Board of Scientific Advisors

Meeting Minutes

November 13-14, 2003

Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI), convened for its 25th regular meeting on Thursday, November 13, 2003, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public from 8:00 a.m. until 5:36 p.m. on 13 November for opening remarks from the Chairman; the NCI Director's report; a summary of Research Project Grants (RPG) Working Group Discussions; perspectives on the Institute of Medicine (IOM) Report; ongoing and new business; and new and reissued Requests for Applications (RFAs), Requests for Proposals (RFPs), and Cooperative Agreements (Coop. Agr.) concepts. On 14 November, from 8:30 a.m. until adjournment at 12:07 p.m., updates were presented on gene expression profiling of lymphoid malignancies and the applications to clinical trials; applications of new technologies in clinical research; evaluating breast cancer screening performance in practice; and management of the Biorepository Initiative.

Board Members present:
Dr. Frederick R. Appelbaum (Chair)
Dr. David B. Abrams
Dr. Hoda Anton-Culver
Dr. Esther G. Chang
Dr. Neil J. Clendeninn
Dr. Thomas Curran
Dr. Mary Beryl Daly
Dr. Raymond N. DuBois, Jr.
Dr. H. Shelton Earp III
Dr. Patricia A. Ganz
Dr. William N. Hait
Dr. Susan B. Horwitz
Dr. William G. Kaelin, Jr.
Ms. Paula Kim
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Dr. Michael P. Link
Dr. Lynn M. Matrisian
Dr. Christine A. Miaskowski
Dr. Enrico Mihich
Dr. Nancy E. Mueller
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal

Board Members absent:
Dr. David S. Alberts
Dr. Hedvig Hricak
Dr. Eric Hunter
Dr. W. Gillies McKenna
Dr. John D. Minna
Dr. Margaret R. Spitz
Dr. William C. Wood
Dr. Robert C. Young

NCAB Liaison:
TBN

Others present: Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives.

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I. CALL TO ORDER AND OPENING REMARKS - DR. FREDERICK APPELBAUM

Dr. Appelbaum called to order the 25th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. He introduced and welcomed new member Dr. William Hait, Director, The Cancer Institute of New Jersey, and Associate Dean, Oncology Programs, University of Medicine and Dentistry of New Jersey/Robert Woods Johnson Medical School. Dr. Appelbaum then reminded Board members of the conflict-of-interest guidelines and called attention to confirmed meeting dates through November 2005. He invited the public to submit to Dr. Paulette Gray, Acting 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 26-27 JUNE 2003 MEETING MINUTES - DR. FREDERICK APPELBAUM

Motion: The minutes of the 26-27 June 2003 meeting were approved unanimously.

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III. NCI DIRECTOR'S REPORT-DR. ANDREW von ESCHENBACH

Dr. von Eschenbach began by acknowledging the contributions to cancer research made by the late Dr. Paul Calabresi as President, American Society of Clinical Oncology (ASCO); Chairperson of the National Cancer Advisory Board (NCAB), NCI Board of Scientific Counselors (BSC), and President's Cancer Panel; and member of the National Dialogue on Cancer (NDC).

Dr. von Eschenbach reported on current NCI initiatives, opportunities, and efforts. He noted that the NCI is an active participant in the NIH Roadmap Initiative, a process to strengthen the national scientific strategic plan by creating a structure to facilitate trans-NIH activities and initiatives. Board members were reminded that the three priority areas identified in the Roadmap are: (1) developing an NIH competing strategy to follow in looking at new pathways to discovery, (2) developing a framework for adapting the new scientific teams to the changing model of how science is conducted, and (3) re-engineering the clinical research enterprise. Dr. von Eschenbach announced that RFAs have been developed and will be announced in the Fiscal Year (FY) 2004 budget to begin engaging the community in implementing Roadmap initiatives. He noted that the initiatives will be of interest to the cancer research enterprise and should be seen as potentially exciting opportunities. At the same time, strategies are being developed for managing these RFAs and integrating them across the Institutes, Centers, and Divisions (ICDs), as well as for providing oversight and leadership.

The NCI Director's Seminars will be re-instituted on January 7, 2004, beginning with a presentation by U.S. Food and Drug Administration (FDA) Commissioner, Dr. Mark McClellan. Subsequent speakers in the series will be Dr. Carl Feldbaum, biotechnology expert, and Dr. Julie Gerberding, Director of the Centers for Disease Control and Prevention (CDC). Members were informed that the speakers represent critical partnerships that the NCI is engaged in, such as the FDA/NCI Task Force to accelerate and streamline the pipeline from scientific discovery to regulatory requirements. Two Task Force initiatives that were announced recently as being ready for implementation in the coming year are: (1) the re-institution and expansion of a joint training program to develop a cadre of investigators versed in regulatory as well as discovery science, and (2) the enhancement of the joint bioinformatics initiative to create an electronic submission process at the FDA for investigational new drugs (INDs) that is linked and

integrated with the NCI's Cancer Bioinformatics Grid (caBIG). The biotechnology partnership will focus on enhancing the development of enabling technologies. In addition to the development of state cancer plans, a particular NCI/CDC/FDA effort under the leadership of the Surgeon General will be the pursuit of opportunities with regard to energy balance to address obesity as a public health problem from the perspective of nutrition and physical activity.

Dr. von Eschenbach reported that a number of workshops and meetings will be implemented in the coming year to bring segments of the cancer research community together for intensive dialogue and discussion between the Director and other NCI leadership. A one day retreat with all Cancer Center Directors will be held in March 2004, and one with the heads of the Cooperative Groups will be held later in the year. Plans are to hold an annual retreat with all Cancer Center Directors. Other meetings in this regard are the think tanks sponsored by the NCI Division of Cancer Biology (DCB), the most recent of which were those on tumor immunology and the tumor microenvironment. Board members were informed that the Director's Corner on NCI's Web Site has been another mechanism for broadening the dialogue, discussion, and interaction with the extramural community.

Future Budgetary Issues. Dr. von Eschenbach addressed significant budgetary challenges brought on by the expected end of double-digit percentage increases in the budget and unique mechanisms in the NCI grant portfolio that require special consideration. He noted, for example, that noncompeting renewals (T5s) are projected to account for about 84 percent of the budget increase proposed in the FY 2004 appropriation, which still is under debate. Moreover, competition for the remaining 16 percent of new money will be shared by competing Cancer Centers, Cooperative Groups, and other large and ongoing commitments in addition to emerging strategic opportunities and NIH Roadmap priorities. Board members were informed that the NCI has been engaged in a long-range financial planning process. The fiscal management team is working to identify mechanisms for enhancing and expanding NCI's ability to make strategic investments and redeploy resources. To further inform this process, Dr. von Eschenbach informed members that a Joint Board (NCAB, BSA, BSC) Retreat would be held discuss long-range financial planning and modeling and strategic investing.

During the RPG Working Group meeting, the discussion centered on the RPG pool and the implications of NCI's success in terms of the accelerating numbers of people who are applying for cancer research grants. Board members were reminded that never before in the history of the enterprise has there been as much money in cancer research and as many investigators, and that the NCI intends to work aggressively to maintain that critical mass of investigators in both the basic and translational sciences to achieve the goal of eliminating the suffering and death due to cancer by 2015.

In discussion, the following points were made:

- Although interdisciplinary research venues have proved, in general, to be productive, their great expense and the resulting impact on individual R01s should be addressed in the proposed retreat.

- The relationship between common and integrated programs between intra- and extramural programs and the perceived uneven access to research dollars also should be addressed.

- Maintaining the R01 payline at 20 percent is a top priority for the NCI.

