EARLY DETECTION IMPLEMENTATION GROUP
National Cancer Institute

The Early Detection Implementation Group (EDIG) was charged with coordinating the implementation of recommendations from the Cancer Prevention and the Cancer Control Program Review Groups in the area of cancer screening and early detection.

To accomplish this task, NCI staff first formed an internal working group that suggested experts in the field of cancer prevention and control to serve on the full EDIG. The internal working group then prepared a working document **(See Attachment A)** that listed all the recommendations relevant to early detection from the reports of the Cancer Prevention Review Group and the Cancer Control Review Group. This was used as the basis for subsequent discussion in the EDIG. The specific recommendations in the area of early detection research from the Cancer Prevention and the Cancer Control Program Review Groups have been extracted from the full reports and listed in **Attachment B**.

The full EDIG consisted of a number of experts whom we felt brought a breadth of knowledge to the field of screening and early detection. These include a number of outside consultants, as well as representatives from several NCI Divisions **(See Attachment C)**. In the course of fulfilling this charge, the EDIG met four times **(See Attachment D)** along with invited representatives and speakers to aid in finalizing the implementation plan.

The following documents represent the combined effort of the EDIG which we feel will have a positive effect in the area of cancer screening and early detection, and which addresses the recommendations of the Program Review Groups.

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EARLY DETECTION IMPLEMENTATION GROUP (EDIG) RESPONSE

INTRODUCTION

Early detection strategies in cancer involve the search for invasive cancers in at-risk populations at curable stages of disease, as well as the search for non-invasive abnormalities which have an elevated probability of progression to invasive cancer. Successful treatment of the latter category of abnormalities is a form of primary cancer prevention. Screening of asymptomatic people is the primary means to accomplish early detection, whether in the physician's office, community invitation programs, or mass population-based organized programs in a national health system. The first two screening settings are often termed "opportunistic," and they are the most common settings in the United States. The third setting, organized population-based screening, is more characteristic of countries with national systems of universal health care, such as the United Kingdom, Scandinavia, and other European countries.

The primary goal of early detection research is to determine if there is a benefit to screening and to determine the magnitude of the benefit. An important theme common to all three screening/early detection settings is that large numbers of otherwise healthy people undergo testing to identify a relatively much smaller number of affected people. This usually involves incurring inconvenience and low levels (hopefully) of morbidity in large numbers of people to avert cancer death in a relatively few. Potential harm to many individuals must be weighed against the benefit to a few.

In any case, screening of large numbers of people involves, in aggregate, substantial resources. The incremental benefit in terms of mortality reduction achievable with these resources should be weighed against the incremental benefits achievable were these resources to be put into other health care strategies. This assessment of "opportunity costs" is also part of early detection research, since these costs can be a hidden "harm" in widespread use of relatively (or completely) ineffective screening strategies.

The cost of doing early detection clinical trials is high relative to most therapeutic trials, due to the large numbers of study subjects and time needed to reach a definitive endpoint: reduction in cancer specific mortality, the underlying goal of screening. Because the costs of doing the trials are substantial, albeit paling in comparison to widespread implementation of screening nationwide, they involve opportunity costs in research investment. Sometimes, these looming opportunity costs give pause to plans for clinical trials, or lead to ending the follow-up phase of a large trial as soon as a primary endpoint has been achieved. Much information can be lost with this strategy, because data on late consequences of screening and subsequent therapy are not collected. Therefore, it is important to develop prioritization criteria by which new research proposals and trials can be measured. (Hopefully, other research strategies would be measured against similar criteria as part of strategic planning.) A potential goal would be to develop a process for receiving and handling investigator initiated ideas for clinical trials. Recent examples for which explicit process would have been useful are proposals for a breast cancer screening trial for women age 40-41 and a colorectal cancer screening trial with colonoscopy. In addition, it may be useful to develop standard guidelines to direct trials in a cost-efficient manner.

New insights into heritable genetic mutations, which confer extremely high risk for some cancers, may allow us to focus screening efforts on particularly high-risk populations. At present, however, it appears that only a minority of cancers are attributable to inherited genetic abnormalities. It is therefore important to focus early detection research efforts upon both "high risk" and "average risk" people. Both were themes of this implementation group.

Other important themes discussed by the EDIG were research on simultaneous assessment of multiple early detection biomarkers for cancer using informatics tools, and extension of research results and benefits to minority and underserved populations.

PROGRAM REVIEW GROUPS RECOMMENDATIONS AND THE EARLY DETECTION IMPLEMENTATION GROUPS (EDIG) CHARGE

The EDIG was charged with coordinating the implementation of the recommendations from the cancer prevention and cancer control program review groups in the area of cancer screening and early detection.

The specific recommendations in the area of early detection research from the Cancer Prevention and the Cancer Control Program Review Groups, fell into five main categories:

1. Advisory Processes, Resources, and Prioritization
2. Screening Studies Design
3. Molecular early detection and exposure/risk markers
4. Behavioral and systems approaches to implementation of effective screening tests
5. Surveillance of the population for screening behavior

The EDIG felt that the last two of the five categories fell under the purview of the behavioral research/cancer control working group, and the cancer surveillance working group, and will not be addressed further in this document. Nevertheless, opportunities for collaboration with cancer control and behavioral scientists were discussed at some length. It was felt that the Early Detection Research Network concept proposed below would offer the opportunity to incorporate studies in basic behavior research (risk communication, risk perception, culturally sensitive communication, etc.) These collaborations should be encouraged and planned in each early detection study involving human subjects.

The EDIG formulated ten primary questions to cover the first three categories. The questions and brief summary of the EDIG response follow:

Question 1. What should be the criteria for starting clinical trials in cancer screening?

Relevant Discussion: The EDIG discussed the prioritization of randomized trials during the first three meetings, especially on March 10 (page 18 of the Minutes) and on May 11 (page 13-14 of the Minutes). The potential use of modeling before new randomized trials are initiated was suggested by a group member. A proposal was made for developing statistical methods and a statistical infrastructure so that the results of a trial could be predicted in order to avoid long-term

expensive trials that may not yield useful information. While there was agreement in the value of this approach, it was felt that it could take several years to develop a successful model.

