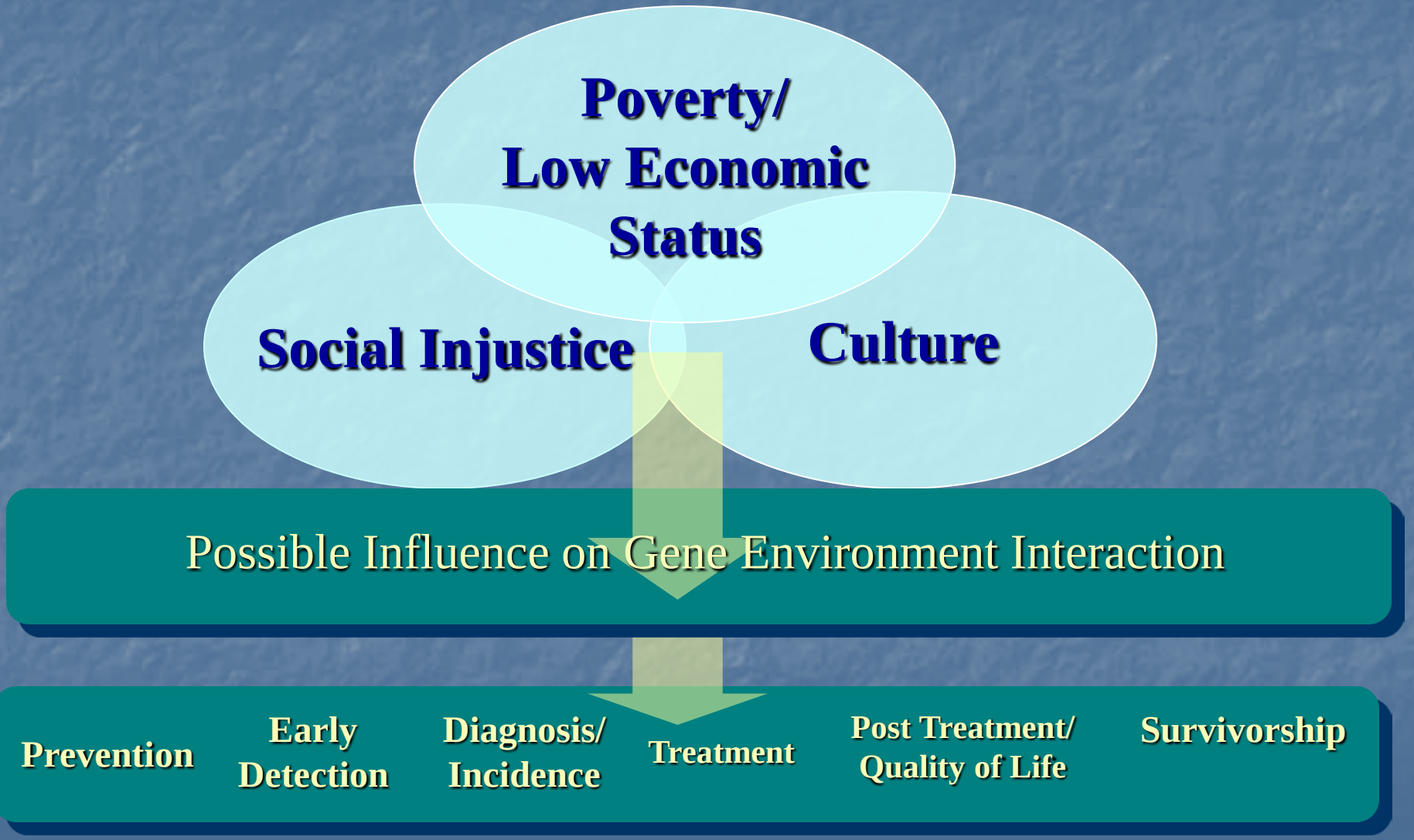
Determinants of Cancer Disparities:

National Cancer Advisory Board Meeting
December 10, 2013

Harold P Freeman, M.D., F.A.C.S.
Professor of Surgery Emeritus, Columbia University

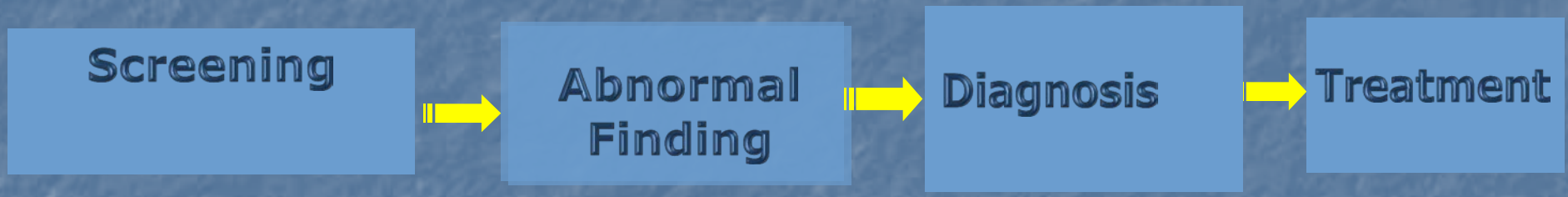
President and CEO, Harold P. Freeman Patient Navigation Institute

Causes of Health Disparities



Freeman, H.P., *Cancer Epidemiology Biomarkers & Prevention*, April 2003 (modified)

The Health Care Continuum



Key Issues:

- What populations suffer with the heaviest cancer burden?
- The Discovery/Delivery Disconnect in the War on Cancer
- What are the principal determinants of cancer disparities?

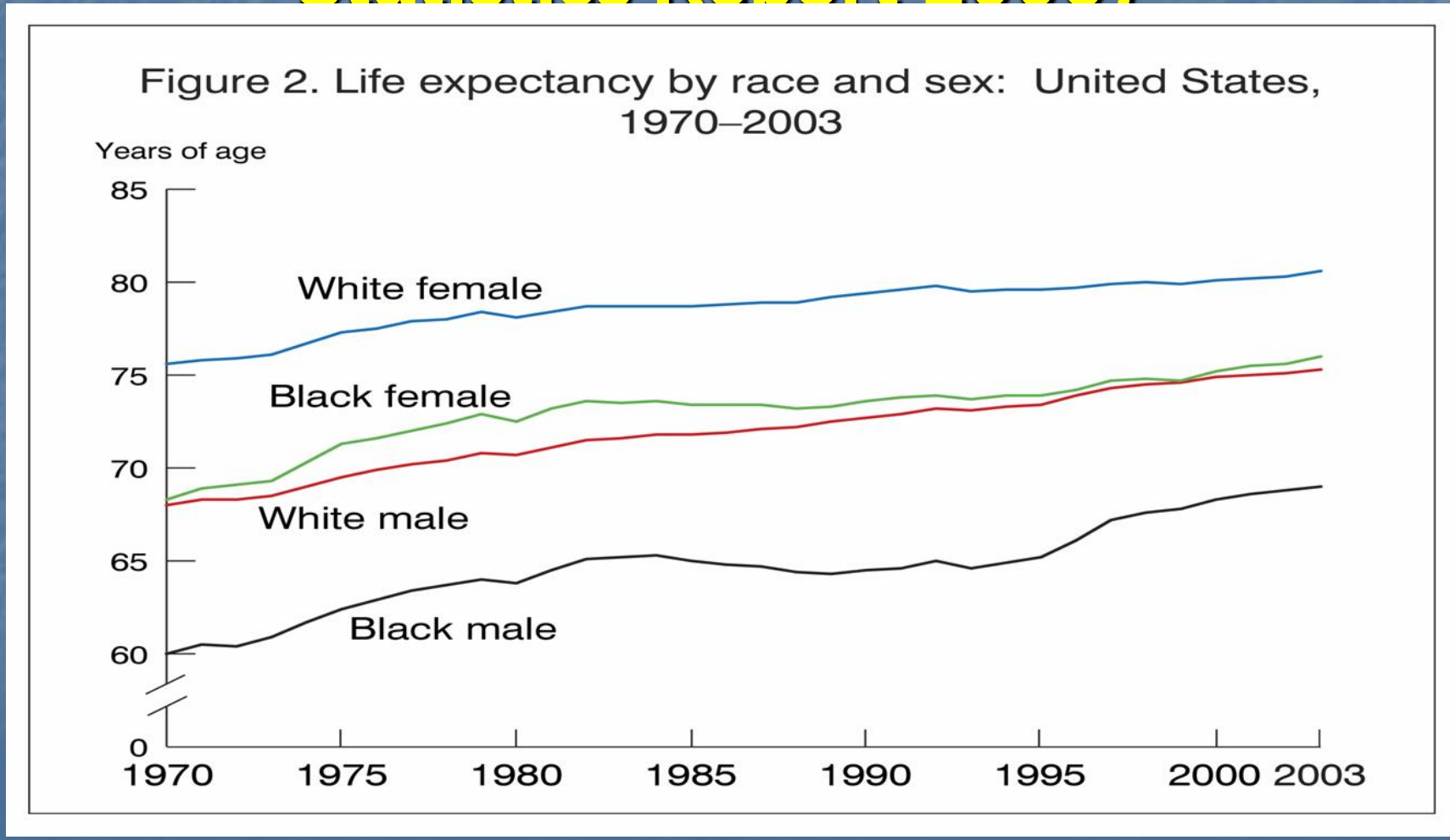
Key Issues:

- Who are the poor and the uninsured?
- What is the meaning of race? Who is black?
- What is Patient Navigation?
- How can we reduce or eliminate cancer disparities?

Disease always occurs within a context
of human circumstances
including economic status, social position, culture, and environment.

These human circumstances are determinants of
survival, and quality of life.

