

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL CANCER INSTITUTE  
122<sup>nd</sup> NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting  
June 11-12, 2002**

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

**NATIONAL CANCER ADVISORY BOARD  
BETHESDA, MARYLAND  
Summary of Meeting  
June 11-12, 2002**

The National Cancer Advisory Board (NCAB) convened for its 122<sup>nd</sup> regular meeting on Tuesday, June 11, 2002, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, June 11, 2002, from 8:45 a.m. to 3:45 p.m. The meeting was closed to the public from 4:00 p.m. until adjournment at 5:00 p.m. The meeting was reopened to the public on Wednesday, June 12, 2002, at 8:45 a.m. until adjournment at 11:00 a.m. Dr. Amelie Ramirez, Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, served as Acting Chair of the NCAB and presided during both the open and closed sessions.

**NCAB Members**

Dr. Amelie G. Ramirez (Acting Chairperson)  
Dr. Samir Abu-Ghazaleh  
Dr. Richard J. Boxer  
Mr. Stephen C. Duffy  
Dr. Elmer E. Huerta  
Dr. Howard K. Koh  
Dr. Frederick P. Li  
Dr. Susan M. Love  
Dr. Sandra Millon-Underwood  
Dr. Arthur W. Nienhuis  
Dr. Ivor Royston  
Ms. Ellen L. Stovall

**President's Cancer Panel**

Dr. Harold Freeman

**Alternate Ex Officio NCAB Members**

Dr. Steven K. Akiyama, NIEHS  
Dr. Herman Gibb, EPA  
Dr. Peter Kirchner, DOE  
Dr. Allison Martin, FDA  
Dr. T. G. Patel, VHA  
Dr. Richard Pazdur, FDA  
Dr. John M. Powers, DOD, OASD, HA  
Dr. George Ruby, DOL, OSHA  
Dr. Anita Schill, NIOSH

**Members, Executive Committee, National Cancer Institute, NIH**

Dr. Carl Barrett, Director, Center for Cancer Research  
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics  
Dr. Peter Greenwald, Director, Division of Cancer Prevention  
Dr. Joseph Harford, Associate Director for Special Projects  
Dr. Marvin Kalt, Director, Division of Extramural Activities  
Dr. Alan Rabson, Deputy Director, National Cancer Institute  
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences  
Dr. Dinah Singer, Director, Division of Cancer Biology

**Liaison Representatives**

Dr. Eve Barak, National Science Foundation  
Dr. Margaret Foti, American Association for Cancer Research  
Dr. Robert W. Frelick, Association of Community Cancer Centers  
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.  
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation  
Mr. William J. Hoskins, Association of American Cancer Institutes  
Ms. Judy Lundgren, Oncology Nursing Society  
Ms. Mary Mitchell, The American College of Obstetricians and Gynecologists  
Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology  
Ms. Kristin Simonson, American Society of Therapeutic Radiology and Oncology  
Ms. Barbara Stewart, Association of American Cancer Institutes  
Ms. Julie Taylor, American Society of Clinical Oncology  
Ms. Pamela Wilcox, American College of Radiology

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**DAY ONE—TUESDAY, JUNE 11, 2002**

**I. INTRODUCTION, WELCOME, AND ACCEPTANCE OF MINUTES—  
DR. AMELIE RAMIREZ**

Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), and Executive Secretary, NCAB, thanked Dr. Ramirez for agreeing to serve as acting Chair of the NCAB for this session and reminded Board members that the open session was being Webcast to various locations on the NIH campus and closed-captioned in real time as required by Federal law.

Dr. Ramirez welcomed Board members, representatives of liaison organizations, and members of the public, and she invited the public to submit to Dr. Kalt, in writing and within 10 days, comments regarding items discussed during the meeting. Dr. Ramirez also reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

A motion was requested and made to approve the minutes of the February 2002 NCAB Meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

Dr. Ramirez reminded Board members that the material furnished for review and discussion during the closed portion of the meeting is considered privileged information.

**II. APPROVAL OF FUTURE MEETING DATES THROUGH 2004—  
DR. AMELIE RAMIREZ**

Dr. Ramirez called Board members' attention to future meeting dates listed in the Agenda. Dates have been confirmed through 2004. She noted that the dates for the September 2002 meeting have been slightly altered so that Federal Government employees can attend the memorial events being planned for September 11, the anniversary of the tragic events that occurred in 2001.

**III. NCI DIRECTOR'S REPORT—DR. ANDREW von ESCHENBACH**

Dr. Andrew von Eschenbach, Director, National Cancer Institute (NCI), began by thanking NCI staff and NCAB members for their support during his first 100 days as NCI Director. He listed several venues at which he had made major presentations since the last NCAB meeting, including a recent meeting of the National Dialogue on Cancer. A major theme during these meetings has been the need to work collaboratively with the cancer research community to translate knowledge into interventions that can be delivered to people in need.

Dr. von Eschenbach reported that NCI is in negotiation with the Institute of Medicine (IOM) so that the latter can continue independently to create a mechanism for reviewing evidence related to mammography and periodically update its findings. The NCI Breast Cancer Surveillance Consortium and the internal Breast Cancer Screening Working Group will continue to evaluate the performance of screening mammography in community practice.

Another issue receiving attention is the early detection of lung cancer. Dr. von Eschenbach said that he had suspended the implementation of the National Lung Screening Trial, which is aimed at comparing spiral computed tomography (CT) to chest x-ray technology, until it is determined that all relevant issues have been addressed. Representatives of the American College of Radiology Imaging

Network (ACRIN) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, the two arms of the trial, were brought together with concerned members of the cancer research community. These productive discussions resulted in some fine-tuning of the study design, including the addition of ten sites to the ACRIN arm. Accrual allocations for sites have been removed so that the study can meet its goal of 50,000 patients as quickly as possible. This will accelerate accrual to the trial and should enable the study to achieve meaningful results faster and at a reduced cost. Rapid accrual should also reduce the likelihood of contamination of the study due to the growing availability of spiral CT.

Partnerships are being pursued to help defray the cost of this \$200M project. The American Cancer Society (ACS) has committed \$1M per year for the first 5 years of the trial and will participate in the promotion of the study to enhance accrual. Discussions are also underway with the American Legacy Foundation that may result in further financial support for the trial.

Within the ACRIN component of this trial, Dr. von Eschenbach continued, a tissue repository will be established. These samples from the early stages of the disease will supplement existing specimens that primarily represent later-stage disease, providing a more balanced portfolio of tissue for the study of fundamental questions about lung cancer pathogenesis and progression.

Dr. von Eschenbach reminded the Board of discussions that have been underway between the NCI Division of Cancer Treatment and Diagnosis (DCTD) and leading pharmaceutical companies to explore the development of a collaborative program to study barriers to clinical trial access. After unsuccessfully examining the Institute's Gift Fund as a possible way to disburse contributions from the companies as supplements for this research project, the DCTD explored the National Institutes of Health Foundation and found it to be a useful and effective mechanism for this effort. The NCI and the pharmaceutical companies will both contribute \$1.5M per year for 2 years, for a total pool of \$6M. Offers for supplements will be issued to Cancer Center grantees to examine barriers to access to clinical trials and develop a mechanism to overcome those barriers. It is hoped that this mechanism will serve as a model for other public-private partnerships.

Dr. von Eschenbach stated that in the course of his orientation to the NCI, he has been looking at the management structure of the Office of the Director (OD), and he plans, within the next 30 to 60 days, to initiate recruitment and reorganization efforts to ensure an effective team with the multiple skill sets required to respond to the needs of the Institute. At the same time, he added, strategic planning efforts are going forward, including development of the Bypass Budget and the scheduling of three Executive Committee (EC) retreats. In the first retreat, the EC will examine progress in oncology in the past 5 to 10 years, develop projections for progress in the near future, and discuss resources that will be needed to support anticipated progress. In the second retreat, the EC will consider operational issues and the kind of team that will be needed, and in the third retreat, the EC will develop a work plan to make anticipated progress a reality.

### **Budget Update**

Dr. von Eschenbach reported that the NCI is waiting for Congress to make a decision concerning the FY2003 budget. Now that all of the testimony has taken place, he said, he is optimistic that appropriations will meet the President's recommendations.

About half of the approximately \$4.2B in the FY2002 budget is obligated for Research Project Grants (RPGs). The NCI expects to award 4,600 RPGs (including 1,280 competing awards), representing

an approximate 10 percent increase over the previous year. Although increases in the number of applications received are an encouraging sign of interest, especially among young investigators, Dr. von Eschenbach noted that these increases present a challenge in maintaining the payline. While NCI has been experiencing budget increases in recent years, the growth curve is expected to flatten out. The President has proposed an FY2003 budget of \$4.7B, but the working budget for FY2004 provided by the Office of Management and Budget (OMB) contains an increase of only 2.2 percent. The combination of growth in awards and flattening of the budget has significant implications for the number of new and competing grants the NCI will be able to award, due to out-year commitments to noncompeting renewal awards over the next several years.

As part of its effort to address these budgetary issues, Dr. von Eschenbach explained, the NCI is paying a great deal of attention to Cancer Centers and Specialized Programs of Research Excellence (SPORes), two areas in which much growth has occurred recently and in which more growth is anticipated in light of various recommendations made by the Progress Review Groups. To ensure careful deliberation concerning immediate and long-term needs in those areas, Dr. von Eschenbach brought together a group of representatives from Centers and SPORes, plus a cross-section from advisory boards such as the NCAB, Board of Scientific Advisors (BSA), and Board of Scientific Counselors (BSC). A small program planning committee is developing an agenda for this working group, which will be chaired by Drs. Nienhuis and Simone.

This group's charge, Dr. von Eschenbach continued, is to project the future of the Centers and SPORes mechanisms in light of the changing funding landscape. Particular attention will be given to opportunities for coordinating and integrating the two programs to further leverage their impact. The fact that most SPORes have been developed within Cancer Centers suggests that synergies between the programs exist. Another goal is to explore ways to integrate these programs with the larger cancer research community, especially with regard to augmenting clinical trials.

Dr. von Eschenbach brought to the Board's attention another initiative that will affect the NCI budget. In 2002, \$21M was transferred from NCI to the new NIH Institute, the National Institute of Biomedical Imaging and Bioengineering (NIBIB); in 2003, an additional \$60M will be transferred from NCI to the new Institute. The NCI performed a detailed analysis of its portfolio to identify biomedical imaging grants that could be transferred to NIBIB; 122 grants totaling \$35M were identified, leaving the NCI short of the expected transfer. A compromise was reached in which \$25M in cash would be transferred, rather than additional grants. Dr. von Eschenbach stated that this compromise helps maintain the integrity of the NCI portfolio while meeting the needs of the new Institute.

Dr. von Eschenbach noted the appointment of Dr. Elias Zerhouni as the new Director of the NIH. He said he looked forward to working with Dr. Zerhouni, who has demonstrated dedication to both basic and translational research, and expressed his thanks to Dr. Kirchstein, who was very supportive of him in her role as Acting Director.