Recommendation: The Group has considered the relevant scientific issues related to randomized trials (Phase III) and endorsed the following criteria for the prioritization of clinical trials in early detection:

- *Strength of Hypotheses* - This dimension measures the degree to which there is genuine uncertainty regarding the question(s) posed by the study. Hypotheses that are supported only by weak evidence would score poorly. Hypotheses that would score highly are those for which substantial evidence exists but is either not strong enough to be conclusive or is contradicted by other substantial evidence. "Proven" hypotheses would not be scored highly.

- *Impact on Public Health* - If outcome of the study were to be positive, how large would the effect on public health be? This would include considerations of disease burden, incidence, mortality, and morbidity as well as potential adverse consequences.

- *Impact on Current Scientific Paradigms* - this dimension measures the importance of the scientific question being asked or the potential impact should the result(s) of the study be positive. Impact includes moving the state-of-the- science forward, paradigm shifts, etc. If the proposal is a large program initiative, rather than a specific study or scientific question, what will be its impact on a field or critical area of science that would not be achieved without this assistance? Opportunities that would score highly are those that cover a range of needs in related or unified scientific, biological, or medical subject areas, rather than a single area in isolation. Areas in which progress is being made, albeit at a less than optimal pace, would be scored based on opportunities and needs to infuse new ideas or technologies in the field.

- *Strength of Study Design* - This dimension measures the degree to which the proposed study is anticipated to provide clear results. Its strength will be measured by important design factors such as randomization, blinding, good power, and good measurement tools, to assess both benefits and risks. Study feasibility and efficiency would also be a strong consideration. Other study strengths will include multiple endpoints, the efficiency of the design in addressing multiple questions and the use of substudies to answer other sub-hypotheses. There would also be attention given to whether the available technology is capable of giving a clear answer.

- *Portfolio Balance* - The existence of several ongoing studies of a similar nature of the same cancer sites and methodology (basic, clinical, population-based) should receive a negative rating. A study that fills an obvious gap -- should score highly. A balance between immediate versus long-term outcomes is also important.

- *Window of Opportunity* - How quickly is the technology, test, or strategy being taken up into community practice? In some cases, delay of definitive testing of a new technology would decrease the likelihood that the technology could ever be tested rigorously, since finding an "uncontaminated" control group would be difficult. It may be important under such circumstances to launch a trial before the medical community and public have made up their minds, right or wrong, to embrace the technology, even if the evidence for launching the trial falls short of ideal.

The trial must have 1) an explicit statement of the objectives of the screening trial; 2) a definition of the population to be screened, the time it will take to screen the population and the screening interval; 3) evaluation of preliminary research studies to assess the usefulness of the early detection test or marker and specific interventions in the population, and; 4) clear indication of endpoints (risks and benefits) to be assessed in the course of the trial. It may not always be possible to acquire sufficient empirical information that will allow decisions to be made. In these cases, the information can be modeled and computer simulations can be used to assess the assumptions of the decision model, if possible. Many approaches to modeling screening have been published, but the assumptions in many models are often not proven in empirical studies.

QUESTION 2. What should be the process for funding decisions on large investigator-initiated cancer screening trials?

Recommendation: Currently, NCI requires that all applications for more than $500,000 (total cost) per year, including those to conduct clinical trials, must be cleared by the appropriate Division for programmatic relevance prior to review either by the Division of Extramural Activities (DEA), NCI, or the Center for Scientific Review (CSR). It is proposed that at such times, when proposals are referred to Program, research proposals on new screening trials be initially reviewed by an ad hoc committee composed of NCI staff and outside members. Review will primarily consider whether the proposed research meets the criteria discussed above. DEA and/or the CSR Initial Review Groups will still have the responsibility to evaluate the scientific merits of the proposals.

QUESTION 3. What is the critical pathway to be followed in validating early detection molecular or secreted protein markers?

Relevant Discussion: The basic steps needed for biomarker research and development were listed as (1) the concept, (2) a new approach, (3) proof of principle, (4) revising or improving the approach, (5) pilot feasibility studies, (6) technology enablement, (7) prospective monitoring trials, and (8) a prospective screening trial. Several research designs for validating biomarkers were proposed (for details, please refer to May 11 Minutes). A discussion came up regarding several “biological foot prints” in biomarkers research - from basic science research to clinical trials, and a prioritized list of biomarkers that may be clinically useful and the types of specimens/patients to be compared for cross-validation. The Implementation Group felt that a stable infrastructure was needed to accomplish the goals of biomarker research including clinical validation. A proposal was made for establishing Centers for Molecular Diagnosis with emphasis on collaboration with industry and development of a national diagnostic trials group with national cohorts and biorepositories. It was further suggested that such a mechanism must be designed to operate generically in order to avoid creating a customized structure for each research issue. The idea of using a vertical approach in the development and validation of biomarkers was discussed (Minutes of April 6 and May 11 meetings)- from the laboratory through implementation, performance characteristic assessment, and initial application in defined populations.
In discussing this concept, the Group noted the need to translate research from the laboratory to clinical application.

Recommendation: Based on the discussion of the Group members and their enthusiasm for a "vertical approach" to biomarker research, Program now offers the concept of a Prevention Research Network for Studies in Biomarkers, Cancer Detection and Risk Assessment as the framework for this approach **(See Attachment E)**. The network approach has many advantages. It is flexible, provides opportunities for conducting biomarker research in an integrated, multidisciplinary environment, and facilitates collaboration among technology developers, basic scientists, clinicians, and other health professionals. Because the Network will include multiple institutions, it will have access to patients, including those with premalignant lesions. The network will establish a stable and reliable connection between basic laboratory research and clinical testing as well as industry, a need that was considered by the Implementation Group.

QUESTION 4. Can surrogate endpoints replace cause specific mortality in definitive screening trials? How would such endpoints be validated?