Life Expectancy at Birth – USA (1970-2003) (CDC/National Center for Health Statistics Report 2006)



SEER Incidence and US Death Rates[a]
All Cancer Sites, Both Sexes
Joinpoint Analyses for Whites and Blacks from 1975-2007
and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 1992-2007

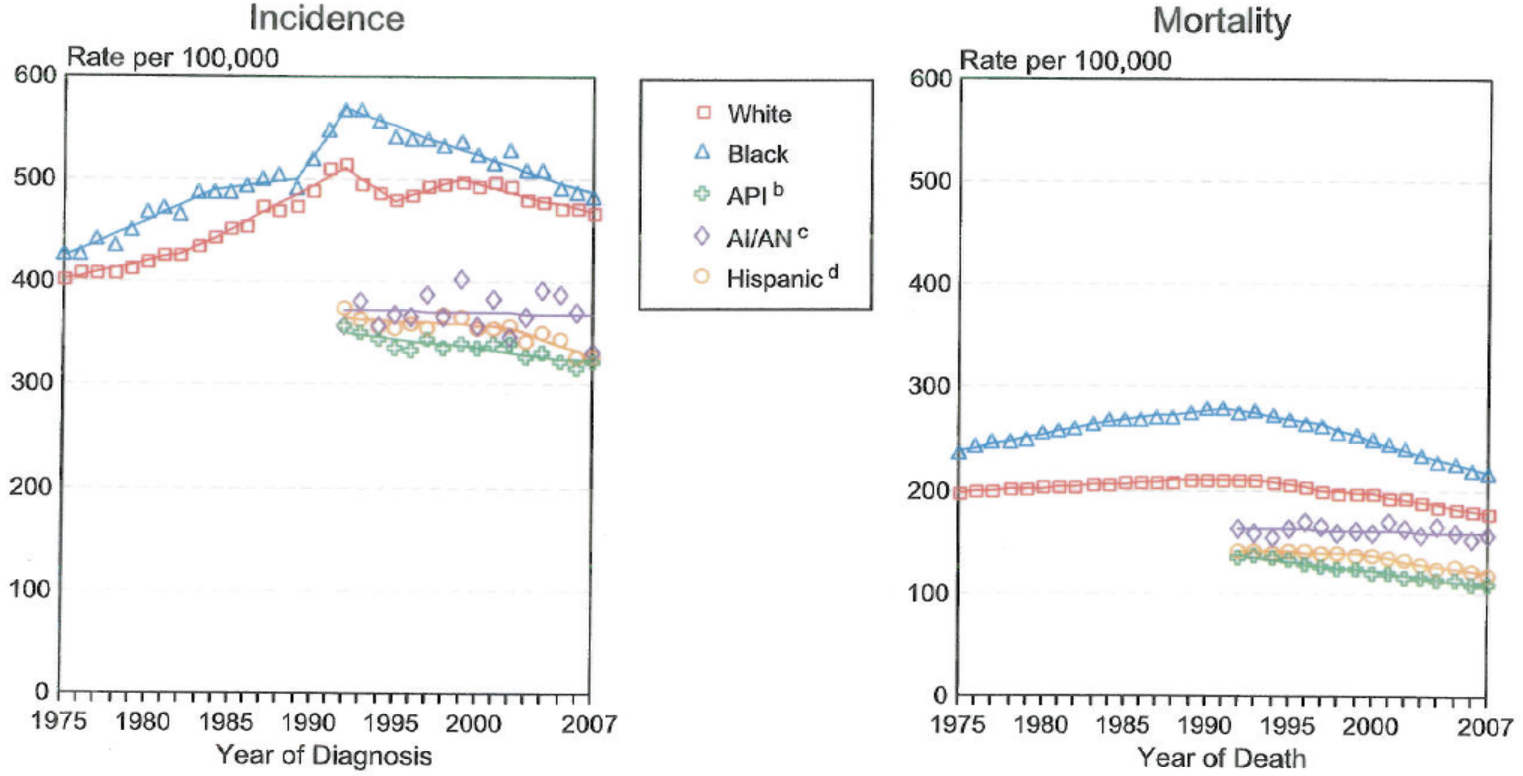


Figure 2.4

Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from US Mortality Files, National Center for Health Statistics, CDC.

[a] Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute. Joinpoint analyses for Whites and Blacks during the 1975-2007 period allow a maximum of 4 joinpoints. Analyses for other ethnic groups during the period 1992-2007 allow a maximum of 2 joinpoints.

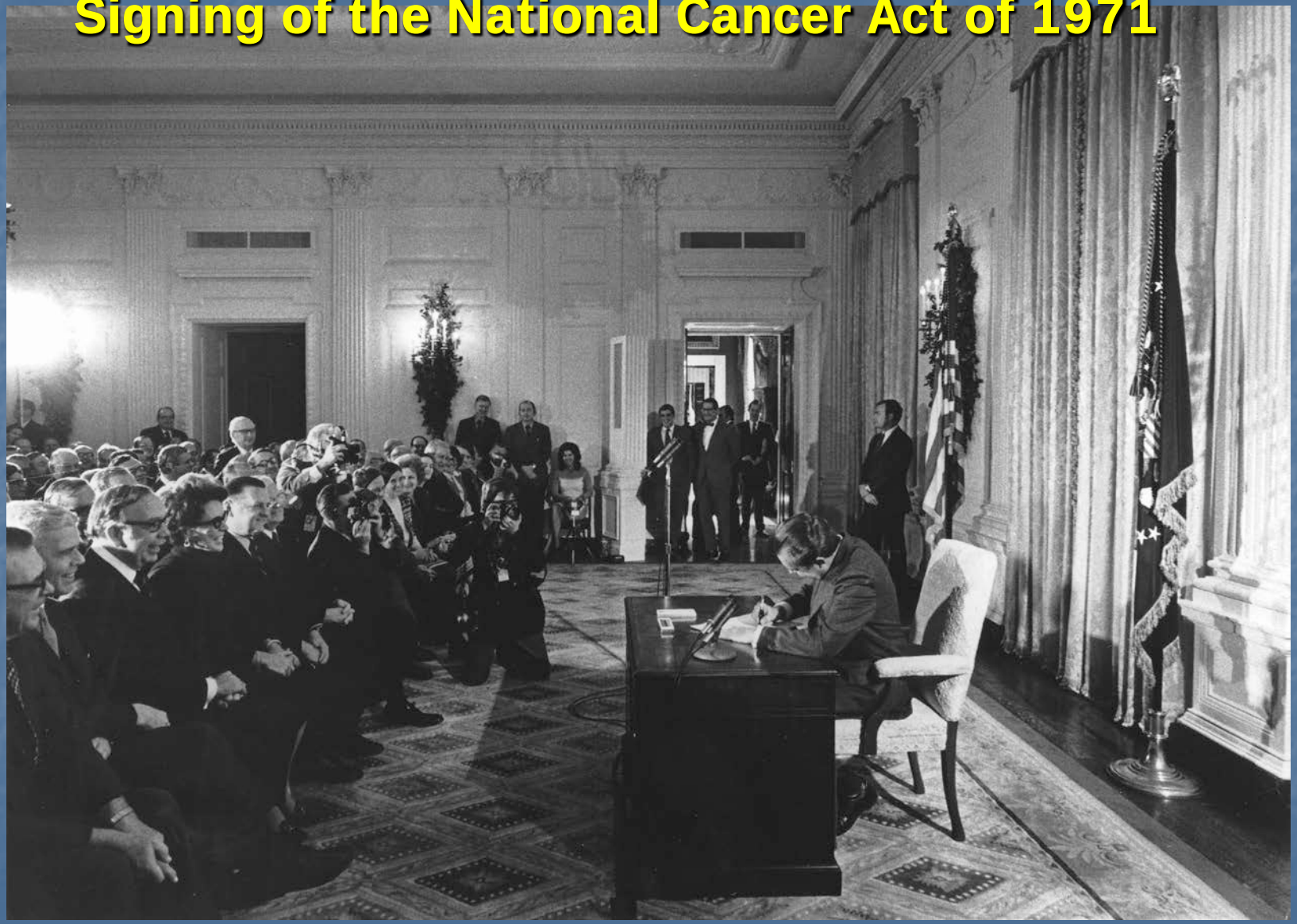
[b] API = Asian/Pacific Islander.

[c] AI/AN = American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

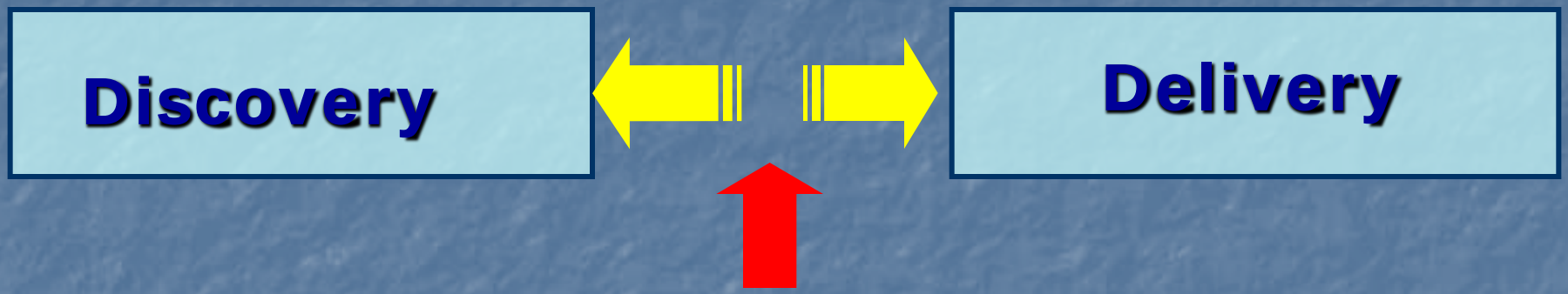
[d] Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from Connecticut, the District of Columbia, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, and Vermont.

The “War on Cancer”

Signing of the National Cancer Act of 1971



The Discovery-Delivery Disconnect



This ***discovery to delivery*** "disconnect" is a key determinant of the unequal burden of cancer.

Voices of a Broken System: Real People, Real Problems, President's Cancer Panel, Freeman, September 2001

There is a need to distinguish between the meanings of:

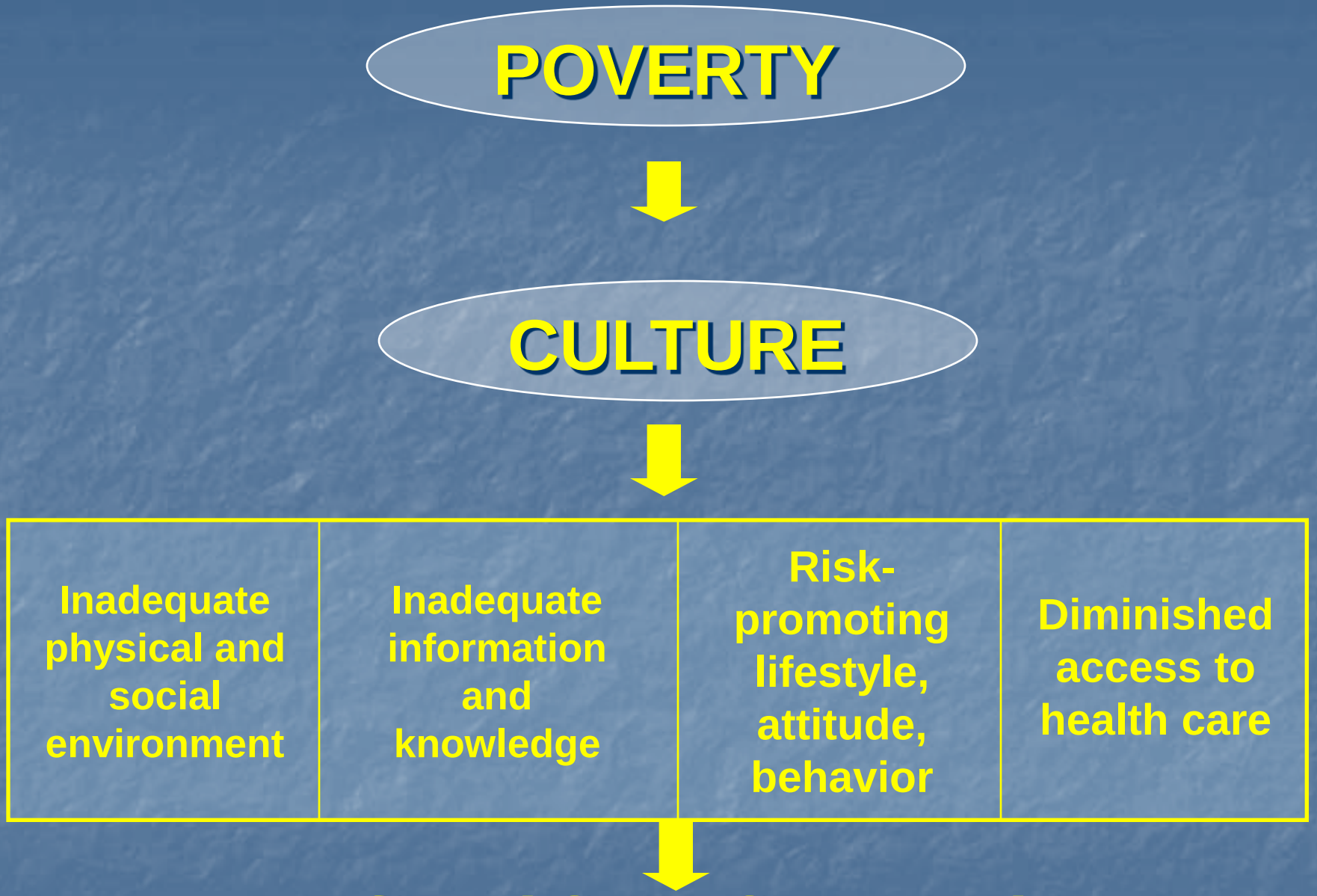
- Class (economic status)
- Culture
- Race
- Social Injustice

