MEETING SUMMARY

PRESIDENT'S CANCER PANEL

THE FUTURE OF CANCER RESEARCH: ACCELERATING SCIENTIFIC INNOVATION

September 22, 2010
Boston, Massachusetts

OVERVIEW

This meeting was the first in the President's Cancer Panel's (PCP, the Panel) 2010-2011 series, *The Future of Cancer Research: Accelerating Scientific Innovation*. During this meeting, the Panel heard expert testimony and moderated discussions regarding scientific progress made over the past four decades and opportunities to enhance the National Cancer Program (NCP) in coming years. The agenda for the meeting was organized into two discussion panels.

PARTICIPANTS

President's Cancer Panel

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair

Margaret Kripke, Ph.D.

National Cancer Institute (NCI), National Institutes of Health (NIH)

Abby Sandler, Ph.D., Executive Secretary, PCP

Speakers

John Auerbach, M.B.A., President-Elect, Association of State and Territorial Health Officials

Edward J. Benz, Jr., M.D., President, Dana-Farber Cancer Institute

Otis W. Brawley, M.D., Chief Medical Officer, American Cancer Society

Bruce Chabner, M.D., Co-Chair, The National Cancer Advisory Board's Ad hoc Working Group to Create a Strategic Scientific Vision for the National Cancer Program and Review of the National Cancer Institute

Gwen Darien, Chair, Director's Consumer Liaison Group, National Cancer Institute

James Doroshow, M.D., Director, Division of Cancer Treatment and Diagnosis, National Cancer Institute

Judy E. Garber, M.D., M.P.H., President-Elect, American Association for Cancer Research

Peter Grevatt, Ph.D., Director, Office of Children's Health Protection and Environmental Education, Environmental Protection Agency

William Hait, M.D., Ph.D., Senior Vice President and Worldwide Head, Ortho Biotech Oncology Research & Development, a Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Brandon Hayes-Lattin, M.D., Senior Medical Advisor, Lance Armstrong Foundation

Michael Kelley, M.D., F.A.C.P., National Program Director for Oncology, Veterans Health Administration, Department of Veterans Affairs

Sharyl Nass, Ph.D., Director, National Cancer Policy Forum, Institute of Medicine

Richard Pazdur, M.D., F.A.C.P., Director, Office of Oncology Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration

Kyu Rhee, M.D., M.P.P., F.A.A.P., F.A.C.P., Chief Public Health Officer, Health Resources and Services Administration

Lisa Richardson, M.D., M.P.H., Associate Director for Science, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention

George W. Sledge, Jr., M.D., President, American Society of Clinical Oncology

Barry Straube, M.D., Chief Medical Officer, Centers for Medicare and Medicaid Services

OPENING REMARKS—DR. LaSALLE D. LEFFALL, JR.

On behalf of the Panel, Dr. Leffall welcomed invited participants and the public to the meeting. He introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings.

Dr. Kripke reported that the Panel held Working Group meetings on February 19, June 30, and September 8, 2010, to discuss policy, research, and program recommendations for the 2009-2010 Annual Report to the President. Dr. Kripke's motion to accept all of the recommendations of the Working Group was unanimously passed.

PANEL I

DR. JAMES DOROSHOW:

CHANGING THE NCI'S CLINICAL TRIALS SYSTEM TO MEET THE NEEDS OF THE 21ST CENTURY: FOCUS ON MOLECULAR CHARACTERIZATION OF TUMORS FOR PATIENTS ENTERED ON CLINICAL STUDIES

Background

Dr. James H. Doroshow has been the Director of the NCI Division of Cancer Treatment and Diagnosis since 2004. From 1983 to 2004, Dr. Doroshow was the Chairman of the City of Hope Comprehensive Cancer Center Department of Medical Oncology and Therapeutics Research. From the time of his first research grant in 1980, Dr. Doroshow was continuously funded by NCI until he moved to NIH in 2004. He is the author of over 300 full-length publications in the areas of anthracycline antibiotic molecular pharmacology, the role of oxidant stress in tumor cell signal transduction, and novel therapeutic approaches to solid tumors. Dr. Doroshow served from 1990–92 as Chairman of the NIH Experimental Therapeutics II Study Section, from 1995–2001 as a member of the Subspecialty Board on Medical Oncology of the American Board of Internal Medicine, from 1999–2000 as Chairman of NCI's Scientific Review Group A-Cancer Centers, and from 2004–2007 as a member of U.S. Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee. From 2004–2005, Dr. Doroshow chaired NCI's Clinical Trials Working Group, which developed a comprehensive set of initiatives to restructure the national cancer clinical trials enterprise.

Key Points

- One of the most important issues currently facing NCI is the need to improve and update its clinical trials system to meet the requirements of the 21st century. Necessary to this endeavor is the collection of biospecimens for research and molecular characterization patients. Facilitation of these activities will be essential to NCI's quest to bring new, effective cancer-fighting treatments to patients.
- The development of predictive therapeutic markers encompasses a broad range of activities that begin in the early stages of drug development. An assessment of NCI's research portfolio reveals a large amount of funding devoted to predictive marker identification, to early-phase feasibility testing, and

to the detection of biomarkers. However, the resources needed to move past early discovery to the development phase are lacking.