Dr. von Eschenbach concluded his report by announcing that negotiations with the Army have resulted in the availability of a parcel of land adjacent to the NCI's Frederick facility, enabling its expansion. When that arrangement has been finalized, he said, the process of refurbishing and redeveloping the Frederick facility will begin. Part of this expansion will involve the creation of a vaccine facility in collaboration with the National Institute of Allergy and Infectious Diseases.



## Questions and Answers

Dr. Richard Boxer, Clinical Professor of Health Policy/Family and Community Medicine, Medical College of Wisconsin, asked whether any transfers were being made by NIH or NCI associated with Federal reorganization related to homeland security. Dr. von Eschenbach replied that no recent decisions have affected NIH beyond the impact that already took place in the FY2002 budget.

Dr. Boxer then asked two questions about the National Lung Screening Trial: Does the lung cancer screening project contain any provisions to provide treatment for uninsured individuals who are found to have lung cancer through the trial? Does the study examine the question of whether early detection has significant value in lung cancer? Dr. von Eschenbach said that he would have to look into the answer to the first question. Concerning the second question, he agreed that overdiagnosis is a critically important part of the study.

Dr. Boxer asked whether new members would be appointed to the NCAB. Dr. von Eschenbach answered that aggressive efforts are underway to select new members. He added that Mr. Lance Armstrong and Dr. LaSalle Doheny Leffall, Jr., have been selected to replace Dr. Dennis Slamon and Ms. Frances Visco as members of the President's Cancer Panel (PCP).

## IV. UPDATE FROM THE OFFICE OF POLICY ANALYSIS AND RESPONSE— MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Policy Analysis and Response, NCI, began her report with the description of a bill that was recently signed into law: the Hematological Cancer Investment Act of 2002. The Act expands research into hematologic malignancies and increases support for cancer education programs. NCI will have primary responsibility for the research component; the educational component, at the discretion of the Secretary of the Department of Health and Human Services (DHHS), is likely to be a collaboration between NCI and the Centers for Disease Control and Prevention (CDC).

Ms. Foellmer then turned the Board's attention to a bill introduced by Senator Dianne Feinstein, the National Cancer Act of 2002, or S1976. This bill is an outgrowth of Senator Feinstein's leadership in co-chairing the Senate Cancer Coalition, her involvement in the National Dialogue on Cancer, and the work of the National Cancer Legislation Advisory Committee (NCLAC), which she convened. The bill has 29 cosponsors and has been referred to the appropriate committees within the Senate.

In terms of NCI appropriations, the bill would authorize \$4.8B in FY2003, \$5.3B in FY2004, \$5.8B in FY2005, \$6.4B in FY2006, and \$7.1B in FY2007. The bill also requires the development of strategic plans in several specific areas: behavior associated with causation and prevention of cancer; disparities among racial and ethnic groups; early detection; palliative care, pain management, symptom management, and quality of life; environmental risk factors; and gene-environment interactions.

The bill contains a provision establishing a national network of about 20 multidisciplinary translational research centers focusing on drug and technology development. A strategic plan would also be required to disseminate results of translational research and to increase participation in clinical trials. The bill addresses career development for cancer researchers and the need to address cancer care workforce issues.

Additional requirements include: an IOM study of cancer care guidelines (under the leadership of the Agency for Healthcare Research and Quality [AHRQ]); a national program of comprehensive cancer control plans (under the leadership of the CDC and NCI); a strategic plan for research on environmental risk factors and gene-environment interactions (under the leadership of the National Institute of Environmental Health Sciences [NIEHS] and NCI); and a colorectal cancer screening demonstration program (under the leadership of the CDC). There are also provisions related to health insurance coverage for clinical trial participation, cancer screening, and a lead physician for cancer care. The bill also names the Food and Drug Administration (FDA) as the primary regulatory authority for tobacco products.

#### **V. NIH LOAN REPAYMENT PROGRAM UPDATE—DR. CAROLYN STRETE**

Dr. Carolyn Strete, Chief, Cancer Training Branch; Office of Centers, Training and Resources; Office of the Deputy Director for Extramural Sciences; NCI, gave an update on NCI progress under the NIH Loan Repayment Program. She reminded the Council that the purpose of this program is to recruit and retain highly qualified health professionals as clinical and pediatric researchers. She further explained that under the terms of the program, NIH/NCI will pay up to \$35,000 of the principal and interest on eligible educational loans to clinical and pediatric investigators for each of the 2 years in which they are required to perform under the program. The NIH will also pay 39 percent of the loan repayment amount per year toward Federal tax liability under this program.

As required by statute, the loan repayment recipients must agree to perform 2 years of research service; thus, these are not grants. Rather, they are contractual agreements, and the terms begin on the date that the loan repayment program award is made. Implementation of this program is an NIH-wide activity.

Dr. Strete reported that for the first round, NCI received 79 applications: 55 were from clinical investigators, and 24 were from pediatric investigators. Of the 79, a substantial proportion, 31 applicants, had as their qualifying mechanism the institutional National Research Service Awards (NRSA) T32 programs. That is, applicants were pre- and postdoctoral trainees.

Dr. Strete reported that the applications deadline was February 28, 2002. The applications were reviewed by an NCI Special Emphasis Panel, and the results were submitted last week. Dr. Strete stated that she and her colleagues are now in the process of determining which applications to support. This activity involves a broader NIH process. Applications will be examined for awards consistent with general parameters to be established across the NIH; the success rate is expected to be relatively high, not just for NCI, but across the NIH.

Dr. Strete then commented that not all Institutes have completed their reviews. When all the reviews are available, she and her colleagues will discuss the applications they may wish to pick up from other Institutes and vice-versa. Dr. Strete stated that she could not at this time precisely state the success rate, but that she would be able to do so in September.

Dr. Strete concluded by stating that, in terms of the future, NIH is committed to expanding the eligibility beyond the qualified NIH grantees selected in FY2002. However, the specifics of the eligibility pool have not yet been established. She mentioned that she and her staff are reviewing different qualifying factors that describe the current applicant pool. There is an NIH committee headed by Dr. Claude L'Enfant, with representatives from throughout the NIH, that is working on defining future criteria, and more details should be available at the September 2002 NCAB meeting.

## **Questions and Answers**

Dr. Sandra Millon-Underwood, Professor, University of Wisconsin–Milwaukee School of Nursing, asked whether there was any information regarding the demographics of the pool of individuals who applied, such as the percentages of men and women, ethnic/racial backgrounds, and professions represented in the pool. Dr. Strete replied that the group has not yet determined these elements because the results were received only last week, but there appears to be a mix. She stated that there were minority supplement applicants, but she did not know the precise numbers. She can make this information available soon.

### **VI. NEW BUSINESS I—DR. AMELIE RAMIREZ AND NCAB MEMBERS**

Dr. Ramirez opened the floor for new business. Dr. Kalt announced to the Board a resolution by NCI to institute a two-phase program for granting NIH Method to Extend Research in Time (MERIT) Awards (also called R37 grant awards) to outstanding researchers who submit R01 applications to NIH. Dr. Kalt explained that from now on, new awardees will be publicly announced at the Board meeting following their selection. In addition, NCI will provide the awardees with a certificate suitable for framing so that they can gain recognition in their own institutions. Dr. Kalt then announced three Principal Investigators who were granted MERIT Award status as a result of actions taken by the NCAB at its February 2002 meeting: Dr. Mary Hendrix from the University of Iowa, whose project is entitled “Endothelial Transdifferentiation of Invasive Tumor Cells”; Dr. Terumi Kohwi-Shigematsu from the University of California Lawrence Berkeley Laboratory, whose project is entitled “Non-B DNA Structure with Chemical Carcinogens”; and Dr. Satya Prakash from the University of Texas Medical Branch in Galveston, Texas, whose project is entitled “Repair of UV Irradiated DNA: Excision Genes of Yeast.”

Dr. Kalt indicated that NCI is open to suggestions from the Board as to other grant award-related activities that might be announced at subsequent NCAB meetings. He noted that the names of the new MERIT award grantees will be posted on the NIH and NCI Web sites.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, expressed concern about the lack of response regarding the inclusion of uninsured and underinsured individuals in the Spiral CT Lung Cancer Screening Trial and their treatment coverage if they are found to have lung cancer after screening. Dr. Ellen Feigal, Acting Director, DCTD, NCI, indicated that it is expected that 10 percent of the individuals in the study will be uninsured, and this has been accounted for in the budget for the screening test. She stated, however, that the cost for follow-up treatment for these individuals has not been addressed. Dr. Huerta stressed the need for addressing health/budgetary issues for uninsured people sooner rather than later. Dr. Feigal reiterated that this is a very challenging issue and NCI is exploring many different avenues (e.g., partnerships with the private sector) to help underwrite some of the costs incurred by individuals who are un- or underinsured.

### **VII. RPG WORKING GROUP REPORT AND FY2003 RFA INITIATIVES— DR. MARVIN KALT AND MR. STEPHEN HAZEN**

Dr. Kalt presented a brief background on the tracking of grant awards. This exercise was developed after a series of year-to-year swings were observed in the NCI budget and grant portfolio funding plans, which confused the extramural community. The NCAB created the Research Project Grant (RPG) Working Group to assist the NCI Director in explaining the parameters the Institute had to deal

with in making awards, defining average cost, and assessing the distribution of awards across the research grant portfolio. The research grant portfolio includes R01 grants, Program Project grants, R03 small grants, and R21 developmental awards.

Because appropriations bills are not often signed by the beginning of the fiscal year (October 1), the NCI must decide on a preliminary funding plan that represents the worst-case scenario, defined as a flat budget from the previous fiscal year, which is then projected forward. When an appropriation is obtained, the Institute liberalizes the payline. The ultimate aim is a consistent payline across all three grant award rounds by the end of the year. The math is not simple. After the budget appears balanced, more applications continue to come in. If there is a fixed number of awards, and applications continue to come in, it will have a negative effect on the overall success rate.

As dollars increase in the extramural budget and the RPG pool, there is not always a concomitant increase in the payline, although there is a concomitant increase in the absolute number of awards or in the average cost. This concept has always been difficult to explain to the extramural community. All parameters require a lot of round-by-round attention in the grant award decision-making process, because the average length of an award is 4 years, and this affects the extramural budget—not just for the fiscal year in which the award is made, but for the following 3 years. Recognizing the confusion caused by these constantly changing parameters, the NCAB formed an ad hoc working group, the RPG Working Group, to look at the direction of the trends in grant awards.

Mr. Stephen Hazen, Chief, Extramural Financial Data Branch, NCI, summarized the recommendations of the June 3, 2002, meeting of the RPG Working Group and presented an overview of the challenges. He showed the operating policies for FY2002 and recommendations for FY2003. Mr. Hazen also reviewed the guiding principles identified and gave a preview of the number of applications for FY2003 as well as a brief history of modular grants.

The budget allocations for FY2003 include an increase of nearly 13 percent under the President's budget request to Congress. For FY2004, there is only a 2.2 percent increase in the budget. This presents a challenge both for the NCI and across NIH. The specific challenge for the RPG pool is that the noncompeting, Type 5 commitments require an 8 percent increase to pay all the prior-year commitments. This will clearly require considerable reduction in the number of competing grants that can be funded.