Relevant Discussion: The concept of intermediate endpoints or surrogate outcomes is based on the multi-stage progression model of cancer. In prevention, they are defined as cellular, biochemical, or molecular changes associated with a stage of carcinogenesis prior to the final endpoint of irreversible cancer. Before these markers can be used as endpoints for early cancer detection or as surrogate outcomes in chemoprevention trials, they must be validated for a well-defined clinical outcome. It was noted (page 15, May 11 meeting) that there are few validated surrogate outcomes at present. One possible surrogate, for instance, in colon cancer is large polyps. It was explained that knowing the natural history helps to validate surrogate endpoints, for which (validation) a sufficient number of subjects are needed.

At least three elements are necessary to use biomarkers as surrogate outcomes: 1) the proper definition of the risk factor and how to detect it, 2) the proper definition of the definitive outcome of interest and a description on how to assess it, and 3) knowledge of the strength and direction of the relationship between the surrogate outcome and the definitive outcome over a specified time interval. For a risk factor to be a useful surrogate outcome it must be strongly connected to the definitive outcome and the probability and direction of the relationship must be known. Surrogate outcomes do not shorten the first investigation because the relationship between the risk factor and the true outcome (cancer) must be known prior to using the risk factor as a surrogate outcome.

Recommendation: Several basic criteria must be met before the potential markers could serve as adequate surrogate endpoints either for risk estimation or clinical outcome: (1) Is the surrogate biomarker differentially expressed in normal and high-risk or tumor tissue? (2) At what stage of carcinogenesis does the marker appear? (3) Does the marker and its assay provide acceptable sensitivity, specificity and predictive value, and (4) How easily can the marker be measured? For biomarkers to serve as intermediate endpoints, it would be desirable to satisfy additional criteria (1) Can the marker be modulated by chemopreventive agents? and (2) Does modulation of the marker correlate with a subsequent decrease in cancer rate? These criteria can be tested and evaluated in animal models and in human tissue specimens. The proposed Prevention Research Network for Studies in Biomarkers, Early Detection and Risk Assessment concept will offer the opportunity to conduct studies to validate such markers in different institutions at the different stages of biomarker development concurrently **(See Attachment E**). Because of its importance, this question is still undergoing Program Review.

QUESTION 5. How can the Institute plan for long-range follow-up in screening trials to detect benefits and risks for screening and treatment?

Relevant Discussion: It was noted that it would be useful to have a stable funding mechanism for long-term projects. Whenever there are budget constraints, it becomes necessary to measure the costs and investment in follow-up versus costs of new projects. The Group reached a consensus on the need to make a commitment to finish trials. Another concern was brought up about the discontinuity in such decision making when a new review group examines the record at the 5-year renewal point.

It was proposed that criteria be established for trial continuation. One member proposed linking this to planning for a trial's progress review, stating that an independent review group should decide if the trial endpoints have been reached.

Recommendation: Develop a prioritization of resources and a stable funding mechanism for long-term projects.

QUESTION 6. How should the Institute prioritize resources for biorepositories attached to screening trials?

Relevant Discussion: One member informed the Group that the Cancer diagnosis Program, Division of Cancer Treatment and Diagnosis is setting up a review committee in the near future, one of whose objectives will be to develop prioritization and evaluation criteria. The EDIG felt this issue should therefore be deferred to that group.

Recommendation: It was noted that Question 6, like Question 5, involves a prioritization of resources. Work is in progress to set up a committee to deal with repository issues. It was suggested that the EDIG defer to the new committee for establishing objective criteria and developing a repository proposal. Such a proposal could then be brought back to this Committee's membership for information.

QUESTION 7. What is the appropriate informed consent for future tests on collected materials in biorepositories?

An EDIG member noted that this question is being addressed by other groups, such as the National Action Plan on Breast Cancer (NAPBC). Therefore, this question was not discussed at great length by the EDIG.

QUESTION 8. **What are the behavioral and systems approaches that can be studied to improve dissemination of screening practices that have been proven to decrease mortality? What special approaches are directed at minority population?**

Relevant Discussion: There was discussion of the need for an analysis of the barriers to early detection in underserved populations and highlighted the need for intervention research designed to find ways to increase the maintenance of cancer behavior that adheres to screening

recommendations. Where possible, collaborations with behavioral scientists should begin early in the evaluation of new screening technologies, so that basic behavioral ancillary studies can be going on in synchrony with technology assessment. It is likely that the Division of Cancer Control and Population Science will take the lead in this area, since the mission of the Division includes behavioral studies.

Recommendation: The following types of behavioral studies are important in the development, testing, and implementation of early detection tests and procedures:

- Recruitment strategies for under-represented populations in trials of promising new tests.
- Adherence behavior issues in the evaluation of efficacy of new tests.
- Studies of the acceptability of new tests given behavioral and cultural norms in particular population subgroups.
- Studies to discover barriers and incentives to screening of tests of proven efficacy and the development and evaluation of interventions to improve adherence to recommend practices.

QUESTION 9. Is the organizational structure of the early detection effort ideally configured for early phase (or preclinical) and clinical screening studies?

The proposed DCP reorganization structure was presented to the EDIG. The new structure is a matrix design of Programs covering the basic foundations of prevention research, and Branches covering disease-specific areas of research (i.e., the "product lines"). The DCP Director will be discussing his proposal with the NCI Director and his advisors in the near future. **(See Attachment F)**

QUESTION 10. What is the role of industry in development of biomarkers and tools for early detection? How can NCI work with industry?

Recommendation: Program plans to include industry as a formal partner within the proposed Prevention Research Network for Studies in Biomarkers, Early Detection and Risk Assessment concept, which will give commercial companies access to organized clinical studies **(See Attachment E).** There will be two major benefits for industry that should be emphasized, 1) industry will have access to patients for clinical studies of products that are developed by the private companies, and 2) industry will have access to new discoveries made by network investigators in academic research laboratories. Since industry will ultimately have the responsibility to produce and market the new tests, it should also be involved in the development and clinical testing.