- Members will be kept informed of progress in designing an organizational structure for Roadmap initiatives, funding mechanisms, and concept review for the resulting RFAs.

- Comments should be extracted about partnerships and collaborations such as trans-NIH, Roadmap, and NCI/FDA initiatives for use in justifying the NCI budget in dealings with Congress, other agencies, and the media.

- Members requested a presentation on the Impact of A-76 and the MEO on the Management of Extramural Activities; Career Impediments to Team Research; an Overview of Career Development Mechanisms for Translational Research; and Career Impediments to Team Research.

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IV. SUMMARY OF RPG WORKING GROUP DISCUSSION- MR. STEPHEN HAZEN

Mr. Stephen Hazen, Chief, Extramural Financial Data Branch (EFDB), Office of the Director (OD), NCI, stated that Working Group discussions focused largely on the competing RPG policy and success rates in 2004, the challenge associated with the influx of applications to the NCI, demographics of the applicants, and an option for sliding scale funding cuts. Mr. Hazen then reminded members that the NCI Executive Committee (EC) has established a policy that will apply to large R01s (requesting more than $700K in direct costs) that are reviewed by the Center for Scientific Review (CSR) and fall within the payline. Beginning in FY 2004, the EC will make selections from among those grants on a case-by-case basis, a policy that currently is applied to program project (P01) grants.

As background for the Working Group discussions, the challenges for FY 2004 were reviewed: (1) high expectations in the grantee community for continuing the payline at the 20th percentile; (2) increases in the numbers of R01, P01, and exploratory grant (R21) applications; (3) increase in average cost requested by R01 Principal Investigators (PIs); and (4) limited new dollars available in the budget request. Mr. Hazen stated that proposed NCI options for addressing these challenges while at the same time keeping the R01 payline at the 20th percentile were to take a greater than 11 percent average cut in the R01 requests and limit the numbers of R21s, P01s, and other mechanisms. Working Group discussion of these options focused on: (1) whether keeping the payline at the 20th percentile is reasonable in light of limited budget growth and many additional scientific opportunities; (2) whether R01s should be increased without proportional growth in the other mechanisms; (3) whether it would be better to reduce the average cost of competing grants below the FY 2003 level, fund more grants, or have a stringent R01 payline and a lower success rate; and (4) whether there are metrics other than the 20th percentile to measure NCI's commitment to research in light of the accelerating number of applications received. The sense of the discussions was that the strategies proposed by the NCI would be a reasonable approach to maintaining the payline if the amounts in the President's budget become a reality.

Mr. Hazen pointed out that an additional $32M in new dollars would be needed to balance the proportions of R01s, P01s, and R21s in FY 2004. He used the example of the explosion in the number of R21 applications since FY 2001 to further illustrate the extent of the FY 2004 challenge as it relates to communication to the research community. Awards increased from 133 in FY 2001 to an expected 210 in FY 2004, but applications over that same time period increased from 440 to 1,411, representing a reduction of the success rate from 30.2 percent to 14.9 percent. A presentation of the overall RPG application receipt and funding history since the National Cancer Act of 1971 showed a similar picture and further underscored the FY 2004 challenges.

In the discussion, the following points were made:

- Success of R21 recipients in obtaining an R01 might be a guideline for determining R21 numbers.

- The increase in the number of applications received during the past 5 years was attributed to investigators submitting second, third, or multiple applications; not to an increase in the number of first-time R01s.

- The NCI remains committed to funding discovery through the investigator-initiated grants and honoring its commitments.

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V. PERSPECTIVES ON THE IOM REPORT-DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Professor, Departments of Oncology and Surgery, University of Wisconsin at Madison, and NCAB Chairperson, presented a summary of the report entitled "Enhancing the Vitality of the NIH: Organizational Challenges to Meet New Challenges," which had been prepared by the Institute of Medicine (IOM) Committee on the Organizational Structure of the NIH. Dr. Niederhuber noted that his objective was to promote an awareness of the report's content as it proceeds through the process of Congressional hearings. To put the NIH in perspective, he cited

its preeminence as a biomedical research institution; the doubling of the NIH budget over the past 5 years as evidence of the public's perception of its success; the fact that this budget represents 80 percent of the federal funding for biomedical research; and the magnitude of the establishment with its 27 Institutes and Centers. He noted that although more than 40 unit heads report to the Director, the OD budget has changed only slightly-from $189M in 1993 to $259M in 2003. Board members were reminded that the NIH mission is to serve as a mechanism for efficiently and effectively deploying federal resources across a wide array of institutions and individuals in the Nation's scientific community to advance the scientific frontier and ensure research training of special relevance to human health needs.

Board members were informed that the current study was requested by Congress in the FY 2001 appropriations with the goal of determining the optimal NIH organizational structure, given the context of the 21st century biomedical research agenda. The charge to the Committee was to address the following questions: (1) Are there general principles by which the NIH should be organized? (2) Does the current structure reflect these principles, or should the NIH be restructured? (3) If restructuring is recommended, what should the new structure be? (4) How will the proposed new structure improve NIH's ability to conduct biomedical research and training and to accommodate organizational growth in the future? (5) How would the proposed new structure overcome current weaknesses, and what new problems might it introduce?

Dr. Niederhuber noted that the Committee sought information and testimony from a variety of sources and organizations. He reviewed the Committee's 14 recommendations, providing comment and emphasizing items of particular relevance to the NCI. The Committee recommended the following: (1) centralize management functions; (2) develop a public process for proposed changes in the number of NIH Institutes or Centers; (3) strengthen clinical research; (4) enhance and increase trans-NIH strategic planning and funding; (5) strengthen the OD; (6) establish a process for creating new OD offices and programs; (7) establish a discrete program?the Director's Special Projects Program?to fund the initiation of high-risk, exceptionally innovative research projects offering high potential payoff; (8) promote innovation and risk-taking in intramural research; (9) standardize data and information management systems; (10) set terms and conditions for

Institute and Center (IC) Director appointments and improve the IC Director review process; (11) set terms and conditions for the NIH Director appointment; (12) reconsider the status of the NCI; (13) retain integrity in appointments to advisory councils and reform advisory council activity and membership criteria; and (14) increase funding for research management and support.

In summary, Dr. Niederhuber noted that the NIH has been productive and immensely successful in part because it is a federation of highly specialized and somewhat independent units. The Committee concluded that widespread consolidation or restructuring would not necessarily be the best means to resolve the management and programmatic challenges presented by a matrix or decentralized structure. The Committee did see opportunities for organizational rather than structural change, which could improve the strength, responsiveness, vitality, and accountability of the NIH. With regard to the latter, Dr. Niederhuber noted that the measures aimed at transcending a decentralized structure to optimize trans-NIH decision-making are important for the NCI advisory boards to consider.

In discussion, the following points were made:

- One area of opportunity for the BSA is to emphasize the need for new resources to help accomplish trans-NIH initiatives that are projected to evolve from the NIH Roadmap planning.

- Another area of opportunity is to promote creative thinking in regard to developing research across institutions and the need for infrastructure and continuity of leadership to support that research.

- There is an opportunity for synergism across NIH ICs to emphasize the transition of research results from the clinic to public health population implementation.

- An *ad hoc* committee of NCI Advisory Board members (NCAB, BSA, BSC, Director's Consumer Liaison Group) should be convened to raise the research community's awareness of the IOM report recommendations and discuss the need for and timing of developing a unified response.