The Meaning of Poverty

- Substandard housing
- Inadequate information and knowledge
- Risk-promoting lifestyles, attitudes, and behaviors
- Diminished access to health care

The Meaning of Culture

- Shared communication system
- Similar physical and social environment
- Common beliefs, values, traditions, and world view
- Similar lifestyles, attitudes, and behaviors



Freeman, HP, *Cancer in the Economically Disadvantaged*, CA, July 1 Supplement, 1999. Presented at the American College of Surgeons/American Cancer Society Workshop on Quality Assurance in Cancer Care, 1988, published Cancer, 1989

Poor Americans have a
10 to 15% lower
5 year cancer survival
compared to other Americans.

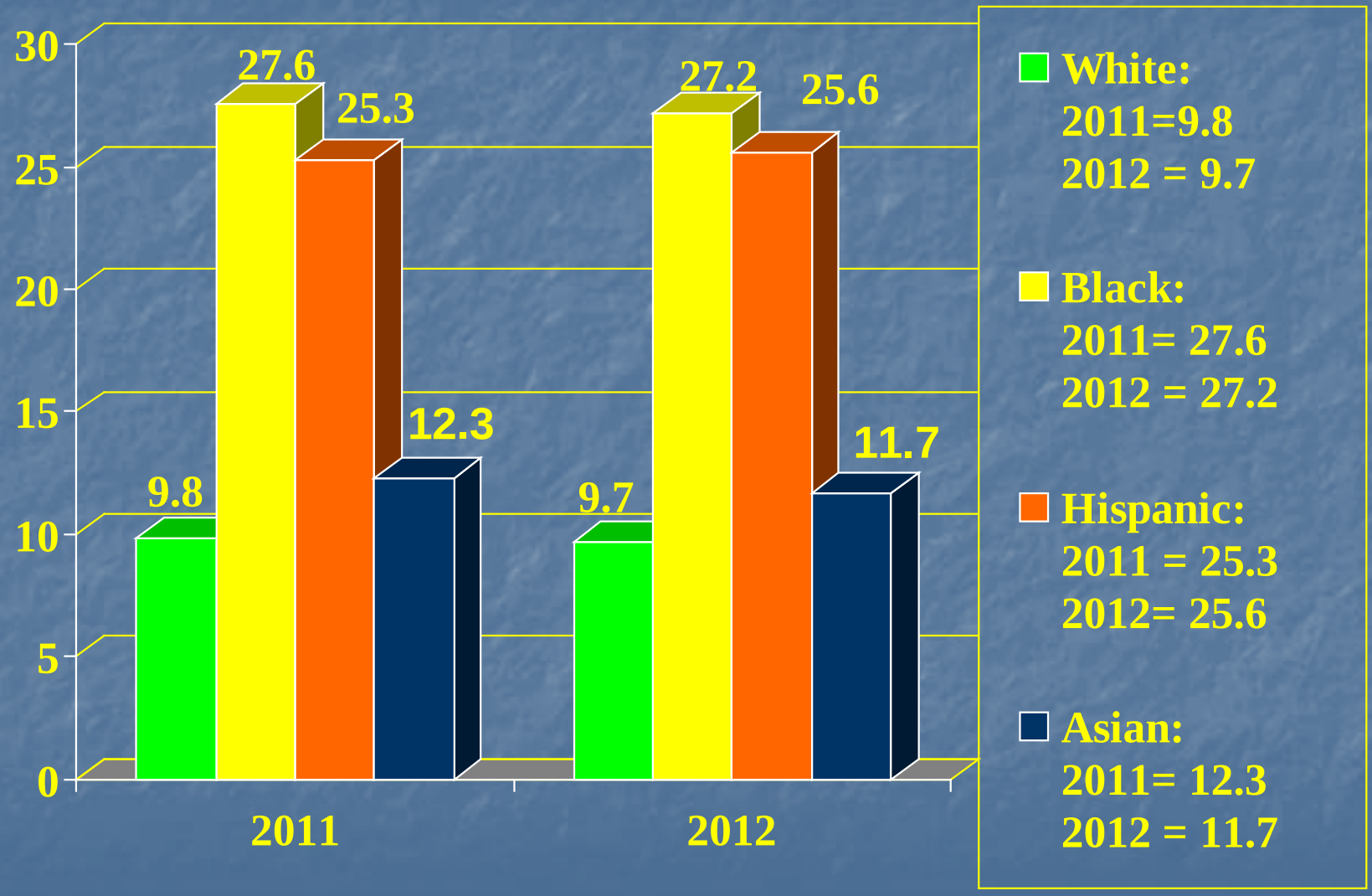
The Poor and Uninsured

- 43M (14%) American are poor.
- 50M (16%) Americans are uninsured.

2010 U.S. Census Bureau Report

Who are the poor?

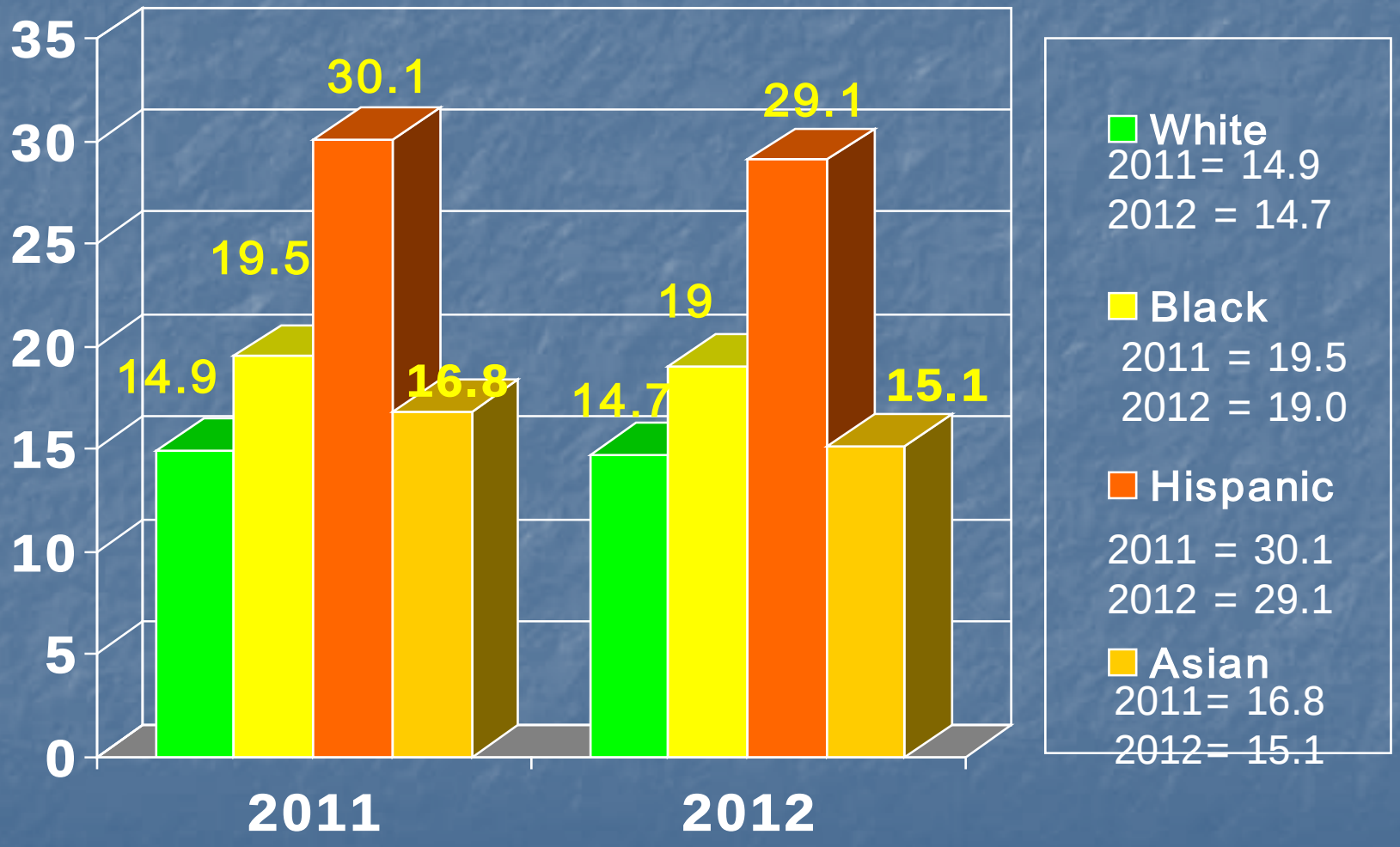
Poverty Rates by Race and Hispanic Origin: 2 Years 2011 and 2012



U.S. Census Bureau, Current Population Survey, 1960 to 2013 Annual Social and Economic Supplements

Who is uninsured?

Percent of People Without Health Insurance Coverage by Race and Hispanic Origin Percentages for 2011 and 2012



U.S. Census Bureau , Current Population Survey 2012 – 2013 Annual Social and Economic Supplements

The Meaning of Race

Who is Black?

The "One Drop Rule"

Black—The American Definition

Identifies as black anyone with even one black ancestor, no matter how remote, and regardless of physical appearance.

Gunnar Myrdal
Sociologist, 1944

Findings of IOM Report on Unequal Treatment, 2003

Bias, stereotyping, prejudice, and clinical uncertainty on the part of healthcare providers may contribute to racial and ethnic disparities in healthcare.

Bach, NEJM, 1999

Black patients were substantially less likely than white patients to have their non-small cell lung cancers surgically removed. (The rate of surgery was 12.7 percentage points lower for black patients than for white patients)...five–year survival for blacks was 26.4% vs. 34.1 percent for whites...