NCI has established a task force to encourage industrial participation in the development of relevant technology in the detection and diagnosis of earlier cancer. In addition, the Institute has issued or will issue several initiatives (R21/33 and R43/44) to encourage participation by industry in cancer detection. There is ongoing discussion among the NCI leadership on directly involving industry in NCI supported projects. A major barrier in bringing industrial partners into

government supported projects relates to intellectual property restrictions. Also, a barrier exists for industrial participation for economic and practical reasons. Diagnostic testing is sometimes a low margin, low profit business and the market size may be relatively small under some circumstances. Practical limitations restrict what can be charged for a diagnostic test. As a result, many companies are backing away from high technology procedures. However, low or modest technology for
screening/early detection may appeal to industry, because testing may be applied to large at-risk populations. The industry also faces difficulty in coordinating its obligation to commercial partners (investors) and NCI. The proposed Network envisages a partnership between industry and academic centers in the early stages of development - discovery, assays, preclinical models, and clinical trial design. Currently, the system does not work effectively - products that should be developed are not, and products that should not be developed often are. This mis-development results from a lack of expertise at the early stages of innovation.

ATTACHMENT A

INTRODUCTION

Strategies in Early Detection Cancer Research

Early detection strategies in cancer involve the search for invasive cancers in at-risk populations at curable stages of disease, as well as the search for non-invasive abnormalities which have an elevated probability of progression to invasive cancer. Successful treatment of the latter category of abnormalities is a form of primary cancer prevention. Screening of asymptomatic people is the primary means to accomplish early detection, whether in the physician's office, community invitation programs, health maintenance organization (HMO) setting, or mass population-based organized programs in a national health system. The first two screening settings are often termed "opportunistic," and they are the most common settings in the United States. The third setting, organized population-based screening, is more characteristic of countries with national systems of universal health care delivery, such as the United Kingdom, Scandinavia, and other European countries.

An important theme common to all three screening/early detection settings is that large numbers of otherwise healthy people undergo testing to identify a relatively much smaller number of affected people. This usually involves incurring inconvenience and low levels (hopefully) of morbidity in large numbers of people to avert cancer death in a relatively few. Harm to the majority must be weighed against benefit to the minority. Of course, it is also an important goal in early detection research to determine if there is a benefit to the minority and to determine the magnitude of the benefit.

In any case, screening of large numbers of people involves, in aggregate, substantial resources. The incremental benefit in terms of mortality reduction achievable with these resources should be weighed against the incremental benefits achievable were these resources to be put into other health care strategies. This assessment of "opportunity costs" is also part of early detection research, since these costs can be a hidden "harm" in widespread use of relatively (or completely) ineffective screening strategies.

The cost of doing early detection clinical trials is high relative to most therapeutic trials, due to the large numbers of study subjects and time needed to reach definitive endpoints: reduction in cancer specific morality, the underlying goal of screening. Because the costs of doing the trials are substantial, albeit paling in comparison to widespread implementation of screening nationwide, they involve opportunity costs in research investment. Sometimes, these looming opportunity costs give pause to plans for clinical trials, or lead to ending the follow-up phase of a large trial as soon as a primary endpoint has been achieved. Much information can be lost with this strategy, because data on late consequences of screening and subsequent therapy are not collected. Therefore, it is important to develop prioritization criteria by which new research proposals and trials can be measured. Hopefully, other research strategies would be measured against the same criteria as part of strategic planning. This will be an additional theme for the committee to address. A potential goal would be to develop a process for receiving and handling investigator initiated ideas for clinical trials. Recent examples for which an explicit process could help are proposals for

a breast cancer screening trial for women age 40-41 and a colorectal cancer screening trial with colonoscopy. In addition, it may be useful to develop standard guidelines to direct trials in a cost-efficient manner.

New insights into heritable genetic mutations, which confer extremely high risk to some cancers, may allow us to focus screening efforts on particularly high-risk populations. At present, however, it appears that only a minority of cancers are attributable to high risk inherited genetic abnormalities. It is therefore important to focus early detection research efforts upon both "high risk" and "average risk" people. Both will be themes of this implementation committee. (missing partial line of text) and the Cancer Control Program Review Groups have been extracted from the full reports. The internal working group placed the specific recommendations into the following categories:

I. Advisory Processes, Resources, and Prioritization
II. Screening Studies
III. Molecular early detection and exposure/risk markers
IV. Behavioral and systems approaches to implementation of effective screening tests
V. Surveillance of the population for screening behavior

The internal committee felt that the last two of the five categories fell under the purview of the behavioral research/cancer control implementation working group, and these categories *will* not be addressed further in this document.

Each of the first three categories and the specific recommendations are discussed below. The results of discussion in the internal working group were only preliminary and served only as a starting point for deliberations by the full implementation group on early detection.

I. Advisory Processes, Resources, and Prioritization

A. Prioritization of Clinical Trials in Early Detection

Proposed primary (dominant) and secondary criteria for explicit prospective prioritization of large studies or projects are listed below. They are currently under discussion by the Extramural Division Directors Committee of the NCI. We would like input from the Early Detection Implementation Group on these criteria.

Primary Criteria

- *Contribution to Portfolio Balance* - the existence of several ongoing studies of a similar nature of the same cancer sites and methodology (basic, clinical, population-based) should receive a negative rating. A study that fills an obvious gap -- should score highly. A balance between immediate versus long-term outcomes is also important.

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- *Strength of Hypotheses Engendered in the Project* -This dimension measures the degree to which there is genuine uncertainty regarding the question(s) posed by the study. Hypotheses that are supported only by weak evidence would score poorly. Hypotheses that would score highly are those for which substantial evidence exists but is either not strong enough to be conclusive or is contradicted by other substantial evidence. "Proven" hypotheses would not be scored highly.

- *Strength of Study Designs/Tools That Can be Brought to Bear to Answer Hypotheses* –This dimension measures the degree to which the proposed study is anticipated to provide clear results. Its strength will be measured by important design factors such as randomization, blinding, good power, and good measurement tools, to assess effects. Other study strengths will include multiple endpoints, the efficiency of the design in addressing multiple questions and the use of substudies to answer other sub-hypotheses. There would also be attention given to whether the available technology is capable of giving a clear answer.

- *Importance of the Scientific Question Being Asked: or if the Project Generates Positive Results. Impact On Public Health or Potential Impact of Program Initiative* - This dimension will measure the importance of the scientific question being asked or the potential impact should the result(s) of the study be positive. Impact includes moving the state-of-the-science forward, paradigm shifts, potential to reduce disease burden, etc. If the proposal is a large program initiative rather than a specific study or scientific question, what will be its impact on a field or critical area of science that would not be achieved without this assistance? Opportunities that would score highly are those that cover a range of needs in related or unified scientific, biologica1, or medical subject areas, rather than a single area in isolation. Areas (missing text) in opportunities and needs to infuse new ideas or technologies in the field.