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VI. ONGOING AND NEW BUSINESS-DR. FREDERICK APPELBAUM

American Association for Cancer Research (AACR) "NCI Listens" Report. Dr. Enrico Mihich, Distinguished Member, Department of Pharmacology and Therapeutics, Professor, Molecular Pharmacology, State University of New York/Buffalo, reported that Drs. John Sogn and Edward Sausville presented an overview of NCI programs and initiatives. Dr. Mihich noted that questions and discussion following the overview focused on funding issues related to Special Programs of Research Excellence (SPOREs) and R01s, prospects for the FY 2004 payline, the status of the NCI bid for the Most Efficient Organization (MEO) Award, the effect of study section restructuring on grant application review, training issues and opportunities related to moving from basic to translational research, career impediments related to opposing requirements of independent versus team research, and the new technologies. Dr. von Eschenbach informed members that the NCI Training Commission is implementing a new training pathway that has the potential to address training issues raised at the meeting.

2004 "NCI Listens" Sessions: Members representing the BSA during "NCI Listens Sessions" at upcoming meetings are: **Society of Behavioral Medicine (SBM)**, March 27-31, Baltimore, MD; Dr. David Abrams (Chair); **American Association for Cancer Research (AACR)**, March 27-31, Orlando, FL; Drs. Hoda Anton-Culver (Chair), H. Shelton Earp, William Hait, and Henry Mihich; . **Oncology Nursing Society (ONS)**, April 29-May 2, Anaheim, CA; Dr. Christine Miaskowski (Chair) and Ms. Paula Kim; **Cold Spring Harbor Laboratory Symposium (CSHL)**, August 18-22, Cold Spring Harbor, NY; Dr. William Kaelin (Chair); **American Society for Therapeutic Radiology and Oncology (ASTRO)**, October 3-7, Atlanta, GA; Dr. Mack Roach (Chair); and tentatively, **NCI Tobacco Control Investigators and Synthesis meeting** in June, San Diego, CA, Dr. David Abrams (Chair).

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VII. RFA/RFP NEW CONCEPTS-PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Prevention

Reducing Barriers to Effective Symptom Management and Palliative Care (RFA). Dr. Ann O'Mara, NCI Palliative Care Working Group, stated that the purpose of the proposed project is to stimulate research on barriers to the delivery of symptom management and palliative care in the health care system and among health care providers, patients, families, and caregivers. To illustrate the scope of the problem, Dr. O'Mara cited recent studies that documented unacceptable prevalence rates of pain, depression, and fatigue symptoms in the cancer population despite the discovery and development of promising interventions. The proposed initiative is a trans-NIH effort (Office of the Deputy Director for Extramural Science, DCP, Division of Cancer Control and Population Sciences [DCCPS], Office of Cancer Complementary and Alternative Medicine, Division of Cancer Treatment and Diagnosis (DCTD)) and would contribute to achieving the NCI challenge goal of eliminating suffering and death due to cancer. Palliative care research would cover the physical, psychological, and social arenas across the entire cancer continuum. Dr. O'Mara noted that critical research gaps in measuring and treating impaired quality-of-life (QOL) and cancer-related symptoms have been identified in three IOM reports, in the 2002 NIH State of the Science Conference, and by each of NCI's organ site-specific Progress Review Groups. Research results of the proposed RFA would: (1) generate knowledge on how to reduce barriers to the delivery of symptom management and palliative care, (2) address barriers for vulnerable medically underserved and special populations to access and receive palliative care, and (3) encourage research collaborations across disciplines and cancer care delivery systems as well as public-private partnerships. Because of the broad applicability of the proposed research, other ICs and government agencies have expressed interest in participating.

A budget of $5M is requested in Year 1 to fund an anticipated 15 awards. The estimated cost for the 5-year project is $25M.

In discussion, the following points were raised:

- Research focused more on addressing patient/family and clinician barriers than health system barriers would make the RFA less diffuse and produce the greatest benefit for the dollar.

- Dissemination of best practices into the community is the key issue, and the amount of money being proposed may be insufficient. A dissemination/implementation arm operating through a different mechanism might be considered in addition to the RFA.

- To eliminate barriers to conducting research in this area, the issue of assigning cancer control points for this type of research should be addressed if the initiative might ultimately be implemented in collaboration with existing networks such as the Clinical Cooperative Groups (CCGs) and the Community Clinical Oncology Program (CCOP). Consideration also should be given to linkage to the Cancer Centers for symptom management and dissemination research.

- The research results should be generalizable for implementation in a representative population of cancer patients.

- A critical issue is to make a clear distinction between research on barriers and mechanisms to effective implementation and dissemination.

Motion. A motion to approve the DCP RFA concept entitled "Reducing Barriers of Effective Symptom Management and Palliative Care" unanimously approved. Staff consideration should be given to coupling with another mechanism (e.g. the contract mechanism) to allow more focus and direction. RFA language should be added to assure a representative sample of diverse populations and the RFA should focus on one or two groups rather than on a broad spectrum of focus groups.

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VIII. WORKING LUNCH

RFA Annual Report. Dr. Paulette Gray, Acting Director, DEA, presented and briefly described the content and organization of the BSA Concepts Review Report, which is prepared annually as requested by Board members. The information dates from 1996, when the BSA was created and became responsible for review of concepts proposed by the NCI extramural Divisions. It is arranged in the following categories: (1) Request for Applications (RFA) Concepts (presented according to meeting dates on which they were reviewed); (2) Request for Proposals (RFP) Concepts; (3) RFA Reissue Report; (4) RFAs in relation to other mechanisms in the NCI grant portfolio, the originating divisions, and RFA allocation by concept area; and (5) BSA Approved Versus Actual Funding. The notebooks also include a CD-ROM containing the abstracts of all RFAs funded from FY 1996 to FY 2002.

In discussing the following point was made:

- A modified version of BSA approved versus actual funding data should be included in the next RFA Annual Report.

Program Project Review Process. Ms. Diane Bronzert, Associate Director, Office of Referral, Review and Program Coordination, DEA, discussed changes being considered in the process for reviewing program project grants (P01s). Ms. Bronzert noted that the changes have become necessary to address challenges presented by an increasing P01 workload, difficulties in recruiting more than 1,200 senior, experienced reviewers needed each year; scoring inconsistency; priority score compression, reviewer and NCI staff time investment, and review costs.

Ms. Bronzert noted NCI will conduct a one year trial of a cluster review process starting with the q 1 February 2004, receipt date (for funding in FY 2005). The trial process will include: (1) review of 2-4 applications on closely related topics by one review panel with appropriate expertise; (2) review of both original and amended applications at the same meeting, with no individual site visits or teleconferences; (3) face-to-face meeting of reviewers in the Metropolitan Washington, DC, area or elsewhere; (4) contact of applicants by tele- or videoconference to ask questions; (5) service

of Parent Committee members on one cluster, rather than several individual review panels; and (6) final scoring by Parent Committees as usual. Expected benefits of the trial process are significantly lower recruiting requirements, scoring consistency and spreading of scores, reduced number of review meetings, provision for triage of poor applications, and increased time and cost savings for all. Ms. Bronzert noted that the Committee is developing a plan for evaluating the impact on the number of reviewers required, review costs, priority score spread, and customer satisfaction.

In discussion, the following points were made:

- For future comparison purposes, Scientific Review Administrators will record the number of reviewers they tried to recruit versus the number who accept.

- Triaging deprives the applicant of the benefit of the Parent Committee discussion.