- This resource need, along with the recent availability of stimulus funds, has led to the creation of the Clinical Assay Development Program (CADP). This program provides intramural and extramural resources to facilitate the efficient development of diagnostic tests needed to speed the evaluation of molecularly targeted therapies. This program also serves to overcome the inefficiencies and lack of support for therapeutic and predictive biomarker development. NCI is creating a rigorous development process that will allow for the use of biomarkers in stratification, treatment assignment, and eligibility assessment in the context of clinical trials. Resources will be provided to optimize analytical performance and establish the clinical validity of biomarker studies.
- The Clinical Assay Development Program (CADP) comprises four parts. The first is the Clinical Assay Development Network (CADN), which is a group of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories in academia and industry with the purpose of facilitating the transition of biomarkers into the clinic in a manner that brings them closer to FDA certification.
- A Patient Characterization Center, the biomarker discovery piece, is being developed on the NCI-Frederick campus. This center will be a model for the development of personalized, highly prescriptive cancer care. This care will be based on traditional epidemiological and risk-factor analysis combined with molecular and pharmacogenomic characterization of patients and their tumors. Ultimately, the Center will have the capacity to perform complete genomic characterization of patient specimens (normal and tumor). All of this information will be publicly available pending patient consent.
- The Clinical Assay Development Centers (CADC) will work in concert with the CADN to create a process to efficiently develop diagnostic tools that will address clinical needs, including but not limited to tools that can assess prognosis, inform patient selection for testing of molecularly targeted agents, and predict response to therapy. Initially, the emphasis will be on evaluating the performance characteristics of assays proposed for use in clinical trials. The CADC and CADN will provide the resources to optimize and validate assays. Project teams that include pathologists, statisticians, and experts in assay development will be formed to design the studies needed to carry the assay development process to completion.
- CADP will utilize an outside peer-review process by a special emphasis panel of individuals from industry and academia. The most highly rated projects will be evaluated for their feasibility by various internal committees and then overseen by a group of project management teams in conjunction with NCI staff and the principal investigators.
- The fourth component of the CADP is the Specimen Retrieval System. A contract has been established with Northern California Kaiser to provide these services.
- To date, eight CLIA-certified laboratories have signed contracts to participate in CADN. About half of the staff for the Patient Characterization Center and CADC in Frederick have been hired and will be operational by January 1, 2011. It is anticipated that the first application for utilization of the CADP will be received in the first quarter of 2011.

DR. LISA RICHARDSON:

ADVANCING CANCER PREVENTION AND CONTROL THROUGH COORDINATION AND DISSEMINATION

Background

Dr. Lisa C. Richardson is the Associate Director for Science in the Centers for Disease Control and Prevention Division of Cancer Prevention and Control (CDC/DCPC). Her research focuses on access to

cancer care, systems of care, health-related quality of life during cancer treatment, health disparities and racial discrimination, and breast cancer treatment patterns of care. Dr. Richardson oversees the research and scientific content of the DCPC products. The Division administers the only organized screening program for low-income uninsured women in the United States (National Breast and Cervical Cancer and Early Detection Program). The Division also administers the National Program of Cancer Registries. This program, in collaboration with the NCI Surveillance, Epidemiology and End Results (SEER) registries, covers 98 percent of the U.S. population for cancer incidence.

Key Points

- The CDC Division of Cancer Prevention and Control provides essential public health services, including monitoring health status; informing, educating, and empowering the public; mobilizing community partnerships; developing policies and plans; linking people to needed services and assuring care; and evaluating health services and conducting research. CDC views research as one of its essential services and may mandate its programs to conduct more research in the future.
- DCPC addresses cross-cutting issues across the cancer continuum, from prevention to diagnosis to survivorship. Some of these issues include communications, surveillance (one of the CDC's core functions), genomics, and policy change. CDC provides health services in the context of the cancer continuum, implementing interventions where the evidence is strongest. For example, evidence for effective intervention for breast cancer may be strongest in the area of early detection, so that is where CDC would devote most of its efforts to make an impact.
- DCPC's largest health intervention initiative is the National Breast and Cervical Cancer Early Detection Program. This program is for under- and uninsured women who would like to be screened for breast and cervical cancer. To date, about 4 million women have been screened.
- DCPC's second-largest initiative is the National Program of Cancer Registries, which collects data on the occurrence of cancer; the type, extent, and location of the cancer; and the type of initial treatment. This program supports 45 state cancer registries, which are complementary to NCI's SEER Program.
- The third-largest DCPC health initiative is the National Comprehensive Cancer Control Program, which currently supports 50 states, the District of Columbia, 7 tribal groups, and 7 U.S.-associated Pacific Islands/territories to establish coalitions, assess the burden of cancer, determine priorities, and develop and implement cancer plans.
- The Prevention Research Centers is a network of public health agencies, community members, and 40 public health schools that conducts applied research in disease prevention and control. Within these Centers, the Cancer Prevention and Control Network was established to provide expertise for research that meets the *Guide to Community Preventive Services* standards. The *Guide* is a free resource that offers program and policy suggestions to improve health and prevent disease in the community.
- CDC cancer surveillance data have been used to inform the Agency for Healthcare Research and Quality's (AHRQ) National Healthcare Quality and Disparities reports and state snapshots, which provide state-specific health care quality information. CDC also provided data for *Healthy People 2020*, which should be released in December 2010.
- CDC's foremost cancer priorities revolve around primary and secondary prevention. Primary prevention involves implementing interventions known to reduce the risk of cancer forming—vaccination (e.g., HPV, HBV), smoking cessation, obesity prevention, and increasing physical activity. Secondary prevention is the early detection of disease, which encompasses the entire cancer care spectrum, from getting screened to being diagnosed and receiving therapy and survivorship care.
- As of 2006, there were nearly 12 million cancer survivors in the United States, which is 4 to 5 percent of the total population. Yet, little research has been conducted on patients' lived experience with cancer. Elucidating the cancer patient's experience and improving the quality of life of cancer

survivors is one of CDC's top priorities. Unfortunately, funding has not yet been provided to truly make an impact in this area.

- The current paradigm for translating research from "bench" to "beside" needs to change. Effective health interventions must be informed by research. However, some public health officials estimate it can take as long as 30 years to translate research into practice. One possible avenue to efficiently disseminate research findings to the public is to utilize the existing public health infrastructure. For example, CDC has cancer control programs in every state, which could serve as a vehicle to disseminate information to the public.
- The CDC National Center for Chronic Disease Prevention has developed its own framework for translating research into practice—the Health Promotion Knowledge to Action Framework. This translation trajectory starts with the research phase and leads to dissemination and then implementation and institutionalization of the evidence. A missing piece of this framework is how health practice in the community can inform the development of interventions and research.
- CDC's future directions in the National Cancer Program include health reform, primary prevention, policy change, protection of social justice, and enhanced surveillance and cancer registry applications (particularly for comparative effectiveness research). Partnerships and collaboration will be key to the accomplishment of CDC's goals. Additionally, across all of its efforts, CDC will encourage programs and researchers to disseminate and implement their findings among all population groups.