- *Incidencel Prevalence/Trends of the Disease(s) in The Population (Burden of Disease)* – This dimension measures the burden of the disease in the population along with trends in incidence and mortality. A large burden and increasing trend is scored highly.

Secondary Criteria

- Uniqueness of the Problem That is not Being Addressed by Other Research Institutions Within the National Cancer Program
- Congressional Interest
- Public Interest

B. Resources: National Databases of Available Screening Trials

The PDQ (Physicians Data Query) is a comprehensive cancer database that contains peer-reviewed statements on treatment, supportive care, prevention, and screening, as well as anti-cancer drugs; a registry of over 1,600 open and 8,000 closed clinical trials from around the

world; and directories of physicians and organizations that provide cancer care, including more than 4,000 FDA approved mammography screening facilities. All NCI sponsored screening and prevention trials are currently part of this database. PDQ was developed and is maintained by the International Cancer Information Center of the U.S. National Cancer Institute (NCI) with the help of cancer experts from across the U.S. All PDQ statements are peer-reviewed and updated every one to three months by five editorial boards of oncology specialists in adult treatment, pediatric treatment, supportive care, screening and prevention, and anticancer drugs.

The PDQ Committee is in the process of forming a panel of experts to update the PDQ database system. The committee will consist of NIH physicians and experts, outside physicians, and community members interested in making the PDQ a more user friendly tool. In addition, input from the Early Detection Implementation Group would be welcome as part of the updating process. If the group wishes, formal presentation by PDQ staff could be arranged.

C. Biorepositories and Tissue Banks

The goals of improving early detection and developing novel molecular markers for cancer which are easily detectable, specific, sensitive and have high predictive value, can best be achieved via systematic evaluation of biomarkers in tissues, sera and other biological fluids collected prospectively from populations at various levels of risk for cancer development. While recent advances in molecular biology allow for measurements of genetic changes that occur during the process of cancer development and progression, the validation of molecular markers requires a complex and lengthy series of prospective evaluation studies. Numerous tumor banks have been established. Nevertheless, specimens in some banks were collected and stored less than optimally or were processed according to a very specific protocol so that such banked specimens, especially tissues, could not be used for a wide range of research. Furthermore many tissue banks contain tissues which could not be linked to patients' prior historical information, to tumor stage and grade and/or to patients' therapies or clinical outcome. In addition, many of the existing biorepositories do not collect and bank samples of uninvolved or histologically normal tissues which are necessary in characterizing "field effects" on the initiation and progression of some epithelial-derived tumors.

Development of a biorepository to serve an early detection program should be carefully planned with attention paid to protocols for sample collection, prevention and storage to assure uniformity of quality of the specimens. Several different procedures may be desired, especially for preservation, so that specimens will be useful for a variety of studies. If specimens are to be collected from participants in screening programs, plans should be made for serial collections. If feasible, an attempt should be made to obtain matched tissues, such as blood and urine in (missing text) addition for each person who serves as a source of specimens.

Existing biorepositories vary in the completeness of the associated clinical and demographic data. Many of the collections have built-in biases that prevent generalization of results from studies of the specimens. Quality control of specimen characterization and preparation varies significantly and users of a resource frequently are not aware of potential problems they may encounter in using

the specimens. All of these issues must be considered in the design of any new repository for early detection research.

At present the existing biorepositories are being reviewed by a panel of NCI extramural scientists and criteria are being developed to measure their success and failure in serving the stated purpose of individual biorepository and their contributions to cancer diagnosis research. The existing biorepositories have limited use in early cancer detection research and therefore the establishment of a biorepository based on uniform protocols and stringent quality controls is needed to serve the extramural scientific community.

D. Ethical Issues and Informed Consent

There is a growing interest and concern in the ethical and legal issues regarding the use of stored specimens. This has primarily occurred due to the increase in the availability of electronic transfer, matching of patient identity with research results, and compilation of data and patient records, and advances in molecular biology and research questions.

To discuss the topic of tissue banking, it is important to understand that there are two ways that specimens are collected and utilized by researcher. One type is a specimen collected and stored from a patient having a routine surgical procedure. The other is a specimen stored from patients participating in clinical research studies. Specimens from both categories have been utilized for medical research for decades. The reason for the relatively recent concern about storage and utilization of specimens is two-fold. One is that patients contributing specimens from routine surgical procedures may not be aware that their specimens may be stored and utilized for future research. This is a concern not only because of the development of electronic records but also because of the potential for discrimination by insurers or employers due to identification of a genetic risk status. The second concern is for the specimen-contributing research participant. Informed consent is obtained for the storage and research use of the specimens, but dependent upon the level of identity attached to each specimen, similar concerns exist regarding disclosure and genetic discrimination.

The National Action Plan on Breast Cancer (NAPBC) has contributed significantly to the discussion to improve the quality and effectiveness of the informed consent process for tissue banking from routine clinical surgical procedures. Their extensive work in this area has benefited the coalescence of issues in both the research and non-research setting of specimen banking.

NAPBC had three goals when undertaking this project:

- To elevate the role of the tissue donor to that of an active partner
- To develop a user-friendly consent process that is meaningful to both patients and researchers.
- To develop a set of standards for specimen use upon which researchers could rely.

ATTACHMENT A

The NAPBC and others have identified the following concerns relating to tissue banking and testing in the research community. These issues continue to generate discussion:

- level of anonymization of the samples
- disclosure of research results
- commercial use of specimens
- tissue bank concerns including the oversight board and duties of the tissue trustee.

The model consent form developed by the NAPBC has attempted to address each of these issues. It was developed by using information and ideas from existing IRB approved forms, discussions with representatives of the breast cancer clinical and research communities, and 27 focus groups that drew from racial/ethnic and socio economic groups of adults within and outside the health care community.