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IX. RFA/RFP NEW CONCEPTS (continued)-PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Control and Population Sciences (DCCPS)

Transdisciplinary Research on Energetics and Cancer (TREC) Centers (RFA). Dr. Robert Croyle, Director, DCCPS, informed Board members that the proposed initiative is the first in the area of energy balance and cancer. Dr. Croyle noted that one of the challenges in developing the RFA was to identify NCI's scientific role and mission in this area. Another challenge was to complement what other Institutes are doing not, only to inform the larger issue of obesity and the role of energy balance and disease, but also to fill the gap of what is known about cancer-related mechanisms. Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS, stated that the proposed initiative was developed after a series of NCI Energy Balance Working Group discussions

on research priorities in the area of energy balance, energetics, and cancer. She reviewed the status of evidence demonstrating the need for transdisciplinary research at the intersection of weight control, physical activity, and cancer incidence in reports of the International Agency for Research on Cancer (IARC) and studies reported in the *New England Journal of Medicine (NEJM)* and other journals. She presented data from the National Health and Nutrition Examination Survey to indicate the extent of the obesity epidemic among both adolescents and adults in the United States. The association between obesity and cancer has been identified as a priority area for research in the NCI Bypass Budget and recent reports of the IOM, IARC, and World Health Organization.

Dr. Ballard-Barbash noted that the proposed initiative is intended to support the creation of TREC Centers to stimulate research on both micro-level factors (physiologic, behavioral, genetic) as they relate to disease risk and macro-level (sociocultural, environmental, and institutional/policy) factors to counter the rapid growth of obesity in the United States. Two major challenges identified in the RFA are to: (1) enhance an understanding of the mechanisms underlying the association between energy balance and carcinogenesis across the cancer continuum and throughout the life cycle; and (2) focus on the development of effective interventions with broad population-level impact at the social, environmental, and policy levels for the prevention of obesity, with particular focus on children and on critical time periods among adults when weight gain is likely to occur. The proposed concept has been designed to complement existing NIH research efforts; other Institutes will be invited to comment or partner.

The proposed P50 mechanism requires at least three projects related to a theme (such as defining mechanisms of energetics and cancer), research that bridges disciplines and levels of analysis, and interactive organization that promotes cross-fertilization and synergy within and across centers. The P20 mechanism also is proposed to accommodate the possibility of research in smaller centers that would advance the field, and the U01 mechanism is proposed for a coordinating center. Two large areas included in the evaluation criteria are: (1) quality and innovativeness of the science, and(2) infrastructure development and capacity building.

The estimated cost for 5-6 P20 awards per year is $15M. Total estimated cost for the 5-year project period is $75M.

In discussion, the following points were made:

- It should be made clear that resources are to be included within each center for coordination, communication, and fostering the interdisciplinary process.

- The importance of conceptual synthesis and an operational definition for evaluating the whole as greater than the sum of the parts should be emphasized as part of the criteria to ensure that transdisciplinary integration is weighted in the review process. An example might be selecting from existing longitudinal epidemiological studies that could be linked to human metabolic and animal research in the laboratory.

- The genetic component should be included in both preclinical and clinical aspects of the research.

- The envisioned components and tasks of the coordinating center should be clarified in the RFA.

- To address broad public health problems such as obesity and cancer, the NCI can create a scientific infrastructure for action and take a leadership role in effecting systemic changes in collaborations with other public and private partners.

- Exit strategies should be considered as part of the initiation of large infrastructure projects.

- There should be a report on large initiatives (e.g., Energetics; Palliative Care, etc.) issued by NCI and and how to make them more intra-institutional)

Motion. A motion to approve the DCCPS RFA concept entitled "Transdisciplinary Research on Energetics and Cancer (TREC) Centers" passed with 13 votes in favor and 9 opposed and 1 abstention..

Support for Human Specimen Banking in the Clinical Cooperative Groups-A Virtual National Specimen Bank (RFP).

Dr. Ellen Feigal, Acting Director, DCTD, stated that the proposed initiative focuses on leveraging the NCI clinical cooperative group (CCG) investment in human specimen banking to make it a more effective resource for the research community. As background, Dr. Sheila Taube, Associate Director, Cancer Diagnosis Program (CDP), DCTD, reviewed the characteristics, access, and use information for all NCI human specimen resources. She noted that CCG human specimen banks are unique in that specimens are collected in the context of clinical trials so they are associated with complete treatment, patient, and followup information. In addition, the specimens represent most organ sites. She reminded members that the Resources Development Branch (RDB) coordinates all NCI specimen resources, initiates and administers public resources, markets resources, and facilitates researcher access through means such as the Specimen Resource Locator Web Site. Board members were reminded that the National Biospecimen Network Blueprint calls for building on available resources and adding new sources of tissue to ensure that special needs for emerging technologies are met.

Dr. Roger Aamodt, Chief, RDB, stated that the purpose of the proposed initiative is to separately fund the CCG specimen banks to ensure that they are able to provide high-quality specimens and data to investigators within and outside the CCGs. CCG specimen banks would be provided with stable support to ensure standardized access procedures, improved coordination of activities, quality of specimens, and utilization for quality science. Metrics have been developed and approved by the EC. The fundamental criterion is whether the resource is effectively meeting a critical scientific need. Performance measures have been developed to provide quantitative data such as utilization figures, cost per specimen, and numbers of research papers published. In addition, impact measures will attempt to evaluate the effect that the resource availability has had on the science. Dr. Aamodt demonstrated the continuing need for the resource in accordance with NCI metrics. He noted that the contract mechanism was being proposed to enable the NCI to define the work scope, monitor work, facilitate "best practices," improve utilization, and set timelines for reaching goals. The Intergroup Specimen Banking Committee has been

proposed as the provider of governance and oversight.

An estimated $9M is proposed for Year 1. A total of $47.8M is estimated for 9 awards for the 5-year project period.

In discussion, the following points were made:

- The CCG specimen banks should receive enough of an increase to supply the infrastructure to maintain and properly inventory the specimens.

- The recommendations of the Intergroup Committee should prevail in regard to the study design, choice of controls, and analysis decisions remaining within the purview of the CCG investigators and statisticians.

- The contract mechanism, which would separate the funding and oversight of the CCG specimen banks from the oversight of the treatment trials, may not be the optimal solution to addressing the problem of ensuring the quality and facilitating the availability of specimens. Moreover, the mechanism may be too inflexible to accommodate different disease subsets, cooperative groups, and organizations that might be involved in the studies. A cooperative agreement should be considered. A workshop involving all CCG Chairs should be convened to define future directions

Motion. A motion to table consideration of the DCTD RFP concept until questions related to the funding mechanism can be addressed was approved unanimously.

Office of the Director (OD)

NCI Interdisciplinary Cancer Research Career Development (K25) Award for Quantitative Scientists (RFA). Dr. Brian Kimes, Director, Office of Centers, Training, and Resources (OCTR), OD, reminded members of the 1998 strategic plan for training and career development based on the principles of protected time, portability, continuity, and selected emphasis. The plan included five career tracks (from basic to transdisciplinary

scientists) with four stages in each track (from predoctoral to established investigator), and the strategy was to build on those career tracks using special career awards. At the same time, the NIH Bioengineering Consortium (BIOCON) created the K25 career development award to support quantitative scientists. In 4 years of participation in the NIH Omnibus Program Announcement (PA), the NCI received 17 applications, of which only two were funded. The training issue with regard to quantitative scientists was revisited within the NCI. Dr. Kimes noted that the proposed concept was developed to complement the DCB's newly established Integrated Cancer Biology Programs (ICBPs) as well as to further integrate quantitative scientists into treatment, prevention, and behavioral and population research. The proposed initiative would create a pilot K25 award in which mentors are matched with candidates through the proactive efforts of cancer centers and ICBPs. The career development program for each candidate would be monitored by cancer center/ICBP personnel to ensure that it is achieving its goals and objectives. Candidates would have the opportunity to compete for a K22 Career Transition Award after completion of the K25. Results would be tested, analyzed, and combined with results from the continued participation in the NIH Omnibus PA to create a new NCI PA or to lobby for a better NIH PA that incorporates what is learned.