Report to the Nation on Cancer and the Poor

Findings

- Poor people meet significant barriers when they attempt to seek diagnosis and treatment of cancer.
- Poor people often do not even seek care if they cannot pay for it.
- Poor people experience more pain, suffering, and death because of late stage disease.

American Cancer Society 1989

Report to the Nation on Cancer and the Poor

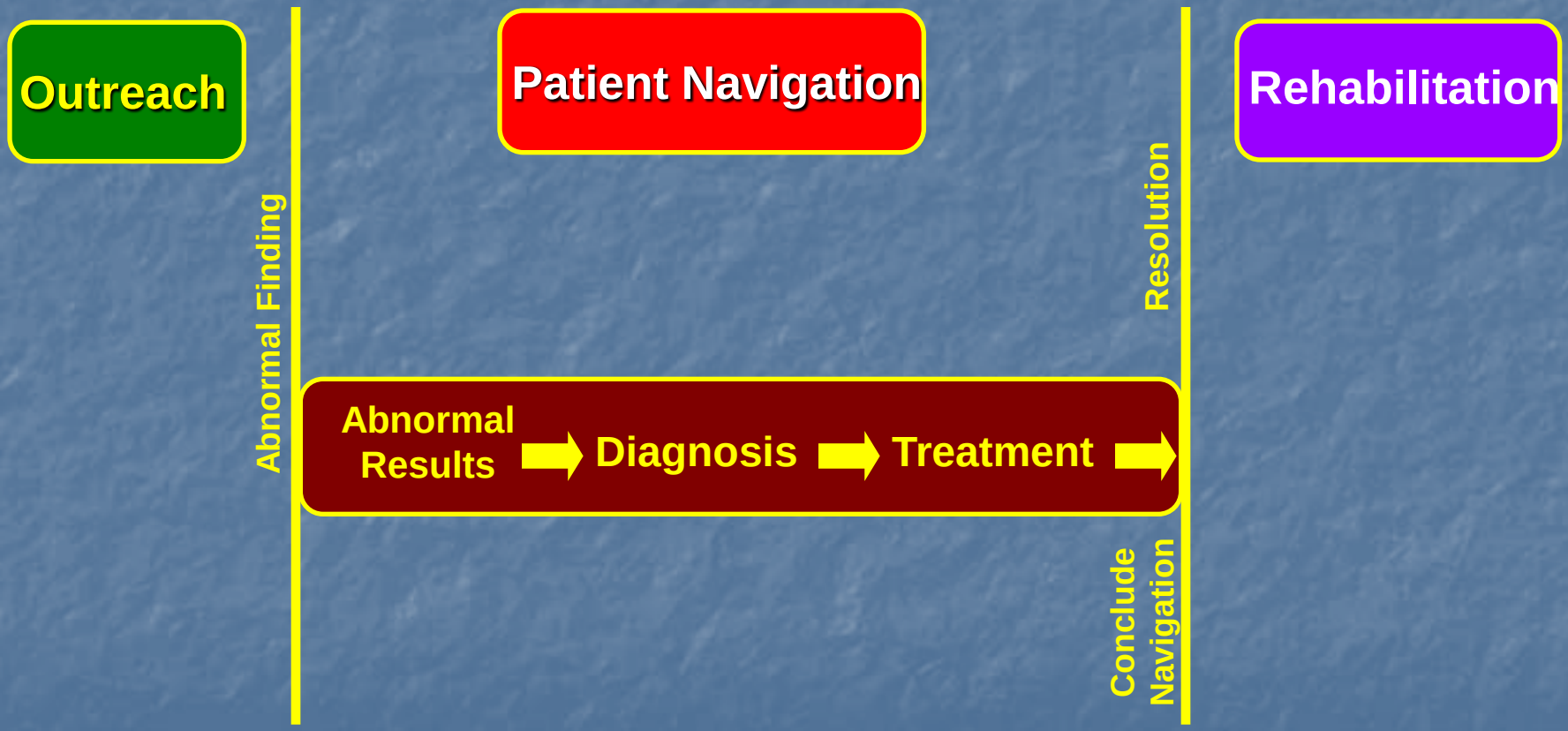
Findings

- Fatalism about cancer is prevalent among the poor and prevents them from seeking care.
- Poor people and their families must make extraordinary and personal sacrifices to obtain and pay for care.
- Current cancer education programs are culturally insensitive and irrelevant to many people.

American Cancer Society 1989

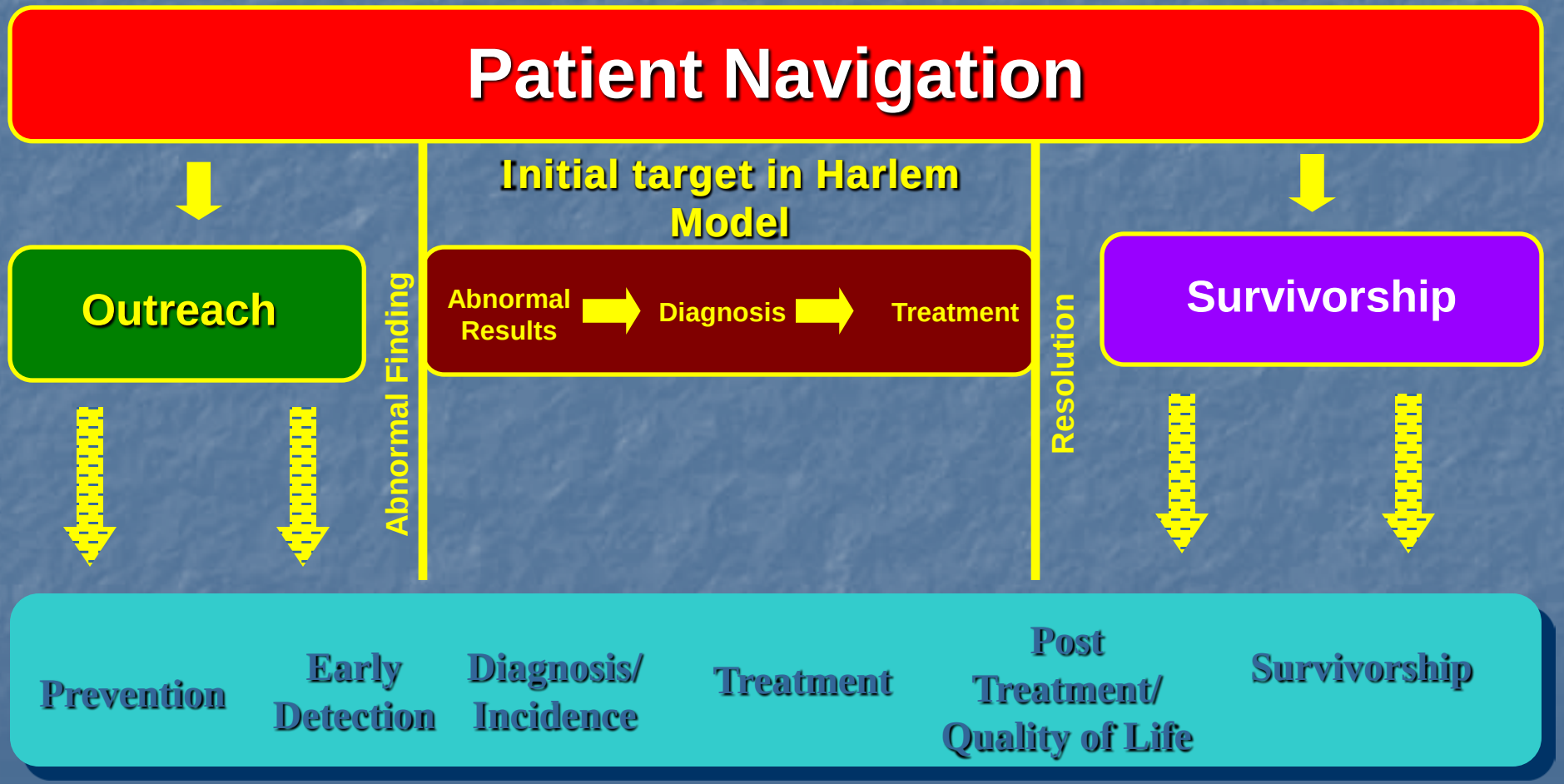
There is a critical window of opportunity to save lives from cancer between the point of an initial suspicious finding and the resolution of the finding by further diagnosis and timely treatment.

Patient Navigation Model



Freeman, et.al., *Cancer Practice*, 1995.

Patient Navigation across the Health Care Continuum



Freeman, 2006.

National Legislation authorizing Patient Navigation Program

Signed into law

June 29, 2005

"Patient Navigator Outreach and Chronic Disease Prevention Act of 2005"
P.L. 109-18

Funding for Patient Navigation

- NCI 9 Demonstration Sites
- CMS 6 Demonstration Sites
- Health Resources and Services Administration 6 Demonstration Sites
- American Cancer Society
- Susan Komen Foundation
- Avon Foundation
- Pfizer Foundation
- Amgen Foundation

American College of Surgeons Commission on Cancer

Cancer Program Standards 2012:

Standard 3.1

American College of Surgeons Commission on Cancer mandated that Patient Navigation is to be a standard of care to be met by cancer programs seeking approval beginning 2015

Affordable Care Act

The ACA requires that states utilize patient navigators to facilitate access to health insurance coverage for uninsured individuals.

How can we eliminate health disparities?

We must apply what we know *at any given time* to *all* people, irrespective of their ability to pay.

Freeman, HP, *Cancer in the Economically Disadvantaged*, CA, July 1 Supplement, 1999. Presented at the American College of Surgeons/American Cancer Society Workshop on Quality Assurance in Cancer Care, 1988, published Cancer, 1989

Provide universal access to health care.

Delineate and target geographic areas with excess cancer mortality with an intense approach to providing culturally relevant education, appropriate access to screening, diagnosis and treatment, and improved social support.

Create a high level of awareness among medical trainees and professionals regarding their role in eliminating bias in medical care delivery.

Provide personal assistance to eliminate barriers to timely care across the entire health care continuum in underserved communities.

Final Thoughts

Disparities in cancer are caused by the complex interplay of low economic class, culture, and social injustice, with poverty playing the dominant role.

There is evidence that race, in and of itself, is a determinant of the level of health care received.

There is a need to disentangle the social and political meaning of race from assumptions about it's biological meaning.

Health disparities exact an extraordinarily high human cost and a significant economic cost to this nation.