In addition to developing a model consent, the NAPBC has provided two other documents: an information sheet about the use of human tissue specimens in research that could serve to answer the types of questions likely to arise from patients and their families and a set of principles designed to assist IRBs in deliberations on tissue banking issues. It is anticipated that these documents will be in final form in the spring.

The National Bioethics Advisory Commission (NBAC) has taken up issues related to tissue banking as a current topic of study and review. They anticipate submitting a report on the topic of tissue banking by early 1998.

II. Screening Studies

A. Ongoing Screening Trials in the General Population

Two DCP-sponsored prospective randomized screening trials are ongoing. The first is the Prostate, Lung, Colorectal, and Ovarian (PLCO) study. Currently conducted at 10 screening centers in the country, nearly 100,000 of a planned 148,000 study subjects have been randomized to the control arm (usual medical care) or to the screened arm (serum prostate-specific antigen, digital rectal exam, in men; serum CA125, transvaginal ultrasound, ovarian palpation in women; chest x-ray, 60 cm flexible sigmoidoscopy in both genders). Primary study endpoints are cause-specific mortality. Together, the PLCO cancers account for about half of cancer deaths in America. The study has been formally endorsed by the American Cancer Society, and partial funding for minority participant accrual is provided by collaboration with the Centers for Disease Control and Prevention (CDC). The prostate screening portion of the trial is part of an international collaboration to combine data from a number of prostate cancer screening studies ongoing worldwide (the International Prostate Screening Trials Evaluation Group.

ATTACHMENT A

The second large ongoing screening trial is the ALTS (*ASCUS/LSIL) Triage Study for cervical cancer. Together, ASCUS and LSIL account for an estimated 3 million cases of cervical abnormalities detected per year on Pap screening in the United States. The natural history of these low-grade abnormalities is unknown, but it is widely recognized that there is substantial over treatment (and some attendant morbidity) of these lesions to prevent the progression of the minority of legions to higher grade or invasive diseases. The ALTS study therefore compares treatment of all such lesions to careful follow-up and treatment of lesions that do not spontaneously regress. In the case of ASCUS, a third comparative study arm is immediate treatment only of lesions than show DNA-based evidence of infection by the oncogenic human papilloma viruses (HPV). Conducted at four screening centers in the U.S., about 2,000 of the planned 6,000 women have been entered onto the study.*

B. Potential Studies

Investigator-initiated proposals have come from the extramural community to perform randomized screening trials addressing two important issues: (l) one-time colonoscopy to screen for colorectal cancer, and (2) initiation of screening mammography at age 40-4l vs. at age 50. Both studies would require substantial resources. Perhaps the implementation committee would like to use such proposals as a focus for practical discussions of a prioritization process.

The Early Detection and Biometry branches are collaborating on the development of decision theoretic methods for guiding the selection of screening technologies, especially biomarkers**,** for randomized clinical trials (RCT) evaluation. They are also collaborating on the development of experimental designs suitable for individual and multi-marker RCTs. The initial applications of these efforts are planned for biomarker evaluations within PLCO trial.

C. Collaboration and Communication Outside NCI

The Early Detection Branch initiated in 1997 regular meetings with the Food and Drug Administration (FDA), Devices Division to trade information and develop strategies for evaluating technologies for early detection, especially in the general population. This effort was built upon a more informal relationship, which has existed for at least the last seven years. FDA has recently intensified this activity and elevated it to a higher organizational level within FDA. Also, the Agency for Health Care Policy and Research (AHCPR) has recently been invited to participate in these regular meetings. Representatives of AHCPR are enthusiastic about the collaboration.

* ASCUS = Atypical Squamous Cells of Unknown Significance. LSIL = Low-grade Squamous Intraepithelial Lesion.

ATTACHMENT A

III. Molecular Early Detection and Exposure/Risk Markers

Three potential applications of molecular markers were identified in the report of the Cancer Prevention Program Review Group:

(1) Early Detection

(2) Surrogate Markers or Intermediate Endpoints
(3) Identification of High Risk Populations or Risk Assessment

Molecular genetic alterations in various types of benign and malignant tumors offer the opportunity to detect specific tumor-related changes in DNA. This approach has the potential to identify specific tests useful for early detection of cancers. For instance, molecular probes could be used to detect altered DNA shed into the feces (colo-rectal cancer and pancreatic cancer), into sputum (lung cancer), into pancreatic juice (pancreas), and in exfoliated cells in bladder washings (bladder cancer) from neoplasms. In addition, correlation of molecular alterations with the demographic data, risk factors, environmental exposure, family history, dietary history, and follow-up events may provide important information on the biology of tumorigenesis. In 1990, the Early Detection Branch initiated several studies under the Early Detection Research Network (EDRN) to characterize preneoplastic stages of epithelial tumors. Several biomarkers, such as crB-2 and crbB-3 in prostate and telomerase in lung cancer, were characterized for the first time as potential early detection biomarkers.

Molecular markers could also serve as surrogate or intermediate endpoints in chemoprevention trials, and could improve surgical and medical management as well as utilization of medical care resources by providing better estimates of prognosis than those based on clinical and pathological staging. Also, surrogate markers, which occur in the early pathogenic pathway, could reduce the cost of and shorten the duration of primary and secondary cancer prevention trials, where the endpoint would otherwise have to be cancer incidence or mortality. An expert panel convened by the NCI included crbB-3 (resulting from the studies conducted under EDRN) in a panel of potential surrogate biomarkers worthy of further development in pilot chemoprevention studies in prostate cancer.

Risk-assessment has greatly benefited from the discovery of genotypic and phenotypic markers that are associated with increased risk of cancer. This is well documented for many inherited cancers, especially breast and colorectal cancer. For instance, the adenomatous polyposis syndrome and hereditary nonpolyposis colorectal cancer (HNPCC), also called Lynch syndrome, are two examples of autosomal dominant inherited disorders. Hypermutable microsatellite sequences and (missing text) disease process observed in HNPCC and perhaps other cancers, as well as for early detection. It is also known that the occurrence of colorectal cancer in first degree relatives of patients with colorectal cancer is 3-4 times the general population without a recognizable syndrome. Molecular technology could significantly advance our ability to assess inherited and environmental/lifestyle risk factors. Recently, a program-sponsored study assessed the molecular damage (loss of heterozygosity in chromosomes 3p and 9p) of lung tissue in response to smoking and concluded that the former smokers had persistent evidence of genetic damage for many years after smoking cessation.