According to various budget models, the same scenario will occur for several years past FY2004. Thus, unless early action is taken, it will take at least 2 years of decompression before the RPG paylines and policies restabilize.

Mr. Hazen presented a matrix of RPG differences expected between FY2002 and FY2003. "Policy" reductions would be about the same for both years. The new Type 1 R01s would have an average reduction of 10 percent from levels approved in peer review. There is a two-tiered policy that cuts smaller grants less than it cuts larger grants. This policy is used for the Type 1s. For the Program Project grants (P01s), which are much larger, the reduction is 15 percent. For the Type 2s, the competing renewal grants, there is a 6 percent reduction. These get a more modest reduction because the NCI limits the amount a Type 2 applicant can request over his or her current budget. Under this scenario, the R01 payline goes from the 22<sup>nd</sup> to the 21<sup>st</sup> percentile. Finally, the Request for Application (RFA) set-aside will increase from \$37M in FY2002 to \$44M in FY2003.

With the projected FY2004 numbers in mind and the expected 2.2 percent budget increase, the Working Group identified six principles to guide the NCI's operating policies: (1) NCI should give special consideration to supporting new investigators; (2) NCI should identify and initiate one-shot supplement initiatives in FY2003; (3) NCI could implement a targeted and more restrictive cap on competing renewal requests (only in case of severe budget restriction); (4) NCI should continue the accelerated executive review process; (5) NCI should review all budgets across the Institute to establish the relative value of different ongoing initiatives; and (6) NCI should strongly oppose any proposed change in the modular grant ceiling.

Mr. Hazen then presented a brief preview of FY2003 in terms of the number of grant applications expected in the first round of the year. He compared the numbers to those estimated for FY2002: nearly a 25 percent increase over the previous October, and at least a 7 percent increase over January's numbers.

Mr. Hazen then displayed a chart showing numbers of applications and amounts of grant awards, broken down into modules. The chart began with FY1999, the last year before the invention of modular grants. At the end of FY2001, the first full year for modular applications, there was a large increase in the number of very large (defined as \$1M) R01 grants; this was a serious concern for the RPG Working Group last year. In FY2002 estimates, there are fewer very large R01 grant applications, but among the regular sized R01s, the average cost has been rising significantly.

Dr. Kalt then added that in any given fiscal year, there is always going to be a certain number of applications awarded at a certain average cost. What the NCI is hoping to do is maintain or reduce the distance between the amount of dollars requested and approved by peers and the amount that is actually paid. If the gap gets too wide, the number of specific aims that cannot be conducted under the research award becomes substantial, and it becomes harder to anticipate whether the research can actually be completed successfully for less money.

Dr. von Eschenbach commented that the NCI and the RPG Working Group must do everything possible to keep the payline from falling below the 20 percent level in outlying years.

Mr. Hazen then asked the NCAB members to comment on the NCI Internet Web page that describes the RPG policy.

### **Questions and Answers**

Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital, asked Mr. Hazen to elaborate on the one-shot supplement. Mr. Hazen answered that it is a supplement to ongoing grants. It would be awarded at one time in FY2003 for a short-term project, to help support infrastructure and other items, such as equipment. Dr. Nienhuis commented that bioinformatics is an area he thinks should be targeted.

Dr. Frederick Li, Chief, Division of Cancer Epidemiology and Control, Dana-Farber Cancer Institute, asked about the indirect costs and their increases. Mr. Hazen replied that they are "creeping up." The average rate of indirect costs for an R01 is around 49 percent. Mr. Hazen said that it has not been a big issue in recent years.

**VIII. FOLLOW-UP ON CANCER SURVIVORSHIP—DR. JULIA ROWLAND AND MS. ELLEN STOVALL**

Dr. Julia Rowland, Director, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences (DCCPS), NCI, presented to the NCAB a summary of material presented at the previous meeting and provided an update on new developments. She stated that during the previous NCAB meeting, she talked about cancer prevalence and the history of the Office of Cancer Survivorship (OCS), in addition to the topics presented by three other speakers.

Regarding prevalence statistics, Dr. Rowland stated that in the past, the NCI relied on the cancer registry in Connecticut—the oldest extant tumor registry in the country, with the longest follow-up of persons diagnosed with cancer—to estimate the number of cancer survivors in the United States. As of April 2002, the Surveillance Research Program within the DCCPS has developed statistical modeling techniques that make it possible for the first time to use the complete Surveillance, Epidemiology, and End Results (SEER) registry database to generate prevalence estimates. Use of this larger data set permits a fuller description of survivors and more generalizable prevalence estimates for the country. In particular, it allows for estimation of cancer prevalence by race/ethnicity, going back 10 years—information previously unavailable using the Connecticut registry alone. The SEER database also tracks the prevalence of cancer by site in the body. Dr. Rowland also noted that while age is the most common factor associated with cancer risk, research is lagging in describing outcomes for the growing population of older cancer survivors.

The OCS was established in recognition of the growing population of survivors. Dr. Rowland praised Dr. Anna Meadows, the initial leader of OCS. Dr. Rowland also praised Dr. Barbara Rimer, Director, DCCPS, NCI, for her leadership, compassion, and support. She noted that in 1996, the amount spent on studies looking at postcancer treatment was \$6M (24 grants), while in 2001, it was \$38M (142 grants)—a fivefold increase in 5 years.

At the last meeting, three presentations were given by researchers funded by the OCS. In summary: Dr. Patricia Ganz talked about some of the late effects of cancer treatment faced by survivors and their families. These include physical effects such as second cancers, pain, cardiac dysfunction, and sexual impairment and psychological effects such as depression, anxiety, and fear of recurrence. She also raised a number of questions about how to follow up such individuals—what interventions can reduce the incidence of adverse sequelae, who should monitor survivors, and how to increase survivors' knowledge about late effects of treatment.

Dr. Tim Ahles spoke about the neuropsychological impact of systemic chemotherapy. There is evidence that long-term cognitive problems may arise in both children and adults subsequent to chemotherapy. The OCS is currently supporting research on interventions to alter the outcomes for individuals undergoing treatment.

Dr. Michael Antoni talked about the effects of cancer on quality of life, or psychosocial variables. He is interested in finding consistent psychosocial predictors of cancer disease progression and developing interventions, such as cognitive behavioral stress management, that have the potential to enhance length and quality of survival.

Dr. Rowland then commented that since the last NCAB meeting, the first large cancer survivorship conference was held jointly with the ACS—a historic meeting that the OCS hopes will

become a biennial event. Preceding the conference, OCS and ACS held a town hall meeting discussion of survivorship that was Webcast on the ACS Cancer Survivor Network. Dr. Rowland also mentioned that she had an opportunity to go before Dr. von Eschenbach and make the case for having cancer survivorship embraced as an Extraordinary Opportunity (EO) in the Bypass Budget for 2004.

Ms. Ellen Stovall, President and CEO, National Coalition for Cancer Survivorship (NCCS), talked about *Imperatives for Quality Cancer Care*, a report on a survey of 300 professionals and advocates in the cancer community. She detailed how Dr. Klausner had read the report and how he and Anna Meadows had established the OCS.

Ms. Stovall gave her perspective on the importance of combining the science of survivorship with what NCCS calls the “art of cancer survivorship.” What is the art of cancer survivorship? Ms. Stovall mentioned an article by Dr. Stanley Reiser, published in 1993 in *JAMA*, in which he wrote about using the experience of illness to shape the mission of health care. She also mentioned Dr. von Eschenbach’s statement that “you cannot solve a problem you fundamentally do not understand” to highlight the collective wisdom of the founders of NCCS who, indeed, defined and solved a problem they fundamentally understood very well. The founding members of NCCS came up with the term *survivor* to describe people diagnosed with cancer, from the moment of diagnosis until the end of their lives, and their caregivers, friends, and families. They defined *survivorship* as the experiences these people go through after a diagnosis of cancer. The *survivor* definition also includes researchers as support elements for those diagnosed. The term *survivorship* has become more widely accepted, since a person’s experience with cancer has evolved to be treated as a chronic illness, rather than as a matter of “death or cure.” Ms. Stovall also mentioned the feeling of abandonment a cancer survivor feels after receiving the final chemotherapy or radiation treatment and how this is not addressed in the medical profession.

Ms. Stovall concluded her presentation by thanking the NCI for the opportunity to serve as an NCAB member for the past few years and speak on behalf of the cancer survivorship community.

### **Questions and Answers**

Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Institute, referred to a chart showing five million white cancer survivors, compared with less than half a million black survivors. He asked Dr. Rowland why the number of black survivors was so much lower. Dr. Rowland answered that the SEER prevalence data by race and ethnicity go back only 10 years, and that the relative percentages did not generally vary that much among racial/ethnic groups; they were about equivalent.

Dr. Millon-Underwood asked if the estimated number of persons diagnosed with cancer in the United States referred only to those with invasive cancer. Dr. Rowland answered yes, although she acknowledged that one could still be considered a cancer survivor with noninvasive cancer (e.g., skin cancer, some breast cancers). Dr. Millon-Underwood then asked if noninvasive cancer were included in the calculations, what the number of cancer survivors in the United States would be. Dr. Rowland acknowledged the relevance of the question, but she indicated that she did not know the amount.

Dr. Millon-Underwood also noted the absence of figures for Native Americans, and Dr. Rowland replied that those populations are too small to capture yet. She indicated, however, that as the database expands, the registry pool should increase.

Dr. Li asked whether there were any studies on the impact of survivorship on family members—children, spouse, etc. Dr. Rowland answered yes, but she did not have the figures with her. She directed Dr. Li to the Survivorship Web site, which lists a number of studies looking specifically at family members.

Dr. Rimer answered Dr. Millon-Underwood’s earlier question about survivors of noninvasive cancers. She said that there were about 56,000 cases of ductal carcinoma *in situ* (DCIS) in the last year, so if one multiplies this by the number of years involved, one can get a sense of how much this group would add. Dr. Rimer also commented on Dr. Millon-Underwood’s Native American question, citing the inclusion of these populations as really important and something that would be able to be done over time with the expansion of the SEER sites.

Dr. Rowland added that with the SEER data will come the ability to do more than just count those living with cancer; one will be able to specify stage of treatment and the nature of the disease.

Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, commented that two-thirds of those with DCIS would never have gotten cancer if they had never been treated; so it is “weird” to call them “survivors.” However, those who have received treatment for DCIS feel like cancer survivors and are made to feel as though they are survivors by others, so defining who is a survivor becomes complicated.

Dr. Howard Koh, Commissioner, Massachusetts Department of Public Health, asked if there were data about whether the stigma of having cancer is being reduced. Dr. Rowland said yes—for some cancers. For example, breast cancer has seen a reduction in stigma for the patients themselves because there is such a strong advocacy for breast cancer survivors. But some survivors feel stigmatized because they may lose job opportunities and insurance coverage and experience prejudicial treatment in the financial arena.

