

Board of Scientific Advisors

Meeting Minutes

June 25-26, 2001

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

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI), convened for its 18th regular meeting on Monday, June 25, 2001, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public from 8:00 a.m. until adjournment on 26 June for opening remarks from the Chairman; ongoing and new business; Director's report; clinical trials restructuring initiative status report; Subcommittee on Training report; Policy Update on Data Safety Monitoring issues; Specialized Programs for Research Excellence (SPORE) presentation; and Request for Applications (RFA) and Request for Proposal (RFP) concepts presentations and discussions; the Division of Cancer Biology (DCB) sexennial review report; and the Early Detection Research Network (EDRN) status report.

Board Members present:

Dr. Frederick R. Appelbaum
(Chair)

Dr. David B. Abrams

Dr. David S. Alberts

Dr. Neil J. Clendeninn

Dr. Hoda Anton-Culver

Dr. Thomas Curran

Dr. Mary Beryl Daly

Dr. Virginia L. Ernster

Dr. Waun Ki Hong

Dr. Susan B. Horwitz

Dr. Louise C. Strong

Dr. Peter K. Vogt

Dr. Barbara L. Weber

Dr. Robert C. Young

Dr. Alice S. Whittemore

Dr. William C. Wood

Board Members absent:

Dr. Esther H. Chang

Dr. Suzanne W. Fletcher

Dr. Herbert Y. Kressel

Dr. Caryn E. Lerman

Dr. Tyler Jacks	Dr. W. Gillies McKenna
Dr. William G. Kaelin, Jr.	Dr. Christine A. Miaskowski
Dr. Kenneth W. Kinzler	Dr. Nancy E. Mueller
Ms. Amy S. Langer	Dr. Daniel D. Von Hoff
Dr. Enrico Mihich	Dr. Elias A. Zerhouni
Dr. John D. Minna	
Dr. Franklyn G. Prendergast	NCAB Liaison:
Dr. Richard L. Schilsky	TBN
Dr. Ellen V. Sigal	
Dr. Joseph V. Simone	

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

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

Dr. Frederick Appelbaum called to order the 18th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Appelbaum reminded Board members of their responsibilities regarding conflict-of-interest issues. Board members' were also reminded of future Board meeting dates, which are confirmed through 2002. He informed members that their term end dates would be distributed by e-mail.

II. CONSIDERATION OF MARCH 25, 2001, MEETING MINUTES -- DR. FREDERICK APPELBAUM

Motion: The minutes of the 5 March 2001 meeting were unanimously approved.

III. REPORT OF THE DIRECTOR, NCI, AND AWARD PRESENTATION -- DR. RICHARD KLAUSNER

Dr. Richard Klausner presented an update on several molecular targeting projects:

Cancer Molecular Analysis Project (CMAP). The CMAP was designed to create an integrated, interactive information infrastructure. CMAP, being launched through the new NCI Center for Bioinformatics, will link individuals throughout the NCI, external organizations and companies involved in informatics. The intent is to provide a means to graphically represent the explosion molecular nature of cancer information; make that information accessible by annotating the molecular pathways of cancer; and link this information to both the availability of, and the need for, drugs, agents, probes, and clinical trials. An important purpose of the project is to begin filling in the gaps in current knowledge concerning the genetic changes associated with particular tumors and particular types of cancer.

Molecular Medicine. Aspects of recent NCI activities related to molecular medicine that have raised questions about how to cope with the information being generated, how to synthesize what has been gained, and how to identify gaps in information were reviewed. Dr. Klausner stated that three critical aspects of molecular medicine are the: 1) ability to profile a disease state in combination with an individual's specific characteristics; 2) use of molecular targets in diagnosis, prevention, and treatment; and 3) development of technologies and approaches referred to as "molecular monitors."

Innovative Molecular Analysis Technologies (IMAT) Program. Members were reminded that IMAT involves a new grant mechanism, the Phased Innovation Award. The IMAT program, a collaborative effort of 116 investigators, is designed to support the development of new molecular technologies by identifying specific goals and laying out milestones. Investigators' goals are to develop assays capable of measuring single molecules or single cells. Members were encouraged to visit the Office of Technology and Industrial Relations Web site for an overview of the IMAT program.

Molecular Signatures. A theoretical breakdown of the components of molecular target-based approaches to cancer diagnosis, prevention, and therapy were presented. Dr. Klausner stated that molecular signatures are described and credentialed as being meaningful for potential interventions, thus turning signatures into targets. Once targets have been identified, clinical trials are designed empirically.

Dr. Klausner reminded the Board of its support of the new molecular targeting programs that are creating information, resources, and the infrastructure necessary to allow these processes to work. This infrastructure, he noted, includes the: Cancer Genome Anatomy Project (CGAP); Director's Challenge: Toward a Molecular Classification of Tumors; Molecular Target Drug Discovery grants; Chemical Biology Centers; changes within the Developmental Therapeutics Program; and a network of Molecular Target Laboratories to develop and evaluate potential targets. He noted that an enormous amount of multidimensional information is being generated.

In discussion, the following points were made:

- The system is expected to go live within the next couple of months.
- The project's cost has been within the budget and it is anticipated that much of the expertise for future development will come from the private sector. Partnerships are being explored with major entities involved in information systems, graphic representation, and other technologies, so that costs can be distributed.
- Ways to interface the CMAP system with tools that the public can use to get information about the clinical trials portfolio will be explored.
- When fundamental targets are identified, there should be a funding mechanism to stimulate companies or universities to synthesize agents directed at those targets.

Director's Service Award. Dr. Klausner recognized and presented Dr. Virginia Ernster, an original BSA member, the Director's Service Award for her outstanding and dedicated service to the NCI and the Board from 1996 to 2001. Dr. Ernster thanked Dr. Klausner and the Board, noting that in her years of service with colleagues on various NCI Boards and committees, she has come to understand just how multidisciplinary cancer research really is.

Budget Report. Dr. Klausner informed the Board that the Fiscal

Year (FY) 2002 NCI budget had not been determined. Initial planning for 2002 will be based on the President's proposed budget request of an 11.8 percent increase, which would bring the Institute's budget total to \$4.177 billion. Information on dollars available compared with dollars already committed and how that relates to the proposed budget increase was presented.