A cost of $700K per year is estimated to support four candidates. The total estimated cost for the 5-year project period is $3.5M.

In discussion, the following points were made:

- Applications received in response to the proposed RFA would be subject to review criteria separate from those of the NIH's Omnibus PA.

- Ensuring the quality of the mentoring component is one barrier that might be addressed by including compensation for the mentors.

Motion. A motion to approve the OD RFA entitled "NCI Interdisciplinary Cancer Research Career Development (K25) Award for Quantitative Scientists" passed unanimously.

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X. RFA/COOPERATIVE AGREEMENT RE-ISSUED CONCEPTS-PRESENTED BY NCI PROGRAM STAFF

Office of the Director (OD)

Community Networks To Reduce Cancer Disparities Through Education, Research, and Training (RFA/Coop. Agr. Re-Issue).
The BSA Committee requested additional information. Dr. Kenneth Chu, Center to Reduce Cancer Health Disparities (CRCHD), presented a brief history of the original grant offering, which established 18 Special Population Networks (SPNs) in FY 2000 and will end in FY 2004. Dr. Chu reviewed SPN achievements as a basis for reissuance in the areas of increased community cancer awareness (through awareness activities, partnerships, and cancer awareness training) and new investigator training and research. The latter included 96 funded research projects of the 196 pilot projects submitted, 150 newly trained minority researchers, and 110 peer-reviewed papers published or in press. In addition, the SPN activities have raised $13M in non-NCI funds for cancer awareness and research activities in 3 years. Board members were informed that the proposed RFA/Coop. Agr. would be reissued under the new name if approved.

The Community Networks program goal would be to reduce cancer disparities in the community by improving utilization of beneficial cancer interventions and through community-based education, research, and training in disparities research. This goal is consistent with the DHHS Healthy People 2010 goals, the NCI Director's 2015 goal, and the NIH Director's Roadmap goals for disparities. The first of the three new program phases is capacity building, with the objectives of creating the core infrastructure; partnering with local prevention, diagnosis, and treatment facilities; collaborating with NCI centers, divisions, and offices; and participating in community-based primary and secondary prevention activities. In the second phase, a disparities research and training program would be developed. The third phase would focus on establishing the credibility and sustainability of the program by demonstrating a reduction in cancer disparities in the community, obtaining non-CRCHD funding for Community Network activities, and informing

policy related to the reduction of cancer disparities. Three new elements added to the organizational structure for the proposed reissuance are the NCI collaborations, a community advisory group, and clinical partnerships. Board members were informed that evaluation metrics have been developed as appropriate for each phase of the program and that the ongoing initiative has been well integrated with other NCI programs on disparities.

Total estimated cost per year is $24.2M, of which $18M will be contributed by CRCHD and $6.2M will be new funding. The estimated cost for the 5-year project period is $126.5M for an estimated 22 awards.

In discussion, the following points were made:

- The original initiative included a significant capacity-building effort as evident from the 18 SPNs that were created. The reissuance therefore should require that already-funded applicants move to the second phase of the program, with the equivalent of exploratory/developmental grant (R21s) proposals in the applications. In the peer-review process, the measurable outcomes then could be evaluated to show that the partnership between the research community and the SPNs was tangible in terms of a scientifically fundable project that can go forward.

- Looking at proximal endpoints in the evaluation would be more valuable than looking at more distant endpoints such as population outcomes. The evaluation should identify approaches that are working well and could be disseminated to other pockets of prevalence in the country.

- A more formal basis for holding meetings and conferences among the centers should be considered to promote feedback, interaction, and the transfer of information.

- Consideration should be given to working with learning institutions that have larger minority representations to provide learning opportunities for graduate students in an effort to draw them into the cancer research arena.

Motion. A motion to concur in the re-issuance of the OD RFA/

Coop. Agr. entitled "Community Networks to Reduce Cancer Disparities Through Education, Research, and Training" passed with 19 in favor and two abstentions.

Division of Cancer Prevention (DCP)

Diet, DNA Methylation and Other Epigenetic Events, and Cancer Prevention (RFA Re-Issue). Dr. Sharon Ross, Nutritional Science Research Group, DCP, presented the request to re-issue the RFA and accompanying PA. The proposed initiative seeks to promote novel and innovative approaches to determining interactions between epigenetic events and diet as they relate to cancer prevention. It is based on the belief that epigenetic processes are fundamental for gene expression and chromosomal stability, and diet is a key regulator. Dr. Ross noted that the BSA approved the original concept in June 2002, to see what the response would be. Fifty-two applications were received and were reviewed in June 2003. Plans are to award the top 10 applicants whose scores range from 123 to 126, equivalent to a payline at the 19th percentile. The NCI and the Office of Dietary Supplements made funding possible. Pending award characteristics include varied model systems, several dietary constituents, differing cancer sites, and collaborations established between nutrition and epigenetic experts. The pending applications are believed to be consistent with the goals of the first issue of the RFA.

Dr. Ross noted that the basis for the re-issue request is to maintain the momentum in this emerging area and foster additional collaborations between these two disciplines. Moreover, the goals are deemed consistent with the 2004 NCI Bypass Budget in the areas of genes and the environment, defining the signatures of cancer cells, and molecular targets of prevention and treatment. Additional issues to be addressed include: (1) how bioactive food components regulate epigenetic processes for cancer prevention, (2) whether bioactive food components alter epigenetic events to restore gene function, and (3) whether bioactive food components circumvent or compensate for genes and pathways that are altered by epigenetic events. Mechanisms proposed for the reissued concept are R01s, R21s, and supplements to existing grants.

The anticipated number of awards is 8 to 10 for an estimated $3.3M per year. The estimated cost for the 4-year project period is $13.8M.

In discussion, the following points were made:

- The original RFA was successful in stimulating research in this particular area. The next step might be to track applications coming into the general R01 pool in the next few rounds to determine whether this activity is sustained.

Motion. A motion to postpone until a later date the reissuance of the DCP RFA concept entitled, "Diet, DNA Methylation and Other Epigenetic Events, and Cancer Prevention," passed with 15 in favor and 4 abstentions. The BSA indicated that the first issuance's track record and success rate should be presented to the Board prior to any additional re-issuances.

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XI. UPDATE: GENE EXPRESSION PROFILING OF LYMPHOID MALIGNANCIES AND THE APPLICATIONS TO CLINICAL TRIALS-DR. LOUIS STAUDT

Dr. Louis Staudt, Chief of the Lymphoid Malignancies Section in the Metabolism Branch, Center for Cancer Research, NCI, discussed bringing molecular profiling into clinical practice and the challenges and opportunities in this area, particularly with regard to gene expression profiling. Gene expression profiling will have applications that will allow clinicians to more effectively select appropriate therapies for cancer patients. Dr. Staudt described microarray work in his laboratory demonstrating that the biopsy on presentation of a cancer patient can predict what will happen years later to that patient, using diffuse lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia as examples. He noted that there are various ways in which the common cellular functions differ between tumors. This heterogeneity has profound influence on all aspects of the biology of the tumor and can be used to predict tumor behavior.

