Board of Scientific Advisors

Meeting Minutes

November 6-7, 2008

Building 31C, Conference Room 10
Bethesda, Maryland

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Meeting Minutes

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 41st meeting on Thursday, 6 November 2008, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, Chancellor, Fox Chase Cancer Center, presided as Chair. The meeting was open to the public from 8:00 a.m. until 4:33 p.m. on 6 November for the NCI Director's report; a report on NCI Congressional relations; an Early Detection Research Network (EDRN) Subcommittee report; a status report on the NCI Community Cancer Centers Pilot (NCCCP) program; ongoing and new business; and consideration of Request for Applications (RFA) new and reissuance concepts presented by NCI Program staff. The meeting was open to the public from 8:30 a.m. on 7 November until adjournment at 12:03 p.m. for reports on the Surveillance, Epidemiology and End Results (SEER) Program; research on RNAi-mediated Epigenetic Control of the Genome and on Nuclear Receptor Interactions; and an update on the Cancer Intervention and Surveillance Modeling Network (CISNET).

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Kirby I. Bland
Dr. Andrea Califano
Dr. Michael A. Caligiuri
Dr. Curt I. Civin
Dr. William S. Dalton
Dr. Robert B. Diasio
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. James R. Heath
Dr. Mary J. C. Hendrix
Dr. Timothy J. Kinsella
Dr. Christopher J. Logothetis
Dr. Kathleen H. Mooney
Dr. James L. Omel

Board Members Present:
Dr. Edith A. Perez
Dr. Richard L. Schilsky
Dr. Stuart L. Schreiber
Dr. Ellen Sigal
Dr. Louise C. Strong
Dr. Jean Y. J. Wang
Dr. Jane Weeks
Dr. Irving L. Weissman
Dr. James K. Willson

Board Members Absent:
Dr. Susan J. Curry
Dr. Leland H. Hartwell
Dr. Leroy Hood
Dr. Marc A. Kastner
Dr. Robert D. Schreiber
Dr. Bruce W. Stillman
Dr. Victor J. Strecher

Others present: Members of NCI's Executive Committee (EC), NCI staff, members of the extramural community, and press representatives.

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IX. Progress Report: Surveillance, Epidemiology and End Results (SEER) Program; Drs. Edwards, Glaser, and Deapen
X. RNAi-mediated Epigenetic Control of the Genome; Dr. Shivinder S. Grewal
XI. Dynamics of Cell-specific Nuclear Receptor Interactions with Regulatory Elements; Dr. Gordon L. Hager
XII. Update: The Cancer Intervention and Surveillance Modeling Network (CISNET); Drs. Feuer, Mandelblatt, Zauber, ad Etzioni

Introduction and Brochure Announcement; Dr. Eric J. Feeuer
Breast Update; Dr. Jeanne Mandelblatt
Colorectoral Update; Dr. Ann Zauber
Prostate Update; Dr. Ruth Etzioni

XIII. Adjournment; Dr. Robert C. Young

I. CALL TO ORDER AND OPENING REMARKS - DR. ROBERT C. YOUNG

Dr. Robert C. Young called to order the 41st regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. He reminded Board members of the conflict-of-interest guidelines and

confidentiality requirements. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

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II. CONSIDERATION OF THE 23–24 JUNE 2008, MEETING MINUTES - DR. ROBERT C. YOUNG

Motion: The minutes of the 23–24 June 2008 meeting were approved unanimously.

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III. REPORT OF THE DIRECTOR, NCI — DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, welcomed new and continuing Board members and thanked them for their service.

Budget. Dr. Niederhuber informed members that research project grants (RPGs) were funded at the 14th percentile with a 20 percent success rate, including exceptions. New investigator awards were funded at an extended payline of 19th percentile. The NCI funded 1,248 competing RPGs and added the Greenebaum Cancer Center, University of Maryland, as a new cancer center. The fiscal year (FY) 2009 President's Budget for the NCI is $4.809 B, a +0.1 percent difference from the FY 2008 funding level. The NCI adheres to NIH policies, including funding non-competing grants at 90 percent of the commitment level and providing a 1 percent inflation allowance in FY 2009. FY 2009 commitments for non-competing grants are expected to decrease by $30 M, but competing grants likely will be funded close to the FY 2008 level. Dr. Niederhuber reminded members that the Congressional appropriations for the NCI is approximately $4.8 B and is expected to remain at that level for several years.

NCI Activities. The NCI supports and often sets the standards for research in a number of fields that span the NIH, such as

information technology through the cancer Biomedical Informatics Grid (caBIGTM), drug development, nanotechnology, proteomics, biorepositories and biospecimens, clinical trials, and translational research. During the past year, the NCI held meetings with experts in the physical sciences to help cancer biologists view cancer from a different viewpoint to intensify and speed up cancer research and therapeutics. Additionally, the Cancer Genome Atlas (TCGA) has made significant inroads in studying sequencing, gene expressions, and DNA copy number and methylation in glioblastoma cancer, and has begun work on ovarian and lung cancers. The challenge with the whole genome association studies, pharmacogenomics, and TCGA is how to monitor the outflow of information and expedite decisions about the emphasis and resources for the assay system to address the genetic and pathway alterations that are discovered by the programs. Another aspect is the involvement of the private sector in the process. Additionally, translational science is undergoing a paradigm shift, with a focus on multiple, highly targeted agents matched to molecularly selected patients. The NCI has begun to consider a new clinical trials structure for this type of drug discovery and patient intervention to facilitate patient-centered cancer research aimed at individual patients.

Clinical Trials System. The NCI is considering ways to refine and change its clinical trials system to attain greater efficiency. One activity involved the CEO Roundtable on Cancer, the Life Sciences Consortium with representatives from 11 pharmaceutical companies, and representatives from the NCI Cancer Centers. The group has 1) identified common language, intellectual property, and antitrust as significant issues; and 2) worked during the past year to analyze clinical trial agreements and to identify key clauses on intellectual property, study data, subject injury, indemnification, confidentiality, publication rights, and biological samples, that need to be dealt with in each contractual relationship. On 17 September, the Department of Justice (DOJ) issued a press release announcing that the DOJ “will not oppose a proposal by the CEO Roundtable on Cancer to develop and publicize model contract language for clinical trials of potential new cancer treatments.”