DR. RICHARD PAZDUR:

THE ROLE OF THE PHARMACEUTICAL INDUSTRY IN THE NATIONAL CANCER PROGRAM

Background

Dr. Richard Padzur has a distinguished career in clinical and academic oncology in addition to his experience as a regulatory expert at FDA. He has served as a practicing oncologist, researcher, and teacher at Wayne State University, where he was director of the medical oncology fellowship program, and at the M.D. Anderson Cancer Center at the University of Texas, where he was a tenured Professor of Medicine and Assistant Vice President for Academic Affairs. He joined FDA in 1999 as the Director of the Division of Oncology Drug Products and was named Director of the Office of Oncology Drug Products in April 2005. He has authored over 160 peer-reviewed papers in the field of oncology, has written chapters for over 30 oncology textbooks, and is the editor of two standard reference oncology texts.

Key Points

- The field of oncology has changed dramatically since the inception of the National Cancer Program in 1971. This transformation is due in part to the emergence of the pharmaceutical industry in the cancer field and the changing role of government in drug development.
- Government-supported drug development trials in the United States currently lack international perspective. The vast majority of applications the FDA receives for new drug approval contain drug development clinical trials and information that are international in scope.
- The internationalization of clinical trials does not create barriers but, rather, opportunities to develop drugs faster. For example, the NCI Clinical Trials Cooperative Group Program could partake in a collaborative effort with pharmaceutical companies in which NCI takes on the domestic components of a trial and the pharmaceutical company handles international accrual of the trial. Such a collaboration could also result in improvement in data quality. It is clear from the FDA perspective that pharmaceutical companies collect an excessive amount of data on clinical trials. On the other hand, trialists from other sectors, including the Cooperative Groups, may not provide all of the

necessary data for timely submission of a new drug approval. Having an active, ongoing collaboration with pharmaceutical companies for this endeavor might expedite drug development.

- There are many benefits to supporting international trials, such as faster trial accrual, especially for rare diseases. Having international access to patients will only become more important as oncology research delves deeper into defining molecular subtypes in smaller numbers of patients on clinical trials. In addition to having access to larger patient populations and faster accrual, international trials also provide information on drug efficacy in various ethnic populations. The U.S. has a large ethnic population, yet representation of these population groups is often missing in trials conducted exclusively in the United States. Additionally, internationalization of clinical trials allows integration of ideas from other countries.
- Pharmaceutical companies that are developing drugs on an international basis must comply with multiple drug regulators, not just FDA. FDA currently holds monthly teleconferences with the European Medicines Agency and Health Canada in an effort to establish relationships with other international drug regulators.
- The field of oncology drug development is also changing with the emergence of biomarkers. Biomarkers inform patient selection for clinical trials. They can also provide insight into drug disposition and activity and help relate these measures to clinical endpoints. Drug development should be partnered with biomarker development very early in the development of drugs or biologics. The use of biomarkers will result in greater efficacy in the population of interest and, possibly, smaller clinical trials.

DR. BARRY STRAUBE:

CMS AND THE NATIONAL CANCER PROGRAM: THE "TRIPLE AIM" GUIDEPOST

Background

Barry M. Straube, M.D., is Chief Medical Officer at the Centers for Medicare and Medicaid Services (CMS). Dr. Straube received an A.B. degree (magna cum laude, Phi Beta Kappa) from Princeton University and received his M.D. degree from the University of Michigan Medical School. He is board-certified in Internal Medicine and Nephrology.

Key Points

- The Centers for Medicare and Medicaid Services provides health benefits for more than 114 million Americans through Medicare, Medicaid, and the Children's Health Insurance Program. In fiscal year 2011, CMS will spend $784 billion on these programs.
- The mission of CMS is to promote and ensure the health and health care of all their beneficiaries across the three aforementioned programs. A goal of CMS is to transform the agency from a passive payor/insurer of health to an active purchaser of high quality and value in health care. CMS follows a "triple aim" approach to improve health services, which focuses on population health, the experience of care, and per capita cost. CMS is particularly focused on reducing per capita costs while maintaining high-quality health outcomes. The agency has multiple drivers or tools to ensure a high level of quality and value.
- The first tool is contemporary quality improvement. Traditional quality improvement involves identifying a problem, measuring it, devising an intervention to improve quality of what is being measured, and implementing the intervention. Contemporary quality improvement entails evidence-based interventions, rapid-cycle quality improvement, and accountability. This concept can best be exemplified by the Quality Improvement Organization (QIO) Program. QIOs are private organizations that are staffed by professionals, mostly doctors and other healthcare professionals, who are trained to review medical care, help address beneficiary complaints about the quality of care, and

implement improvements. CMS contracts with one organization in each state, as well as the District of Columbia, Puerto Rico, and the U.S. Virgin Islands to serve as that state/jurisdiction's QIO contractor. QIO contracts are three years in length. The current cycle began August 1, 2008, and includes a number of cancer quality improvement tasks focused on prevention and the use of health information technology.

- Early results after two years of the current QIO contract cycle reveal that over 96 percent of the 1,500 physician offices involved with the program are successful in reporting cancer rates and cancer screening rates via direct submission of records from electronic health records (EHRs). All offices using EHRs have been successful in increasing colorectal screening rates by at least 9 percent and breast cancer screening rates by a minimum of 6 percent. These rates were calculated against a control group of offices that do not track or report via EHR systems.
- The second CMS health improvement driver is transparency, which involves public reporting and making healthcare data readily available. CMS has 17 separate prospective payment systems used to pay for different clinical areas, such as doctors' offices, hospitals, home health agencies, and nursing homes. Quality measures are being reported through a host of tools on CMS.gov that allow comparisons of different sites. Some CMS programs (e.g., physicians' offices) have many cancer-related measures to report, whereas others (e.g., inpatient hospitals) have none.
- There is a gross need to develop more measures for quality of cancer care and treatment. Currently, the Hospital Inpatient Reporting Program has no cancer-related quality measures. The Hospital Outpatient Reporting Program has one cancer-related measure to report mammography follow-up rates. The Nursing Home program reports rates of chronic pain and post-acute pain, which abstractly link to cancer. The Home Health program only measures rates of pain control and Hospice Care reports symptomatic measures of some cancer types.
- CMS is sponsoring development of a host of cancer-related measures for the Hospital Outpatient Reporting Program. Some of these measures include: a companion measure of the rate of breast cancer detection following repeat imaging; adjuvant chemotherapy for colon and breast cancer; and needle biopsy to establish cancer diagnosis prior to surgical excision.
- In the physicians' office program, there are currently 22 measures that address cancer-related diagnoses to some extent, but they are primarily process measures. Outcome measures and measures of patient experience of care are needed.
- The third health improvement tool CMS utilizes is financial incentives. Value-based purchasing is being implemented in hospitals, physicians' offices, home health agencies, nursing homes, and other types of sites to promote higher quality of care. More money will be given to those clinical settings that exhibit better treatment and care outcomes, and less money will be given to those that have worse outcomes.
- Regulation is the fourth improvement driver. CMS writes conditions of participation or conditions for coverage for all 17 clinical settings through which health care is delivered. These conditions set and demand basic levels of care and quality outcomes. A survey and certification process is implemented to ensure provider settings are compliant with the conditions. These regulations are a powerful tool that ought to be harnessed specifically to improve cancer care.
- The fifth CMS tool is coverage decision-making. CMS has an active role in the evaluation of published evidence regarding the effectiveness of diagnostic and therapeutic modalities in cancer care. Regular meetings of the Medical Evidence Development and Coverage Advisory Committee (MEDCAC) are held to elicit advice from scientific experts in a public forum. Recent MEDCAC meetings have been held on pharmacogenomics, biomarkers and cancer therapeutics, radiation therapy for prostate cancer, and screening computed tomography colonography for colorectal cancer. CMS also commissions technology assessments by the Agency for Healthcare Research and Quality and other organizations on cancer topics.