## **IX. MINI-SYMPOSIUM ON EARLY DETECTION AND SCREENING FOR BREAST CANCER—DR. AMELIE RAMIREZ**

Dr. Ramirez introduced the topic of the mini-symposium: the benefits of screening for breast cancer. Recently, scientific publications have questioned how results of mammography trials have been interpreted. DHHS and NCI have worked together to reassure the public of the benefits of early detection of breast cancer through mammography, as well as to improve current detection strategies. Dr. Ramirez introduced the first two speakers, Drs. Greenwald and Rimer, who further discussed these topics.

### **INTRODUCTION AND OVERVIEW—DRS. PETER GREENWALD AND BARBARA RIMER**

Dr. Peter Greenwald, Director, Division of Cancer Prevention, NCI, introduced the recent controversy surrounding mammography studies. This past October, a paper was published by Gotzsche and Olsen in the *Lancet* that criticized trials on mammography detection performed from the 1960s through the 1980s. The elements critiqued included randomization methods and baseline comparability of mammography groups and controls, exclusion of data after randomization, and biased assessment of outcomes. The lay press reported this review along with comments from the Physician Data Query (PDQ) Screening and Editorial Board. The PDQ is NCI’s comprehensive cancer information database, and within the PDQ, an independent group summarizes evidence from cancer screening. The statement from



the PDQ Screening and Editorial Board questioned the “variable quality of the evidence and the inconsistency of results across studies.”

Dr. Greenwald listed a number of groups that have come forward with statements in opposition to the *Lancet* review. After reviewing the evidence in question, NCI has reaffirmed the benefits of screening mammography and recommended that women have a mammogram every 1 to 2 years, beginning in their 40s. The U.S. Preventive Services Task Force (USPSTF) and the DHHS have both taken a similar position. This past spring, the International Agency for Research on Cancer (IARC) established a working group that reviewed the available evidence on breast cancer screening and found the criticisms of the studies to be unfounded. This group recommended that women between 50 and 69 years of age undergo screening mammography.

Dr. Greenwald concluded that the consensus of the various groups involved in cancer screening was to continue the promotion of screening mammography. In addition, NCI has set up a working group to monitor mammography issues, new screening technologies, and basic biology as they relate to breast cancer screening. In the future, this working group will report to the IOM as well as to the NCAB.

Dr. Rimer provided an overview of how NCI funding in FY2001 was invested in the area of breast cancer detection and screening. The largest portion of the budget, \$118M, was invested in funding RPGs, with \$39M of that amount going to projects focused on the treatment and diagnosis of breast cancer. The majority of grants in this area focus specifically on imaging analysis. Dr. Rimer emphasized that most of the budget for breast cancer screening and detection is invested through RPGs, with a much smaller fraction directed to cooperative agreements, contracts, and research program projects and centers.

Within the RPG pool, 44 percent of the budget for FY2001 was invested in imaging and new technologies—including proteomics—with smaller fractions covering mammography, surveillance, epidemiology, basic biology, and other screening methods. The majority of these grants were investigator-initiated research project grants, with a limited amount designated for Requests for Applications (RFAs) and 31 percent for Program Announcements. Dr. Rimer concluded her talk by pointing out that this brief overview was important to ensure that the NCAB understands how NCI distributes and invests its monies.

#### **U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS— DR. STEVEN WOOLF**

Dr. Steven Woolf, Professor, Department of Family Practice, Virginia Commonwealth University, presented a brief background on the USPSTF, which was established in 1984 by the U.S. Public Health Services. The mission and purpose of the USPSTF is to develop “evidence-based recommendations on hundreds of clinical preventive services that include screening tests, counseling on lifestyle and health behaviors, immunizations, and chemoprophylaxis.” The Task Force makes recommendations on a range of diverse topics that include cancer, mental health, and substance abuse, as well as pediatrics and obstetrics, and comprises generalists with expertise in analytical sciences.

Dr. Woolf reviewed the USPSTF’s 1996 recommendations on breast cancer screening. The USPSTF gave an *A* recommendation for women aged 50 to 69 to receive a mammogram every 1 to 2 years, as there was sufficient evidence to support this intervention. For women aged 40 to 49 and aged 70 and older, the USPSTF gave a *C* grade due to insufficient evidence to recommend for or against screening. Clinical breast exams and the teaching of self-examination also received a *C* grade. Since

1998, the USPSTF has created a new approach to analyze evidence and assign grades. The new rules rate the quality of the evidence—good, fair, or poor—in relation to the magnitude of the benefit—substantial, moderate, small, or zero/negative. Each piece of evidence is analyzed based on these two separate rules before assigning a recommendation of *A*, *B*, *C*, or *D*. In addition, a new grade, *I*, has been added for instances in which evidence is insufficient as a result of conflicting results, inferior quality of results, or an absence of studies on the subject. A detailed explanation of the USPSTF methodology can be found at [www.ahcpr.gov/clinic/uspstfix.htm](http://www.ahcpr.gov/clinic/uspstfix.htm).

The Oregon Health and Sciences University performed a review of breast cancer screening for the USPSTF, and the results were released along with the new USPSTF recommendations. Mammography screening received a *B* recommendation, with screening every 1 to 2 years—with or without clinical breast exam—for women aged 40 and older. Routine clinical breast exam and teaching/performing breast self-exam both received an *I* recommendation, since there was insufficient evidence to justify a higher rating. These recommendations were based on meta-analysis results on the mortality rate from a number of breast cancer trials that investigated mammography alone or in conjunction with breast exam. Eight trials were investigated, and combined data from all the studies yielded a pooled relative risk reduction of 0.77 for mortality due to breast cancer. This rate changed little regardless of whether mammography was performed with or without clinical breast exam.

Dr. Woolf pointed out that the major change in the recommendations was that women were advised to receive mammography screening starting at age 40. This change was based on the fact that longer follow-up data suggested a mortality benefit in five of seven trials that enrolled women in this age group; these data were not available when the previous recommendations were published. The relative risk reduction for women in their 40s is similar to that of older age groups, but because the absolute risk for breast cancer increases with age, the absolute benefit from mammography functions as a continuum and is smallest for younger women. The change in the recommendations would also allow patients and physicians to make decisions based on personal preference and patient history.

Dr. Woolf briefly discussed the review by Gotzsche and Olsen in the *Lancet* and stated how the USPSTF had used the same trials that were identified as having imperfections in the development of the new recommendations. The USPSTF agreed that there were imperfections and design flaws in the breast cancer trials, but while Gotzsche and Olsen rejected some of the trials, claiming there were “fatal flaws,” the USPSTF accepted those trials because it determined that the design flaws did not bias or change the findings of the studies. Dr. Woolf pointed out that, based on the quality of the trials combined with the changes in the USPSTF rules of evidence, the present recommendation for a mammogram was rated *B*, compared to an *A* in 1996. An *A* recommendation would require that the quality of evidence be good and the net benefit substantial. The flaws in the trials affected the rating of the evidence, resulting in the downgrade from an *A* to a *B*.

Dr. Woolf concluded his talk by briefly discussing the justification the USPSTF used to rate clinical breast exams as an *I*. The majority of trials included clinical breast exam with mammography, making it difficult to separate the two methods. Three trials on breast self-exam alone found no benefit in decreasing breast cancer mortality; however, the trials had either not followed the patients for an adequate period of time or were not designed to correctly determine the actual benefit. For these reasons, the USPSTF did not have sufficient information on the effectiveness of breast self-exam to recommend any rating other than an *I*.

## Questions and Answers

Dr. Harold Freeman, Member, PCP, and Director, Center to Reduce Cancer Health Disparities (CRCHD), NCI, commented on the lack of mammography screening in third-world countries. Dr. Freeman stated that breast self-examination and clinical examination could be used in these countries, but he asked what the USPSTF recommends in those situations. Dr. Woolf replied that in countries where limited mammography is available, he would recommend selectively screening women in the highest-risk groups and who would gain the greatest benefit. In countries with limited resources, priorities would need to be set to determine the form of intervention that would result in the greatest reduction in morbidity and mortality.

Dr. Abu-Ghazaleh asked about the size of the lesions detected in the breast self-examination trials and how those findings would relate to the detection of breast cancer lesions in women living in countries that lack resources for mammography. Dr. Woolf stated that early detection studies, similar to screening studies, result in detection of smaller lesions that are less advanced in stage and grade. However, the USPSTF does not feel comfortable inferring a benefit from those findings—even when such trials include mortality as an endpoint.

Dr. Li inquired why the USPSTF was composed mainly of generalists with expertise in analytical sciences rather than a broader array of experts. Dr. Woolf explained that the judgment of the USPSTF was that the evidence could best be examined using members whose expertise was not related to the field they were studying, but who were experts at the critical appraisal of studies. In cases where the Task Force requires clarification on content or science, content experts are engaged to review the information to ensure that the USPSTF is reviewing the evidence correctly. The USPSTF believes that this method of review is the best approach considering that the recommendations developed cover hundreds of health care topics.

Dr. Freeman explained that there are women in the United States who undergo mammography screening but do not follow up with the proper medical treatment. The USPSTF uses mortality as the endpoint to measure the success of a screening trial, and Dr. Freeman asked how the inclusion of these women would change how a trial was scored under the rules of quality and benefit. Dr. Woolf replied that the mission of the USPSTF is to determine how effective the interventions are under optimal conditions. Optimal conditions would include adequate follow-up care, which is lacking at this time and needs improving; however, that is not the mission of the USPSTF. In terms of the impact that the inclusion of these patients would have on the analysis of the trial: In a truly randomized trial, those types of problems would be included and equally distributed among the groups. However, Dr. Woolf agreed that improving follow-up care and treatment would decrease the mortality rate and change the benefit assessment.

Dr. Koh asked Dr. Woolf to make a general comment on the Canadian trials that were excluded from the pooled effect-size analysis. Dr. Woolf did not list any specific problems with the trials, but he indicated that some groups have reported that there were design flaws. Some people believe that based on these flaws, the trials are *completely* invalid, while others have refuted the criticisms. The USPSTF performed analyses both with and without the Canadian trials data to create a balanced picture.

**QUANTIFYING POPULATION EFFECTS OF MAMMOGRAPHY—  
DR. RACHEL BALLARD-BARBASH**

Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS, NCI, gave a brief overview of the data collection studies organized by a number of groups throughout the world. In the early 1990s, the U.S. Breast Cancer Surveillance Consortium (BCSC) initiated pilot studies to examine the performance and outcome of screening mammography. These studies continue today in seven sites throughout the United States. In addition, the International Breast Cancer Screening Network (IBSN) has 25 countries collaborating to evaluate the effects of population screening. NCI has collaborated with the Health Care Finance Administration (HCFA) to create the SEER-Medicare linked database. This database provides a resource for investigators throughout the country to analyze the patterns and the quality of care given to cancer patients in the United States. Finally, the National Health Interview Survey has provided information on trends in cancer screening at the national level, and recently, NCI has initiated the California Health Interview Study (CHIS) to analyze similar data on specific populations at the state level.