Impact of Federal Dollars. Dr. Niederhuber encouraged members to consider the impact of federal dollars invested in communities. In 2007, the NIH awarded close to $23 B in research grants and contracts, which created more than 350,000 jobs nationwide, generated more than $18 B in wages from those jobs, and spurred

more than $50 B in business activities. NCI funding represented 13.3 percent of the NIH research grants and contract funding, and expenditures generated $7.8 B in state economic output, which is approximately $2.57 of increased economic activity for every dollar of NCI research funding. In FY 2007, NCI funding supported more than 54,000 jobs, which generated more than $2.84 B in wages and salaries. Thus, in addition to curing cancer, the federal investment is about the creation of new knowledge and understanding of biology and biologic processes, behavior, disease prevention, education, and communication. The NCI continues to face multiple challenges, including more years with less-than-inflation budgets, providing leadership and resources to academia and industry, attracting the bright young investigators to work in biomedical research, building the translational program of the future, understanding knowledge management at the NIH, and finding new ways to think about cancer.

In discussion, the following point was made:

- A future agenda item should be an update on proteomic initiatives supported by NCI and the NIH.
- The BSA requested that staff provide sources for data on the impact of NIH and NCI dollars invested in communities, including employment and wages as well as any additional data on the economic impact of prevention or early detection

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IV. NCI/CONGRESSIONAL RELATIONS - MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on the status of FY 2008 and 2009 appropriations, as well as legislation of interest to the BSA and recent Congressional hearings. New public laws include the Caroline Pryce Walker Conquer Childhood Cancer Act (H.R. 1553, PL 110-285), which was signed into law on July 29, 2008, expands pediatric cancer research, facilitates early access to treatment, makes treatment available to underserved patients, and mandates a national childhood cancer registry, and the Breast

Cancer and the Environment Research Act (H.R. 1157). Ms. Erickson described other legislation of interest and recent Congressional hearings on biospecimen resources and cell phone usage. Testimonies for hearing are available on the OGCR web site: http://legislative.cancer.gov/hearings.

In discussion, the following point were made:

- The Childhood Cancer Act and the Breast Cancer and Environment Research Act are authorization bills but do not provide appropriations.

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V. EDRN SUBCOMMITTEE REPORT - DR. SANJIV S. GAMBHIR

Dr. Sanjiv S. Gambhir, Professor, Department of Radiology and Bio-X Program, and Director, Molecular Imaging Program, Stanford University School of Medicine, reported on the Subcommittee's review of the Early Detection Research Network (EDRN). Dr. Gambhir informed members that the Subcommittee was charged with reviewing the program based on the BSA's earlier concerns about: 1) the program productivity and return on investment; 2) the processes for initiating projects; 3) assurance of a fair and open process for competition for funding that includes appropriate extramural participation; 4) decision points for validation and application phase and the decision to continue funding specific projects for marker development; and 5) EDRN governance and the functioning of the committees.

The Subcommittee met three times by conference call with program staff. After the review of the written report and the initial conference call, the Subcommittee requested more concrete examples of the EDRN processes, as well as additional information on productivity, decision points, and the review process. Following the second call where investigators presented their science and described how the EDRN was assisting them, the Subcommittee became confident that the EDRN project was functioning properly.

The EDRN program has developed an infrastructure that allows

investigators to rapidly put forward new biomarker discoveries through the validation process, trials, and licenses. The Subcommittee also examined issues of discovery and developmental projects, EDRN's support of different projects, international outreach, flexibility and capability to work on several markers simultaneously, and the significance of biospecimen reference sets, as well as inclusiveness and use of core funds to support collaborative activities with investigators outside the EDRN. The EDRN has developed more than 84 biomarkers, launched five validation studies, two of which are completed, published 500 papers, and approved more than 28 patents and 14 licenses.

To refine the EDRN functionality and the perception of how EDRN works, the Subcommittee recommended: 1) that the term of the steering committee chair be limited to 5 years; 2) establishment of a BSA EDRN subcommittee to meet periodically and function as an external advisory group; 3) that the EDRN steering committee serve as a governance body, and review of the current steering committee and executive committee to enhance inclusiveness and transparent management of the program; and 4) improvement of overall communication of the program as well as internal communication.

In discussion, the following point were made:

- Patient advocacy groups should be involved in EDRN outreach campaigns and other activities.
- NCI should consider establishing a BSA subcommittee to provide input to the EDRN with reviews occurring from twice a year to once every 2 years.
- EDRN's use of statistical and modeling techniques should be strengthened to ensure that the correct biomarkers are selected.
- The EDRN should be brought more effectively into the issues related to understanding dynamic modulation and the biology of cancer and clinical trials outputs. Subcellular imaging likely will be meaningful as a biomarker of targeted therapy.

Motion. A motion to accept the report of the BSA Early Detection Research Network (EDRN) Subcommittee was approved with 27 yeas, 1nay, and 1 abstention.

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VI. STATUS REPORT: NCI COMMUNITY CANCER CENTERS PROGRAM—DRS. JOHN NIEDERHUBER, MAUREEN R. JOHNSON, MARK KRASNA, THOMAS PURCELL, AND STEVEN CLAUSER

Dr. Niederhuber introduced the NCI Community Cancer Centers Program (NCCCP) as a pilot project that allows the NCI to have a presence in the communities where cancer patients live, work, and receive their care. Dr. Maureen R. Johnson, Project Officer, NCCCP, provided an overview of the Program and introduced the speakers: Drs. Thomas Purcell, NCCCP principal investigator (PI) and Director of the Billings Clinic Cancer Center, Division Chief, Service Lines; Mark Krasna, PI and Medical Director, St. Joseph Medical Center Cancer Institute, PI, Catholic Health Initiative (CHI); and Steven Clauser, Chief, Outcomes Research Branch, NCI Project Officer, NCCCP Evaluation.