Knowing is not enough; we must apply

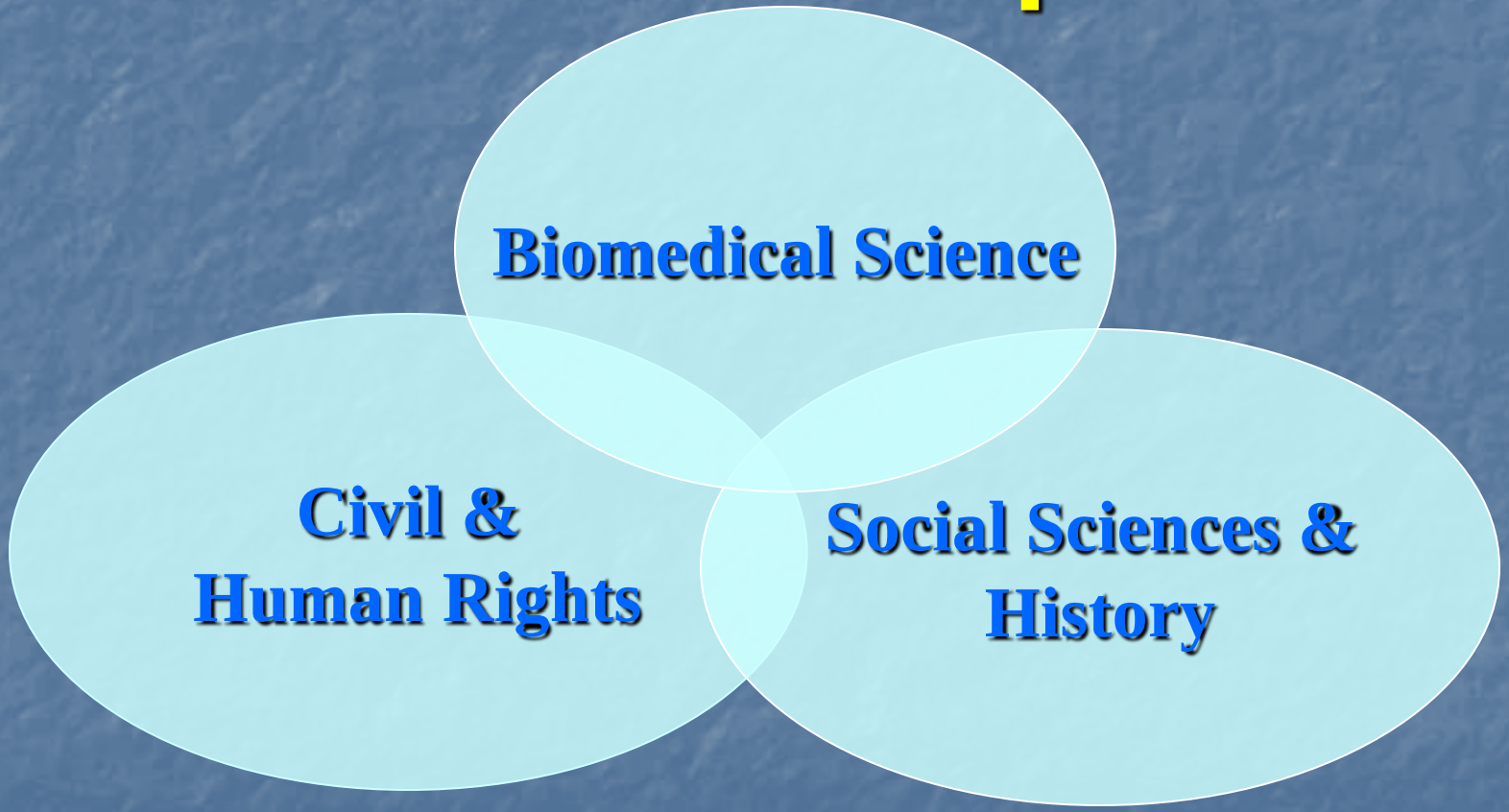
"Willing is not enough;

We must do."

Johann von Goethe

The unequal burden of disease in our society is a challenge to science and a moral dilemma for our nation.

A New Paradigm to Reduce Health Disparities

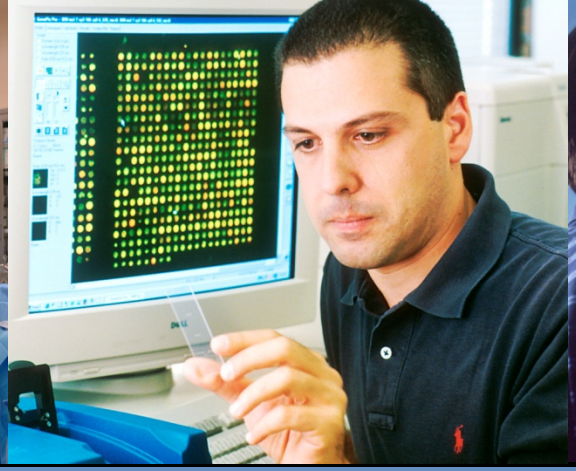
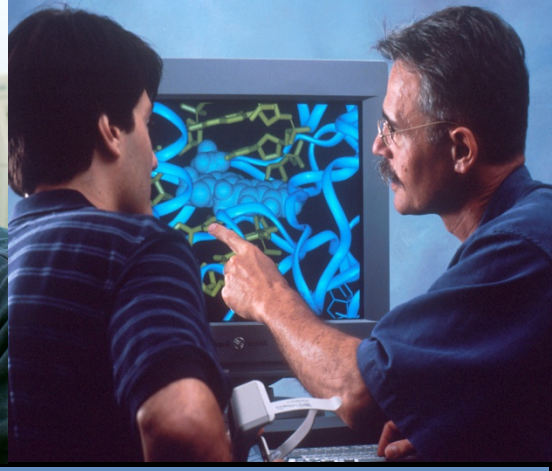


Freeman, HP, 2005

“What you see depends on where you stand.”

Albert Einstein

National Cancer Institute

Genomic Clinical Trials: NCI Initiatives

James H. Doroshow, M.D.
Deputy Director for Clinical and Translational Research
National Cancer Institute

National Cancer Advisory Board
Washington, DC
December 10, 2013

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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NCI Precision Medicine Initiatives

- Help to advance molecular profiling from research use into the clinic
- Genotype to Phenotype
  - Develop portfolio of trials across spectrum from early stage to advanced disease
  - Screen for molecular features that may predict response to a drug with a given mechanism of action
  - Analyze tumor specimens at relapse to define mechanisms of resistance
- Develop public database that links clinical outcomes with molecular tumor characteristics

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NCI-Supported Genomic Clinical Trials: Overview

- ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
- SWOG1400: Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer
- M-PACT: Molecular Profiling Based Assignment of Cancer Therapeutics
- NCI-MATCH: Molecular Analysis for Therapy Choice:
  Dr. Barbara Conley
- Dr. Elizabeth Mansfield: FDA Division of Devices

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Lung Cancer Epidemiology in US

	New Cases / Yr	Deaths / Yr
Male	116, 470	87,750
Female	109,690	72,790
Total	226,100	160,340

Incidence/Mortality: ACS Cancer Facts and Figures/ SEER 2012

	Local	Regional	Distant	Unstaged
Stage at Dx	16%	22%	56%	7%
5 year survival	52%	24%	4%	--

Stage at Dx: SEER Cancer Statistics, 1999-2007
5-yr Survival: Adjusted for normal life expectancy & based on cases diagnosed in SEER 17 areas from 2001-2007 & F/U 2008

5 year survival after lobectomy (Stage IA, IB): 45-63%

5-yr survival for stage 1A and 1B NSCLC – Ou SH, et al, Cancer 2007, California Cancer Registry (19,702 pts) 1989-2003. Similar findings to Raz, DJ et al, Chest 2007: 54%.

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ALCHEMIST: Project Goals, Design, & Operational Assumptions

Goals:

- Conduct one integrated program for screening the target patient (regional disease) population to identify the patients with tumors with EGFRmut & ALK rearrangements for assessment for enrollment on either of 2 specific adjuvant trials testing the benefit of adding erlotinib or crizotinib to adjuvant therapy (respectively) combined with a research component for screened + and screened neg patients
- Define biologic/molecular progression of non-squamous NSCLC (both +/- screened pts)
- Evaluate two promising therapies in adjuvant setting targeted for specific molecular subsets of the disease
- Provide public resource for research community w/ genomic characterization tied to detailed clinical annotation, epidemiology data, & long-term outcome data

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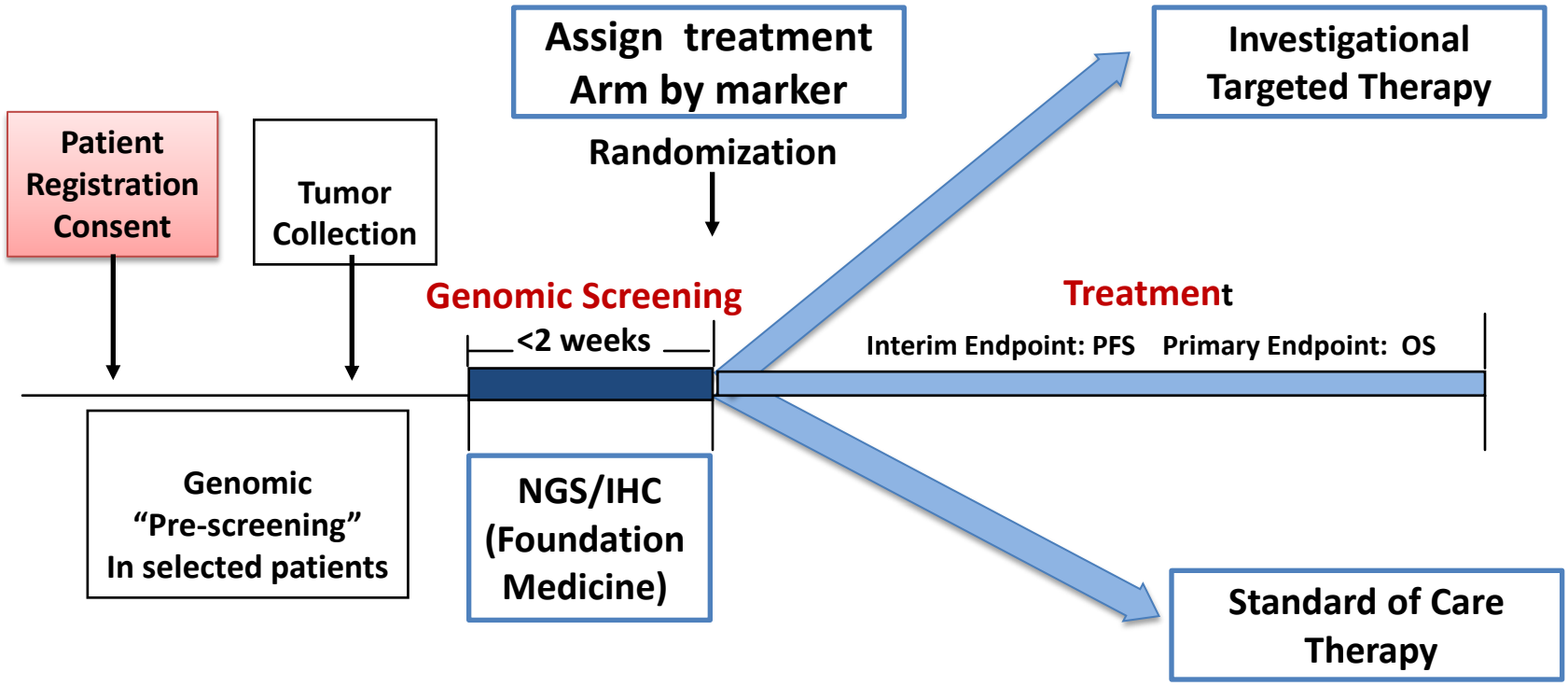
Protocol Details – Trial Design