- Some recent national coverage decisions related to oncology involve allogeneic hematopoietic stem cell transplantation (allogeneic HSCT), autologous stem cell transplantation (AuSCT), autologous cellular timmotherapy treatment for metastatic prostate cancer, cryosurgery ablation for prostate cancer, and liver transplantation for malignancy, among others.
- CMS also has a Medicare Clinical Trials Policy, by which costs incurred during treatment for clinical trials are paid. CMS will soon be implementing an FDA-CMS parallel review to streamline the coverage and approval of oncology drugs.
- Under the Affordable Care Act, CMS will be implementing the Center for Medicare and Medicaid Innovation (CMI). CMI will research new ways to encourage evidence-based coordinated care for CMS beneficiaries.

DR. MICHAEL KELLEY:

IMPROVING CANCER CARE: LESSONS FROM VA

Background

Dr. Michael Kelley, M.D., F.A.C.P., is National Program Director for Oncology at the Veterans Health Administration, U.S. Department of Veterans Affairs (VA). Dr. Kelley is also an Associate Professor of Medicine in the Hematology and Medical Oncology department of Duke University School of Medicine.

Key Points

- The Veterans Health Administration (VHA), part of the Department of Veterans Affairs, provides health benefits and care to the nation's 24.8 million veterans. Currently, there are over 5 million veterans enrolled in the VHA; 95 percent of those enrollees are male. The VHA comprises 153 hospitals, 951 clinics, and 21 regional networks and provides care for approximately 3 percent of all cancer cases in the United States.
- Comparisons of care inside the VA system with that outside the VA have been conducted for an impressive number of diseases, including cancer. The results of these comparisons show that care in the VA is as good, if not better, on all the metrics used. The quality of VA health care is touted in Phillip Longman's book, *Best Care Anywhere: Why VA Health Care Is Better Than Yours*.
- With regard to cancer, the main focus of the VA is on primary care—screening and prevention. Data from the June 2010 *VHA Facility Quality and Safety Report* reveal that women in the VHA system receive breast and cervical cancer screening at a rate at least 10 percent higher than outside of the VA. For colorectal cancer, the screening rate is 20 percent higher in the VHA than outside the VA system.
- The VA is particularly noted for its data systems, which entail a completely integrated and comprehensive electronic health record (EHR), a central cancer registry, and extensive administrative databases.
- The VA EHR system identifies patients, based on age, who may require specific health care services and alerts providers that those services are needed. These alerts arise in the Clinical Reminder Panel and the healthcare provider can then indicate that screening has been done, directly order screening tests, or indicate that the patient declines screening.
- High-quality health care requires healthy information systems. Effective electronic health systems support efficiency, virtual clinics, cancer registry data (e.g., identification of clinical trials), and patient centeredness. The VA systems allow patients access to EHRs at home or in the clinic or hospital. My Health***e***Vet (http://www.myhealth.va.gov) is a Web portal where veterans can access and download all of their health information.
- There is a great need to improve the clinical trials system across the country. Within the VA, the enrollment rate to NCI Cooperative Group studies is about half the rate of the rest of the United

States. However, the rest of the nation is not faring well, either; less than 1 percent of cancer patients enroll in NCI Cooperative Group trials. The barriers leading to these low enrollment rates include low funding, narrow enrollment criteria, and unintended effects of well-intentioned regulation. New regulations, from Institutional Review Boards (IRBs) or Health Insurance Portability and Accountability Act (HIPAA) privacy and security rules, reduce the number of trials approved, resulting in a loss of clinical trial expertise.

- Future therapeutic interventions in oncology must be "high yield," meaning that they decrease mortality by at least 25 percent. Historically, some chemotherapy agents have improved survival by a much greater margin—chemotherapy agents for small-cell lung cancer improve survival by fourfold—than more recent therapeutic treatments that have been less and less effective in terms of improving survival.
- The few recent, successful high-yield therapeutic interventions have been biomarker-drug combinations specifically related to single genetic alterations and associated tyrosine kinase inhibitors. One such example is the development of the enzyme-inhibiting drug imatinib for treatment of chronic myelogenous leukemia. These successful biomarker-drug interventions need to be replicated and expanded to other tumor settings.
- The challenge with extending high-yield treatments to other cancer types is that many cancer cell mutations are pharmacologically difficult to target (e.g., ras, p53, p16 mutations). Overcoming this barrier requires alternative technological approaches to targeted cancer treatment, such as nanoparticles and siRNAs (small interfering RNAs), which both may soon become clinically applicable. When developing alternative interventions, cancer researchers must also consider that cancer types with multiple mutations may be susceptible to multiple drugs.
- A major barrier to biomarker-drug clinical trials is access to high-quality tissue specimens. The cost is high for obtaining tissue samples to conduct research on personalized therapies, and the use of bioinformatics to interpret trial results is very challenging. These barriers will become even more pressing to overcome as The Cancer Genome Atlas (TCGA) progresses. TCGA is a comprehensive and coordinated effort to accelerate understanding of the genetics of cancer using innovative genome analysis technologies.