Overview - Dr. Maureen R. Johnson

Dr. Maureen Johnson informed members that the NCCCP's focus on disparities, quality of care, and information technology (caBIGTM) addresses the full cancer continuum. Dr. Johnson stated that the program complements many NCI initiatives through its development of a strong hospital-based community center network that support the research infrastructure and involves hospital management to address sustainability. Six community hospitals in urban and semi-rural areas, two rural hospitals that serve Native Americans, and two multistate health systems with multiple program locations participate in the program which has sixteen hospital sites.

NCCCP sites have specific deliverables with metrics for each core component. Deliverables for health care disparities include: an increased outreach to disparate populations; increased community partnerships; increased primary care provider linkages, screening resources, and capacity; and expansion of patient navigation

programs. Clinical trials are expected to experience an increase in overall accruals, increased physician participation, identification of infrastructure needed to conduct early phase trials in community hospitals, and identification of patient and physician barriers to enrollment. Quality of care deliverables involve the increase of multidisciplinary, organ site-specific care as well as use of evidence-based guidelines, expansion of genetic and molecular testing programs, and adoption of cancer center-specific medical staff conditions of participation. Additional deliverables focus on biospecimens, information technology (IT), survivorship, and palliative care.

Progress has been made in building a NCCCP network, as well as establishing collaborations in the community and across the cancer enterprise. Hospitals are sharing tools, protocols, program, and approaches to overcome barriers. The NCCCP model addresses a major block in the cancer research continuum, that is, the translation of clinical trials into everyday clinical practice and decision making, and provides a multidisciplinary model for use in community settings that is applicable to other chronic diseases.

Billings Clinic NCCCP Site — Dr. Thomas Purcell

Dr. Thomas Purcell stated that the Billings Clinic in Montana, which is an NCCCP site, is a multispecialty clinic with an academic-like structure. Dr. Purcell informed members that the Clinic's work as a NCCCP member is synergistic with that of the Montana Community Clinical Oncology Program (CCOP), with the CCOP providing a foundation for clinical trials and the NCCCP providing regional research infrastructure, as well as "outreach" to rural, underserved populations, that would otherwise not be present. In addition, the NCCCP offers a unique opportunity to serve American Indian populations, particularly for cancer and cardiovascular care. NCCCP metrics for the Billings Clinic pilot project are to increase cancer screenings in rural areas, increase accrual for clinical trial patients with specific emphasis on the American Indian population, and increase the number of physicians participating in multidisciplinary care across the region. The program also aims to create new NCI-NCCCP collaborative trials and increase the number of patient samples entered into the biospecimen repository.

The NCCCP has been a significant factor in galvanizing cancer care for the entire region as well as in the Billings Clinic's growth. The Billings Clinic is now a regional leader in cancer research, with the resources needed to conduct high-level and complicated clinical trials and to offer unique oncology therapy that would not otherwise be available. It has created access to NCI sponsored clinical trials, including phase I, II and III trials, in rural areas and access to NCI biospecimen and caBIG technology expertise. The NCCCP helps overcome challenges faced in delivering care to the American Indian and rural populations, including lack of access to prevention/screening services and treatments because of inadequate Indian Health Service (IHS) funding, as well as long distances and cost of travel. Understanding tribal cultural norms and gaining individuals' trust is critical to the Program's outreach. Dr. Purcell noted that the implementation of telemedicine in most rural communities has helped improve access to care.

Catholic Health Initiative (CHI) NCCCP System Site — Dr. Mark Krasna

Dr. Mark Krasna described the CHI which provides cancer care for nearly 250,000 patients per year in 80 hospitals in association with 45 cancer centers across 20 states. Five hospitals are participating in the pilot: St. Joseph Medical Center, an urban Baltimore facility that assists patients from large African American, Hispanic, and Latino communities; Penrose-St. Francis Health Services, which services a low-income, medically underserved area of Colorado Springs; and a consortium of three hospitals in rural Nebraska, a region with limited access to cancer care.

In its first year, Dr. Krasna reported that the CHI NCCCP has made progress in promoting multidisciplinary care through its work in health disparities, biospecimens, quality of care, survivorship, and accruals to clinical trials. Specifically, outreach and screening have been expanded at all sites, cancer information services were implemented, and patient navigator programs were created that integrate the clinical aspects of multidisciplinary management and reduce disparities in health care. Monthly conference calls between the CHI sites and quarterly retreats have allowed consistent sharing

of best practices. Through the group cooperative mechanism, the CHI NCCCP has expanded access to clinical trials. A new center for translational research at St. Joseph's Cancer Institute will collect tissues from the 250,000 cancer patients seen at CHI sites and store them in one unique facility, governed by Office of Biorepositories and Biospecimen Research (OBBR) Best Practices. Additionally, the CHI Oncology Network (CHON) is bringing NCCCP best practices into other CHI cancer programs.

The NCCCP pilot provides a new way to promote a public-private partnership, brings translational research to the community, and offers a model for widespread dissemination of patient-centered, multidisciplinary cancer care.

NCCCP Evaluation — Dr. Steven Clauser

Dr. Steven Clauser described plans for the evaluation of the effectiveness of NCCCP pilot sites, particularly in relationship to clinical practice and improvements of health in the population. Dr. Clauser informed members that the evaluation will consider changes in the six program components (i.e., health care disparities, clinical trials, quality of care, survivorship, biospecimens, and information technology) and changes in the cancer service line overall that NCCCP facilitates; organizational requirements, including establishment of partnerships within communities and with other pilot sites; and issues surrounding program sustainability and replication. The evaluation will consider case studies involving quantitative and qualitative measures of sites, as well as patient surveys and economic studies. All NCCCP sites were visited in the spring of 2008, and coding and analysis of Year 1 data are underway. The results of NCCCP's evaluation on cross site studies, patient surveys, and economic study reports will be regularly disseminated to NCI leaders and advisory boards.

Following the presentations, Drs. Carolyn Compton, Director, NCI OBBR, and Kenneth H. Buetow, Director, NCI Center for Bioinformatics, commented on the NCCCP in terms of NCI's efforts in biospecimens and bioinformatics. The program has provided a critical prerequisite to directly connect to the care delivery community and create the next generation of infrastructure

to access information on biospecimens and patient encounters, and support clinical trials that are driven by molecularly characterized markers. Dr. Niederhuber noted that the NCCCP has provided a means for local communities and their leaders to participate in the national cancer program and feel a connection to the NCI.