The commitment base, Dr. Klausner explained, is the amount of money committed to out-year spending for previously funded multi-year grants within the Research Project Grant (RPG) pool, the single largest item in the RPG budget. He noted that although the proposed total budget increase is 11.8 percent. The projected increase in the commitment base is 16.5 percent, which presents a set of dilemmas for the NCI in developing grant funding policies. The biggest issue, however, affecting the Institute's ability to project costs and to fund at a particular payline is the increase in the average cost per grant.

Dr. Klausner stated that traditionally, study sections have provided the NCI with a recommended funding level, usually about 5 percent lower than the requested amount. Last year, that difference virtually disappeared, and so the NCI has been paying a fraction of the level recommended by peer review as determined by downward negotiations. He noted that it is important for NIH to continue linking evaluation of science with evaluation of the budget.

Data showing an increase in the downward negotiation was shown. If this reduction was not made, Dr. Klausner emphasized, fewer grants would be funded. He explained that every percentage point of reduction in R01s represents about \$3 million, and a percentile point on the payline represents about \$10 to 12 million. Thus, he concluded, this year's projected downward negotiation of between \$35 million to \$45 million represents 3 to 4 percentile points on the payline. This affects not only the payline, but also the NCI's access to exception dollars.

Data illustrating trends in requested costs per application was presented. In one recent year, the total dollars requested for large, unsolicited R01s rose from \$15 million to \$50 million. The largest single conceptual area that requested these funds was epidemiologic research. In response to these trends, a cap has been placed on competing continuation (Type 2) Program Project (P01) grant applications so that requests cannot exceed a 20 percent

increase over the direct costs awarded in the last noncompeting (Type 5) year; however, if all applicants make requests utilizing the full increase allowed by this cap, the disparity between requested funding and the downward negotiation will be even greater. He stated that to achieve some predictability concerning large demands on the budget, the Institute could issue a program announcement with an annual set-aside to create a single review group for large individual cohort applications.

During the question and answer session, the following points were made:

- Many epidemiologic researchers are putting together multidisciplinary studies that cost more than an R01. If caps are placed on grants, the studies may not be effective.
- Caps are used to control costs that have grown out of proportion to the growth of the overall budget.
- Placing a cap on grants does not mean that projects will not be funded. Successfully reviewed grants under the cap will be funded and exceptions can be considered.
- Downward negotiations would be easier to accept if applicants were allowed to negotiate with Program Directors to revise applications and remove specific scientific aims that could be transferred to other grants.
- Downward negotiations provide more opportunities for young investigators. Maintaining the success rate of new R01 investigators is one of the most compelling reasons for some of the Institute's decisions.
- When caps were first reported, there was almost a sense of panic. If there had been more public relation efforts to explain the percentage of affected grants and that large grants can be negotiated, the near-panic could have been avoided.

IV. ONGOING AND NEW BUSINESS --DR. FREDERICK APPELBAUM

Dr. Appelbaum noted that BSA representatives participating at 2002 "NCI Listens" sessions of annual meetings of cancer-related societies will be determined at the November BSA meeting.

BSA at National Meetings

American Association for Cancer Research (AACR). Dr. Susan Horwitz reported that participants who attended the "NCI Listens" session expressed concern about downward negotiation of their grants. Dr. Horwitz indicated that budget issues and downward negotiations are not well understood in the investigator community. Other topics discussed during the session included funds for young investigators and more public discussion of NCI achievements. She noted that concern about the issue of funding those who serve on institutional review boards (IRBs) was also expressed. Serving on an IRB requires a major commitment of time.

American Society for Preventive Oncology (ASPO). Dr. Mary Beryl Daly informed members that the "NCI Listens" session was very well received, and attendees encouraged such sessions at future meetings. Training grants and funding for research were major issues of discussion. One ASPO activity that might present an opportunity for NCI is the organization's support of a Junior Investigators' Committee. She indicated that this committee is very active and plans to sponsor its own symposium in the near future; thus, it could serve as a worthwhile forum for NCI and the BSA to reach young investigators and solicit their input.

Society for Behavioral Medicine (SBM) and Society for Research on Nicotine and Tobacco (SRNT). Dr. David Abrams noted that the "NCI Listens" session was well attended. Dr. Abrams reported that a wide-ranging discussion covered four major topics:

1. *Enhancing Communication and Public Relations.* Less than 20 percent of the attendees were aware of NCI initiatives for its grantees, such as accelerated review processes, grant negotiations, and Extraordinary Opportunities.

2. *Incorporating Behavioral Science into such NCI programs as the Community Clinical Oncology Programs (CCOPs).* Attendees expressed interest in participating in national research efforts such as the Cancer Family Registries and the Cancer Genetics Network. They also expressed interest in the SPORE program, but concerns were raised about the SPORE grant process, which requires inclusion of laboratory research components. Such requirements tend to preclude involvement of behavioral scientists.
3. *Encouraging the Participation of Behavioral Scientists in Issues Involving Health Disparities, Health Outcomes, and Health Services.* Dr. Abrams noted that a new generation of behavioral science investigators is specializing in many aspects of health services delivery.
4. *Applying for NCI Training Grants.* Participants expressed concern that the low indirect cost rate for NCI grants is a disincentive to applying for such grants.

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V. STATUS REPORT: CLINICAL TRIALS RESTRUCTURING INITIATIVE -- DRS. ROBERT WITTES AND MICHAELE CHRISTIAN

Dr. Robert Wittes, Director, Division of Cancer Treatment and Diagnosis, reminded the Board that the Cancer Therapy Evaluation Program (CTEP) is obligated to update the BSA annually on the important aspects of restructuring both multicenter and single-site clinical trials. He introduced Dr. Michael Christian, Associate Director, CTEP, who reported that the multicenter trial restructuring initiative has four basic parts: strengthening and enhancing the science of NCI's clinical trials; streamlining and increasing efficiency; broadening access; and addressing adequate compensation. Pilot programs to address these goals were presented:

Strengthening and Enhancing the Science. "State of the Science" meetings were described as national forums to identify new clinical

research opportunities, important gaps in knowledge, and the most critical research questions for clinical trials. Five meetings, attended by clinicians, basic scientists, and consumers from a wide variety of backgrounds, have been held. A Web site that features meeting highlights, including audio and video excerpts has been created. Out- comes to date are the establishment of a national tumor bank for research on small-cell lung cancer and the inception of phase I and II clinical trials of anti-VEGF antibodies for the treatment of non-small-cell lung cancer. Additionally, an initiative to strengthen the science of clinical trials is the creation of multidisciplinary Concept Evaluation Panels (CEPs) that review phase III clinical trials proposals. Membership includes NCI staff and representatives of NCI-sponsored Cooperative Groups and Cancer Centers, as well as other sources. Formation of a new rare diseases CEP is under consideration.