Trial Category	ALCHEMIST SCREEN Component A151216	ALCHEMIST - ALK E4512	ALCHEMIST – EGFR A081105
Target	Registry/Intervention with biopsy at recurrence	ALK+	EGFRmut
Prevalence	all comers	~5%	~10%
Total Sample Size	6000 – 8000	378 (5% ineligible)	430 (5% ineligible)
Primary Endpoint	N/A	Overall Survival	Overall Survival
Power	N/A	80%	85%
One-sided α	N/A	0.025	0.05
Hazard Ratio	N/A	0.67	0.67

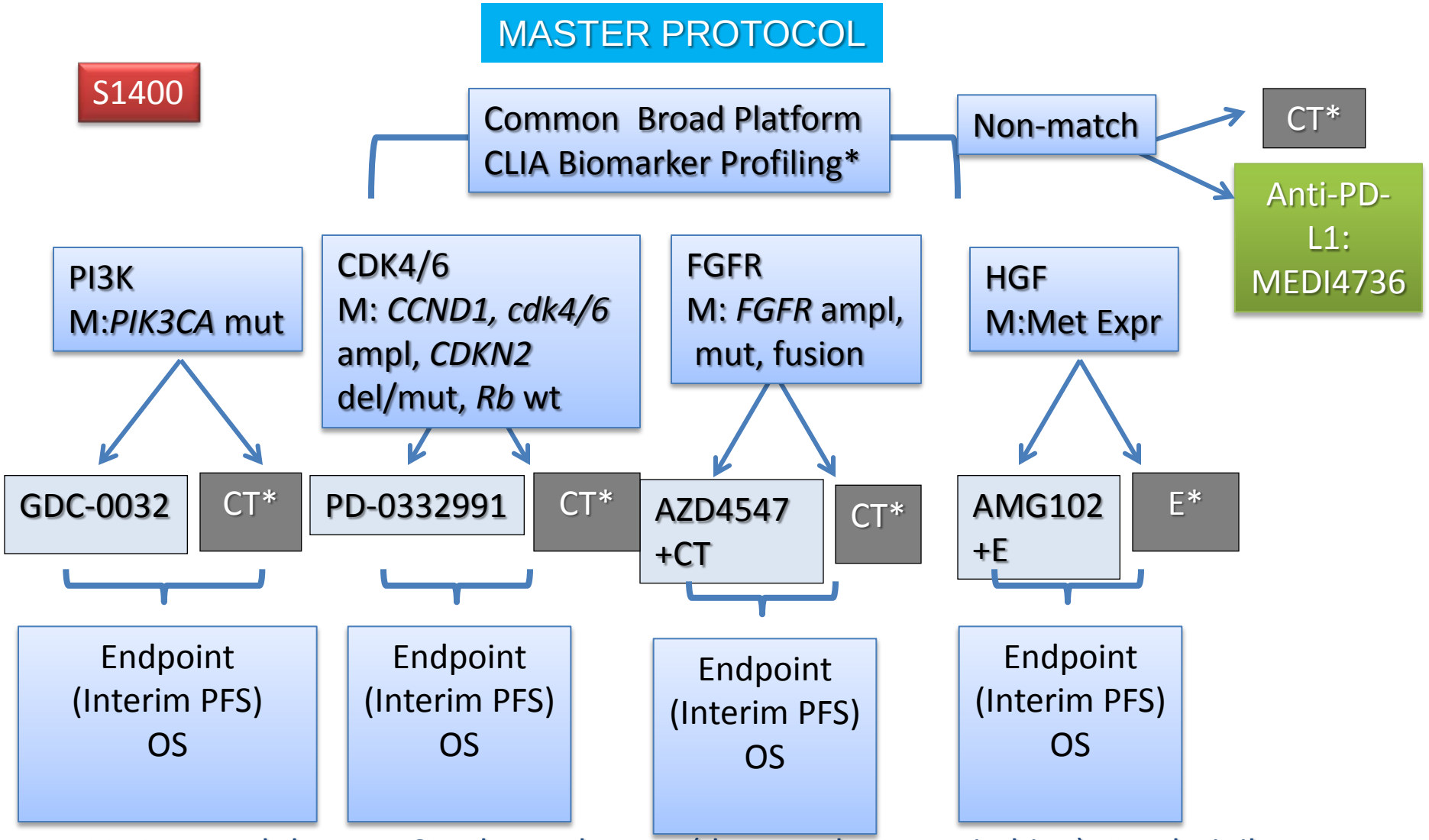
S1400: Rationale for Master Protocol Design in SCCa Lung

- Lung SCCA "orphan" group- substantial developments in therapeutics have yet to be seen versus Lung adenocarcinoma (multiple independent mutations & targets for Rx)
- Subgroup selection (genotype or phenotype-driven) refined strategy in a Multi-arm Master Protocol with improved operational efficiency: homogeneous patient populations & consistency in eligibility from arm to arm. Phase II-III design: rapid drug/biomarker testing for detection of "large effects"
- Grouping multiple studies: reduces overall screen failure rate , multi-target screening by NGS platform: sufficient "hit rate" uninterrupted accrual.
- Bring safe and effective drugs to patients faster, ineffective drugs are replaced by new improved candidates.
- Designed to allow FDA approval of new therapeutics.

MASTER PROTOCOL



- Organizers: FOCR,NCI-TMSC, FDA, FNIH
- Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
- Screening: 500-1,000 patients/year
- With 4-6 arms open simultaneously, "hit" rate ~70% in matching a patient with a drug/biomarker arm.



TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

*Archival FFPE tumor, fresh CNB if needed

Target/M: Drug target and biomarker

M-PACT: Molecular Profiling based Assignment of Cancer Therapeutics

Pilot Trial to Assess the Utility of Genetic Sequencing to Determine Therapy and Improve Patient Outcome in Early Phase Trials Independent of Tumor Histology

Objective

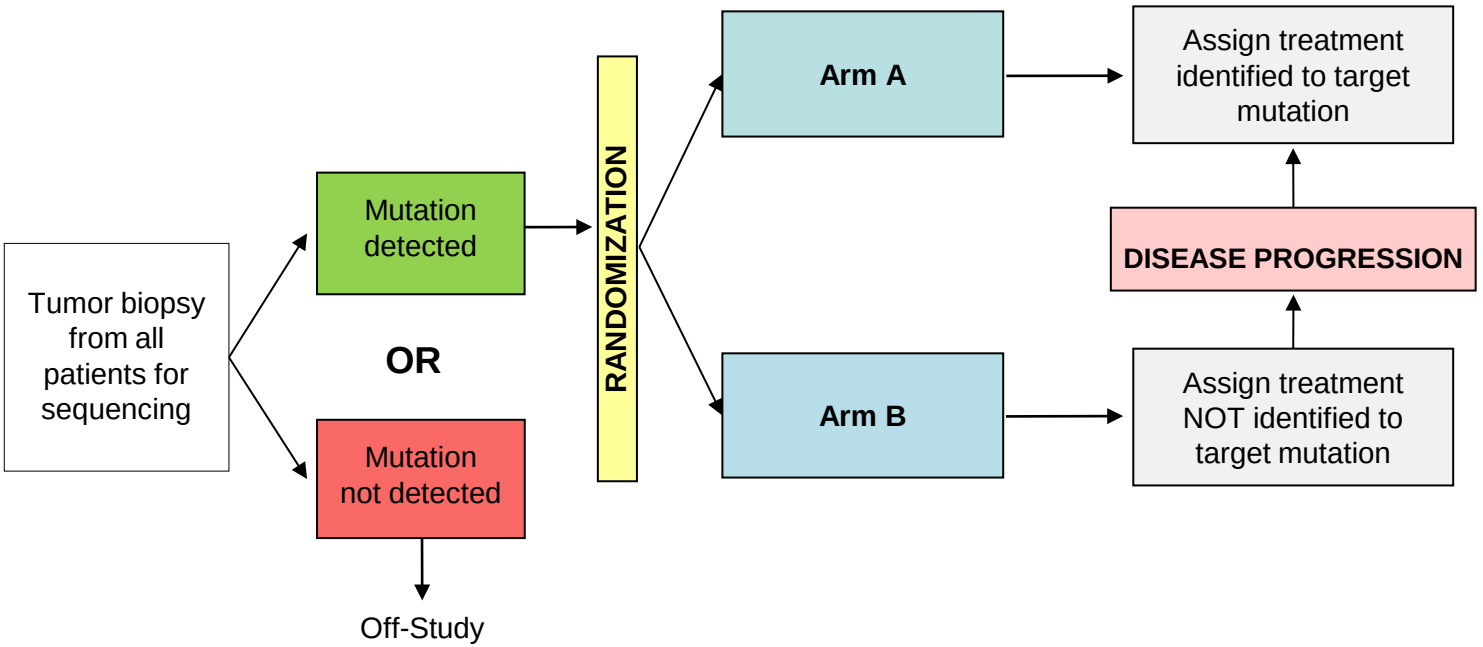
- Assess whether the response rate (CR+PR) and/or 4-month PFS is improved following treatment with agents chosen based on the presence of specific mutations in patient tumors.
  - Only patients with pre-defined mutations of interest will be eligible
  - Study treatments, regardless of cohort, will be chosen from the list of regimens defined in the protocol
  - Arm A: Receive treatment based on an study agent prospectively identified to work on that mutation/pathway
  - Arm B: Receive treatment with one of the study agents in the complementary set (identified to not work on one of the detected mutations/pathways)

Patient Population

- Patients with refractory solid tumors that have progressed on at least one line of standard therapy or for which no standard treatment is available that has been shown to improve survival.
- Adequate organ function (AST/ALT<3xULN, Bil < 1.5 xULN, S. Cr < 1.5 x ULN, platelets > 100K, ANC> 1500)
- Study regimens: As long as the same set of protocols are offered to a given set of patients, the number and actual treatments regimens can vary over time

Mutations in DNA repair pathways	Veliparib+ Temozolomide MK1775 + carboplatin
Mutations in the PI3K pathway; loss of PTEN, Akt amplification	mTOR inhibitor -Everolimus
Mutations in the RAS pathway	GSK 1120212 (MEK inhibitor)

NCI's M-PACT Clinical Trial: Study Design



- Fresh tumor biopsy on-study and at progression
- Primary endpoint response (CR + PR) and 4-month PFS improved for agents chosen on the basis of specific mutations
- Crossover from Arm B (non-mutation–directed) to Arm A (mutation-directed) treatment at progression
- Trial open across NCI's Phase I/II network (>30 NCI-designated Cancer Centers)
- Accrual expected to begin Q1-2014

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- Dr. Elizabeth Mansfield: FDA Division of Devices

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NCI-Supported Genomic Clinical Trials

Extra Slides

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ALCHEMIST TRIAL – SCREENING COMPONENT

Eligibility:

NSCLC, non-squamous

Resectable

Clinical TNM Stage for Pre-Op Option

~ OR ~

Pathologic TNM Stage for Post-Op Option

Stage 1B>4 cm, Stage IIA - IIIA

PS 0-1; Age ≥ 18

Adequate organ function

Adequate tissue for central EGFR & ALK genotyping must be available

Not known to be EGFR & ALK neg, *or* KRAS pos, on local testing

Willing to answer epidemiology questionnaire and donate de-identified data, tissue, & blood for research

If only slides are available in post-op option, only genotyping for EGFR & ALK will be done for possible assessment for adjuvant trials if positive, otherwise patient is off-study (no CCG research component)

PRE-OP (Intra-OP)

FFPE Block

Epi Questionnaire

Blood

If patient is not resectable and/or pTNM does not fit eligibility criteria, the patient is off-study

POST-OP

FFPE Block

Epi Questionnaire

Blood

OR

Slides for genotyping

Scrolls for genomics

Epi Questionnaire

Blood

Blood

Blood Sent Directly to BCR

For DNA germline analysis on patients associated with genomic research

Tissue to BCR from RGI or site

Genomic Research:

Deep sequencing; whole exon sequencing, etc.