In discussion, the following point were made:

- The NCCCP brings a specific focus on health disparities and quality of care in rural settings that the CCOP funding does not provide.
- NCCCP sites should consider partnerships with other cancer centers to assist in providing researchers access to NCCCP specimens, such as viable cell suspensions frozen in small aliquots from Native American populations.
- To ensure the sustainability of improving access and delivery, the NCI should develop a business plan to identify stakeholders, such as third-party payers and the pharmaceutical industry, to assure the private sector about the return on its investment. Also, engage the Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), or other agencies in public health delivery components to determine other ways that NCCP could help move health services forward.
- The NCCCP evaluation plan should be revised to examine research metrics (i.e., defined as taking established knowledge with a firm evidence base and studying how to get it out to the world), rather than quality improvement and public health delivery.
- The various systems used by NCCCP sites to maintain electronic health records are compatible with caBIG to facilitate collaboration and possibly populate clinical trial case report forms.
- This program is a great opportunity to study how personalized medicine and genome based diagnostics will be applied in the community setting. It was noted that the NCI is considering the creation of several state-of-the-art technology centers that would serve as a resource.
- The NCI should appoint a task force to develop a plan to address needed improvements to the quality of care for cancer patients and investment in health service research, as well as to create a strategy to involve other stakeholders to assume public health responsibility.

- Evaluation of the NCCCP pilot should cover productivity, sustainability, exportability to other communities, and leverage. NCI should consider defining what constitutes a successful community oncology program.

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VII. ONGOING AND NEW BUSINESS

BSA Annual RFA Concept Report — Drs. Robert C. Young and Paulette S. Gray

Dr. Young presented the annual report on RFA concepts from 1996 through June 2008. Information is reported by the date the concept was presented to the Board and by the Division in which the concept originated. Also included in the report are: 1) RFA grant funding and overall NCI grant funding, BSA-approved RFA concept set-asides by Division, RFA allocation by concept area, and total NCI grant and RFA funding by concept area as a percentage of total NCI grants; 2) a listing of funded grants; and 3) abstracts of the funded grants in hardcopy and CD-ROM formats. The report has been generated annually since the initial BSA request in 1999, to provide background information relevant to the concept review role played by the BSA. Dr. Gray provided examples of how members could use the book and briefly explained the internal process for concept development and review at the NCI.

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VIII. RFA/COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Office of the Director

Physical Sciences – Oncology Center (RFA/Coop. Agr.)

Dr. Anna D. Barker, Deputy Director, Office of the Director, stated that recent advances in defining the range of changes in cancer cells have emphasized the need to understand the physics of these highly complex systems. Dr. Barker described a series of three meetings held with the extramural communities, including physicists, mathematicians, physical chemists, engineers, cancer biologists, and oncologists, to explore the physics of cancer, complexity and evolution of cancer, and coding/decoding/transfer of information. The overall theme that emerged from the meetings was that the perspectives of the physical sciences would provide new conceptual approaches that could lead to major advances in the understanding of cancer.

The NCI proposes to build a collaborative network of Physical Sciences – Oncology Centers that will bring physical scientists and cancer researchers together to address key questions in cancer research that involve physical laws and principles. New teams in the collaborative centers would develop and carry out projects in four research theme areas: 1) understanding the physics of cancer; 2) exploring and understanding evolution and evolutionary theory in cancer from a physics perspective; 3) understanding the coding, decoding, transfer, and translation of information in cancer at the molecular and submolecular levels; and 4) “de convoluting” the complexity of cancer through the development of physics-based modes of understanding cancer complexity. Each center would adopt two to four synergistic theme projects and research capabilities would be collaboratively linked through multiple centers. It is proposed to develop four to six centers, to be funded for 5 years beginning in 2009, with each center consisting of one to three institutions, with two to four synergistic theme projects and shared resources and capabilities.

Subcommittee Review. Dr. James R. Heath, Elizabeth W. Gilloon Professor and Professor of Chemistry, California Institute of Technology, said that the subcommittee supported the framework that had been proposed. The physical sciences represent a community that has not been engaged significantly in most areas of cancer research, but has much to contribute. Theorists from the physical sciences may be able to develop a theoretical framework for incorporating vast amounts of data. Enthusiasm was expressed about the potential value of rational engineering—an approach that

may allow for an exponential increase in scientific progress, rather than the incremental gains usually seen in cancer research. A potential argument against the concept is that it is less concrete in its specific goals than some other proposed initiatives. However, the potential for gain is so great, the risk is likely to be worthwhile.

The first year cost is estimated at $21M for 4-6 awards and a total cost of $105 M for five years.

In the discussion, the following points were made:

- The merits of establishing a center structure versus investing in individuals who want to apply their knowledge of the physical sciences to cancer were discussed. The center model may be more conducive to large jumps in scientific progress and offers flexibility and an infrastructure for continued research.
- The Web site URL for the Physical Sciences meetings should be distributed to the BSA.
- This program might be enhanced by the involvement of other agencies, including the Defense Advanced Research Projects Agency (DARPA), the Department of Energy (DOE), and the National Science Foundation (NSF).
- A potentially limiting factor in the application of the physical sciences to cancer research is the difficulty of measuring physical environments in vivo in humans.

Motion. A motion to concur with the Office of the Director's (OD) Request for Application (RFA)/Cooperative Agreement (Coop. Agr.) entitled "Physical Sciences – Oncology Center" was approved with 22 yeas, 4 nays, and 0 abstentions.

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Division of Cancer Control and Population Sciences and Division of Cancer Biology

Stress Regulation of Tumor Biology (RFA/Coop. Agr.)

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), introduced the concept by reminding members that one of the most common questions cancer patients ask their physicians is whether stress influences the progression of their disease. Dr. Croyle stated that the NCI has sponsored a series of workshops and meetings on stress and cancer and is now proposing to further explore this controversial, high-risk area of research.