Dr. Staudt described a new molecular profiling predictor of survival in follicular lymphoma, a cancer that has no curative therapy. He informed members that his group is preparing to conduct a clinical trial using gene expression profiling in a set of patients with diffuse large B cell lymphoma, which will involve genomic-scale profiling on as many patients as possible. Then, a predictor of survival will be generated, similar to the one for follicular lymphoma, which would be ready to be turned into a deliverable diagnostic of survival (e.g., a diagnostic mini-array, multiplex PCR, protein-based methods) and for routine clinical use. It is hoped that gene expression profiling in cancer clinical trials will identify subsets of patients that respond better to one treatment arm than another so that patient-specific treatments can be developed; this study represents a step in that direction. Gene expression profiling also may prevent promising new anticancer drugs from being discarded and would allow for a comparison of large clinical trials from around the world.

Dr. Staudt briefly described impediments to bringing molecular profiling to clinical trials. One is that most patients have their first consultation and biopsy in a community setting and their lymph node is placed in formalin, causing it to lose all of its RNA content. Therefore, in many cases, a second biopsy will be needed, which will require additional funding. Furthermore, the biopsy specimens must be adequately handled to maintain RNA, DNA, and protein integrity, so a dedicated research nurse or technician at each site would be needed. Additionally, physicians and patients need to be educated and informed that this activity is worthwhile. Seminars and outreach activities involving patient advocacy groups that promote molecular profiling are needed.

To eventually achieve routine molecular diagnosis of cancer in clinical oncology, molecular diagnoses that influence treatment or prognosis need to be delivered to patients as soon as possible. A mechanism to move from the research laboratory to patients needs to be developed. It also would be helpful to promote the fact that having a molecular profile of tumors could help pathologists resolve a large proportion of the approximately 10 percent of cases that are difficult to diagnose. Molecular profiling also provides a cost-effective alternative to multiple existing diagnostic tests in that many diagnoses can be made with profiling that currently are being made using other expensive means. Dr. Staudt outlined a number of routes that the NCI can take to advance the molecular diagnosis

of cancer, including: (1) supporting the inclusion of gene expression profiling in clinical trials and the establishment of clinical genomics centers that would work in collaboration with clinical trial groups to provide technical bioinformatics and statistical support for gene expression profiling; (2) providing education for clinicians, pathologists, and patients about the value of molecular diagnosis and the need to store frozen biopsy samples; and (3) supporting the development of molecular diagnostic platforms that are suitable for routine clinical use. Dr. Staudt noted the importance of collaborating with the FDA to address problems related to standards in this area so that this technology can move into routine clinical use.

In discussion, the following points were made:

- Although development of a paraffin-based assay for lymphoma might have more widespread use, its cost is prohibitive. To deliver approximately 20 markers would cost between $1,000 and $2,000 per patient; molecular profiling will deliver hundreds of markers for developing the lymphoma diagnosis, well beyond the range of paraffin-based technologies.

- Biopsies are a unique resource in follicular lymphoma because the slow pace of the disease means that a long follow-up is needed, and there is no therapy that currently improves the length of survival of these patients. A single-core needle biopsy combined with a simple, reproducible amplification technique is more than sufficient for obtaining enough tissue for molecular profiling; it is three times more than what is needed to obtain a full genome microarray analysis of gene expression. Fine needle aspirates yield too small of a sampling of the tumor and are too variable.

- Although 430 patients are needed to provide the diffuse lymphoma study proposed by Dr. Staudt's group with enough power to determine which therapy is effective, similar studies with patients who have solid tumors, new drugs, different chemotherapies, targeted agents, etc., will require an enormous number of patients and may be difficult to conduct from a logistical standpoint.

- The NCI cannot be the sole educators of the medical community in this regard. The American Cancer Society has been a leader in community and physician education and could be tapped to help promote molecular profiling. NCI-designated Cancer Centers also could take a leadership role in molecular profiling.

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XII. CONTINUED DISCUSSION ON SUPPORT FOR HUMAN SPECIMEN BANKING IN THE CLINICAL COOPERATIVE GROUPS-A VIRTUAL NATIONAL SPECIMEN BANK (RFP)-DR. FREDERICK APPELBAUM

The previous day's discussion on the virtual national specimen bank RFA was continued. Dr. Appelbaum noted that the Board was unanimously in favor of funding to allow for increased annotation for the development of common data elements among the Cooperative Group tumor banks and to allow them increased funding to make those specimens more available to the community at large. However, there were serious concerns about the funding mechanism and what it would entail (e.g., a contract versus a Cooperative Agreement, etc.).

Motion. A motion for the Board to philosophically approve the DCTD RFP concept entitled "Ensuring the Availability of Critical Human Specimens: Support for Specimen Banking in the Clinical Cooperative Groups" was unanimously approved. Prior to the Board's final approval, the funding mechanism for this concept should be proposed by the Executive Committee (EC) for consideration and concurrence by a BSA subcommittee (Drs. Appelbaum, Hait, Clendennin, and Horwitz). The subcommittee's concurrence with the EC's recommendation will constitute full BSA concurrence. If the subcommittee does not concur with the EC, the concept should be presented at a subsequent BSA meeting for further discussion. [Note: The EC proposed mechanism was the RFA/Cooperative Agreement. The BSA subcommittee concurred with the recommendation

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XIII. APPLICATIONS OF NEW TECHNOLOGIES IN CLINICAL RESEARCH-DR. FRANK BALIS

Dr. Frank Balis, Pediatric Oncology Branch, NCI, noted that biological sciences have moved well beyond the use of single-gene or single-protein approaches to studying biological events to methods that incorporate genomic techniques to measure whole-genome transcriptomes or proteomic techniques to examine proteomes to measure biological events. These new technologies eventually also will aid in the detection and diagnosis of cancer, potentially providing new classifications for prognostic factors, selecting therapies, and even monitoring the course of therapy. A primary mission of the Center for Cancer Research's (CCR) Clinical Research Program is to develop new ways to apply these technologies in clinical research. Dr. Balis briefly described a number of CCR programs, initiatives, and facilities that have been made available to NCI clinical researchers to promote the use of these new technologies. These include the joint NCI-FDA Clinical and Biomedical Proteomics Initiative, the joint NCI-NHGRI Tissue Array Research Program, and the Diagnostic and Molecular Oncology Imaging Program (which is in the process of being established).

Dr. Balis discussed a number of technologies that are complementary to the application of microarrays, focusing primarily on proteomics and the CCR's Clinical Proteomics Program. Dr. Balis described how protein microarrays are developed at the CCR. He also presented a summary of the serum proteomic patterns that have been studied in different tumor types by CCR groups. It was noted that important endpoints for these new technologies include monitoring drug effects or pharmacodynamic studies. Researchers can examine the target proteins specifically, but also all of the other proteins, for example, if it is a molecularly targeted drug that targets a signaling pathway. These new technologies can be used for cancer screening in the future. Current applications have focused primarily on serum proteomic profiles, but applications will be developed for cancer identification and for using these techniques with new biomarkers. These technologies also will be useful in terms of molecular diagnosis and classification of tumors using either gene expression or proteomic profiles as the primary means to establish diagnosis in patients rather than relying on histochemical techniques. Another potential use is the selection of targeted therapies based on

activated pathways in individual tumors so that therapies can be individualized. In addition, it may be possible to: (1) monitor response to therapy in a much more rapid fashion than waiting for tumor shrinkage or, in the longer term, waiting for survival; (2) predict resistance based on the effects these agents have on profiles and move to other therapies; and (3) discover new targets for therapy from these clinical specimens.