Dr. Ballard-Barbash introduced the initiatives of the BCSC. The BCSC's main focus is to evaluate the performance and practice of screening, especially in terms of quantifying the effects on both stage shift and mortality. Studying these effects will allow the BCSC to track new technologies of breast cancer screening as they emerge. These technologies include imaging as well as new tissue and molecular markers. In addition, the BCSC is presently collaborating with numerous organizations involved in health care delivery throughout the country in an effort to standardize how screening data are collected and reported.

As of July 2001, almost four million mammograms had been performed in the United States. Dr. Ballard-Barbash described data that analyzed screening mammography on women according to their age, the density of their breast tissue, and whether the women were receiving hormone replacement therapy (HRT). Regardless of age or use of HRT, screening mammography was not as efficient in detecting cancer in women with dense breast tissue as it was in women with more adipose tissue in their breasts. Dr. Ballard-Barbash commented that a number of recent reports have indicated that women receiving HRT are at higher risk for breast cancer. She discussed data from one study performed by the BCSC that found breast cancer patients who were receiving HRT had a *more* favorable prognosis compared with patients not receiving HRT.

Dr. Ballard-Barbash explained the difficulty in determining a relationship between screening mammography and mortality rates. A screening program begun in the mid-1980s by the Group Health Cooperative found that by 1992, approximately 80 percent of the female population had undergone mammography screening. Even with this high level of screening, the group was unable to track its effect on the mortality rate, although researchers did detect a decline in the rate of late-stage tumors. More recently, Dr. Taplin's group has analyzed the incidence of late-stage breast cancer through 1998 and found a significant decline in women aged 50 and older, with a less significant decline in women aged 40 to 49—but this age group was less likely to have undergone screening.

Dr. Ballard-Barbash briefly discussed studies published by the IBSN demonstrating a stage shift and other surrogate endpoints for mortality reduction. All the studies documented a shift to earlier-stage disease among screened women. A separate study performed by the National Health Services (NHS) found a 21 percent decrease in mortality among women aged 55 to 69 who underwent breast cancer

screening. Breast cancer screening contributed to 6 percent of the 21 percent decrease, with the remainder of the decrease due to other forms of early detection and treatment.

Dr. Ballard-Barbash summarized her talk by pointing out the advances that have been made in the analysis of population-level data and the linkage of cancer outcomes to defined populations.

Dr. Ballard-Barbash also emphasized the need to decrease false-positive rates and improve accuracy and performance in clinical practice. Finally, finding new statistical methods to evaluate population data at the individual patient, health professional, and facility or system level is also a priority.

### **Questions and Answers**

Dr. Freeman asked why more diverse population groups were not included in the analyses of mortality and incidence of cancer outside of the age-group distribution, tissue density, and HRT data that were shown. Dr. Ballard-Barbash explained that other populations have been analyzed with respect to mammography screening studies, and the upcoming CHIS will allow a breakdown of populations according to other factors, such as social levels and economic status. However, a number of practices resist collecting all of this information during screening, and this alters the degree to which the populations can be analyzed. Dr. Freeman followed up his question by commenting that the SEER does not collect socioeconomic data; without this information, it is more difficult to understand how to achieve the best outcome with various populations.

Dr. Koh was interested in obtaining more information on the other early detection methods to which the NHS attributed reductions in mortality. Dr. Ballard-Barbash responded that the other detection methods included procedures resulting from physical examinations or interactions of patients with their family practitioners; however, these forms of early detection do not fall within the realm of true screening programs. In response to another question from Dr. Koh, Dr. Ballard-Barbash commented that due to the quality and the variability of self-reported data—specifically with respect to the recall of screening among specific population groups—this information is useful mainly for looking at trends over time.

Dr. Ballard-Barbash then presented a talk on behalf of Dr. Eric (Rocky) Feuer, Chief, Statistical Research and Application Branch (SRAB), Surveillance Research Program, DCCPS, NCI. The first topic Dr. Ballard-Barbash discussed was the statistical methods and modeling efforts undertaken by NCI to analyze trends in breast cancer mortality in the United States. Comparison of the breast cancer mortality rate from 1992 through 1999 to the percentage of women who underwent screening in individual states found that there was a significant correlation between the decline in mortality rate and the prevalence of screening. A second effort by the SRAB has been to analyze the impact of observed stage shift on breast cancer mortality. Dr. Ballard-Barbash presented data that compared actual trends in the incidence of late-stage disease against that of early-stage disease, or that looked at the estimated versus observed incidence of stage shift. Statistical analyses of these data over the past 30 years indicated that breast cancer screening—as well as improvements in treatment of the disease—has had a net beneficial impact on the decline in mortality.

Dr. Ballard-Barbash concluded with an overview of the Cancer Intervention and Surveillance Modeling Network (CISNET), which was established by NCI in 2000. CISNET was created to model the impact of cancer control interventions on current and future trends so that cancer control planning could be improved. A unique feature of the CISNET modeling effort is that it includes preclinical natural history parameters. In addition, an interface between CISNET and the BCSC database has been created, allowing both groups to access data on screening and screening characteristics. At this time, nine

investigators have been funded through CISNET: seven working on breast cancer models; one working on colorectal models; and one working on prostate models. However, a second round of funding starts this summer that will include increased funding for modeling on prostate cancer, colorectal cancer, and lung cancer. In terms of breast cancer screening, CISNET has attempted to use population modeling to address the effects of dissemination of screening, dissemination of adjuvant therapy, changes in background risk, and mortality from other causes on the predicted incidence and mortality from breast cancer. The predictions that CISNET makes on the incidence and the mortality of breast cancer should help investigators better evaluate community effectiveness and interventions.

### **NEW APPROACHES TO IMAGING—DR. MITCHELL SCHNALL**

Dr. Mitchell Schnall, Vice Chair of Research, Department of Radiology, University of Pennsylvania, emphasized how critical imaging is in every aspect of breast cancer care—starting with screening and diagnosis and, subsequently, in its use in follow-up examinations for the detection of recurrence. However, mammography does have a number of limitations. The main problem with film-screening mammography is that while it is capable of distinguishing adipose tissue from calcifications, it does not discriminate among different types of tissue. In addition, the image of the entire breast is projected in one dimension, making it difficult to view abnormalities—especially in a dense breast. Another problem is that the limited specificity of mammography, combined with the demand in the United States for high sensitivity, results in a large number of biopsies per cancer identified. Dr. Schnall stated that these issues provide justification for the new techniques he would be reviewing.

In the past 15 years, a number of advances in breast imaging have occurred, the majority of which are computer-based. Dr. Schnall mentioned that these advances include increased sensitivity with digital mammography, the use of computers to aid in diagnosis, and contrast-enhanced digital subtraction that can detect small changes in breast tissue and areas of vascular engorgement, which is often associated with areas of cancer. Dr. Schnall discussed an example of digital mammography called tomosynthesis that works in a manner similar to a CT scan. This process improves the acuity of findings by evaluating an image of the breast that is generated from a number of different images, highlighting subtle changes that could be missed in standard projection-image mammography.

Dr. Schnall introduced breast sonography as one of the new applications used to improve mammography. Breast sonography uses the reflection of sound waves as they pass through the breast tissue to create an image of the anatomy of the breast. The advantages of sonography are that there is no ionizing radiation; the examination occurs in real time, allowing it to be coupled with minimally invasive therapy or as a means to guide a needle when isolating a biopsy; and it is portable and inexpensive. The downside of sonography is that analyses can take up to 30 minutes per examination, and it requires a highly trained ultrasonographer; the quality and training of the ultrasonographer can affect the results of the exam. Breast sonography has been used in clinics to clarify whether a woman who had a positive finding as detected by x-ray mammography should have a biopsy. Sonography has also been used to detect fluid-filled cysts in the breast. A study by Kaplan in 2001 tested the ability of sonography screening to detect breast cancer in mammographically dense breasts. Kaplan's study found sonography detected cancer in 0.3 percent of women who tested negative for breast cancer by mammography. While there was a 3 percent biopsy rate for women in this study, 1 of 20 abnormalities was cancerous. Dr. Schnall explained that while sonography can detect occult cancers that other screening exams do not find, the speed and specificity of sonography screening needs to be improved.

Dr. Schnall spoke about a number of other innovations to improve sonography that are presently being tested. Doppler blood flow quantification is a technique that is able to measure frequency shifts that occur when ultrasound hits a moving object; this would identify areas of high vascularity in the breast. This technique, coupled with information from a regular sonogram, could increase the specificity of the screening examinations. Two other new techniques include the use of ultrasound contrast agents that measure the elasticity of a lesion by changing the ultrasound characteristics and 3-D ultrasound that detects calcifications when sound waves resonate off them.

The American College of Radiology Ultrasound Breast Lexicon Working Group (ACRUBL) and ACRIN—a multicenter clinical trial network—have clinical trials underway to improve ultrasound studies. ACRUBL is working to standardize the nomenclature used to describe ultrasound findings in an effort to improve how ultrasound data are interpreted by different centers. ACRIN, in collaboration with the Avon Foundation, is organizing a clinical trial to study sonography screening using high-risk cancer patients. Dr. Schnall explained that one of the major problems encountered with clinical trials of new techniques is that the studies must be very large in order to include sufficient cancer events. The strategies used to ensure that statistical analysis of a trial is useful include making sure the technology itself and the interpretation of the results are clearly understood before the trial begins and using high-risk cohorts of women so that sufficient cancer events occur in a study.

Dr. Schnall then discussed how magnetic resonance imaging (MRI) has been used in breast screening. MRI uses radio waves to collect signals emitted from protons, using contrast agents such as gadolinium to provide three-dimensional images of high-vascularity regions within breast tissue. MRI analysis is an extremely useful technique for detecting cancer in the soft tissue of the breast, especially invasive breast cancer. The downside of MRI is that it is incapable of differentiating between malignant and benign lesions, and it is an expensive technique. While it will most likely never replace mammography as a general screening method, MRI has been extremely useful when used in high-risk populations that have had lesions identified by other screening methods. As with sonography, numerous methods are being tested to improve MRI analysis. New contrast agents are being tested with the use of pharmacokinetic modeling to increase imaging time; spectroscopic imaging is being used to determine whether markers of cancer are present in a lesion; and low-cost scanners are being developed that could be used on the general population.

Dr. Schnall discussed a number of MRI screening clinical trials presently underway. The International Breast MRI Consortium (IBMC) is a multicenter cooperative group funded by the NCI. This group recently finished a study on 1,000 women in an effort to establish criteria for the interpretation of breast MRIs and to establish accuracy in differentiating benign from malignant lesions. A smaller risk-screening pilot study by the same group is screening the contralateral breast of women with cancer to follow up on data that suggest a higher incidence of contralateral breast cancer in women with primary breast cancer. The Cancer Genetics Network and the IBMC are also developing a high-risk program using both ultrasound and MRI to determine which technique is more useful with different populations.

Dr. Schnall then described how nuclear imaging is used in the screening of tumors. Nuclear imaging detects radioactive tracers that can target tumors. Nuclear imaging is an expensive technique, with the imaging agent alone costing \$350 for a single routine whole-body scan. Initiatives are underway to develop dedicated detectors that would be able to identify smaller lesions that presently go undetected; in addition, these new detectors would be more affordable than present nuclear imaging devices and would require a lower dose of imaging agent.