Dr. Paige McDonald, Chief, Basic and Biobehavioral Research Branch, Behavioral Research Program (BRP), DCCPS, informed members that the purpose of the proposed RFA is to increase understanding of how chronic stress may influence the course of disease in cancer. More specifically, the RFA would seek to support research on the biological and clinical relevance of stress mediators and corresponding receptors within tumors and to investigate the molecular mechanisms and signal transduction pathways by which stress may influence tumor progression and metastasis. The RFA would support transdisciplinary collaborations of cancer and stress biology experts to expand the range of tumor types and tumor biology parameters analyzed for regulation by stress biology.

Using both the R01 and R21 funding mechanisms, the proposed RFA would support 8 to 10 awards, The R01 applications would be required to use human/clinical samples, and encouraged to use the multiple PI designation and include comparative studies with other model organisms. The RFA would be evaluated by determining whether it promoted the discovery of tumor types most subject to influence by stress, the mechanisms involved in that influence, relevant biomarkers of stress in tumor tissue or serum, and molecular and therapeutic targets.

Subcommittee Review. Dr. Mary Hendrix, President and Scientific Director, Children's Memorial Research Center, and Professor of Pediatrics, Feinberg School of Medicine, Northwestern University, informed members that the subcommittee had concluded that the RFA was premature because of a lack of convincing evidence of a direct relationship between the biology and clinical outcome. A program announcement (PA) may be more appropriate to help identify investigators interested in this research area. Moreover, the currently available evidence does not support a

RFA because of the limited ability to assess associations between stress and tumor biology and link them to human disease endpoints. The types of assessments used in previous studies, such as questionnaires and measurement of serum cortisol levels, are not sufficiently focused to allow conclusions to be reached about human disease; more specific methodology is needed.

The first year cost is estimated at $4.5 M for 10 awards and the total cost at $14.6 M for 2-year R21 awards and 4-year R01 awards.

In the discussion, the following points were made:

- Standing study sections may not have the appropriate expertise to review proposals on the relationship between stress and tumor biology. A special emphasis panel or additional ad hoc experts may be needed.
- The proposed focus on the neurobiology may be too narrow. A broader concept may encourage other scientists to pursue research in this area.

Motion. A motion to concur with the Division of Cancer Control and Population Sciences' (DCCPS) and Division of Cancer Biology's (DCB) RFA entitled "Stress Regulation of Tumor Biology" was deferred. A BSA subcommittee composed of Drs. Mary Hendrix (Chair), Michael Caliguiri, Susan Curry, and Kathleen Foley was established to work with NCI program staff to address issues raised in discussion.

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Office of the Director

The Cancer Genome Atlas (TCGA) Network: Genome Characterization (GCCs) and Genome Data Analysis Centers (GDACs) (RFA/ Coop. Agr. Reissuance)

Subcommittee Review. Dr. Stuart L. Schreiber, Morris Loeb Professor and Chair, and Director, Chemical Biology Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Harvard University, informed members that the subcommittee enthusiastically concurred with the proposed competitive one-time reissuance of the TCGA RFA Network. Dr. Schilsky noted that the mission of the Network's pilot project was to assess the feasibility of a full-scale effort to identify and catalogue genomic alterations, including mutations, translocations, methylation of chromatin marks, and gene expression, using three different cancer types: brain, lung, and ovary. The pilot studies already completed have provided valuable information, despite the difficulty in obtaining high-quality tissue, and have demonstrated that the requisite infrastructure for creating the network is now in place. He stated that the network has tremendous potential for transformative advances in the classification and improved treatment of cancers. The goal of four to six tumors per year in the proposed RFA is both ambitious and realistic. Other groups working in the same area, outside of TCGA NCI-funded projects, have developed alternative approaches with different results; thus, openness to a variety of strategies is appropriate. An effort should be made to consider any mechanism that would enable the joining together of data be publicly accessible.

The first year cost is estimated at $18 M for 10 to 12 U24 awards, and the total cost is estimated at $100 M for 5 years.

In the discussion, the following points were made:

- Future updates on TCGA's progress should be provided to the BSA.
- Specimen acquisition will be funded in a separate request for proposal (RFP).
- Coordination with other NCI programs, such as the Special Programs of Research Excellence (SPORE), NCCCP, and CCOP, could enhance the acquisition of pathological samples of appropriate quality and quantity.
- The next research phase should allow open competition for investigators to submit candidate genes.
- The renewal should address the issue of providing investigators with better access to the data in a form that is easy to analyze.

Motion. A motion to concur with the OD's RFA/Coop. Agr. re-issuance entitled "The Cancer Genome Atlas Network: Genome Characterization (GCCs) and Genome Data Analysis Centers (GDACs)" was approved with 24 yeas, 0 nays, and 2 abstentions.

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Division of Cancer Biology

The Integrative Cancer Biology Program (ICBP): Centers for Cancer Systems Biology (CCSB) (RFA/Coop. Agr. Reissuance)

Subcommittee Review. Dr. Jean Y.J. Wang, Distinguished Professor of Medicine, University of California at San Diego (UCSD), School of Medicine, and Associate Director of Basic Research, Moores UCSD Cancer Center, reported that the subcommittee strongly supports reissuance of the CCSB Coop. Agr. Dr. Wang stated that the concept is timely, and the centers are very well managed, with a variety of disciplines working well together to address different aspects of the cancer problem from initiation to progression to metastasis, using interdisciplinary approaches involving experts in a variety of fields. The goal of the re-issuance, to continue developing cancer systems biology and to create predictive mathematical models for experimental cancer research, is clear. The ICBP and TCGA are complementary and important programs since both generate functional data, rather then simply mutation-based. The reissuance is well justified and is planned as a full and open competition.

The BSA requests a written report from NCI staff on how many applications were reviewed and selection criteria for funding after awards are made.

The first year cost is estimated at $22.5 M for 8 to 10 U54 awards, with an estimated total cost of $112.5 M for five years.

Motion. A motion to concur with the Division of Cancer Biology's

(DCB) RFA/Coop. Agr. reissuance entitled “The Integrative Cancer Biology Program: Centers for Cancer Systems” was approved with 16 yeas, 0 nays, and 4 abstentions.