In discussion, the following points were made:

- Many of the studies described by Dr. Balis were done in collaboration with other institutions. For example, the screening studies were conducted with Duke University, the University of Minnesota, and the University of North Carolina at Chapel Hill. A number of these facilities also are available to provide extramural investigators access to these technologies, particularly the tissue arrays that are being developed.

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XIV. EVALUATING BREAST CANCER SCREENING IN PRACTICE

Breast Cancer Surveillance Consortium: A Decade of Progress. Dr. Rachel Ballard-Barbash explained that the Breast Cancer Surveillance Consortium (BCSC) began with pilot projects in 1992 and was fully formed in 1995. The purpose of the BCSC is to evaluate the performance of screening and practice at the individual health professional and system levels. Work conducted by the Consortium allows researchers to try to quantify the population effect of screening as it currently is implemented in the United States and to track new technologies in screening. NCI's role in the BCSC is to provide research that helps to identify the targets for improving delivery of screening and rapidly working with partners in understanding how policy and other factors can be influenced to ensure that those targets are utilized in improving care. Currently, there are more than 4.5 million mammograms in BCSC's database; approximately 85 percent are screening mammograms, reflective of the distribution of mammography in U. S. clinical practice. Among this sample of women who have been

undergoing mammography, there have been more than 46,000 breast cancers diagnosed, and slightly more than 16 percent of these are carcinoma in situ.

BCSC data are used within another NCI initiative, the Cancer Intervention and Surveillance Modeling Network. Investigator-initiated research through NCI-funded and NIH-funded R01s, and research funded by the Agency for Healthcare Research and Quality and the Department of Defense, have utilized this research resource as a basis for grant development. It also has been a source for the career development of junior investigators and is drawing individuals into health services research. Over a 7-year period, there have been approximately 150 publications from the individual BCSC sites. There are now 12 publications in press and a number that are actively in preparation. BCSC research has been utilized by the American College of Radiology in creating clinical guidance and has contributed to federal policy and reports. In addition, the Consortium is working actively with software vendors to enhance data collection throughout clinical practice.

Understanding How Mammography Works in Practice. Dr. Stephen Taplin, Senior Scientist, Applied Research Program, DCCPS, discussed some of the factors that might affect mammography and how the BCSC has considered them within its research effort. BCSC researchers intent was to create a dataset that would allow for comparison across regions and around the country and allow an examination of outcomes from stage of diagnosis to cancer rate to biopsy yield in sites around the country. The following factors were considered in building the dataset: (1) the ability to examine women and understand the factors in women that affect overall radiologist/mammography performance; (2) the need for information on radiologists (the BCSC created a data collection form to collect the assessment and followup recommendations in a standardized way); (3) the need for information about the facility, because the facility in which the radiologist operates also affects performance; and (4) the ability to compare regions within the country and to compare the United States to other countries.

One central question that the dataset is intended to answer is how well radiologists discriminate between women who do not have cancer and women who do have cancer in a single measure. BCSC researchers examined a number of characteristics for the dataset,

including breast density. Breast density differs by age. It is not a single, fixed characteristic, and the proportion of women with high-density breasts decreases as women get older. In separating out density and age, it was found that sensitivity increases as women get older, and sensitivity decreases with more dense breasts.

BCSC researchers also examined facility characteristics. In terms of clinical image quality, it was found that, with poor positioning, sensitivity drops substantially and the risk of missing a cancer increases. Another characteristic is the use of computer-assisted diagnostics, which are used by some facilities but not others. Additionally, although the cancer rate is not substantially different between generalists and specialists, the rate of recall and rate of abnormality is much higher among generalists, and the proportion of mammographies that are called abnormal clearly drops with volume. Work recently published in JAMA compared BCSC findings with those from the United Kingdom and found that the proportion of abnormalities was substantially lower and the cancer detection rate was higher in the United Kingdom than in the United States.

Biology of Breast Cancer Detection and Risk. Dr. Karla Kerlikowske, Associate Professor, Medicine, Epidemiology, and Biostatistics, University of California at San Francisco, explained that, by pooling data from the seven mammography registries, the BCSC conducted one of the largest studies of ductal carcinoma in situ (DCIS) in a screened population. Results showed that DCIS has become a common disease in a screened population, with 1 in 1,300 screening mammograms actually leading to a diagnosis of DCIS. The detection of DCIS increases with age, but for each decade of age, the prevalence does not differ significantly between first and subsequent screens, suggesting that the development of DCIS to a point that actually is detectable on mammography is not time dependent. This differs from invasive cancer, the prevalence of which is twofold higher in first screens than subsequent screens.

Dr. Kerlikowske noted that mammography preferentially identifies tumors that have favorable prognostic features. Among women with screened detected cancers versus those who have interval cancers, a higher proportion of the interval cancers have cells with a high proliferation rate, indicating that mammographers may not be missing cancers-it is just that the cancers are developing or growing rapidly between screening exams. The sensitivity of

mammography to detect estrogen receptor (ER)-positive cancers is higher than ER-negative cancers. Older women have a preponderance of ER-positive cancers, and this may explain in part why mammography is somewhat more efficacious in older women (mammography is better at detecting ER-positive tumors). Previous research on groups of women taking hormone replacement therapy (HRT) has suggested that HRT actually may promote tumor growth. Because breast density is important in detection and risk, several BCSC sites have examined what influences breast density and how breast density might influence risk. As mentioned by Dr. Taplin, one of the biggest factors that affects breast density is age, such that as women age their breast density decreases. However, for women who take HRT, the therapy stops the effect of aging on the breast and results in a higher proportion of women with very dense breasts. This suggests that breast density can be modulated and has prompted researchers to ask whether it is one of the mechanisms by which HRT might increase breast cancer risk.

Dr. Kerlikowske and colleagues have been developing a technique to measure density in the compressed area of the breast relative to a phantom that is 100 percent fat versus 100 percent glandular. This method has many advantages compared to the standard research method and is totally objective, automated, reproducible, and can be used on a standard mammography machine. Because it requires digitation of the film, those who perform digital mammography likely would be among the first to implement this technology in clinical practice. In closing, Dr. Kerlikowske told members that breast densitometry should be integrated into routine mammography screening because it can better estimate a woman's risk of breast cancer than current methods. The BCSC could provide the infrastructure to implement this in a rapid, effective manner.

BCSC Statistical Coordinating Center. Dr. William E. Barlow, PI, BCSC Statistical Coordinating Center, Center for Health Studies, Seattle, WA, described the activities of the Statistical Coordinating Center. Dr. Barlow noted that the Center's original purpose was to standardize data collection and the definitions being used by the Consortium. More recently, its mission has evolved to analyzing the pooled data and providing scientific input for interpretation of that data, as well as developing innovative statistical methods that are appropriate for analyzing the short-term and long-term evaluation of mammography. The BCSC has seven

mammography registries located throughout the United States, which are connected to cancer and pathology registries. Nested under those seven mammography registries are 231 mammography facilities, and nested under these facilities are approximately 1,300 radiologists. Currently, there are approximately 1.6 million women in the database for whom the Consortium collects risk factor and demographic information; the BCSC has roughly 4.3 million mammographies from those women. At three of the BCSC mammography registries, additional radiologist survey data are collected, and the Statistical Coordinating Center links the survey data to the mammographic outcomes and has the ability to perform a hierarchical analysis that examines facility-level, radiologist-level, and woman-level covariates in the same analysis.