Improving Efficiency and Streamlining. A new joint protocol development and review process has been initiated to reduce the time between concept and protocol approvals. When a concept is approved, NCI sends the investigator a template for the protocol; upon its completion, CTEP and the study team review the protocol simultaneously, rather than serially. The ultimate goal is to reduce to 60 days the time between concept and protocol approvals. Three protocols that have undergone this process have taken about 80 days for approval, compared with prior periods of approximately 352 days.

Additionally, the Cancer Trials Support Unit (CTSU) was designed to create a national network of investigators and consolidate duplicative administrative and regulatory activities across Cooperative Groups. A database of information on all protocols and staff, including credentialing records, such as conflict-of-interest disclosure forms, IRB records, and a standardized audit system is being developed. Electronic data transfer systems are in place to facilitate data capture and transmission. The CTSU also accrues patients to clinical trials.

A BSA request regarding restructuring the CTSU initiative projected costs in the fifth year of its current contract, FY 2003, were compared with current costs from an academic research organization and two Cooperative Groups. The CTSU contract costs for FY 2003 is \$5.4M, the academic research organization's estimated costs were \$7.6M, and the Cooperative Groups'

estimated costs were, respectively, \$3.9M and \$1.06M. Although the number of sites, investigators, and patients vary in this comparison, the costs were generally in the same range.

Broadening Access. Dr. Christian discussed the Expanded Participation Project (EPP), which is an effort to create a structure to attract new physicians to NCI clinical trials. The program currently has 26 active partners at 55 sites in 19 states. EPP participants have accrued 369 patients to 21 different protocols. CTEP recently surveyed the partners to learn what support would be helpful. IRB submission, protocol, and patient materials were among the items most frequently mentioned. Dr. Christian observed that the EPP experience demonstrates that patient accrual through previously nonparticipating physicians is possible.

In collaboration with the Office of Human Research Protection, NIH, in August 1999, CTEP developed a central IRB. Dr. Christian informed the Board that the central IRB does not replace local IRBs but, rather, works in tandem with them. The central IRB's role is to approve protocols. If the central IRB approves a protocol and the local IRB accepts that decision, then the central IRB becomes the IRB of record, with the responsibilities for amendments, continuing reviews, etc. The local IRB continues to monitor compliance and study conduct. Dr. Christian described this initiative as an important model for improving patient protection while facilitating clinical research.

Adequate Compensation. The Cooperative Groups budget has grown by 55 percent to \$150.8M in FY 2001, i.e., from a baseline of \$97.3M in FY 1998. The additional funding has enabled CTEP to increase the per-case reimbursement for clinical trial patients from \$1,500 to \$2,000; fully fund statistical offices; provide followup funds for 200,000 patients; and support informatics efforts.

Common Data Elements. Dr. Jeffrey Abrams, Medicine Section, CTEP, described the Common Data Elements initiative, which would create a common language with respect to clinical trials and data collection. He explained that this effort is essential to CTEP's ability to automate many of its processes. The benefits of this initiative are that it: (1) enables the development of uniform case report forms; (2) has the potential to reduce the amount of data collected; (3) can facilitate automated data sharing and scientific

pooling of results; and (4) can reduce training and monitoring costs. Common data elements are identified and defined by Disease-Specific Development Committees (DSDCs) composed of clinicians, statisticians, research nurses, and Clinical Research Associates (CRAs). Each committee extracts essential points from existing data collection forms and develops a spreadsheet that displays data elements, definitions, and logical categories for the common Case Report form. Common data elements have been identified for adjuvant and advanced trials in breast, lung, colorectal, bladder, and prostate cancers, and for acute and chronic leukemias. Work on data elements for three gynecologic cancers will be completed by the end of June. Future work involves data elements for melanoma, gastrointestinal tumors, lymphomas, sarcomas, and head-and-neck and brain tumors. Working with the SPORE Pathology Committee and the Cooperative Group Intergroup Specimen Banking Committee, plans are to develop common data elements for pathology specimen submissions. Dr. Abrams announced that the *Common Data Elements Dictionary* was migrating to a new standards-based repository, a metadata management system designed to adapt as science evolves. The ultimate goal is the development of a common Case Report form.

Dr. Christian concluded the presentation by briefly describing additional informatics initiatives, such as common toxicity criteria now accessible via a Web-based interactive application; the clinical update system; and the Adverse Event Expedited Reporting System (AdEERS). She noted that the Food and Drug Administration (FDA) has expressed interest in common toxicity criteria and AdEERS for industry-sponsored studies as well as for investigational agents.

In discussion, the following points were made:

- FDA representatives should be involved in Concept Evaluation Panels. The success of innovative trial designs might be improved if there is a demonstration that the FDA is interested in them.
- Cooperative Groups should be involved in the planning and evaluation of the restructuring effort, not just the implementation. Continuous evaluation is needed for a project of this scope.

- The CTSU has not been successful in patient accrual, and it stands in the way of accruing patients through traditional means. Its database of protocols and investigators is, however, a powerful tool for making the process of protocol approval more efficient.
- Despite having been recently increased, reimbursements for clinical trials are still too low. One institution's costs were estimated at \$5,000 per patient, while the available reimbursement is \$2,000. Without a new infusion of dollars, raising the per patient reimbursement will reduce the number of trials.
- The centralized IRB concept, in conjunction with efforts of the national coalition of cancer cooperative groups and various new NCI informatics initiatives, can help improve public access to clinical trials information by compiling IRB approval, insurance plan coverage, and doctor participation information.

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VI. WORKING LUNCH

Subcommittee on Training -- Dr. Robert Young

Dr. Robert Young reminded Board members that the goal of the "NCI Listens" sessions at annual meetings of cancer-related societies is to listen to comments and criticisms from the investigator community and report back to the BSA on frequently heard issues. Concerns about training support for young investigators have been expressed consistently. Dr. Young presented for Board consideration three draft letters designed to address two separate issues. The first issue is the lack of success in advertising the availability of K series training grants to their intended audience, the young investigator community. In response to this issue, one letter, addressed to academic institutions, deans of schools of medicine, and vice chancellors of research, requests assistance in publicizing the K awards and offering to send summary information about them upon request. Another draft letter

was addressed to national cancer-related organizations, volunteering to provide an article or letter about the K awards written for their journals by NCI staff.