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Office of the Director

NCI Alliance for Nanotechnology in Cancer (RFA/Coop. Agr. Reissuance)

Dr. Piotr Grodzinski, Director, Nanotechnology for Cancer Programs, Office of the Director, provided an overview of the program which consists of an integrated model of centers, platforms, and training programs that have been successfully established. Dr. Grodzinski stated that the key accomplishments include: 1) establishing multi-disciplinary teams around scientific focus areas; 2) publication of over 600 peer reviewed papers; and 3) clinical translation with 50 industrial partnerships associated with program diagnostics and therapy. Reissuance will provide for an increased focus on complete technology solutions leveraging collaborative efforts within the centers and across centers and platforms, including a redesigned training program.

Dr. Grodzinski responded to questions submitted by the subcommittee concerning relationship between platforms and centers, balance between technology development and translation, Alliance Challenge projects, clinical input, and the training component. He indicated that the: 1) centers are a network of multidisciplinary hubs consisting of multiple projects ranging from early pilot to mature, with shared resources; 2) platforms represent a “pipeline” of innovative nanotechnologies and topically focused projects that require substantial collaborative development and thus must interact with the centers; and 3) alliance will continue to embrace technology development and will further increase the number of projects with strong potential for clinical translation. Translation will be pursued through the academic medical center/ cancer center that is working as part of a specific project and/or

through spin-off companies established through licensing of the technologies developed in the program. He also stated that the joint Alliance Challenge projects will provide resources and a mechanism to enable groups of investigators representing more than one center or platform to work together on major problems.

In response to an inquiry about changes in the program's training component, Dr. Grodzinski stated that the training component will use the R25 mechanism, which funds training centers, and a K99/R00 component, which can include foreign nationals. Through interaction with the Center to Reduce Cancer Health Disparities (CRCHD), the Centers for Nanotechnology Excellence (CCNEs) will continue to reach out to underserved communities.

Subcommittee Review. Dr. Richard L. Schilsky, Professor of Medicine, Section of Hematology and Oncology, Biological Sciences Division, University of Chicago Pritzker School of Medicine, reported that NCI staff had addressed the subcommittee's concerns, and that the subcommittee unanimously concurred with the re-issuance. Dr. Schilsky informed members that the program also had undergone an internal NIH evaluation which resulted in a positive report with a number of insightful comments. The technology developed under this program is very impressive; its direction toward diagnosis and treatment of cancer and its coupling to clinical work would not be happening at this level without the program. He also noted that in response to the lack of involvement of the clinical oncology community in this alliance, a Clinical Advisory Committee was added to obtain input from clinical oncologists.

The first year cost is estimated at $35 M for 5 to 8 U54 awards, 8 to 12 U01 awards, 4 to 5 K99/R00 awards, and 4 to 6 R25 awards. The total cost is estimated at $170 M for 5 years.

In the discussion, the following points were made:

- The intramural clinical program should become more involved with CCNE products that are approaching the point of clinical development and require a sophisticated level of clinical investigation.
- NCI should consider ways to involve the extramural community as nanotechnology products are prepared for the

clinical.

Motion. A motion to concur with the Office of the Director's RFA/ Coop. Agr. reissuance concept entitled "NCI Alliance for Nanotechnology in Cancer" was approved with 22 yeas, 0 nays, and 2 abstentions.

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IX. PROGRESS REPORT: SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM DRS. BRENDA K. EDWARDS, SALLY GLASER, AND DENNIS DEAPEN

Drs. Croyle and Brenda K. Edwards, Associate Director, Surveillance Research Program (SRP), DCCPS, introduced the SEER program, which was established in 1973 as part of the 1971 National Cancer Act's mandate to collect, analyze, and disseminate data to support the prevention, diagnosis, and treatment of cancer. Dr. Edwards introduced the speakers: Drs. Sally Glaser, Research Scientist, Northern California Cancer Center, and Director, Greater Bay Area Cancer Registry; and Dennis Deapen, Professor, Division of Biostatistics, University of Southern California.

The SEER program is a network of population-based cancer registry programs that provide essential data to inform cancer health policy and practice. Since the SEER program was established, the number of registries has grown to 17, covering 26 percent of the U.S. population, with certain population groups of special interest (such as American Indians, Asians and Pacific Islanders, and members of low-income and rural populations) being intentionally overrepresented. SEER data 1) have validated that people from low-income populations may have lower cancer incidence rates, but are diagnosed with cancer at later stages of the disease and have less favorable outcomes; 2) are widely cited, with more than 5,000 entries in the SEER online bibliography and with tens of thousands of citations of SEER data in publications; and 3) have been used in many landmark scientific studies, including studies on endometrial cancer and estrogen, environmental tobacco smoke and cancer, non-steroidal anti-inflammatory drugs

(NSAIDs) and cancer prevention, and AIDS-related cancers, among other topics.

Dr. Sally Glaser presented examples to illustrate the scientific value of the SEER data and emphasized the program's ability to detect short-term changes in cancer rates, to distinguish among a wide variety of population subgroups, and to monitor rare cancers. Dr. Glaser stated that SEER data have: 1) documented the year-to-year impact of the AIDS epidemic on rates of Kaposi's sarcoma and non-Hodgkin's lymphoma; 2) demonstrated a decrease in breast cancer incidence within a quarter year after discontinuation of postmenopausal hormone replacement therapy in response to the results of the Women's Health Initiative study; 3) demonstrated a significant increase in rare neuroendocrine/carcinoid tumors; and 4) allowed comparisons of rates of specific lymphoma subtypes in different racial groups. The research breadth of the SEER program is enhanced by its linkage to other data sources, including census data, AIDS registries, and Medicare claims. Recently, for example, SEER-Medicare data have been used to analyze the benefits and risks of androgen deprivation therapy (ADT) in men with prostate cancer, demonstrating no survival benefit of ADT among men with localized cancer.

Dr. Dennis Deapen provided information on how the research community can access SEER data using the interactive public portal (seer.cancer.gov), and described the SEER* Stat package and other statistical modeling applications. Dr. Deapen told members that SEER data can be combined with biomedical, behavioral, and risk factor data through the caBIG™ and visualized using new, state-of-the-art tools. Emerging opportunities for the SEER program include the development of faster, efficient, privacy-friendly tools to capture patient data, as well as the integration of SEER data with other data systems to provide support for clinical trials, public information, and pharmacogenomics research. Members were asked for their input regarding how the SEER program might best be leveraged as a resource for the national cancer program, additional data that the SEER program could provide, and additional services that the SEER program could provide to researchers, clinicians, and the public.