The Center has done work on mammography performance after several screens, modeling the interval between screens, joint modeling of recall rate and positive predictive value (which is the probability of breast cancer given a positive mammography), and has examined the variability among radiologists. Using the radiologist survey data, it is possible to determine how many mammographies radiologists read in the last year and examine whether volume affects performance. The data indicate that volume affects recall, the rate of calling a mammography positive, and has an impact on sensitivity and specificity. However, the data indicate that true discrimination does not change with the number of mammographies read in the last year. Center researchers also are working to develop a model that is similar to a Gail Risk Model in which there is a prospective collection of covariates, whereas Gail used a retrospective collection of covariates. The Center has four times the number of breast cancers that was used in the Gail model. An interaction between age and breast density was found, and the effect of breast density decreases slightly with age.

Next steps for the Statistical Coordinating Center and the Consortium are to develop a public Web site that will have interactive graphics and tabulations that are intended both for the public and for radiologists. The Center is modeling long-term screening effects, survival, and mortality in this population and intends to expand data collection on some women to collect more risk factors or potential biomarkers.

Influencing Clinical Practice. Dr. Constance Lehman, Associate Professor of Radiology and Director of Breast Imaging at the

University of Washington-Seattle Cancer Care Alliance, described BCSC efforts to influence clinical practice. Dr. Lehman stated that one of the Consortium's most productive collaborations has been with the American College of Radiology (ACR). The BCSC started working with the ACR in 2002 to develop more accurate and more efficient methods of collecting information and streamlining the data collection process for the organization's data dictionaries and forms. The BCSC also created guidance for software companies that partner with the ACR. One overall goal of the Consortium is to improve the efficiency and the accuracy of data collection, both through data standardization as well as by creating more specific automated data collection systems. The group has explored innovations through the NCI Small Business Innovation Research Program and has worked with software vendors at local sites to enhance their existing systems, again in an effort to promote more accurate and more efficient data collection.

One example of a BCSC pilot project is a hand-held tablet computer. All of the information that patients have given in the past on their forms can be downloaded into this hand-held computer, and the patient can use a touch screen system to answer the questions that are being asked. This technology also is available for the radiologist and the technologist. The radiologists and technologists have access to these tablets on which the patient's information is downloaded into the computer, providing more efficient and accurate data collection. Another Consortium-sponsored project involves a tablet that has been translated into a variety of other languages for the multilingual and ethnically diverse population in San Francisco. These plastic templates are used on top of the English language form, are cost effective, and are an efficient approach to collecting information from a variety of women.

The BCSC also has contributed to federal reports and policymaking and has worked with a variety of groups, including the General Accounting Office, the International Breast Screening Network, the International Agency for Research on Cancer, and the IOM. The BCSC locally partners with federal and state groups. There is an interactive feedback for practices and radiologists on their audit performance, which has been extremely helpful both to sites and to radiologists. The research generated by the Consortium has been presented at grand rounds, and the data have been used in the development of training sets for improving interpretive

performance at specific sites. There are newsletters for radiologists and facility staff that provide updates on the information that the BCSC collects and analyzes. The Consortium also is developing an interactive Web site that will allow radiologists to see how they compare to similar practices across the country.

In discussion, the following points were made:

- In addition to mammography, there is a very active new development program at the Consortium, and the BCSC is collecting information related to magnetic resonance imaging (MRI), ultrasound, and other new modalities. The database is updated continuously, and as those modalities enter into clinical practice, this information is collected and examined relative to standard practices.

- Little is known about breast density. Using benign biopsies and examining percent collagen versus fat versus epithelium, it is clear that women who have mammographically more dense breasts have
- more collagen and more epithelium, but a greater increase in collagen out of proportion to epithelium. Molecular, proteomic, and genomic studies may be needed to assess these biopsies.

- The four main reasons that radiology residents are not interested in moving into breast imaging are: (1) the types of people that are drawn to radiology often are not those interested in patient care, and breast imagers deal with patients every day; (2) legal aspects-there is more malpractice in breast imaging than any other area; (3) reimbursements are very low when compared to other areas of radiology; and (4) a negative reputation has developed and some radiologists have a relative lack of respect for the subspecialty.

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XV. MANAGEMENT OF BIOREPOSITORY INITIATIVE- DR. ANNA BARKER

Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives, NCI, explained that the NCI, in collaboration with a research team from the NDC, is trying to do more at the discovery-development interface to enable R01 investigators, translational investigators, and clinical investigators to carry out more of the critical postgenomic science and to accelerate and optimize their work in some of these areas as well as to accelerate the movement of these technologies into patient care. Dr. Barker informed members that resources for cancer research have never been more needed, and the science has never been more optimized to make significant progress against this disease. An evolving barrier to realizing this progress is how researchers get, store, quality assure, distribute, and have access to the biospecimen resources that are needed. In an effort to overcome this barrier, the National Biospecimen Network (NBN) created a Blueprint with guidance for handling the biorepository issue on a national basis. Informing the Blueprint is a case study performed by the RAND Group. In this study, it was found that there are approximately 300 million specimens stored in this country that represent approximately 150 million cases, and there are about 20 million new specimens added each year.

Advancing the science of genomics and proteomics will depend ultimately on the availability of uniformly collected, processed, annotated, and stored samples. This has become a commercial area in some respects; and there are some very good small companies that provide these tissues, and some of the Cancer Centers make money by selling tissues. As those tissues migrate into the private sector, however, those data are no longer available in a precompetitive way.

A more consistent, uniform approach to handling and storing biospecimens is needed. She noted that experts from the United Kingdom have been extremely helpful in collaborating with and teaching investigators in this country lessons they have learned regarding these types of efforts. Dr. Barker explained that the NBN would be a new, overarching initiative. The repositories would grow and, over time, it is hoped that the database will grow to a point where in silica biology can become a reality. The Blueprint and the best practices identified by the RAND study evolved sequentially and led to the development of an organizational framework. The RAND study examined a broad range of 12 repositories and identified as many best practices as possible.

In light of the RAND study, the NBN has proposed creation of a national resource in addition to current resources that would standardize biospecimen collection, storage, and distribution. It also would standardize data collection, including longitudinal data. In addition, there would be some standardization of ethical clearance and stringent protection of patient confidentiality. One future critical issue is determining how access to this resource will be granted-it is intended to be an open system based on supporting the best science through peer review. Currently, there are a large number of existing high-quality tissue repositories in the United States. What is lacking, however, is a standardization to integrate them into a single system.

The NDC, working closely with the NCI, has developed a report outlining a strategy for the National Biorepository Initiative. The report will undergo a 45-day public comment period and will be made available on the Internet. Dr. Barker emphasized the importance of the NCI maintaining an active presence in this area and suggested that an inventory of old and new NCI repositories be created to aid in this process.

In discussion, the following points were made:

- Determining how to best provide access to biospecimens is a critical issue facing existing repositories. This issue must be resolved for a successful National Biorepository Initiative.

- It is hoped that, if this Blueprint is adopted, regardless of what biorepository is created by what group, and as long as there is a common platform with a bioinformatics grid that would enable communication to occur, it may be possible to integrate information and create a "virtual" biorepository.

- When this initiative comes up for review for funding, it would be useful to have background information that illustrates current sample processing, attainment, and banking, as well as the relationship of this initiative to the existing one. This type of information is necessary for the Board to provide informed advisory guidance.

- This topic will be discussed at a future Board meeting, where it is hoped the Board will be in a position to provide guidance on how the NCI should proceed in this area and next steps will be discussed.

A BSA Subcommittee (Drs. Anton-Culver (Chair), Appelbaum, Schilsky, and DuBois, and Ms. Kim) was established was established to review the National Biospecimen Network Blueprint to ascertain BSA participation and support in the formation of such a network.

Adjournment. The meeting was adjourned at 12:07 p.m. on Friday, 14 November 2003.

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