Dr. Schnall concluded his talk by describing some more speculative technologies that could be very useful but are still under development. Optical imaging is based on the fact that light is refracted through the breast at different wavelengths. How light refracts through healthy tissue, lesions, and even hemoglobin can be used to detect breast cancer. Extrinsic contrast agents can also be detected by optical imaging. Recently, imaging agents have been developed that are capable of binding specific proteins expressed on the surface of a tumor. One example of this is a probe developed by Weissleder et al. that is specific for metalloproteinase. Metalloproteinase is a surface protein required to destroy tissue so that cancer cells—for example, metastatic cells—can continue to grow. Other speculative technologies that Dr. Schnall briefly touched upon included electrical impedance imaging, infrared thermography, electrical potential measurements, and electronic palpation.

### **Questions and Answers**

Dr. Greenwald commented that with the numerous new technologies coming to the forefront and the ability to detect cancer at earlier stages, a large number of clinical studies are going to be required to examine how these methods prevent mortality. He emphasized the need to determine the most efficient method to analyze the various techniques and provide convincing evidence on how they affect mortality rates.

### **MOLECULAR PROFILING OF BREAST CANCER—DR. CHARLES PEROU**

Dr. Charles Perou, Departments of Genetics and Pathology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, discussed the use of genomics to classify tumors and guide therapy. Dr. Perou described histological sections of breast tissue from four patients with grade III breast cancer who received tamoxifen. Even though all four of the patients presented with the same tumor classification, two of them died within 2 years of treatment. Genomic profiling technology can be used in such cases to find genetic differences between patients who present with similar tumors.

Dr. Perou reviewed the technique of cDNA microarray analysis used to detect the expression of different genes in unique samples. RNA was isolated from different breast tumors, and messenger RNA was transcribed into cDNA using fluorescently labeled nucleotides; two uniquely labeled nucleotides were used to differentiate one cDNA sample from another. In addition, RNA was isolated from a common reference sample. Since all the tumors are compared to the same reference sample, there is no need to perform pairwise comparisons. After the cDNA from one tumor sample was mixed with the cDNA from the reference sample, the mixtures were hybridized to a glass cDNA microarray. The color and intensity of the regions emitted from the microarray correlated with the level of expression of a specific gene contained in a given sample. The fluorescent emissions were converted to numeric data, using the ratio of one fluorometric color to another as a data point. A computational tool developed by Mike Eisen used cluster analysis to analyze all of the data acquired from the cDNA microarrays performed on the various tumor samples. In the colorimetric display, each column represents a different experiment, and each row represents a unique gene. How a specific gene behaved in a specific experiment is represented by a colored square at the point at which the column intersects with a row. By comparing one display to another, Dr. Perou continued, one could determine the various levels at which the specific genes were expressed in different tumor samples. Finally, in each row, genes are grouped according to their similarities. A phylogenetic dendrogram placed next to each row creates branching patterns of varying lengths based on how the rows are related to one another. These dendrograms aid in identifying coordinately regulated sets of genes and sets of samples that share common expression patterns. With this



background on the methodology explained, Dr. Perou described a number of studies his laboratory has performed.

The first study analyzed 60 breast tumor samples; 40 of these were provided by a Norwegian group collaborating with Dr. Perou and consisted of samples isolated before and after treatment with a specific chemotherapy. The study revealed that each tumor had a unique gene expression pattern; however, common trends identified relevant subsets of tumors. Dr. Perou explained that eight different clusters were identified, representing eight different cell types present in the tumors. Comparison of the gene expression pattern in a tumor with the expression pattern from cell lines identified the cell type from which the tumor was derived. Immunohistochemistry performed on tissue samples from the original tumor corroborated this information.

Dr. Perou briefly discussed a group of genes located in an area referred to as the “proliferation cluster,” since this region contains genes that either regulate or are regulated by the cell cycle. Expression of the genes in this cluster has been linked to two different indices of tumor proliferation. Expression of these genes correlated with how quickly the cells proliferated. In an effort to ensure that this set of genes was involved with the regulation of the cell cycle, the expression of the proliferation cluster was analyzed using HeLa cells. After cells were arrested in the G1 phase, there was a periodic expression of the proliferation genes as the HeLa cells were allowed to progress through the cell cycle.

Dr. Perou introduced how microarray technology has been used to classify tumors. The breast tissue is composed of luminal epithelial cells, which are estrogen receptor (ER)-positive and produce milk; and basal epithelial cells, which are ER-negative and produce the basal lamina. Each cell type produces a unique microarray pattern. Dr. Perou showed how some tumors express genes associated with luminal cell lines while other tumors express genes associated with basal cell lines. He then commented that even though the tumors were derived from different cell types, the same therapy was administered. These data need, however, to be applied in the clinical setting to determine which treatment is most appropriate for each tumor.

A study done in collaboration with the Norwegian group focused on the tumor samples taken from patients before they underwent any treatment. The majority of the tumors were derived from luminal cells. Some of these tumors expressed HER2, but expression of this gene was not a requirement for classification into this group. Dr. Perou stated that when these tumors were analyzed for ER expression, his group found a set of genes associated with tumors that were ER-positive, but *in vitro* experiments have determined that these genes are not regulated by estrogen. Dr. Perou commented that the expression of genes linked to ER expression could be important in determining how tumors are treated clinically and how rated diagnostically.

Dr. Perou ended his discussion on these studies by focusing on patient outcomes in relation to the status of the genes expressed by the tumors. Fifty-one patients from the Norwegian study were rated based on ER status, HER2 status, and grade of the tumor. All these subtypes were statistically significant predictors of survival. The results of this study showed that ER-positive luminal subtype B tumors, HER2-positive tumors, and basal cell-derived tumors had the worst survival rates. Dr. Perou emphasized again that this information needs to be applied in a clinical setting so that treatments can be used appropriately for tumors associated with subtypes with low survival rates.

Dr. Perou discussed work done in collaboration with the Mouse Models of Human Cancer Consortium (MMHCC) and a group of SPORC investigators. These groups were interested in identifying

mouse models that could be used to model human cancer subtypes. Three mouse tumor subtypes were analyzed. One of these three types proliferated rapidly and showed expression of many similar genes as were expressed in the human tumor proliferation cluster. Dr. Perou noted that the studies on the subtypes of gene expression in the mouse correlated with the information his group had ascertained from the microarray studies on individual human breast tumors.

Dr. Perou's final topic involved a paper published this year in *Nature* that reported on studies that used gene expression to profile clinical outcomes of breast cancer patients. The patients involved all had small tumors, had no metastases to the lymph nodes, and received no therapy. The patients were followed for 5 years, grouped according to whether or not metastasis had occurred; microarray analysis was then used to identify genes that correlated with one group or the other. Dr. Perou indicated that the predictions based on this study correlated with the data from his group that he had presented earlier: Mainly, based on the *Nature* studies, high expression of genes located in the proliferation cluster predicted a propensity to develop metastases, while his studies showed that the same genes were linked to tumor proliferation and short survival time.

Dr. Perou concluded his talk by discussing the future clinical implications of gene profiling: First, whether or not a patient is treated, and with what chemotherapeutic, will be determined based on the genes his or her specific tumor is expressing. Second, a "cell biology" approach needs to be taken in which multiple assays are performed on a set of tumors to create predictive models. Third, validation of the existing findings will need to be performed on large clinical cohorts of homogeneously treated patients. Fourth, funding agencies will need to mandate the full release of genomic data. Finally, therapies will be developed based upon the cell type of origin and a molecular understanding of the altered pathways in the tumor.

### **Questions and Answers**

In response to Dr. Greenwald's request to comment on DCIS, Dr. Perou commented that while he is interested in performing expression profiling on DCIS patients, the main problem is to be able to follow the patients for long enough periods. In addition, there is the problem of getting access to samples from the patients over time.

Dr. Freeman commented that a lot of the work Dr. Perou is presently working on could result in practical information once the data are analyzed. He asked if there is a way that the clinicians—who are actually treating the patients—could get access to the information to aid in finding potentially practical ideas instead of having to wait for the data to be published. Dr. Perou answered that the first step would be to classify distinct subsets within groups that are presently being treated as one group. This would help guide how patients are treated. Second, genomic and proteomic analysis of tumors will, hopefully, identify markers that could be quickly taken to the clinical setting.

### **SUMMARY AND DISCUSSION—DR. BARBARA RIMER AND NCAB MEMBERS**

Dr. Rimer briefly outlined all the information presented in this mini-symposium. She encouraged Board members to visit the USPSTF Web site to review the recommendations on breast cancer screening described by Dr. Woolf, as NCI will be updating its recommendations in the next few years. The take-home message from Dr. Ballard-Barbash's talk, along with the modeling data from Dr. Feuer, indicated that there is a population effect on screening. The presentations by Dr. Schnall and Dr. Perou provided a sense of future screening technologies. Dr. Rimer stated that "mammography will at some point be a

thing of the past, but at this time, NCI is committed and obligated to improve the present technology while working on new technologies.”

Dr. Greenwald and Dr. Rimer together have chaired an internal breast cancer screening working group to look at the various aspects of mammography screening. The group will identify and recommend the areas of new technology and basic biology that NCI needs to explore in the coming years. Dr. Rimer discussed a mammography survey done in collaboration with the Office of Communications. The results showed that minority women and women with lower incomes and less education were more confused about mammography than women in other populations. Dr. Rimer commented on the need for NCI to improve communication with the public, following up on comments made by Dr. Freeman during Dr. Ballard-Barbash’s talk.

Dr. Rimer closed by mentioning that the presentations today cover only a small portion of NCI’s research portfolio on breast cancer detection and screening.

Dr. von Eschenbach commented how insight into the biology of cancer is dependent upon the collaboration and sharing of ideas among a number of disciplines. The U.S. Government is presently trying to determine how to process the intelligence information related to biodefense and ensure that all of the agencies involved are sharing information and working to the same end. In the same manner, scientists need to work together to ensure that biological information is properly presented and accessible. Dr. von Eschenbach emphasized to Board members that NCI is looking at collaborations that will provide information such that everyone can benefit from it.

#### **X. PORTFOLIO TRANSFERS TO NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING—DR. ELLEN FEIGAL**

Dr. Feigal stated that it was important for the Board to hear about the new NIBIB and future interactions between this Institute and the NCI.

The NIBIB is the newest of the 27 NIH components. Its founding was mandated by the National Institute of Biomedical Imaging and Bioengineering Establishment Act, which was signed into law by President Clinton on December 29, 2000. The Institute’s mission is to improve health by promoting fundamental discoveries, design, development, translation, and assessment of technological capabilities in biomedical imaging and bioengineering. This mission will be carried out through an assessment of relevant areas of information sciences, physics, chemistry, mathematics, materials science, and computer science.