The second issue was that the indirect cost rate of 8 percent for K awards is lower than that of other Federal grants. A third letter, addressed to the NCI Director requested that consideration be given to raising the indirect costs percentage, since the 8 percent rate might be a disincentive to applying for these grants, especially in institutions that lack resources to cover indirect costs.

In discussion, the following points were made:

- Career development awards are unique because they fund individuals, not institutions.
- Increasing reimbursement for indirect costs might result in fewer grants for training, because the funds for both direct and indirect costs come from one source.
- Information regarding R25 training grants should be added to the academic institutions, deans of schools of medicine, and vice chancellors of research letter and to the national cancer-related organizations letter concerning the availability of "K" Awards.

Motion: A motion to withdraw the letter drafted to the Director, NCI, on issues related to indirect cost rates for "K" Awards was approved.

Policy Update: Data Safety Monitoring Issues -- Dr. Robert Wittes

Dr. Wittes explained that new Department of Health and Human Services (DHHS) requirements for data safety monitoring (DSM) are no longer limited to phase III clinical trials but have become a more comprehensive requirement for clinical trials of all types. Well-publicized lapses in clinical trials procedures, resulting in increased public awareness of clinical trials, have prompted the Federal Government to increase its surveillance level of DHHS sponsored clinical trials, including those carried out by NIH-funded

researchers. The NIH has indicated that each Institute can decide how best to implement DSM plans. He noted that this approach will allow each Institute to implement policies appropriate to the kinds of trials it typically conducts.

Members were informed that clinical researchers must submit a satisfactory DSM plan as a condition of funding. Trials involving Investigational New Drugs (INDs) are subject to FDA monitoring and reporting regulations, but many NCI-funded trials do not involve INDs (e.g., bone marrow transplant studies and nutrition research). To help institutions meet these requirements, NCI has prepared a document explaining these issues and describing four essential elements of a DSM plan. If an institution's plan is sufficiently clear and thorough, it could serve virtually all of its investigators engaged in clinical trials, with only minor modifications. It was emphasized that the NCI is not looking for minute detail but, rather, the assurance that an institution has a reasonable and thorough DSM procedure in place. Internal NCI reviewers are working with institutions to modify such plans, and samples of approved plans and actual review criteria are being sent to institutions to assist in the development of their DSM plans.

In discussion, the following points were made:

- The NCI guidelines lack specificity with regard to which kinds of trials are covered.
- Since implementation of a DSM system will require institutions to incur associated costs, the NCI plans to invite institutions to submit reimbursement requests for those costs.

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VII. SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE --DRS. BRIAN KIMES AND JORGE GOMEZ

Dr. Jorge Gomez, Chief, Organ Systems Branch, Office of Centers, Training, and Resources, Office of the Deputy Director for Extramural Science, informed members that the Specialized

Programs of Research Excellence (SPORE) program had undergone several changes since it was last presented to the BSA in 1998. Dr. Gomez reviewed recommendations made by Board members at that time, which included extending the program to cover more organ sites and making the program more accessible by converting it from an RFA to an investigator-initiated award. A 5-year transition plan to implement the Board's recommendations included 1) the development of new SPORE grant application guidelines; 2) ensuring that applications meet NIH translational research requirements; 3) refining the definition of translational research; and 4) working to ensure consistency in the peer-review process. The *definition of translational research* was modified to: "Translational research uses knowledge of human biology to develop and test feasibility of cancer-relevant interventions in humans or determines the biological basis for observations made in people with cancer or in populations at risk for cancer."

Dr. Gomez informed the Board that the goal of the SPORE program is to apply knowledge of the biology of human cancer to diagnosis, prevention, risk assessment, early detection, and therapy. The SPORE program has grown rapidly since its inception in 1992, from 9 programs covering 4 organ sites in 1992 to 31 programs covering 7 organ sites (breast, prostate, lung, gastrointestinal, ovarian, genito-urologic, and skin cancers) in 2001. Its budget was \$20M in 1992 and \$68M in 2001. The most likely areas for expansion in coming years include leukemia, lymphoma, and head and neck cancers. He noted that for an institution to be eligible for a SPORE award, a base of funded research in a given organ site, an active clinical research program, and a multidisciplinary team of investigators is required. Dr. Gomez stated that NCI-designated Cancer Centers play a major role in creating the environment required for a SPORE award; i.e., 29 of the 31 programs are located at Cancer Centers.

In discussion, the following points were made:

- The planning for the evaluation of the SPORE program in 2003 should be included on the calendar for Board action in 2002.
- The guidelines prepared by the Board in 1998 for the evaluation of the SPORE program should be sent to Board members.

- The SPORE program successfully brings new investigators to NCI and creates opportunities for research that would not exist through traditional funding mechanisms.

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VIII. PROPOSED RFA/COOPERATIVE AGREEMENT AND RFP CONCEPTS PRESENTED BY NCI STAFF

Division of Cancer Treatment and Diagnosis

Pilot Program for Underserved Medical Institutions: Radiation Oncology Partnerships (RFA). Dr. Norman Coleman, Associate Director, Radiation Research Program (RRP), DCTD, indicated that the title of this concept has been changed to "Cancer Disparities Research Partnerships Program (CDAP)." Dr. Coleman stated that the concept is designed to develop or expand radiation oncology clinical trials infrastructure in institutions serving populations with cancer-related health disparities. The intent is to foster the development of long-term research mentoring partnerships with established NCI-affiliated research organizations. Changes made in response to Board members' comments were: (1) broadened eligibility, so participating institutions could take part in NCI-sponsored clinical trials; (2) defined target populations more specifically; (3) adopted a more specific methodology for evaluating institutional eligibility; (4) refined content and chronology metrics; (5) added institutional baseline metrics to the application process and timeline; (6) included a description of partner relationships in the application; (7) began the mentoring process at the beginning of the grant; (8) focused goals and outcomes more clearly; and (9) increased funding for partnership institutions to \$100,000.

He stated that radiation oncology was an appropriate specialty for this concept because: (1) for underserved populations, radiation oncology is a major treatment alternative, since patients often do not seek treatment until their disease has progressed; (2) it is computer-based and easily lends itself to training; (3) it supports the goal of creating long-term credible institutional partners with

the NCI; and (4) it has the potential to increase the number of clinical and translational scientists in areas with health disparities. [Extraordinary Opportunity in Cancer Imaging]

The proposed length of award for this one-time solicitation is 5 years with a first year set-aside of \$3.2M and a total cost of \$21.3M for an estimated 6 awards.