In the discussion, the following points were made:

- Consideration should be given to developing a SEER

program that presents the data in a comprehensible public health message for the media and the public. Additionally, NCI should consider strategies for ensuring that SEER data are acknowledged as an NCI product.

- The SEER program should dialogue with the Google Foundation to have the SEER Web site noted as a primary data source in search engines. Also, consider linkage to data for patients younger that Medicare age as well as pursue linkages with HMOs and other insurance providers.
- SEER data may be helpful in investigating whether the recent increase in neuroendocrine tumors might be linked to imaging technologies and screening.
- The issue of whether SEER findings on the effects of ADT use in prostate cancer have led to changes in physician behavior should be addressed.
- More SEER data should be collected on side effects, toxicity, and morbidity.
- Some SEER registries are beginning to address capturing genomic and molecular data on patients.

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X. RNAi-MEDIATED EPIGENETIC CONTROL OF THE GENOME—DR. SHIVINDER S. GREWAL

Dr. Shivinder S. Grewal, Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research (CCR), described recent investigations on RNAi-mediated epigenetic control of the genome. Dr. Grewal informed members that a significant proportion of the human genome consists of repetitive DNA elements, some of which serve as sites for recruitment of protein complexes involved in chromosomal processes and maintenance of higher order chromatin structure. Chromatin structure maintains correct gene expression, prevents inappropriate recombination in repetitive regions of the genomes, and is required for appropriate chromosome segregation during cell division.

Centromeric proteins (CENP-Bs) are highly conserved proteins with DNA binding and dimerization domains and play an important role in genome organization and silencing retrotransposons. In *Schizosaccharomyces pombe*, CENP-Bs localize at and recruit other proteins to TF2 retrotransposons and initiate formation of

repressor complexes at solo long terminal repeats (LTRs) and LTR-associated genes. Loss of CENP-B function is associated with upregulation of genes involved in the cellular stress response and meiosis. CENP-Bs function in protein complexes that are involved in positioning of nucleosomes along the DNA, which is important for maintaining genomic integrity and proper gene regulation. CENP-Bs recruit histone deacetylases (HDACs) and cluster with them at sites called TF bodies. Formation of TF bodies occurs in response to environmental conditions, and modification of the TF bodies correlates with upregulation of genes associated with retrotransposons and genomic stability.

Dr. Grewal described a different mechanism for controlling silencing of repeat elements by CENP-Bs which involves heterochromatin nucleation by an RNAi-dependent mechanism. RNAi targets the CENP-B protein complexes to the correct loci for post-transcriptional gene silencing. Methylation of histones allows RNAi to stably associate with the chromosome and process transcripts produced by the repeat elements to generate more small RNAs. This leads to spreading of heterochromatin and epigenetic gene silencing. Although once thought to be an inert part of the genome, heterochromatin is highly dynamic platform of the genome which allows large protein complexes to be targeted across extended chromosomal domains. These complexes are required for DNA repair, gene expression and silencing, and correct replication and segregation of chromosomes during the cell cycle. Aberrant chromosome segregation or silencing of tumor suppressor genes has implications for the development of cancer and other human diseases.

In the discussion, the following points were made:

- Many human gene promoters are derived from transposable elements; thus yeast studies may be useful for understanding how transposons affect gene expression and genome organization.
- Important future research directions include studying how different sequence specific factors localize to different parts of the genome and how protein complexes play an important role in organizing the genome into higher order chromatin structures.

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XI. DYNAMICS OF CELL-SPECIFIC NUCLEAR RECEPTOR INTERACTIONS WITH REGULATORY ELEMENTS
DR. GORDON L. HAGER

Dr. Gordon L. Hager, Laboratory of Receptor Biology and Gene Expression, CCR, discussed three related topics on: 1) the dynamics of nuclear receptor interaction with regulatory elements in living cells; 2) importance of rapid glucocorticoid receptor (GR) dynamics for functional gene regulation; and 3) the global interaction of nuclear receptors with chromatin. Dr. Hager explained that nuclear receptor interactions with regulatory elements represent the integration of a large number of rapid events that occur in individual cells. Using high speed ultraviolet (UV) laser cross linking techniques, the highly dynamic process of proteins moving on and off chromatin is linked to the chromatin remodeling process and involves the constant turnover of proteins and switching of nucleosome modification states. Constant sampling of regulatory elements by nuclear receptors leads to transitions in promoter structure, resulting in altered promoter activity.

Members were told that this phenomenon has been explored using the GR and its binding element as a model system. Administration of glucocorticoids to cells in a pulsating pattern showed that GR binds its regulatory element during the pulse and comes off when glucocorticoid is absent. In contrast, GR does not disengage from its regulatory element when the synthetic corticosteroid dexamethasone is pulsed, since dexamethasone's high binding affinity for GR prevents the receptor from disengaging before the next pulse is delivered. Thus, nuclear receptors cycle on and off regulatory elements as they release and regain ligand.

The dynamic movement of proteins on and off regulatory elements is linked to chromatin remodeling. DNase I hypersensitivity profiles indicate sites of chromatin remodeling that occur in response to a nuclear receptor or by constitutively active remodeling systems. The majority of GR binding events occur at preexisting hypersensitive sites; however, the receptor can induce hypersensitivity at other sites in a cell type specific manner. For

example, GR can induce hypersensitivity and upregulate expression of the glycocalin 2 gene in mammary, but not pituitary cells. Global analysis of hypersensitivity showed that a given cell type has approximately 100,000 hypersensitive sites, but little overlap exists between cell types.

Cell-specific factors recruit remodeling systems to create constitutively accessible chromatin that permits access by regulatory proteins. DNA and chromatin epigenetic modifications also regulate access of these proteins to their binding sites in a highly cell-specific manner. This concept can be explored in different types of cancer cells to learn whether the epigenetic environment of a critical regulatory element varies in a particular cancer type, providing clues regarding the etiology of various cancers.

In the discussion, the following points were made:

- The regulation model described for GR also applies to the estrogen receptor and the other major steroid receptors.