DR. PETER GREVATT:

UNDERSTANDING EARLY-LIFE SUSCEPTIBILITY TO CARCINOGENS

Background

Peter Grevatt, Ph.D., is Director of the Office of Children's Health Protection and Environmental Education, Environmental Protection Agency (EPA). He is also the Senior Advisor to EPA Administrator Jackson for Children's Environmental Health. He is responsible for ensuring that all EPA decisions are protective of children's health and that EPA is an international leader on children's environmental health issues. Dr. Grevatt served as the Senior Science Advisor in EPA's Office of Solid Waste and Emergency Response and as the Senior Health Scientist in EPA's Region 2 office. In these roles, Dr. Grevatt was responsible for ensuring that science, public health, risk assessment, environmental justice, and children's health were fully considered in relation to a range of critical issues such as asbestos, polychlorinated biphenyls, lead, and arsenic. Dr. Grevatt led the National Water Quality Monitoring program in EPA's Office of Water. More recently, as Director of the Economics, Methods and Risk Analysis Division in EPA's Office of Resource Conservation and Recovery, he provided leadership to the regions and states on Resource Conservation and Recovery Act implementation, and provided health risk assessments and economic cost-benefit analyses on major rulemakings. Dr. Grevatt received his B.A. degree in biology from Earlham College and his M.S. and Ph.D. degrees in basic medical sciences from New York University Medical Center.

Key Points

- Ensuring that chemicals are safe and noncarcinogenic is one of EPA's top priorities. EPA is particularly concerned with understanding the role of chemicals in increasing cancer risk to children and other vulnerable populations—not just childhood cancers but cancers that can occur throughout life that may be initiated during the childhood years. Cancer risk data are integral to the implementation of multiple environmental statutes; however, in most cases, manufacturers are not required to submit these data to EPA.
- The EPA is working with Congress, members of the public, the environmental community, and the chemical industry to reauthorize the Toxic Substances Control Act (TSCA). Several essential principles of reform have been developed by the Administration to inform these efforts. First, chemicals should be reviewed against safety standards that reflect protective risk-based criteria. Second, manufacturers should provide EPA with the necessary information to conclude that new and existing chemicals are safe. Third, risk management decisions should take into account the following: sensitive life stages and vulnerable populations, cost, availability of substitutes, and other relevant considerations. Fourth, manufacturers and EPA should assess and act on priority chemicals, both existing and new, in a timely manner; in particular, for those that might impact sensitive life stages and population groups. Fifth, green chemistry should be encouraged and provisions assuring transparency and public access to information should be strengthened. Finally, EPA should be given a sustained source of funding to implement TSCA.
- Individuals at certain life stages, such as fetal development and early childhood and puberty, may be more susceptible to the carcinogenic effects of certain chemicals. For example, more frequent cell division during development can reduce the time available for DNA repair, resulting in the perpetuation of genomic mutations. Some embryonic cells, such as brain cells, lack key DNA repair enzymes. Some components of the immune system are not fully functional during early development, and hormonal systems operate at different levels during different life stages. Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life.
- A 1994 report of the National Research Council (NRC) recommended that EPA assess risk to infants and children whenever it appears that risk among these populations may be greater than that among adults. However, it is usually difficult to ascertain whether elevated risk exists. Standard cancer bioassays involve sexually mature rodents, which provide little insight into early-life susceptibilities.
- In response to the NRC report, EPA revised its cancer guidelines in 2005. These guidelines state that direct data should be utilized whenever available and that "defaults," or uncertainty factors, should be employed only in the absence of critical information. Unfortunately, critical data are frequently lacking when considering the potential susceptibilities of populations at different life stages. The guidelines also emphasize that efforts should be made to understand the modes of action by which chemicals are operating (i.e., the key events and processes that mediate the adverse events caused by chemicals).
- In the process of implementing the 2005 guidelines, EPA conducted a review of the scientific literature. The review identified 27 rodent studies for 18 chemicals (a majority were mutagenic) that had sufficient data reflecting postnatal and adult exposures to quantitatively estimate potential increased susceptibility from early-life exposures. Ratios of juvenile to adult cancer potencies were calculated for three study types: acute dosing, repeated dosing, and lifetime dosing. Most studies demonstrated the perinatal period as a time of enhanced sensitivity to carcinogens.
- Based on these findings, EPA issued guidance recommending the use of age-dependent adjustment factors (ADAFs) to provide additional protection, but only for carcinogens with a mutagenic mode of action since most of the early-life studies involved such carcinogens. EPA also announced that it could develop additional "supplemental" guidance should new data become available to address other modes of action. In addition, California and Minnesota have taken a more precautionary approach by

applying ADAFs to all carcinogens regardless of mode of action unless data are available to show that additional protection is not necessary.

- Of the numerous compounds in the EPA Integrated Risk Information System database, only eight are either currently undergoing external peer review or have been concluded to have a mutagenic mode of action. These include 1,2,3-trichloropropane, dichloromethane, acrylamide, polycyclic aromatic hydrocarbon mixtures, ethylene oxide, formaldehyde, chloroprene, and trichloroethylene.
- EPA is not only concerned with the potential potency of compounds, but with the differences in how people are exposed to chemicals throughout different life stages. Young children, for example, have higher exposures to many substances than do adults because this life stage is associated with hand-to-mouth behavior, crawling on floors, and other behaviors that may increase exposure.
- An improved understanding of early-life susceptibility to carcinogens in the environment is critical. To meet this challenge, several approaches are necessary. First, the high-throughput toxicity testing assays that are currently under development in EPA's Computational Toxicity Center, as well as those under development at NIH and at academic centers across the United States, will help yield a better understanding of cancer risks and the environment. Second, additional data are needed to improve estimates of infant and toddler exposures to chemicals. Third, data are also needed to reduce uncertainty in estimating the impact of cumulative exposures to multiple toxicants. Fourth, an improved understanding of the metabolic differences among different life stages is needed. Fifth, methods for assessing cancer risk in clusters or "hot spots" must be developed. Sixth, an improved understanding of why cancer risks may differ for children in socioeconomically disadvantaged as opposed to more advantaged communities is critical. Finally, childhood cancer surveillance must be improved so that data can be linked among studies in the United States and internationally.