Blocks & Slides Sent to RGI

Quality control and CLIA testing for EGFR & ALK

Scrolls and remaining tumor blocks sent to BCR

Patients whose tumors cannot be evaluated by the CLIA Central Lab for EGFR & ALK (test failures) would go off-study

If EGFR or ALK pos with CLIA Central Lab or Local Lab Testing*

If EGFR & ALK neg with CLIA Central Lab Testing

Recurrence biopsy sent to BCR

Genomic Research: comparison to baseline specimen

Assessment for Adjuvant Tx Trials

If EGFR or ALK pos but not able to go on adjuvant tx trial

Follow to recurrence or for 5-years (whichever 1st) with abbreviated collection of treatment data & annual F/U form

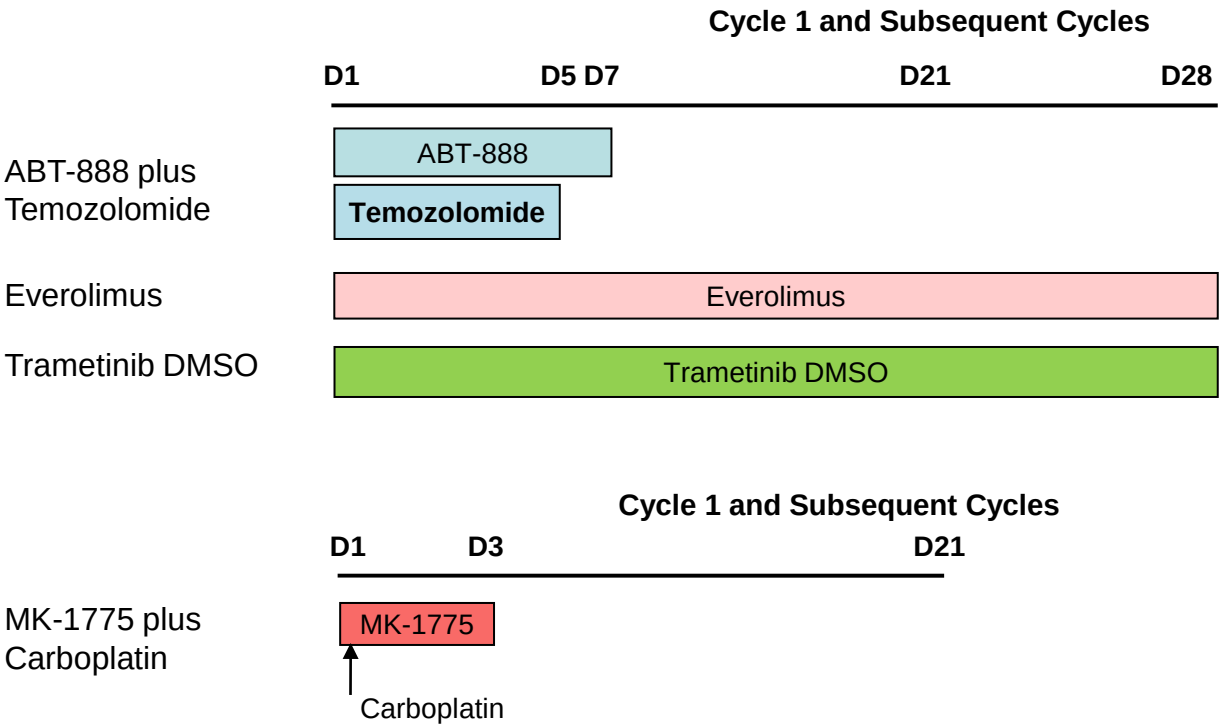
At recurrence, patients should undergo biopsy to confirm recurrence if deemed clinically appropriate by treating clinician

**Primary endpoints of the treatment trials are based on patients with EGFR or ALK pos by CLIA Central Lab; however, those pos at Local Lab but neg at Central Lab may still be randomized and followed as an exploratory subset*

Proposed initial agents

Target	Biomarker	Agent	Description/Background
PI3K	*PIK3CA* mut	GDC-0032	Small molecule PI3-kinase alpha inhibitor, increased activity in *PIK3CA mut+,* Phase I
CDK4/6	*CCND1, cdk4/6* ampl, *CDKN2* del/mut, *Rb* wt	PD-0332991	Orally active, highly selective inhibitor of CDK4 and CDK6 kinases, Ph II in NSCLC
FGFR	*FGFR* ampl, mut, fusion	AZD4547 + Docetaxel	Selective FGFR 1, 2, 3 inhibitor, phase I, Phase II NSCLC, FGFR FISH
HGF	MET Expression	AMG102 + Erlotinib	Neutralizing Ab against HGF/SF, phase III gastric Ca, MET IHC assay
PDL-1	None-"Non-match arm"	*MEDI4736*	Anti-PDL1 monoclonal antibody, phase I

13-C-0105 MPACT Clinical Trial



Patients with specified mutations of interest will be assigned to receive **<u>one</u>** of the following study drugs or drug combinations at the assigned dose. Cycle length is +/- 1 day for scheduling:

- **ABT-888** 40 mg orally BID qd days 1-7 plus **temozolomide** 150 mg/m^2 orally qd days 1-5 (no food restrictions) in 28-day cycles
- **Everolimus** 10 mg orally each day (no food restrictions) in 28-day cycles
- **Trametinib DMSO:** 2 mg orally each day either one hour before or two hours after a meal in 28-day cycles
- **MK-1775** 225 mg orally BID for 5 doses either at least two hours before or two hours after a meal plus **carboplatin** (AUC 5) IV on day 1 every 3 weeks (21-day cycle)

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Molecular Analysis for Therapy Choice (NCI-MATCH)

National Cancer Institute

NCI-MATCH rationale

- Molecularly targeted therapy benefits patients with defined molecular features:

  within individual tumor types:

  - imatinib in CML (bcr-abl)
  - imatinib in GIST (CKIT & PDGFRα)
  - erlotinib in NSCLC (EGFR)
  - crizotinib in NSCLC (EML4-ALK)

  and, across tumor types:

  - trastuzumab in breast & gastric (Her-2)
  - vemurafenib in melanoma, thyroid & NSCLC, but not colon cancer (BRAF)

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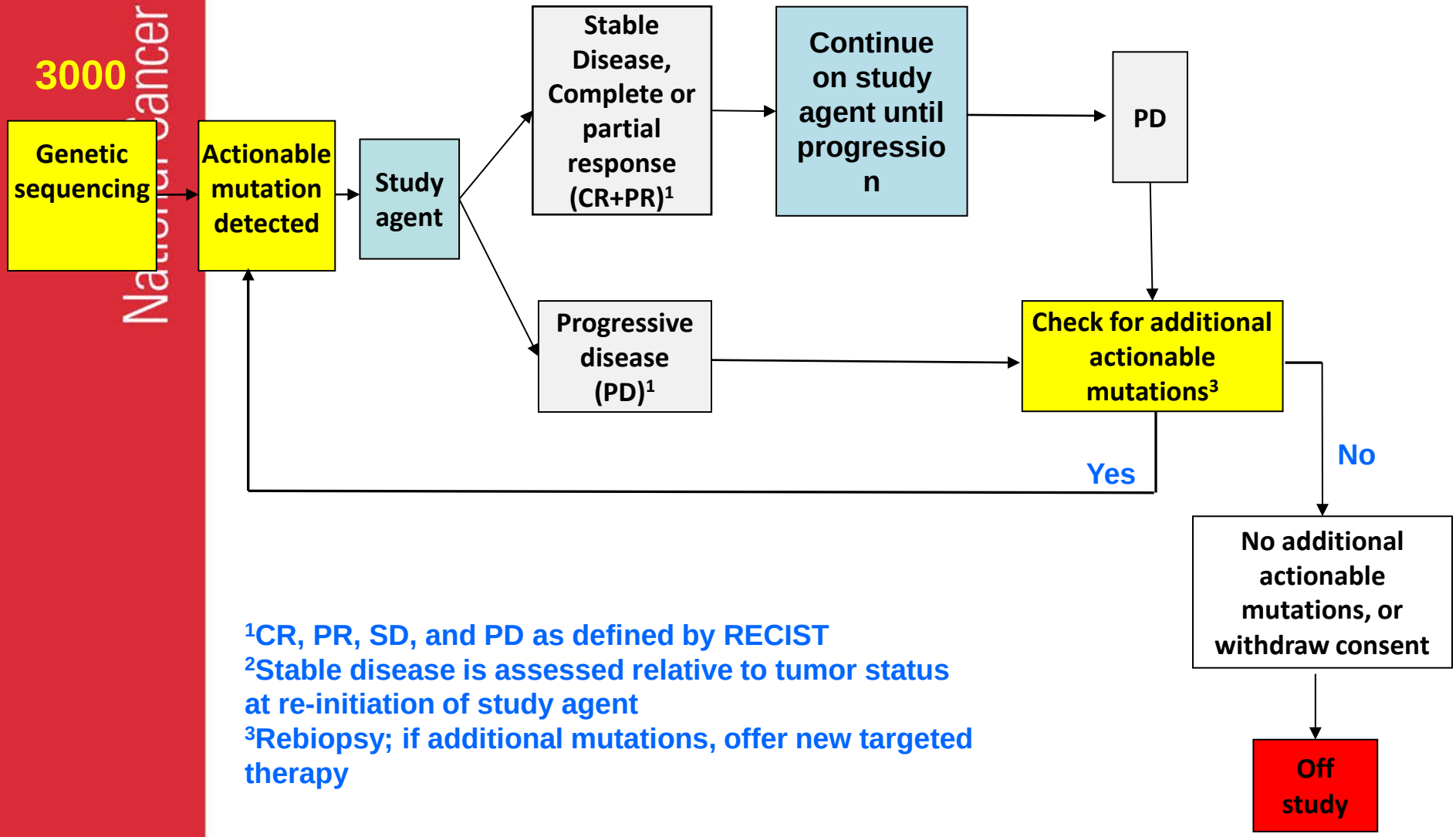
NCI MATCH