ATTACHMENT A

The Early Detection Branch has ongoing activities in many areas of molecular markers, especially for identifying high-risk populations. The program has coordinated and facilitated the development of the "Bethesda Guidelines" for the molecular diagnosis of HNPCC and International Guidelines for the nomenclature for microsatellite instability (MSI), and assay and quality control of MSI assessment. These guidelines have been endorsed by the International Collaborative Group on HNPCC (ICG-HNPCC) whose members are drawn from more than 50 countries.

Future development of new generations of molecular markers will be guided by the following principles: (1) The markers should be associated with the development of cancer; (2) Alterations in the markers, such as mutations, should occur early in the development of the cancer; (3) These alterations/mutations should be clonally preserved; (4) Assays for these markers should be minimally invasive, simple, cost-effective and reproducible; and (5) the performance characteristics, such as sensitivity, specificity and positive predictive value of these markers should be high. Epithelial cell carcinomas, for example, offer opportunities for early detection because; i) the transition time from precancerous lesion to malignancy is relatively long, sometimes 10 to 15 years, thereby providing a window of opportunity for detection; ii) cells are shed into biologic fluids allowing DNA-based molecular detection and; iii) protein products may be released in cells or body fluids in the early phase of tumor progression. Detection of molecular markers in biologic fluids is likely to be acceptable to patients and physicians, is less invasive and is practical. Therefore, the detection of molecular markers shed in biological fluids is being given high priority.

In the short term our focus would be on those molecular markers which have been proven biologically relevant and have high levels of reproducibility and accuracy. Markers such as p53 mutations, ras mutations, proliferation markers, telomerase, and microsatellite instability (MSI), for example, must move beyond their current status as interesting laboratory correlation and observations in small numbers of samples to establishment of the range of results in various at risk groups in preparation for population-based validation studies. It will be necessary to organize the burgeoning number of candidate markers and to categorize the relevant markers for each tumor site (e.g., a range of genetic markers, differentiation markers, or other markers). Additionally, new generations of gene expression markers are likely to be discovered from the NCI Cancer Genome Anatomy Projects (CGAP). Program will continue to interact and collaborate with CGAP investigators on potential early detection markers. It should be, however, noted that prior to introduction of molecular markers into population screening, they should be validated as screening tests, if possible, by evaluation of the test's efficacy in reducing mortality and morbidity. The ultimate evaluation of the efficacy of screening tests remains the controlled clinical trial.

In the long term, the major research initiatives addressing the development of molecular markers will need to combine basic science discoveries concerning early events in cancer with new detection technologies. Potentially useful detection technologies could then be evaluated using clinically well defined normal tissue (histologically normal), preneoplastic and neoplastic lesions, collected with ancillary demographic and epidemiological data. These studies need to focus on the identification, characterization, and validation of molecular markers in high-risk individuals and

accompanying demographic and epidemiologic data that could lead to the successful development of early detection markers for high-risk subgroups drawn from the population. The translational strategies needed to achieve these goals may fall into several critical areas: 1) tissue acquisition, 2) resource development, 3) technology development, and 4) major research initiatives. An additional important resource necessary for developing and validating molecular markers may be model (missing text) epithelial cell types, 2) whole organ culture systems which mimic the structure, cellular interaction, and growth of whole organs, and 3) animal models where the development of epithelial tumors is frequent and can be followed through various stages.

The linkage of early detection research to ongoing screening trials or prevention studies could accelerate the validation of molecular markers. Examples are planned and ongoing ancillary substudies in the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial; the Breast Cancer Prevention Trial (BCPT); and the Prostate Cancer Prevention Trial (PCPT). Both molecular markers and interventions may be evaluated in the same study or trial, potential savings in time and resources. The program will also initiate collaborations with various programs in NCI and other federal agencies, such as Food and Drug Administration and Agency for Health Care Policy and Research. The program will seek joint initiatives with industry, using the CRADA mechanism, to accelerate the development of new generations of molecular markers for early cancer detection.

RECOMMENDATIONS FROM THE PREVENTION REVIEW GROUP ON EARLY DETECTION

Advisory Processes and Resources

- Develop and expand biorepositories and provide new access with appropriate consent for testing of molecular detection strategies.

Biomarkers and Intermediate Endpoints

- Intermediate biomarkers for exposure and biological effects applicable in prevention studies, and validate use in parallel studies in animals and people.

Early Detection and Diagnosis

- Develop new molecular markers for early detection.
- Develop high-throughput test for implementation of promising molecular diagnostic approaches in clinical and population-based trials.

Advisory Processes and Resources

- Develop databases of a) clinical cancer prevention trials (objectives, target populations, methodologies, successes, failures); b) tissue resources associated with clinical trials accessible to research community through peer-reviewed mechanisms.

Collaboration and Communication Outside NCI

- Work with FDA on matters affecting prevention (e.g. validation of biomarkers).

Clinical Trials

- Comprehensive trials in high-risk populations for validation and potential integration of novel prevention and detection strategies.
- Do RCTs in prevention and establish a process for deciding how, when, with what, and in whom to do them.

Tobacco (DCCPS)

- Priority on preventing tobacco use in the young, encouragement of cessation in heavy smokers and women, increasing use of recommended early detection tests, and improvement of behavioral outcomes of genetic testing for cancer susceptibility.

CANCER CONTROL REVIEW GROUP RECOMMENDATIONS

- Ensure that the new Deputy Director coordinates research on cancer screening throughout NCI.
- Develop mechanisms to assist decisionmaking regarding the initiation of randomized clinical trials of screening technologies.