In discussion, the following points were made:

- Reviewers will need clearer criteria to determine which applications should be successful. Patient followup and compliance should be among the metrics used to judge the success of the projects. Baseline metrics should reflect 5-year metrics.
- Radiation oncology is used as a model to test how community outreach can be done more effectively. The partnerships to be generated in this project will make participants part of a larger intellectual team that can improve cancer care in general.

Motion: A motion to approve the RFA/Cooperative Agreement concept entitled "Pilot Program for Underserved Medical Institutions: Radiation Oncology Partnerships" was unanimous.

Division of Cancer Prevention and Division of Cancer Treatment and Diagnosis

Lung Screening Study II (LSS II) and Overview of ACRIN Lung Screening Study

Lung Screening Study II (LSS II) (RFP). Dr. John Gohagan, Supervisory Health Science Administrator, Early Detection Research Network, Division of Cancer Prevention, NCI, informed the Board that many cancer specialists believe that spiral chromatography (SCT) could reduce mortality from lung cancer by as much as 50 percent compared with reductions in mortality from chest x-ray (CXR) screening. Dr. Gohagan noted that the population at high risk for lung cancer is large and the target population of this study includes approximately 20 million current and former smokers with a 30-pack/year history who have quit

within the past 10 years.

Dr. Gohagan presented recent and ongoing research in early detection of lung cancer. He noted that the Lung Screening Study I (LSS I) screened 3,000 randomized subjects, roughly half of whom received CXR and the other half SCT. Subjects screened with CXR showed a 10 percent positive rate for possible lung cancers. SCT screening showed a positive rate of 21 percent. The Early Lung Cancer Action Project (ELCAP) administered both CXR and SCT to about 1,000 individuals. SCT detected more than three times as many noncalcified nodules and nearly four times as many cancers as CXR. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial will screen approximately 154,000 individuals for lung cancer by CXR only.

Dr. Gohagan indicated that SCT research is timely because industry representatives indicate that SCT technology is unlikely to change over the next 5 years and by the time a large trial is completed, the results will not be obsolete. Additionally, since SCT is a relatively new detection tool, the problem of "crossover" is reduced. He noted that because of these two factors, beginning the screening as soon as possible is important.

Dr. Gohagan explained that the Lung Screening Study II (LSS II) would be a randomized controlled trial adding about 12,000 subjects to LSS I over a 12-month period. The study would involve two annual screens for subjects. Data from the screens would be analyzed for positive rates, detection rates, diagnostic followup, and mortality. A reduction in mortality of as much as 68 percent by the time 12,000 subjects have received two annual screens is anticipated. The trial's statistical power would be approximately 0.90, and to strengthen the results, the LSS II team would work with other countries that are also conducting SCT trials. Extraordinary Opportunity on Research on Tobacco and Tobacco-Related Cancers]

The proposed length of award for this one-time solicitation is 4 years with a first year set-aside of \$16.3 M and a total cost of approximately \$52M.

ACRIN Lung Cancer Screening Trial. Dr. Daniel Sullivan, Associate Director, Biomedical Imaging Program, Division of

Cancer Prevention, explained that the American College of Radiology Imaging Network's (ACRIN) Lung Cancer Screening Randomized Control Trial proposal is for a cooperative group trial and would not normally be presented to the BSA for a vote. However, the ACRIN trial would require a significant increase in funding. The ACRIN proposal had originally been submitted in 1998 and, following peer review, was reviewed by the Cancer Therapy Evaluation Program (CTEP). CTEP's principle concern was the study's statistical power, which proposed screening 7,000 subjects accrued over an 18-month period. In response to the CTEP's concern(s), ACRIN added CXR for the control arm subjects, reduced the number of annual screens from five to three, and harmonized the data fields so that mortality data could be obtained by merging ACRIN data with LSS data. The ACRIN protocol suggests followup protocol for positivity, and would collect additional data for a biorepository from blood, urine, and tissue samples. In addition, investigators would obtain questionnaire data on quality of life and behavior, as well as data for analysis of cost-effectiveness.

The proposed length of award for this solicitation is 6 years with a first year set-aside of approximately \$8.5 M and a total cost of \$43.7 M.

In subsequent discussion, the following comments and points were made:

- The stakes involved are huge, because lung cancer is the leading cause of cancer death, and effective therapies are scarce. Moreover, if SCT is proved an effective tool for lung cancer screening, the cost of applying the screening to 20 million current and former smokers is great enough to affect the share of the Gross Domestic Product (GDP) spent on health care in the United States.
- The trial benefits may be greatly overestimated. In the first year of the trial, the screening will likely detect large numbers of prevalence cases, but in subsequent years, the screening will detect incidence cases, which will be fewer in number.
- The proposed sample might not be large enough to produce

meaningful results. Thus, a treatment algorithm to determine which types of lesions detected would be rescreened later and which would be biopsied, because followup treatment would have a large effect on mortality rate, should be determined.

- The benefits of SCT as a screening device are not well understood and the proposed trial would add to the knowledge base for SCT. Biomarkers expressed in sputum should be part of the screening and a smoking cessation component added.
- Since SCT would detect a large number of small lesions that could be difficult to investigate via biopsy, there will be the cost of followup care for those who test positive. Patients will need to know whether their health insurance providers would pay for rescreening or biopsy. A clear cost estimate is needed.
- Many women in their fifties who quit smoking during their childbearing years are now contracting lung cancer. The 10-year cutoff specified in the experimental design would not accommodate this group.
- NCI's SPORE program has several initiatives for genetic predisposition to lung cancer. It is hoped that such a large study would incorporate research on susceptibility genes and perhaps yield findings that would help distinguish among different types of lung cancer.
- The goal of reducing mortality by 50 percent may be too ambitious. The study should be designed to detect a 25 to 30 percent reduction in mortality.
- The sample should be larger. Increasing the sample size will result in greater statistical power without raising costs proportionately.
- The benefits of the study as measured by gains in years of life or by dollars saved are not articulated in the proposal.
- Lung cancer is one of the most preventable cancers, and the

problems it represents are not cancer detection and treatment, but smoking prevention and cessation. Moreover, the cost of morbidity and mortality associated with smoking is not limited to lung cancer, but includes heart disease, stroke, and many other diseases. The resources to be expended on LSS II might be better spent on more effective cessation and prevention programs or on better therapies.