DR. KYU RHEE:

SAFETY NET OPPORTUNITIES FOR THE NATIONAL CANCER PROGRAM

Background

Dr. Kyu Rhee serves as the Chief Public Health Officer of the Health Resources and Services Administration (HRSA). Prior to joining HRSA, Dr. Rhee was Director of the Office of Innovation and Program Coordination at the NIH National Center on Minority Health and Health Disparities. Before that, he was Chief Medical Officer of Baltimore Medical System, Inc., the largest network of Federally Qualified Health Centers in Maryland. In addition, Dr. Rhee served five years as a National Health Service Corps Scholar and Medical Director at the Upper Cardozo Health Center in Washington, DC. Dr. Rhee is board-certified in internal medicine and pediatrics. He received his medical degree from the University of Southern California and did his residency in internal medicine and pediatrics at Cedars-Sinai Medical Center in Los Angeles. Dr. Rhee also holds a master's degree in public policy from the John F. Kennedy School of Government, Harvard University. He received his bachelor's degree from Yale University in Molecular Biophysics and Biochemistry.

Key Points

- The mission of HRSA is to improve health and achieve health equity through access to quality services, a skilled health workforce, and innovative programs.
- Nearly 19 million patients are served through the more than 8,000 sites affiliated with the HRSA-funded Community Health Center Program. Over 500,000 people living with HIV/AIDS receive services through more than 900 HRSA-funded Ryan White Clinics; two-thirds are members of minority groups. Thirty-four million women, infants, children, and adolescents benefit from HRSA's maternal and child health programs. About 14,000 safety net providers participate in HRSA's

discount drug program. More than 6,700 National Health Service Corps clinicians are (or will be) working in underserved areas in exchange for loan repayment or scholarships.

- HRSA's Community Health Center Program is the largest primary care system in the United States. Nine of every 10 patients served are below 200 percent of the poverty level, 4 out of 10 are underserved, and 1 out of 3 are children. HRSA expects in the next five years to nearly double the number of patients served, from close to 19 million to close to 40 million people. Half of these health centers have electronic health records, offering the infrastructure to conduct research that relates to cancer screening and other issues related to cancer care. HRSA aims to implement electronic health records for 100 percent of its health centers by 2014.
- HRSA is involved in a number of cancer screening, prevention, and treatment initiatives. For example, the Community Health Center program has a referral network in place to provide services like mammograms and colonoscopies, as well as other interventions to screen for cancer. The HIV/AIDS Bureau has programs aimed at smoking cessation. The Maternal and Child Health Bureau has a number of programs that relate to breast, cervical, and colon cancer screening. The Bureau of Health Professions has a patient navigator program that sponsors community health workers to promote cancer screening. The National Health Service Corps comprises a large cadre of individuals who treat primarily those populations that experience health disparities, including disparities related to various cancers. Many HRSA-funded community-based centers are doing important work to promote healthy behaviors—such as screening, healthy eating, and tobacco cessation—through primary care and public health interventions.
- A report published recently in the *American Journal of Public Health* analyzed statistics on several leading causes of death in the United States over the last 50 years. It was found that most of the diseases for which at least a 50 percent reduction in age-adjusted death rate occurred between 1950 and 2000 exhibited "triangulation," meaning that researchers, public health professionals, and primary care providers worked together to ensure that innovations were developed and disseminated.
- The research innovations driven by NCI are critical to reductions in cancer-related mortality and morbidity. HRSA, as a health care delivery system, can use its infrastructure to support research and help widely diffuse the results of this research through its primary care and public health channels.
- HRSA is poised to make contributions to the NCP in key areas. Chief among those are addressing longstanding research challenges—such as establishing and maintaining trust with safety net communities and improving enrollment of more diverse populations in research—and building evidence not just through research but through practice.

DR. GEORGE SLEDGE:

THE CLINICAL TRIALS INFRASTRUCTURE AND THE FUTURE OF CANCER RESEARCH

Background

Dr. George W. Sledge, Jr., is President of the American Society of Clinical Oncology (ASCO). He is also the Ballve-Lantero Professor of Oncology and Professor of Pathology and Laboratory Medicine at Indiana University School of Medicine and the Simon Cancer Center. He received his undergraduate degree from the University of Wisconsin and his medical degree from Tulane University. He completed his residency at St. Louis University and his fellowship at the University of Texas, San Antonio. Dr. Sledge's research interests include molecular and tumor biology, growth factors, and cytokines related to breast cancer.

Key Points

- It has been stated that the field of cancer research has entered a revolutionary era, made possible by the proliferation of so-called "omics" (i.e., genomics, proteomics, metabolomics), the availability of new compounds through computational chemistry, the increase in data availability for all cancer researchers, and the digitization of scientific information, which has the potential to exponentially increase the ability to collaborate . However, revolutionary progress has not occurred in the clinic.
- The time to develop, initiate, and complete Phase III trials has increased steadily in recent years and, not coincidentally, has been associated with an increase in the regulatory burden on those performing trials. The U.S. clinical trials workforce has shrunk in the face of increasing globalization of clinical research science. NCI funding for the Cooperative Groups has significantly declined over the last decade. As a result, the number of new molecular entities reaching the clinic has decreased in recent years.
- A biomarker-driven approach to cancer research adds additional burdens to the clinical trials infrastructure. Biomarker research, for example, necessitates special requirements for the collection, transportation, and analysis of samples, as well as special regulatory requirements. In addition, identifying and accruing patients to trials testing drugs that target specific mutations found in only small populations is difficult, particularly for cancers that are not diagnosed in a large number of people. Finally, the issue of "genomic chaos"—the fact that there are multiple drivers for most cancers but not the same multiple drivers in most patients within a cancer— presents immense challenges.
- Underlying these challenges is the need for a trained clinical trials workforce. Unfortunately, participation in national Cooperative Group trials is detrimental to one's career. There are conflicting demands on time, even within academia: clinicians in hospital systems have heavy patient-care and administrative workloads and share teaching roles with their laboratory colleagues. Clinicians also face lack of career advancement for participating in these trials. These problems are exacerbated in nonacademic settings.
- Solutions exist to overcome these challenges. First, the Cooperative Group system must be revamped with the input and active cooperation of FDA, CMS, academic and practice sites, and the Cooperative Groups themselves. Second, health information technology should be used to drive clinical research; the systems used by the VA and CMS are models for this. Third, the regulatory landscape within which clinical trials are conducted must be reenvisioned. Fourth, novel clinical trials methodologies must be developed. Finally, the clinical trials workforce must be revitalized.