Dr. Roderic Pettigrew has been named first Director of NIBIB. The Deputy Director is Dr. Donna Dean. There are presently about 20 staff members, with interim NIH staff assisting during the transition period. As for a research portfolio: In 2001, a trans-NIH review committee surveyed bioengineering and biomedical imaging activities across NIH and recommended that some current projects and grants funded by other NIH Institutes be moved to the NIBIB. An external task force also examined the research across NIH and identified grants that would be appropriate for transfer to NIBIB.

In FY2002, NCI transferred \$21M in grants, a total of 61, to NIBIB. In FY2003, NCI will transfer an additional \$60M: \$35M from 122 grants and \$25M not tied to specific grants. Of the \$35M, 56 percent will come from the DCTD’s Biomedical Imaging Program. Other programs have been affected as well.

Dr. Feigal explained that there will be an increased focus at NIH on bioengineering and imaging sciences. NIBIB will coordinate the biomedical imaging and engineering programs at agencies and NIH Institutes to support imaging and engineering research that has potential medical applications and will facilitate the transfer of such technologies to medical applications.

Dr. Feigal then presented a brief background on the NIBIB and its establishment. In July 1998, NIH correspondence to Rep. Bilirakis in Florida reported FY1997 spending on biomedical imaging; this report was subsequently sent to the full House of Representatives. It listed about \$325M and more than 1,500 awards; about two-thirds of this was allocated to bioimaging research and about one-third to using bioimaging as a tool. Over the next 2 years, the NIH stated that, rather than establish a new Institute, it needed to coordinate the various existing imaging programs. However, the House of Representatives maintained that NIH needed a strong central focus for imaging and bioengineering research and that simply coordinating existing programs across the NIH was not enough. This led to the Act and the signing of the bill.

A trans-NIH group identified about \$66.9M in bioimaging and bioengineering, representing 300 grants. However, in November 2001, during conversations among the acting NIH Director, the acting NIBIB Director, Rep. Tauzin of Louisiana, and Rep. Burr of North Carolina, it was stressed that, based on early reports by the NIH, the suggested amount to be transferred to NIBIB was not a true reflection of what could be provided for the new Institute. This resulted in the need for an outside group of experts to re-review the research portfolio.

The external group directed the NIBIB to establish a task force to review all existing imaging and bioengineering grants and identify those appropriate for transfer to the new Institute. The selection criterion was that these research projects should have applications to multiple disease processes or organ systems.

A nine-member task force reviewed all the grants and compiled a list of potential transfers. This list was sent to the different Institutes, and each Institute transferred some money or grants to the new Institute. The major Institutes with significant imaging portfolios were the NCI; National Heart, Lung, and Blood Institute (NHLBI); National Institute of General Medical Sciences (NIGMS); National Center for Research Resources (NCRR); National Institute for Neurological Diseases and Stroke (NINDS); and the National Institute of Mental Health (NIMH). For FY2003, transfers to NIBIB include approximately \$15M from NHLBI, \$25M from NIGMS, \$25M from NCRR, and \$10M from NIMH; this is in addition to NCI's commitment to transfer \$60M.

Dr. Feigal then discussed future interactions between NCI and NIBIB. The plan is to work with NIBIB and other NIH Institutes to ensure that the research being done is complementary to other NIH research and is enhanced for bioengineering and biomedical imaging. NCI staff will meet with NIBIB's new Director and discuss plans and opportunities to work together on areas of mutual interest.

Dr. Feigal concluded her presentation by praising the Biomedical Imaging Program staff for assisting staff at NIBIB during the transition period.

**CLOSED SESSION**

**REVIEW OF APPEALS, INTRAMURAL SITE VISITS, TENURE APPOINTMENTS,  
PERSONNEL, AND PROPRIETARY ISSUES**

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

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

The en bloc vote for concurrence with all other IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,347 applications were reviewed requesting support of \$387,641,195. Funding for those 1,347 applications was recommended at a level of \$387,685,161. The meeting adjourned at 4:30 p.m.

**DAY TWO—WEDNESDAY, JUNE 12, 2002****XI. NEW BUSINESS II AND SUBCOMMITTEE REPORT—DR. MARVIN KALT**

Dr. Kalt summarized the two main topics discussed at the previous day's meeting of the Subcommittee on Cancer Centers. The first topic concerned the development of the Ad Hoc Working Group on Cancer Centers. This Working Group will provide an important platform for translational research by assessing the award mechanisms and the role of NCI Cancer Centers and SPOREs. A report on the Working Group's recommendations will be presented to the NCAB in approximately 6 months.

The second topic of discussion covered proposed annual modifications to the guidelines for NCI-supported Cancer Research Centers. Modifications to the P20 planning grants include increasing the direct cost cap and providing specific benchmarks for the 3-year interim review. It has been recognized that small research-focused Cancer Centers may need up to 5 years for development before they qualify for a P30 Cancer Center Support Grant. Involvement of these smaller Centers is encouraged because the narrower focus of small Centers helps broaden the overall diversity of the patient population, both geographically and through the addition of patients with special characteristics.

The motion to approve the minutes was postponed until the document could be finalized. Dr. Kalt announced that the minutes will be sent to NCAB members by mail. Questions and comments on this document should be e-mailed to Dr. Kalt or Dr. Kimes, Executive Secretary of the Subcommittee on Cancer Centers.

**XII. NCI CENTER FOR BIOINFORMATICS—DR. KENNETH BUETOW**

Dr. Kenneth Buetow, Director, Center for Bioinformatics, and Chief, Laboratory of Population Genetics, NCI, provided an overview of the NCI Center for Bioinformatics (NCICB) by citing some of the problems experienced by the Center, as well as approaches to addressing these problems and preliminary solutions. He likened the magnitude of data descending on the NCICB to a tsunami and stated that he could envision drowning in the very data and research the Center is helping to generate.

Twenty-four months ago, NCI formed the NCICB to provide bioinformatics support and help integrate key research initiatives undertaken by the NCI. By building an infrastructure with common architecture among initiatives, and by using common tools and standards, the Center can act to catalyze bioscience discovery. However, significant hurdles must be surmounted.

Dr. Buetow cited the goal of bioinformatics as generating key insights into the etiology, treatment, and prevention of cancer by integrating information from various foundations of molecularly driven medicine, including: components (genes, proteins), context (pathways, ontologies), agents (therapeutics, probes), and states (human trials, animal models). Unfortunately, the diversity of the different scientific disciplines involved in understanding cancer presents substantial barriers. Terminology differs among fields, and data collections are disjointed. Dr. Buetow outlined the method used by the Center to try to interrelate the concepts from different areas of cancer research and medicine. He described the construction of a knowledge stack, a term from the computer field that describes processing steps required to translate data from one plane to another. The three components of a stack include controlled vocabulary, common data elements, and biomedical information. Dr. Buetow indicated that he believes that by translating information through this stack, it is possible for a genomic researcher to communicate with an experimental animal modeler or clinical trial investigator without having to learn a

different scientific vocabulary. Most importantly, Dr. Buetow stated, the bioinformatics stack will facilitate cross-discipline reasoning.

Dr. Buetow described individually the three components of the stack. On the first level, the “controlled vocabulary,” an NCI meta-thesaurus maps many of the vocabularies in biomedicine, and the thesaurus provides definitive terminology to enable description of different concepts using the same collection of words. Onto this controlled vocabulary foundation, common data elements are amassed. Currently, 3,000 elements can be used to generate case report forms that permit comparison across clinical studies. Accrual is underway of elements common to epidemiologic and basic science research studies. The last component of the stack is biomedical information. Dr. Buetow defined this information as pieces of computer code that capture and allow presentation of data in many different contexts. This flexibility enables the information to be accessed by disparate disciplines.

Dr. Buetow compared nature’s strategy for information management using the gene to that of a fundamental bioinformatics tool of an object (Java Bean). In the use of both genes and computer objects, complexity is built by creating interrelationships and infrastructure so that the resulting system has emergent properties. The current NCICB collection contains objects from genomics, gene expression experiments, cancer animal models, clinical trials, and even experiences in the composition of laboratory information management systems. Dr. Buetow noted that all of these objects can be accessed on line by the cancer research community.

Dr. Buetow spent a few minutes describing the NCICB strategy for collecting the data for conversion into the biomedical information component of the knowledge stack. He noted that a key strategy is in the building of Web portals through which individual research communities supported by NCICB can share information and where data integration can occur. The interface of these collections of data has been constructed within the past 12 months.

Dr. Buetow suggested that through the NCICB Web site, the context of how information is to be recovered can be defined by tissue type, molecular significance, gene expression patterns, cell cycle checkpoint genes, cytogenetic location, cellular pathways, functional significance of gene or protein polymorphisms, etc. Even information about reagents can be detailed. Furthermore, Dr. Buetow announced, the prototype effort by the NCICB integrates biomedical data—from molecular data to clinical trial information. Soon, additional data beyond the key data sources will be incorporated, such as data from the Director’s Challenge microarray experiments, the MMHCC, SPOREs, NCI’s Molecular Target laboratories, and others. Dr. Buetow envisions NCICB as catalyzing an open bioinformatic infrastructure that will be enhanced by other members of the NCI research community and strategic partners in government and industry. Dr. Buetow concluded by stating that in using a bioinformatics “surfboard,” the Center will ride the “data tsunami” in to the beach.

### **Questions and Answers**

Dr. Buetow made it clear that everything, from the Center’s bioinformatic architecture to the computer code and data, is publicly accessible. When asked about incentives for industry to contribute data, Dr. Buetow cited the value-added infrastructure that the NCICB is creating. Many companies recognize that the value of their data increases by “plugging and playing” into the bioinformatic space created by NCICB. However, Dr. Buetow acknowledged the fine balance that exists between the business world’s desire to create a drug or otherwise profit from a patent on a human element and the Government’s endeavor to advance scientific and medical advances as rapidly as possible. However, he

felt that companies with appropriate products and sound business plans can still attract customers without feeling competition from the Government. Dr. Buetow revealed that a significant number of visitors to the NCICB Web site are from the pharmaceutical industry. He hoped that companies would not only take, but would give as well.

### **XIII. CENTER FOR CANCER RESEARCH MOLECULAR DIAGNOSTIC REFERENCE LAB—DR. LANCE LIOTTA**

Dr. Lance Liotta, Chief, Laboratory of Pathology, Center for Cancer Research, NCI, reported on the progress made by the NCI-FDA Clinical Proteomics Program in developing a new technology for early detection of cancer. The promise of this technology will lead NCI's Reference Laboratory to the preparation of an expedited premarket application (PMA) and submission to the FDA for prompt approval. Both these endeavors will help speed the new technological advance to public benefit while at the same time ensuring its evaluation with the highest levels of scientific rigor.