- The proposed budget for LSS II does not include further diagnostic evaluation or medical care. Third-party payors would be expected to cover the costs. The proposal does call for referring smokers to smoking cessation programs.
- SCT is already in use as a screening device for lung abnormalities, but interpretation of the results lacks a scientific basis. LSS II would provide the opportunity to develop such a basis for interpretation.
- A significant associated benefit of the research is that participating institutions would have access to a large sample of three-dimensional images of lesions. Investigators could learn much about growth and shape patterns and which patterns are associated with lung cancer.
- Screening, either alone or coupled with educational material, is ineffective in persuading people to change their behavior or seek treatment. Reductions in mortality cannot be achieved without followup diagnostic and treatment protocols.
- The study offers the opportunity to study a variety of conditions, such as heart disease, in addition to lung cancer. Adding new study sites, however, would increase costs substantially.

Motion: A motion was made to approve the RFP concept entitled "Lung Screening Study II" provided the sample size was increased to improve statistical power. In subsequent discussion, a motion was made to table the first motion and form a subcommittee to assist staff in revising the concept. The motion to table failed to receive the required two-thirds majority, 15 in favor, 8 opposed and 1 abstention. The original motion was submitted to a vote and was defeated, 12 in favor and 12 opposed.

Motion: A motion to appoint a subcommittee to work with NCI programmatic staff to revise the concept and submit it for approval by the full Board via e-mail was approved, 21 in favor, 2 opposed and 1 abstention. The subcommittee consists of Drs. Hong, Abrams, Wood, Anton-Culver, Schilsky, Minna, and Whittemore. [Note: Drs. McKenna and Kressel are also on the subcommittee. A vote by the full Board will occur at the November 2001 meeting.]

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IX. DIVISION OF CANCER BIOLOGY PROGRAM AND SEXENNIAL REVIEW REPORT --DR. DINAH SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), informed members that the DCB's mission is to ensure stability and continuity in ongoing cancer biology research while fostering the emergence of novel areas of investigation. Dr. Singer stated that the DCB administers more than 2,200 grants and an approximately \$650 M budget. She noted that the majority of the grants are investigator-initiated and represents over half of NCI's R01 and P01 grants portfolio.

Members were told that DCB staff identify emerging scientific research areas through a variety of approaches. The Division organizes its own workshops and conferences; develop new funding mechanisms; and oversees the Mouse Models of Human Cancer Consortium (MMHCC) and the construction and operation of a beamline at Argonne National Laboratory (cofunded with the National Institute of General Medical Sciences (NIGMS)).

In discussing DCB's staffing and organizational structure, Dr. Singer stated that the Division's 25 Program Directors, responsible for administering the active grants portfolio, are senior doctoral scientists. These individuals provide grantees with advice, feedback, and assistance. They are also responsible for identifying and initiating any new Divisional RFAs or PAs.

Sexennial Review. Dr. Singer explained that the original concept for this review was that it would be conducted by a BSA subcommittee and would consist of four components: 1) analysis of

the grants portfolio to identify gaps; 2) assessment of value added by DCB programmatic activities; 3) conduct of a site visit; and 4) a draft report that would incorporate the subcommittee's findings and the Division's response. Because of conflict of interest regulations, NCI grantees could not serve on a review panel that would evaluate DCB or any extramural Division. Thus, most of the reviewers were extramural scientists funded by other Institutes and tended to focus more on Divisional administrative responsibilities than on the scientific aspects of the Division. Because a consensus report could not be written, the final report consisted of individual reviewer comments rather than specific recommendations. Several themes that resulted from the review and DCB's response were presented:

1. *The DCB should increase communication with grantees, particularly new grantees.* The DCB has instituted new grantee workshops to advise them on the best strategies for achieving their goals. The DCB Web site has been updated and a listserv has been established. An ombudsman has been appointed to help grantees with issues that they are reluctant to discuss with their program directors and staff visit grantees at their home institutions.
2. *The DCB should enrich the scientific opportunities available to staff.* A separate budget for staff enrichment has been established. Outside speakers are invited to present their research and DCB sponsors seminars in which every Program Director gives an annual presentation on an area of interest within his or her field. A basic science seminar series has been instituted for support staff, and the DCB is considering a Visiting Scholars Program.
3. *The DCB should develop approaches for self-evaluation.* The DCB has sought feedback from grantees, but with little success. Dr. Singer expressed hope that the ombudsman and a broad survey might elicit better feedback. The DCB is undergoing a results-based management analysis to determine whether it is structurally organized to perform core functions and goals.

Dr. Singer stated that other comments from the reviewers pertained to NIH-wide or NCI-wide issues not under the Division's control. She expressed regret that the review could not be carried out as originally envisioned, but that the process nonetheless was helpful.

In discussion, the following points were made:

- Given the constraints imposed by conflict-of-interest issues, the increased staff time required to prepare for the review, and the quality of the results, it is doubtful that this type of review will be repeated for other programmatic areas.

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X. STATUS REPORT: EARLY DETECTION RESEARCH NETWORK -- DRS. RICHARD KLAUSNER, PETER GREENWALD, SUDHIR SRIVASTAVA, DAVID SIDRANSKY, LANCE LIOTTA, AND MARK THORNQUIST

Dr. Peter Greenwald, Director, Division of Cancer Prevention, provided an overview of the progress of the Early Detection Research Network (EDRN), which involves biomarker investigation and validation. Dr. Greenwald stated that biomarker research has central importance in cancer prevention, diagnosis, and therapy. In prevention, biomarkers have the potential to make clinical prevention trials more efficient by providing validated surrogate endpoints and by shortening the size and duration of the trials; in diagnosis, they provide opportunities for true early detection, when therapy is most successful; in therapy, biomarkers can aid in the development of better informed and more individualized interventions.

Dr. Greenwald noted that the EDRN was initiated in 1999 and that it supports a network of competitively funded investigators, with each assuming a specific responsibility that relates to the overall success of the Network. The EDRN is based on the premise that integration of discovery, evaluation, and clinical validation is more likely to succeed when these phases are carried out in a coordinated, systematic fashion.