DISCUSSION AND CONCLUDING COMMENTS:

PANEL I

Key Points

- The operational definition of the NCP should be to extend life through prevention and treatment of cancer and to improve quality of life for those living with cancer. Attention should also be paid to reducing the costs of cancer control and treatment.
- The NCP seems to lack a set of priorities, goals, and objectives. The Affordable Care for America Act charged the Secretary of the Department of Health and Human Services (HHS) to determine national priorities for quality of care and to collect and report quality-related data. Identified priorities and a strategic plan for achieving them will be delivered to Congress by January 1, 2011. A strategy for disease prevention is currently being developed through a similar process and should be made public by March 2011. The Affordable Care Act also called for the formation of an Interagency Working Group chaired by the President to oversee the implementation of the components of the Act. The

Panel should consider recommending to the President that cancer be included as a major focus in these efforts.

- The current administration has implemented a number of trans-HHS working groups to address a number of areas of interest, including tobacco, obesity, and hepatitis infection. The Panel may want to consider recommending the formation of a trans-HHS group focused on cancer. It is important that trans-HHS and other coordinated efforts be focused on specific goals (e.g., improving certain processes) and be transparent to those outside of the Federal Government.
- There are many competing requests to serve on committees related to various aspects of health care. People and organizations would be more likely to participate in an effort to build a collective vision for the NCP if the call to do so came from an influential source such as the President. In addition, strong leadership and resources (including support staff) are needed.
- It is important that any NCP strategy address the entire cancer continuum. In addition to improving treatment, efforts should be made to implement proven interventions to address known risk factors (e.g., smoking, obesity) in meaningful ways in order to reduce the risk of cancer. In addition, there should be frank discussions about end-of-life care so that patients are not given unnecessary chemotherapy and are provided appropriate palliative care services. Although this could result in considerable cost savings, cost is not the only reason for having these discussions—they will also result in more appropriate patient care.
- When envisioning the future of the NCP, it is important to ensure, to the extent possible, that the strategies implemented will be sustainable over time. This includes strategies related to health care costs, drug development, treatment, regulation of potentially carcinogenic chemicals, and quality improvement.
- When considering the future of the NCP, stakeholders should identify and clearly define the most urgent problem or a small number of problems that need to be solved. Identifying these priorities by committee—particularly a trans-agency committee—may not be the most effective approach; such groups often work slowly, with participants' interest waning over time. It is sometimes useful to have a priority identified by someone in an influential position, such as the First Lady championing work in the area of childhood obesity.
- Identification of priorities for the NCP is complicated by the fact that cancer is a set of diverse diseases. It may be more effective to develop priorities for more granular components of cancer (e.g., advanced breast cancer). The cancer control continuum graphic may be a useful tool for helping to identify the most promising opportunities for evidence-based intervention for various cancer types and subtypes.
- A vision for the NCP should include efforts to address the delivery of care. The elements of effective care delivery environments must be identified in order to facilitate quality improvement and cost reduction. Consideration must also be given to how to ensure that guidelines and recommendations for best practices are followed in the diverse care delivery environments and populations across the United States.
- There seems to be a lack of coordination and communication among the federal agencies and programs that address cancer. At a minimum, the HHS components involved in cancer (e.g., NCI, FDA, CMS, CDC) should be aware of ongoing relevant activities across HHS. This knowledge will likely lead to opportunities for collaboration, which should enhance the quality of the work being done. In particular, there should be links between research, practice, policy, and education.
- There are silos within the Federal Government—people view themselves as employees of a certain agency, even within HHS, rather than part of a cross-cutting team working within the larger context of a National Cancer Program. Agencies and programs also often feel intense pressure to accomplish the tasks that have been assigned to them. This can result in very focused activity that does not facilitate collaboration or information sharing among federal entities.

- There are rules and regulations in place that prevent agencies from working in concert. If these agencies were better able to communicate and work together, it is likely that effective therapies would get to patients more quickly and ineffective therapies would be recognized and discarded earlier. One option would be for HHS to have a small number of employees who are able to float between different agencies. This could foster communication and collaboration not just among high-level leadership, but among program staff who are more closely engaged in day-to-day activities.
- There should be standing agreements between federal agencies regarding communication. FDA has established policies regarding communication with Canadian and European regulatory agencies, which facilitates interaction. It was noted that in many instances, FDA communicates more effectively with these foreign entities than with other U.S. agencies. Written agreements regarding communication between HHS divisions are currently generated on an ad hoc basis but it would be useful to have standing agreements that address issues such as confidentiality.
- It is important that partnerships be forged among the various NCP stakeholders, including federal agencies, the private sector, and the public. It was noted that grantees of some community-based federal programs, including the National Comprehensive Cancer Control Program, are required to form multidisciplinary collaborations and engage minority and ethnic populations in order to receive funding. However, the federal agencies and programs working on a national level often fail to create these types of collaborations.
- Staff members from the NCI Division of Cancer Treatment and Diagnosis have monthly conference calls with FDA representatives to provide information to and solicit input from FDA regarding ongoing clinical trials. This type of regular communication is what is needed to achieve functional coordination. Less frequent interactions (e.g., yearly meetings) are not sufficient to meet this goal.
- A collaborative approach to dissemination is being conducted as part of the Cancer Prevention and Control Research Network, a joint effort of CDC and NCI. CDC, NCI, and other federal and nonfederal partners also jointly sponsor Cancer Control P.L.A.N.E.T., a Web portal that provides access to data and resources that can help planners, program staff, and researchers to design, implement, and evaluate evidence-based cancer control programs. In addition, the CDC Division of Cancer Prevention and Control and the NCI Division of Cancer Control and Population Sciences have recently initiated regular conference calls to discuss ongoing activities.
- A memorandum of understanding (MOU) was recently developed between FDA and CMS that will facilitate information sharing between the two agencies regarding the review and use of FDA-regulated drugs and devices. The goal is that drug and device manufacturers will be able to meet simultaneously with FDA and CMS to ensure that clinical trials are designed in a way that addresses the concerns of both agencies. It took approximately five years to generate the MOU, which is currently open for public comment.
- EPA depends heavily on data generated by NIH, academia, industry, and other organizations. There are also some task forces that include representation from EPA and other federal agencies, including the President's Task Force on Environmental Health Risks and Safety Risks to Children, which is co-chaired by EPA and HHS, and the Environmental Justice Taskforce.
- Information about ongoing activities within the NCP is often presented at meetings of the National Cancer Advisory Board (NCAB). Although the NCAB is an advisory board for NCI, these meetings often include discussion of a wide range of activities that would also be of interest to other NCP stakeholders.
- Adoption of electronic health records across the NCP is not an option—it is a necessity. The emergence of high-throughput diagnostic tests such as whole-genome sequencing will generate data that will be unmanageable with current data management and health delivery systems. Robust health information technologies are needed and will ultimately become an integral part of all aspects of research and clinical care. Widespread implementation of EHRs will benefit quality assessments and