- Identify mutations/amplifications/translocations in patient tumor sample - eligibility determination
- Assign patient to relevant agent/regimen
- Need to sequence large numbers of tumors and need to have large numbers of targeted treatments
- Tumor biopsies & sequencing at progression to illuminate resistance mechanisms
  - De-identified samples submitted to central labs
  - Whole-exome sequencing (research purposes) to detect nonambiguous germline variants

NCI-MATCH SCHEMA

National Cancer Institute

3000



[1]CR, PR, SD, and PD as defined by RECIST
[2]Stable disease is assessed relative to tumor status at re-initiation of study agent
[3]Rebiopsy; if additional mutations, offer new targeted therapy

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NCI-MATCH

- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- CTEP-IND for protocol template
  - Arms could be added or deleted without affecting other arms
  - Device discussions with CDRH
- Initially focused on single-agents (commercial or experimental)
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- Study will be reviewed by the CIRB

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Eligibility

- Solid tumors and Lymphomas that have progressed following at least one line of standard therapy
  - Exclude histologies from a given arm if already FDA approved for that indication or lack of efficacy documented
- Tumor accessible for biopsy and patient willing to undergo biopsy
- At least 18 years of age
- Performance status ECOG 0-2
- Adequate organ function

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Patient population considerations

- Target: at least 25% of total enrollment to be patients who have “rare” tumors
- “Common” defined as breast, NSCLC, colon, prostate
- Terminate enrollment to an arm if accrual on pace to require > 5 years to accrue

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Statistical Design

(within each mutation-drug match)

- **Dual Primary Endpoints: ORR 5% vs. 25% or PFS 6 months 15% vs 35%**
- **Simon 2-stage design 30 patients total**

ORR = proportion of patients with objective response (PR+CR) on initial course of study agent

PFS6 = proportion of patients alive and progression free at 6 months from initiation of study agent

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Study Participation

- ECOG-ACRIN to lead with full cooperation of NCTN
  - individual PIs for each arm to rotate leadership positions
- National access through CTSU
- CCOPs

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Levels of Evidence: Drugs

- Level 1: FDA approved; evidence of target inhibition, or proof of mechanism; demonstration that patient selection with CDx are more likely to respond
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS); with evidence of target inhibition; plausible evidence of a predictive or selection assay/analyte
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition; some evidence of a predictive or selection assay/analyte
- Level 4: Preclinical evidence of anti-tumor activity and evidence of target inhibition; hypothesis for a predictive or selective assay/analyte

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Levels of Evidence: genes

- Credentialed for selection of an approved treatment target in a particular malignancy (e.g., ERBB2 amplification and trastuzumab; BRAFV6003 and vemurafenib)
- Credentialed for selection of an approved treatment target in any malignancy but robust clinical data are lacking re: efficacy in other cancer subtypes harboring that variant.
- Gene/variant is an eligibility criteria for an ongoing clinical trial
- N of 1: response (e.g. TSC1, everolimus)
- Preclinical data
  - a. Response in at least 2 xenografts with the mutation AND no response in 2 xenografts without the mutation OR
  - b. Response in several cell lines with the mutation AND no response in cell lines without the mutation

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Team Approach

- Agent & Gene Selection Committee vetting actionable genetic alterations and most robust agents
  - May need to recruit additional agents
  - Essential targets/pathways include: RTK, MAPK & PI3K
- Genetic platform developed and validated at NCI-Frederick & responses to RFA being review for extramural diagnostic centers

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Over 40 drugs pledged

COMPANY

- Abbvie
- Amgen
- Ariad
- Biomarin
- BMS
- Boehringer Ingelheim
- Clovis

COMPANY

- Genentech
- JNJ
- Millenium
- Pfizer
- Sanofi
- Tesaro
- Tracon
- Verastem

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In progress

- Currently 20 “arms”
- EGFR, HER2, MET, BRAF, NF1, GNAQ, GNA11, TSC1/2, PTEN, Patch, NF2, ALK, ROS, FGFR

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Eligibility Assays

- NGS: Ion Torrent PGM with custom Ampliseq panel of 200-300 actionable genes
  - Single nucleotide variants
  - Amplifications
  - Selected translocations
- Validation in network of CLIA certified labs: RFP thru Leidos
- IHC, FISH as needed
- Rule driven treatment assignment

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NGS Assay Details

- Central pre-analytic pathology laboratory
  - Biopsy receiving, specimen processing, H&E assessment, enrichment (if needed) & extraction of nucleic acids
  - Shipment to MATCH Clinical Laboratory Network for NGS assay
- Standardized SOPs for targeted Ion Torrent AmpliSeq NGS Assay
- Standard Assay report (CLIA)

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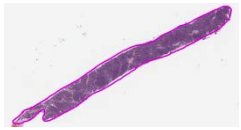
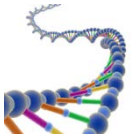
Workflow and Turnover Time of the Assay System



Tissue Fixation Path Review

Tumor content >50%



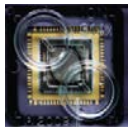
Nucleic Acid Extraction

DNA yield > 20 ng

Library/Template Prep

Library yield > 10 pM

Test fragments: A/D > 80% AQ17, Read Length > 90 bp
Reads per sample: >350, 000
Read Length: 140-160 bp
Coverage: " >80% of amplicons coverage >450X
Positive: detect all true positive variants
Negative: detect no false positive aMOI
NTC: total reads < 2% of lowest sample library read



Sequencing

Data Analysis

aMOI Report Review

Final Report

aMOI = actionable mutation of interest

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In progress

- Nomination of investigators to guide optimal target/agent selection
  - Will become authors and PIs of study arm
- Continued engagement with patient advocates to ensure that design is responsive to patients' needs/concerns
- Develop master protocol including elements that pertain to all arms
  - Tissue submission, result reporting, response criteria, QOL

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

On the Horizon: NGS as Companion Dx

Elizabeth Mansfield, PhD
Director, Personalized Medicine Staff
OIR/CDRH/FDA

History of Companion Dx

- Prior to formal policy
  - ER/PR to direct therapy?
    - Not approved with a specific drug
  - Her-2/Herceptin
  - c-Kit, EGFR IHC, etc with respective drugs
- Dawning recognition that tests can be drivers of therapy

History of Companion Dx

- Policy needed
  - Patient safety
  - Predictability—plan for device element
  - Support for therapeutic approvals
- Policy creation
  - Change in drug development strategies to account for genetic information
  - PGx, VXDS discussions
  - Drug approvals without explicit direction to test

Changing Landscape of Companion Dx

- Multiple drugs with same/similar indication
- Multiple drugs within disease area
- Potential for “molecular diagnosis”
  - Drugs may cross disease lines easily

- Multiple tests for single disease
- Limited tissue
- Reimbursement

Challenges

- Minimize
  - Number of different tests needed
  - Tissue requirements
  - Incremental regulatory requirements
- Maximize
  - Information content per test

Next Generation Sequencing

- What it is:
  - Collection of technologies that enable rapid, affordable nucleic acid sequencing with improved sensitivity*
  - System: nucleic acid preparation, sequencer/reagents, several levels of software
    - Provide for sample to result capabilities

*theoretical; platform dependent

NGS as Companion Dx

- A model
  - Validated platform used to identify appropriate patients for clinical trial
    - Investigational mode
  - Data submitted to FDA in PMA to establish companion use
    - First PMA contains base set of information
  - Build panel over time, as new markers are identified
  - Single platform used to test for all relevant markers
    - Investigation-to-clinical use simplified
    - One platform needed in a lab to run all tests
  - Standardized, validated (national level?)

ABL1 BTK CTNNB1 FGF23 IL7R MLH1 PDGFRA SMO
AKT1 CARD11 DAXX FGF3 INHBA MLL PDGFRB SOCS1
AKT2 CBFB DDR2 FGF4 IRF4 MLL2 PDK1 SOX10
AKT3 CBL DNMT3A FGF6 IRS2 MPL PIK3CA SOX2
ALK CCND1 DOT1L FGFR1 JAK1 MRE11A PIK3CG SPEN
APC CCND2 EGFR FGFR2 JAK2 MSH2 PIK3R1 SPOP
AR CCND3 EMSY
(C11orf30) FGFR3 JAK3 MSH6 PIK3R2 SRC
ARAF CCNE1 EP300 FGFR4 JUN MTOR PPP2R1A STAG2
ARFRP1 CD79A EPHA3 FLT1 KAT6A
(MYST3) MUTYH PRDM1 STAT4
ARID1A CD79B EPHA5 FLT3 KDM5A MYC PRKAR1A STK11
ARID2 CDC73 EPHB1 FLT4 KDM5C MYCL1 PRKDC SUFU
ASXL1 CDH1 ERBB2 FOXL2 KDM6A MYCN PTCH1 TET2
ATM CDK12 ERBB3 GATA1 KDR MYD88 PTEN TGFBR2
ATR CDK4 ERBB4 GATA2 KEAP1 NF1 PTPN11 TNFAIP3
ATRX CDK6 ERG GATA3 KIT NF2 RAD50 TNFRSF14
AURKA CDK8 ESR1 GID4
(C17orf39) KLHL6 NFE2L2 RAD51 TOP1
AURKB CDKN1B EZH2 GNA11 KRAS NFKBIA RAF1 TP53
AXL CDKN2A FAM123B
(WTX) GNA13 LRP1B NKX2-1 RARA TSC1
BAP1 CDKN2B FAM46C GNAQ MAP2K1 NOTCH1 RB1 TSC2
BARD1 CDKN2C FANCA GNAS MAP2K2 NOTCH2 RET TSHR
BCL2 CEBPA FANCC GPR124 MAP2K4 NPM1 RICTOR VHL
BCL2L2 CHEK1 FANCD2 GRIN2A MAP3K1 NRAS RNF43 WISP3
BCL6 CHEK2 FANCE GSK3B MCL1 NTRK1 RPTOR WT1
BCOR CIC FANCF HGF MDM2 NTRK2 RUNX1 XPO1
BCORL1 CREBBP FANCG HRAS MDM4 NTRK3 SETD2 ZNF217
BLM CRKL FANCL IDH1 MED12 NUP93 SF3B1 ZNF703
BRAF CRLF2 FBXW7 IDH2 MEF2B PAK3 SMAD2
BRCA1 CSF1R FGF10 IGF1R MEN1 PALB2 SMAD4
BRCA2 CTCF FGF14 IKBKE MET PAX5 SMARCA4
BRIP1 CTNNA1 FGF19 IKZF1 MITF PBRM1 SMARCB1

NGS Outstanding Issues

- Sponsor must choose to come to FDA
- Unknown how many platforms could meet FDA Quality System requirements
- Approved test systems tend to be static
  - Versus constant rev cycle of research use
  - Ability to rev at intervals will need to be worked out
- Validate NGS systems against already approved tests
- Can’t substitute for IHC or other non-nucleic acid tests

- Thanks for your attention
- Elizabeth.mansfield@fda.hhs.gov