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XII. UPDATE: THE CANCER INTERVENTION AND SURVEILLANCE MODELING NETWORK (CISNET) DRS. ERIC J. FEUER, JEANNE MANDELBLATT, ANN ZAUBER, AND RUTH ETZIONI

Introduction and Brochure Announcement — Dr. Eric J. Feuer

Dr. Eric J. Feuer, CISNET Program Director and Chief, Statistical Research and Application Branch (SRAB), DCCPS, reviewed the activities of the CISNET, an NCI-sponsored consortium of modelers who are investigating the impact of cancer control interventions on public health using modeling techniques. Dr. Feuer told members that the CISNET was recompeted in FY 2005, with 15 grants funded in breast, prostate, colorectal, and lung cancer and eight affiliate members funded through other mechanisms. The CISNET involves a comparative modeling

approach where all CISNET modeling groups use a common set of inputs and outputs, thus avoiding the differences in target population, sensitivity, and other variables that may lead to disparate results in modeling efforts. Dr. Feuer introduced the other speakers: Drs. Jeanne Mandelblatt, Associate Director for Population Sciences, Lombardi Comprehensive Cancer Center, Georgetown University; Ann Zauber, Associate Attending Biostatistician, Sloan-Kettering Institute for Cancer Research; and Ruth Etzioni, Full Member in Biostatistics, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center.

Breast Update—Dr. Jeanne Mandelblatt

Dr. Jeanne Mandelblatt described the major scientific accomplishments of the breast group within the CISNET, highlighting two results: the evaluation of U.S. mortality trends as affected by screening and adjuvant therapy for breast cancer and the comparison of various screening policies. Dr. Mandelblatt informed members that mortality from breast cancer has declined since the mid-1980s, but it is uncertain whether the decrease was a result of improved treatment, including the use of adjuvant therapy, increased screening by mammography, or both. Using common population input data, the results of the seven CISNET modeling groups indicated that screening and adjuvant therapy each accounted for about one-half of the decline in breast cancer rates. All of the modeling groups found some benefit from mammography, solidifying the evidence in favor of this screening modality.

A variety of schedules and strategies for screening mammography have been proposed. The CISNET modeling groups evaluated the impact of six different strategies on mortality and found that the most intensive screening strategy (annually between ages 40 and 84 years) had the greatest effect, but that biennial screening approaches are the most “efficient”. A small benefit was gained with screening beginning at age 40, and not much additional benefit was demonstrated after age 69. The results of this collaborative modeling effort can inform policy and clinical recommendations.

Colorectal Update — Dr. Ann Zauber

Dr. Ann Zauber described the projects undertaken by the CISNET colorectal group, including microsimulation modeling of the sequence by which precancerous colorectal adenomas develop into colorectal carcinomas and prediction of the extent to which cancer control interventions could reduce colorectal cancer mortality by 2020. Dr. Zauber stated that in the CISNET's microsimulation models, the adenoma carcinoma sequence is represented as a series of stages from the adenoma phase to preclinical cancer (detectable by screening but without symptoms) to clinical (symptomatic) cancer. Using this type of modeling and simulating a group of individuals from the U.S. population, modelers have been able to evaluate the impact of screening and treatment interventions on colorectal cancer death rates. These models are being used to evaluate the age to begin and stop screening, intervals of screening, potential cost savings, and assess new technologies.

The CISNET modelers have evaluated the impact of changes in risk factors, screening, and treatment on colorectal cancer rates and determined that fuller utilization of screening with existing technologies could decrease colorectal cancer mortality by almost one-half by 2020. Without an aggressive approach to increasing the utilization of the interventions, however, only a 25% decrease would be expected. CISNET modeling is also being used to evaluate CT colonography compared to optical colonoscopy for cost effectiveness, life years gained, and screening strategies.

Prostate Update — Dr. Ruth Etzioni

Dr. Ruth Etzioni described the challenges facing prostate cancer modeling and the accomplishments of the CISNET prostate group. Dr. Etzioni stated that clinical advances in prostate cancer have been hindered by 1) a lack of definitive trials of prostate-specific antigen (PSA) screening benefit, 2) lack of completed trials which show benefits from different treatment strategies, and 3) the failure to track screening dissemination trends in real time. The CISNET modelers have quantified the decline in mortality due to PSA

screening and demonstrated that other factors are also involved. New models that study the change in treatment options are being developed. The CISNET models have estimated the extent of overdiagnosis of prostate cancer due to PSA screening in the United States. The CISNET models clearly show that some, but not all, of the decline in prostate cancer mortality rates in recent years is attributable to PSA screening but also show that a substantial proportion of cases detected by screening (between 23 and 42 percent) would never have become symptomatic.

Dr. Etzioni emphasized the need for evidence-based policies for prostate cancer screening and treatment. The CISNET models integrate all of the available data sources to address policy questions with currently available information. As further information becomes available from clinical trials and other sources, it will be integrated into the models to provide an even better picture of the patterns of prostate cancer incidence and mortality and the impacts of screening and treatment.

In the discussion, the following points were made:

- The CISNET models are ideally suited for answering questions at the population level and informing policy decisions, but are not individual decision-making tools. Nevertheless, they can be of value in clinical practice by illuminating overall trends.
- CISNET is encouraged to consider strengthening interfaces with existing NCI databases (TCGA, SEER, etc.) and to assist investigators in ascertaining how CISNET modeling could be used for the development and use of therapy.
- CISNET models can guide technology development by providing insight into how successful a new technology would be in impacting mortality rates.
- Consideration should be given to modeling the effectiveness of breast cancer screening in estrogen receptor (ER)-positive versus -negative breast cancers.
- CISNET models could: 1) be used to help discern the potential impact of specific agents on tumors, and 2) assist investigators in setting priorities by modeling the potential outcomes of different courses of action, which provide a more reasoned basis for study designs and clinical decisions.
- A progress report on NCI’s internal pharmco-epidemiology group should be given at a future meeting.

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XII. ADJOURNMENT—DR. ROBERT C. YOUNG

There being no further business, the 41sr regular meeting of the Board of Scientific Advisors was adjourned at 12:04 p.m. on Friday, 7 November 2008.

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