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EDRN Management and Oversight of Scientific Directions

Dr. Sudhir Srivastava, Chief, Cancer Biomarkers Research Group, DCP, presented three goals of the EDRN: encouraging interaction among academic, clinical, and industrial leaders for the development of biomarkers; establishing scientific criteria to evaluate biomarkers as indicators of early cancer, prognostic factors, and markers of risk; and developing and instituting a quality assurance program for biomarker testing and evaluation. The result will be the ability to provide the cancer research community with referenced reagents and standardized assays for biomarkers.

Dr. Srivastava stated that the EDRN had brought together more than 12 industrial partners, 31 research institutions, and 3 Federal agencies for various aspects of biomarker research, including bioinformatics, basic science, and clinical science. Each research institution has its own consortium, for a total of approximately 120 laboratories and 300 investigators. With such a large and diverse group of organizations, management is a critical issue. The EDRN is overseen by a steering committee, a network of policy-setting subcommittees, and a Clinical and Epidemiologic Working Group. Subcommittee chairs constitute an Executive Committee. A Network Advisory Consulting Committee provides advice on science, and a data management and coordination center not only manages data but also helps in the development of tools for biomarker and data analysis. In addition, collaborative groups promote areas of research where collaboration will enhance sharing of technology, resources, and information among EDRN members and nonmembers alike. They are organized around specific cancer sites. The EDRN communicates with the research community by holding annual workshops.

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EDRN Research Spotlights

*Dr. Srivastava described three analytical validation studies being carried out under the auspices of the EDRN:

1. *Chromosomal Hotspot Assay and Lung Cancer Risk.* This study has demonstrated that sensitivity to bleomycin- and benzopyrene diol epoxide (BPDE)-induced DNA damage can measure the risk of lung cancer in vitro. This assay measures the levels of BPDE- and bleomycin-induced chromosomal breakages of DNA adducts. A positive correlation has been observed between the levels of chromosomal breakage and risk for lung cancer, suggesting that subjects very susceptible to BPDE- and bleomycin-induced DNA damage may have a suboptimal DNA repair mechanism.
2. *Serum Telomerase Capillary Electrophoresis.* This study is an effort to develop high-throughput assays to detect telomerase which is expressed in a variety of tumors. EDRN researchers have been successful using capillary gels, which require only small amounts of tissue samples, instead of slab gels for these assays, increasing the number of samples that can be tested simultaneously.
3. *Mitochondrial DNA Mutations Sequence Prevalidation.* Mitochondrial DNA (mtDNA) mutations serve as powerful markers for early detection since they are readily detectable in bodily fluids and are more abundant than other molecular changes. Research is underway to check for heteroplasmy using various technologies; establish threshold concentrations below which mtDNA cannot be reliably sequenced; and determine if standard PCR/sequencing protocols reliably detect mtDNA present in original DNA samples and are optimal for primer pair sequences.

Dr. Srivastava described the EDRN's resource network, other informatics initiatives, and summarized EDRN accomplishments.

* Dr. David Sidransky, Director, Head and Neck Cancer Research Division, Johns Hopkins University, and Chairman of the EDRN Executive Committee, described the EDRN's view of cancer as a genetic disease involving several genetic changes in its progression. Often, cancers produce no symptoms until the disease has progressed. The EDRN's premise is that early genetic changes, along with RNA and protein changes, provide useful markers that can be used to detect the disease at various stages of preclinical

development, when therapy is most effective. Dr. Sidransky discussed three promising biomarkers currently under study and their uses in the early detection of lung cancer:

1. *Mutant mitochondrial DNA*. This marker is particularly useful in detecting lung cancer, because assays of bronchoalveolar lavage (BAL) in patients with lung cancer tend to detect only about 1 cancer cell among as many as 1,000 normal cells. BAL assays reveal a 200-fold increase in mutant mitochondrial DNA in patients with lung cancer.
2. *Promoter hypermethylation*. Recently, a highly sensitive assay that detects methylated DNA and readily distinguishes between unmethylated and methylated DNA was developed. Methylated DNA affects several fundamental pathways in cancer: cell cycle control, DNA damage repair, apoptosis, tumor architecture, and growth factor response. Methylation tends to block transcription, and high-density promoter hypermethylation acts in the same manner as chromosome deletion and halts gene function. Questions being studied with respect to methylated DNA as a lung cancer biomarker are: a) Is methylation present in nonmalignant lung tissue adjacent to lung cancers? b) Are there geographic, histologic and smoke exposure-related differences in the methylation patterns of resected non-small-cell lung cancers? c) Is there a correlation between methylation status and clinical characteristics of the patients? d) Can methylation be detected in smoke-damaged oropharyngeal and bronchial epithelium from clinically cancer-free smokers?
3. *Identification of lung cancer proteins that induce an antibody response*. This technique involves separating proteins from tumor tissue and, using a Western blot analysis, testing the resulting gels with sera from both cancer patients and cancer-free individuals. Several candidate markers from the annexin family have been identified. Among 54 cancer patients, 16 were positive for annexin I antibodies, and 18 were positive for annexin II antibodies. All cancer-free controls were negative.

Dr. Sidransky concluded his remarks by observing that there is a tremendous array of potential markers, and he praised his

colleagues for their willingness to focus efforts on those that are most promising.

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Application of "Artificial Intelligence" Genetic Algorithm to Proteomics

Dr. Lance Liotta, Chief, Laboratory of Pathology, Center for Cancer Research, reported on new technology that employs artificial intelligence and a bioinformatics tool to discover biomarker patterns in serum. Development of these technologies is through the Clinical Proteomics Initiative (CPI) and in response to the Director's Challenge to move promising laboratory data quickly into practical assays for the clinic.

For 3 years, CPI has received support to develop protein analysis and discovery technologies and apply these tools to exploring biological and clinical questions with collaborative investigators. Patterns of biomarker proteins, both known and unknown, can be distinguished by examining microdissected tissues and body fluids using 2D gel analysis, protein microarrays, and Surface Enhanced Laser Desorption/Ionization (SELDI) data to characterize the patterns using an artificial intelligence (AI) algorithm. The ultimate goal is to use the proteins and peptides patterns as diagnostic markers.

Following a brief presentation of successful collaborations with other EDRN investigators on various research projects, Dr. Liotta summarized the AI algorithm mechanism as an iterative process in which a large number of prospective protein patterns are analyzed with a mating recombination test and a fitness test to develop a "survival-of-the-fittest" pattern. The "trained" algorithm can then categorize unknown samples as healthy, diseased, or new and it refines its discriminatory power as more samples are analyzed. He emphasized that this technology is especially outstanding for analysis of low-molecular-weight proteins and peptides not visualized in 2D gels. Low-molecular-weight proteins and peptides offer a wealth of new diagnostic information not yet fully explored.