may help contain costs. It is important that EHRs be easily transferred between institutions (i.e., systems must be interoperable). It was noted that although the VA has EHRs for care delivered within the VA system, it is not possible to electronically capture information about care patients receive outside of the VA system.

- If interoperable EHR systems were adopted across the country, there would be technological solutions to some of the health care delivery problems facing the NCP. Algorithms could be developed to help providers make decisions about care based on the characteristics of their patients and their patients' tumors.
- The Federal Government should not attempt to create EHR software but should instead create standards and require interoperability of EHR systems.
- The costs of health care cannot be ignored. The VA delivers health care at a rate that is slightly less than half that of health care outside the VA system.
- There should be continued and increased investment in research into the basic biology of cancer. Importantly, a functional, not just descriptive, understanding of cancer biology is needed. This knowledge should inform research, regulatory systems, and delivery of care. A greater understanding of disease biology will lead to development of novel drugs. Many drugs currently under development are "me-too" drugs that are similar to those already in use and are unlikely to transform cancer treatment. It is also essential that mechanisms be developed and sufficient resources be devoted to the translation of scientific findings from the discovery phase to something that can be implemented to reduce cancer risk or effectively treat cancer.
- It is important to focus resources on primary risk factor reduction (e.g., smoking cessation, reduction of obesity). In this regard, more community-based research is needed to identify the environmental factors that can help reduce risk.
- A more refined approach is needed for the management of chemicals. Under the current system, chemicals can be in use for several decades before their ill effects are documented. The burden of establishing the safety of chemicals should be shifted from the government to industry.
- The current clinical trials regulatory system is the result of sequential changes often made in response to unfortunate events and is not effective or efficient. It is particularly ineffective for multicenter, international trials for which the IRB review and adverse event reporting process can be very cumbersome. The regulatory system needs to be redesigned for the 21st century based on thoughtful consideration of what needs to be accomplished. Trials need to be activated more quickly and need to be available where patients are being treated, even though there will be only a few eligible patients at any given site. This is even more critical as marker-based trials become the norm, as there will likely be fewer eligible patients at any given site. Although challenging, it is possible to resolve the problems with the clinical trials regulatory system.
- Researchers working in the realms of discovery and development need to consider how their findings will be translated and or disseminated. Research will not benefit the public unless it can be successfully applied in real-world situations.
- There is often discussion of the importance of translating from the "bench" to the "bedside," but it is also important to conduct "curbside" research to gain practical information about the populations being served by the NCP. Curbside research has relevance to cancer prevention, identification of environmental factors in cancer, dissemination of interventions, and cost reduction.
- The NCP cannot ignore the factors outside of the health care delivery system that influence cancer, including the widespread availability of fast food and the need to further decrease smoking rates, particularly among young people.

- Researchers from disciplines that are not normally involved in cancer research should be engaged in order to gain fresh insights into factors that can influence cancer risk reduction, development of treatments, and delivery of care.
- The costs of cancer care must be brought under control. Many patients who should not be treated are being given medications, and more expensive drugs are often used even when less expensive alternatives exist.
- The President's Cancer Panel should be given the resources necessary to facilitate some of the activities that have been described during the discussion.
- There should be a national program or project devoted to reducing cancer health disparities.

PUBLIC COMMENT

Key Points

- Researchers should develop the discipline of predictive oncology in order to predict the cancer risk of individuals based on their genetic predisposition, environmental exposures, and other factors.
- The National Aeronautics and Space Administration (NASA) has a history of bringing together individuals from various backgrounds to solve problems using a systems approach.
- Rather than working to fractionalize cancer by defining more and more disease subtypes, there should be investment in discovering the underlying mechanisms that drive many types of cancer. In this regard, cancer biology research needs to look beyond the genome and single cell and consider microenvironment and multicellular dynamics.
- The Department of Defense (DoD) has always involved patient advocates in research and invests heavily in cancer research. Representatives from DoD should be involved in conversations about the future of the NCP. DoD was invited to send a representative to this meeting; however, a representative did not attend.
- There is some evidence that cancer is biphasic, with an early initiating event causing the formation of a cancer lesion that may lie dormant and/or undetectable for several years and later exposures or events causing the preexisting lesion to "reawaken" and progress to clinically detectable cancer. Evidence for this notion comes from autopsy analyses of individuals who died as a result of trauma and had not been diagnosed with cancer before their death. A large portion of these individuals were found to have cancerous lesions but it is likely that only a small percentage of these would have eventually progressed to clinically detectable cancer. It may be possible to identify ways to prevent or reduce the risk of these types of early lesions from progressing to a life-threatening stage.

PANEL II

DR. JUDY GARBER:

THE FUTURE OF CANCER RESEARCH: ACCELERATING SCIENTIFIC INNOVATION

Background

Judy E. Garber, M.D., M.P.H, is Director of the Center for Cancer Genetics and Prevention at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School. She is President-Elect of the American Association for Cancer Research, the largest organization of cancer researchers in the world. Dr. Garber is a medical oncologist and clinical cancer geneticist. Her work has focused on the genetics of breast and ovarian cancer and the management of individuals at increased risk for these diseases. Her translational research has recently included the evaluation of novel agents targeting DNA