Dr. Liotta outlined the basic scientific hypothesis behind the Proteomics Program. He and the Co-Director of the Proteomics Program, Dr. Chip Petricoin, Laboratory of Immunology, Division of Therapeutic Proteins, Office of Therapeutics Research and Review, Center for Biologics and Research (CBER), FDA, believe that the serum proteome, which consists of thousands of proteins and peptides from every tissue in the body, is modified by the pathologic state of the tissues, resulting in telltale proteomic patterns. Dr. Liotta noted that the problem was to discover these diagnostic proteomic patterns without knowing the identities of the proteins. This issue was addressed through a collaboration with Correlogic Systems, Inc., to develop bioinformatics software, and through the use of a mass spectroscopy system by Ciphergen Biosystems. A drop of unprocessed serum contributes proteins to a chip that is inserted into the Ciphergen surface-enhanced laser desorption and ionization (SELDI) system. The output is a spectrum that can be used to discern the health status of unknown samples. The artificial intelligence (AI) algorithm developed by Correlogic establishes protein patterns derived from two training populations: healthy persons and cancer patients. Dr. Liotta emphasized that the system can learn and become more accurate depending on the feedback it is provided and the number of samples entered into the training set.

A recent paper published in the *Lancet* described the results from a study of ovarian cancer. Patients from a high-risk ovarian cancer clinic provided serum samples. In a 5-year follow-up, the classification derived by the new technology in the NCI-FDA Clinical Proteomics Program was 99 percent accurate in diagnosing cancer. Importantly, the technology correctly diagnosed—with 100 percent sensitivity—stage I disease. Patients treated at this early stage show increased 5-year survival rates, making detection at this stage of great clinical importance.

Dr. Liotta reported that the testing has been extended to prostate cancer screening. He cited 71 percent specificity and 95 percent sensitivity as the results of a blinded test series. A study is now underway to test patients with levels of prostate specific antigen (PSA) in an intermediate range (4.0 to 10.0 serum PSA ng/mL) because this is the stage at which clinical decisions must be made.

Dr. Liotta outlined plans to make the test publicly available. The proteomics system will be offered out of the NCI's Intramural Research Program, using as a reference laboratory the Laboratory of Pathology, which is already CAP/CLIA certified. Moreover, in a unique arrangement, the FDA has agreed to allow the FDA-NCI Proteomics Program to obtain an expedited PMA since the test meets the FDA's specific criteria: the classification of the test as a breakthrough technology, since no approved



alternative exists; the fact that the availability of the test is in the best interest of the patients and provides a specific public health benefit; and that there are a number of cooperative groups willing to provide samples. The expedited review of the application will decrease time for approval of a new diagnostic test from 3 to 6 years to 1 to 2 years. The hope is that after the test has been sanctioned by the FDA, it will be coupled with current diagnostic modalities in screening for breast, prostate, and pancreatic cancer.

### **Questions and Answers**

In response to a question from Dr. Abu-Ghazaleh, Dr. Liotta noted that the technology could be made available to everyone in the country either through central diagnostic laboratories or through the NCI Reference Laboratory. Alternatively, the Internet could be used to send spectra to a central database, which is under continuous expansion, and have a classification sent back to the referring physician. When asked about cost, Dr. Liotta replied that he would be meeting with the American Medical Association to discern what reimbursement code this test would be cited under. He emphasized the need to make the test available with the greatest speed to obtain the greatest public benefit.

Other diseases that this technology will be applied to are pancreatic, lung, and breast cancer; infectious disease; and cardiac disease. Dr. Liotta acknowledged that it could be extended to a wide variety of diseases and made into a new diagnostic paradigm. The technology also shows promise in monitoring therapy. Dr. Liotta affirmed that development was being moved forward with the highest scientific rigor and objectivity. When asked about the quantitative aspect of the assay, he responded that quantification is possible, but that no studies have been conducted to date.

#### **XIV. IMPLEMENTATION OF NIH HUMAN EMBRYONIC STEM CELL POLICIES— DR. GREGORY DOWNING**

Dr. Gregory Downing, Special Assistant to the Deputy Director for Extramural Research, OD, NIH, and Chair of the Implementation Committee at NIH, noted that he was representing Dr. Wendy Baldwin, the Deputy Director for Extramural Research, NIH. For his presentation, Dr. Downing reviewed the activities associated with implementation of the new NIH policies on human embryonic stem (ES) cells and spoke briefly about future endeavors. He highlighted not just the role of stem cells in regenerative and reparative medicine, but also in understanding cell cycle regulation and development. A list of Web-accessible resources was provided to NCAB members for reference.

Dr. Downing defined stem cells as primitive undifferentiated cells that have the potential to become a wide variety of specialized cell types and that have the capacity to proliferate infinitely. However, use of these cells is limited by the individual researcher's ability to grow them in culture and, at least initially, by the 6- to 9-month timeframe needed for development of a new line before distribution can begin. Moreover, human ES cell creation and use was limited by the decision of President Bush to fund research, as announced on August 9, 2001. The criteria for federally funded research include: Only stem cell lines developed before the President's August 2001 announcement can be made available to researchers receiving Federal funds; the embryos from which the cell lines are derived can be created only for reproductive purposes, and used after they are no longer needed for that purpose; informed consent must be obtained from donors to use the cells for research; and no financial inducements can be used for the donation.

Since the President's announcement, the NIH has been actively developing the infrastructure to support the research community. So far, a human embryonic stem cell registry was published on

November 7, 2001; initial research grant applications were received in November 2001; and the availability of infrastructure awards and training grants to help advance the field was announced in February 2002. Dr. Downing acknowledged two areas of weakness in the emerging field of stem cell research: a lack of investigators skilled in handling these cells and a paucity of cell lines available for research. Currently, the NIH has agreements with 4 sources of approved stem cell lines, allowing for use of 17 readily available cell lines. Ultimately, Dr. Downing noted, there may be up to 80 cell lines eligible for use upon completion of their developmental phase.

Dr. Downing discussed the administration of the cell lines. A unique code identifies approved stem cell lines. Infrastructure awards provide assistance for scaleup and distribution of these lines. Material Transfer Agreements have been generated that have no restriction on the intellectual property developed from use of the cells. Training and short courses in the care of the stem cell lines are being organized. Finally, guidance by the Office of Human Research Protections helps institutional review boards (IRBs) understand the circumstances under which they will be required to evaluate a research proposal using the ES cell lines for patient anonymity.

Dr. Downing also highlighted other administrative issues concerning stem cell line use. For ES cell lines developed after the August 9, 2001, deadline, investigators must keep careful accounting records to demonstrate that private funds cover the cost of the research. Issues about international transport of biological tissues have led to cooperation with the CDC and U.S. Department of Agriculture (USDA) to streamline development of standard shipping agreements for importation of ES cell lines. Discussion about the patent currently held by the University of Wisconsin on human ES cells requires separating basic research applications from those that are commercially oriented. Dr. Downing affirmed that these issues were being addressed.

As of the time of his presentation, Dr. Downing noted, only 24 peer-reviewed scientific publications include data on human ES cells. These cells have been well described for only about 3 years. More research is needed to evaluate their potential; investigate the differences between adult stem cells and ES cells; and derive benefits from the interactions among researchers from different disciplines, such as genetics, cell biology, developmental biology, and bioengineering. The hope is that after an anticipated lag of 1 to 2 years, results of fundamental research will begin to appear in the literature.

To conclude, Dr. Downing referred to two Web sites as sources of additional information. For general information, the URL is: <http://www.nih.gov/news/stemcell/index.htm>. For information about research applications, the URL is: [http://www.grants.nih.gov/grants/stem\\_cells.htm](http://www.grants.nih.gov/grants/stem_cells.htm).

### **Questions and Answers**

Dr. Downing responded to a question about secondary distribution of ES cells after acquisition from the originating laboratory. If the researcher wants unmodified ES cells, he or she should go to the original source of those cells. If, however, the cells are modified in any way, the researcher is not restricted in distribution, as these cells are considered a new entity. Policy about derivations of original cell lines is yet to be set.

**XV. POLICY UPDATE ON PEER REVIEW INVOLVING HUMAN SUBJECTS, DATA SAFETY MONITORING, AND DATA SHARING—MS. DIANE BRONZERT**

Ms. Diane Bronzert, Associate Director, Office of Referral, Review, and Program Coordination, DEA, NCI, provided an update on the changes in policy associated with grant applications. She focused first on the evaluation of research involving human subjects. With the publication of a new grant application form in the past year, instructions have been clarified and centralized in the “Human Subjects” section. In addition, the Center for Scientific Review has made available on the NIH Web site instructions to reviewers for evaluating and coding human subjects. Ms. Bronzert noted that in a new procedure announced at the beginning of June 2002, the grant application will be returned if all sections have not been completed before initiation of the peer-review process. Moreover, lack of adequate plans for human and animal subjects can negatively impact the grant’s priority score or result in a bar to the award.

Ms. Bronzert also reported on the more user-friendly format of the summary statement. A new “Résumé” section at the end consolidates opinions about use of human subjects and animals and provides committee budget recommendations. She illustrated her discussion with an example and urged review of this section of the summary statement by the reviewers if questions arise about an application.

Ms. Bronzert next discussed the progress on the NIH draft Statement on Data Sharing. This policy will be enacted on January 1, 2003. The new policy will require that applicants include a plan for data sharing or state why data sharing is not possible for their application. It encourages the timely release and sharing of final research data for use by other researchers. This policy allows the sharing of large, expensive data sets and those that cannot readily be replicated. One exception to the data sharing policy will be if the identity of human subjects cannot be protected. The manner in which the data should be shared is not specified by the policy, but Ms. Bronzert listed several appropriate methods, including using restricted-access data servers or enclaves.

Ms. Bronzert noted that in critiquing data sharing plans, reviewers should be aware that the budget request may include costs of data sharing. Such requests need to be considered against the standards within the research community.

A few of the benefits of data sharing include generation of new or alternative hypotheses and methods of analysis. New data sets can be created from common data. Topics not envisioned by the initial investigator can be explored. Ultimately, data sharing promotes more and better research.

**Questions and Answers**

Ms. Bronzert responded to a question about the extent of data sharing, especially before publication of the research, by commenting that more discussions will be held with researchers to implement the data sharing policy. Importantly, a requirement for data sharing on NIH grant applications will stimulate greater dialogue within the research community. The role of peer reviewers will soon include a responsibility to oversee implementation of the longstanding expectation of the NIH that awardees will share research results.

**XVI. SUMMARY AND ADJOURNMENT—DR. AMELIE RAMIREZ**

Dr. Ramirez thanked the speakers for their ongoing work and their excellent presentations, and the outgoing Board members for their service on the NCAB. Dr. von Eschenbach echoed her thanks and extended his personal gratitude to the outgoing Board members for their service and assurance of continued support to the NCI beyond their term on the NCAB. He extended special thanks to Ms. Martha Fewell, NCI staff in the Office of the Director, for postponing her retirement plans to assist him in his transition as Director of the NCI, and asked the Board's permission to privately present her with a gift of appreciation from the NCAB, since she could not be present at the meeting.

There being no further business, the 122<sup>nd</sup> meeting of the National Cancer Advisory Board was adjourned at 11:00 a.m. on Wednesday, June 12, 2002.

September 9,  
2002  
\_\_\_\_\_  
Date

/s/  
\_\_\_\_\_  
Amelie Ramirez, Acting Chairperson

September 9,  
2002  
\_\_\_\_\_  
Date

/s/  
\_\_\_\_\_  
Marvin R. Kalt, Executive Secretary