Members were told that the patterns for either ovarian or prostate cancer were applied to unknown, blinded cases. The resulting accuracy in detecting cancer ranged from 97 percent in cases of biopsy-proven prostate cancer to 100 percent accuracy in biopsy-proven ovarian cancer. Moreover, patients with healthy prostates were determined with 100 percent accuracy, and patients with no evidence of ovarian disease were detected 94 percent of the time.

Dr. Liotta concluded that discovery of low-molecular-weight proteomic patterns using a bioinformatics tool that evolves and learns the most-fit solution shows promise in detecting ovarian and prostate cancer and may have promise for other cancers. Proteomic patterning offers both a new window into the physiologic state of organs and a new paradigm for disease diagnosis.

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Statistical, Computational And Informatics Tools For Biomarker Analysis

Dr. Mark Thornquist described work being done by the Data Management and Coordinating Center (DMCC) for the EDRN. Dr. Thornquist informed members that the DMCC provides support to the EDRN infrastructure, facilitates communication among EDRN members by providing access to their secure Web site and listservs, and coordinates multisite research. When requested by EDRN investigators, the DMCC also provides assistance with statistical analysis. His presentation focused on: 1) the design of a phase structure for biomarker research; and 2) use of analytical methods for working with high-dimensional data sets.

Phase Structure for Biomarker Research. The DMCC is in the process of designing a new five-phase structure for biomarker research that is similar to the three-phase structure for clinical or therapeutic trials. The new structure incorporates well-defined objectives for each phase, but is flexible to allow for studies that span one or more phases, as is done in phase I/II clinical trials. The phases proceed in a logical order, which should lead to the development of good biomarkers. Dr. Thornquist briefly described the five phases as: 1) discovery phase; 2) develop an assay to

determine and standardize the marker characteristics in an established disease; 3) determine if the marker can be used to detect preclinical disease and define what it means for the marker to be considered positive or negative; 4) prospective screening to determine the marker's effectiveness at detecting disease at earlier stages than existing detection methods; and 5) evaluate the marker for its effectiveness in decreasing disease burden and the effectiveness of the protocols used to treat people who have had their diseases detected at an early stage. Phases I and II were discussed in greater detail. Details of the proposed phase structure will be published in an upcoming issue of the *Journal of the National Cancer Institute*.

Analytical Methods for Working with High-Dimensional Data Sets. A study that looked at serum samples from approximately 300 patients with prostate cancer or benign prostatic hyperplasia (BPH) and approximately 100 patients with no cancer was described. The study included 99 patients with early-stage prostate cancer, 98 patients with late-stage prostate cancer, 96 controls, and approximately 100 patients with BPH. Proteomic analysis of the serum samples was performed using SELDI. The SELDI data included 48,000 mass/charge points over a range of 200,000 kD. A portion of the data was given to a third party, and only that party knew the cancer status of the individuals. The remaining data were used to develop biomarkers to discriminate among cancer cases, BPH, and control cases, the goal of the study. Two approaches to analyzing the data were described: binary marker combinations (BMCs) and wavelets.

Binary Marker Combinations. BMC is a method for combining peaks from SELDI data. Peak identification is the first step; then there is a process of eliminating peaks that are low and can be adequately identified from one another. The data are then recalibrated to account for the smoothed peaks. A key to BMC is in finding different peaks or markers and combining them using a Boolean AND statement. Thus, the new marker is found to be positive when both peaks are present, creating a much more specific, yet less sensitive, marker. Combined markers are then recombined using an OR statement to make them more sensitive. In this particular study, 19 highly specific markers were created using the AND statement and then combined with an OR statement to add sensitivity. The resulting rule establishing the positive result was complicated, but when applied to the test data set, resulted in

87% sensitivity and 100 percent specificity.

Wavelet Analysis. Wavelet analysis has three steps. The first step is to reduce the amount of data. This is important because tens of thousands of observations are made for only a few hundred individuals, making over fitting the data highly likely. The reduction can be accomplished by using wavelets to represent the original data plot. By selecting the 1 percent of wavelets that contain the most data, 96% of the energy of the original data can be captured. The second step is to determine the wavelets that distinguish between subgroups. The third and last step is to define discriminating functions based on the distinguishing wavelets. Using this method, researchers were able to reduce the 12,400 observations to 3,400 wavelet coefficients. They further refined those to 17 coefficients that distinguish among the three states, prostate cancer, BPH, and normal tissue. Using their classification function, they achieved 93 percent sensitivity in determining prostate cancer, BPH, and normal tissue. None of the patients with cancer was classified as normal, and 90 percent were correctly classified as having cancer.

Dr. Thornquist stated that both the wavelet and BMC approaches could be applied not only to continuous data, but also to microarray spot data. He described a study using a publicly available data set in which 7,500 gene spots were reduced using wavelet analysis.

In discussion, the following points were made:

- Many different working groups and consortia deal with overlapping issues, for example, the NCI Program on Assessment of Clinical Cancer Tests (PACCT) deals with issues similar to those of the EDRN. NCI has tried to facilitate communication among these groups by internal sharing; however, some of these groups are so new that development of their own procedures and policies must be accomplished before they can interact with other groups.
- Investigators can become associates of the EDRN by submitting a proposal for a biomarker and inviting collaboration from an EDRN institution. The process from the time of proposal submission to approval is about 3 months.

- Wavelet analysis is useful for differentiating between persons with cancer and those without cancer; however, it has not been reliable in distinguishing between patients with BPH who are cancer-free and those who do have cancer. To obtain the best analysis, serum from large numbers of people need to be tested and with long-term follow-up.
- The patterns currently displayed in the SELDI data cannot be used to determine specific proteins; however, new technology to do that is being developed.
- SELDI data patterns have been shown to differ after treatment, and these patterns are being studied to determine if they can be used as early predictors of recurrence.
- Further studies using these analytical methods need to be completed with various serum collection samples to determine if they are consistent in detecting cancer with respect to changing hormone status and other biological variables.
- Larger studies and more data sets should enable researchers to discriminate among subclasses of cancer and histologic types and to correlate those with outcome data.

Adjournment: The meeting adjourned at 1:00 p.m. on Tuesday, June 26, 2001.