Early Detection Implementation Meeting
Building 31, C-Wing, Conference Room 8
March 10, 1998, 8:30am - 4:00pm
Bethesda, Maryland

AGENDA

		Time
1. Introduction	Dr. Barnett Kramer, Chair Deputy Director, Division of Cancer Prevention, NC	8:30 - 8:40
	Dr. Bernard Levin, Co-Chair Vice President for Cancer Prevention, MD Anderson	8:40 - 8:50
2. Orientation on Committee Operations	Ms. Sue Feldman Office of Advisory Activities	8:50 - 9:05
3. PLCO Screening Trial & Attached Biorepositories	Dr. John Gohagan Chief, Early Detection Branch	9:05 - 9:35
	Open Discussion	
4. Informed Consent	Dr. Leslie Ford Associate Director, Early Detection & Community Oncology Program	9:35 - 10:05
	Open Discussion	
5. NC Supported Biorepositories	Dr. Roger Aamodt Chief of Resources Development Branch	10:05 - 10:35
	Open Discussion	
6. Biomarker Initiatives	Dr. Sudhir Srivastava Program Director, Early Detection Branch	10:35 - 11:05
	Open Discussion	
7. PDQ Initiative and Protocol Listing	Dr. Anne Thurn Chief, International Cancer Research Data Bank Branch	11:05 - 11:35
	Open Discussion	
8. General Discussion	All Participants	11:35 - 12:05
9. Lunch		12:05 - 1:30
10. Early Detection Imaging Progress Review Committee	Dr. Dan Sullivan	1:30 - 1:45
11. General Discussion/Future Plans	All Participants	1:45 - 4:00

April 6, 1998
BLDG. 31 Conference Room 10 C Wing
31 Center Drive
Bethesda, MD 20892

TIME: 8:00 a.m. to 4:00 p.m.

AGENDA

				Time
1.	Introduction	Chair	Barnett Kramer, MD Deputy Director, Division of Cancer Prevention, NCI	8:00 - 8:10
		Co-Chair	Bernard Levin, MD Vice President for Cancer Prevention MD Anderson	8:10 - 8:20
2.	DCCPS Activities in Behavioral/Systems Approaches, Cost & Cost Effectiveness		Bob Hiatt, MD, Deputy Director Division of Cancer Control & Population Sciences, NCI	8:20 - 8:50
			Discussion	8:50 - 9:00
3.	Accessing Communities, and Facilitating and Disseminating Early Detection Tests of Proven Efficacy		Paul Van Nevel, Associate Director for Cancer Communications/ Nelvis Castro, Chief, Health Promotions Branch	9:00 - 9:30
			Discussion	9:30 - 9:40
4.	Cancer Screening Activities		Lisa Richardson, MS, MPH Kevin Brady, MPH Division of Cancer Prevention and Control, CDC	9:40 - 10:10
			Discussion	10:10-10:20
5.	General Discussion			10:20-11:20
6.	Lunch			11:20 - 12:20
7.	General Discussion			12:20 - 4:00

EARLY DETECTION IMPLEMENTATION MEETING

May 11, 1998

Executive Plaza North, 6130 Executive Blvd.
Rockville, MD 20852

TIME 8:30 a.m. to 4:00 p.m.

AGENDA

			Time
1. Introduction	Chair	Barnett Kramer, MD Deputy Director, Division of Cancer Prevention, NCI	8:30 - 8:40
	Co-Chair	Bernard Levin, MD Vice President for Cancer Prevention MD Anderson	
2. Strategies On How To Develop a Biomarker		David Sidransky, MD	8:40 - 9:10
		Discussion	9:10 - 9:30
		Sheila Taube, PhD	9:30 - 10:00
		Discussion	10:00 - 10:10
3. Family Registeries/Cancer		Susan Nayfield, MD	10:10 -10:40
		Discussion	10:40 -10:50
5. Cancer Genome Anatomy Project (CGAP)		Robert Strausberg, MD	10:50 - 11:20
		Discussion	11:20 - 11:30
6. Lunch			11:30 -12:30
7. General Discussion			12:30- 4:00

EARLY DETECTION IMPLEMENTATION MEETING

August 13-14, 1998

Building 31, C Wing, Conference Room 6

Time 5:30 a.m. to 4:00 p.m.

August 13, 1995	**AGENDA**		**Time**
1. Introduction	Chair	Barnett Kramer, MD Deputy Director, Division of Cancer Prevention, NCI	8:30 - 8:35
2. Some Statistical Issues In Early Detection of Cancer		Stuart Baker, ScD Discussion	8:35 - 9:05 9:05 - 9:15
3. Microsimulation Cost-Effectiveness Analyses in Screening (MISCAN)		Martin Brown, PhD Discussion	9:15 - 9:45 9:45 - 9:55
4. Break			9:55 - 10:10
5. Cancer Genetics		Dr. James Hanson Discussion	10:10 -10:40 10:40 -10:50
6. General Discussion: Implementation Strategies			10:10 - 11:30
7. Lunch			11:30 - 12:30
8. General Discussion: Implementation Strategies (continued)			12:30 - 4:00

August 14, 1995	**AGENDA**		**Time**
1. Introduction	Co-Chair	Bernard Levin, MD Vice President for Cancer Prevention, MD Anderson	8:30 - 8:35
	Chair	Barnett Kramer, MD Deputy Director, Division of Cancer Prevention, NCI	
2. General Discussion: Proposal for an Early Detection Network			8:35 -10:00
3. Break			10:00 -10:15
4. General Discussion (continued)			10:15 - 11:30
5. Lunch			11:30 - 12:30
6. General Discussion (continued)			12:30 - 4:00

National Cancer Institute (NCI)/Division of Cancer Prevention (DCP)

EARLY DETECTION IMPLEMENTATION COMMITTEE MEETING
August 13-14, 1998

MEETING REPORT

Introduction and Welcome on August 13

Dr. Barnett Kramer welcomed the members and speakers to the fourth meeting of the Early Detection Implementation Committee. He explained that Dr. Bernard Levin, who co-chairs the Committee, will be present on August 14 and will lead the discussion of an early detection consortium, which has been rescheduled for that day. Dr. Kramer suggested that if the Committee is comfortable with the level of achievement over the next 2 days, it might be possible to complete any subsequent business through teleconferences and electronic communications rather than schedule another meeting.

The meeting packet containing a draft agenda, the Committee's draft response to the 10 questions about implementation, the proposal to establish a prevention research network, and the draft May committee meeting report was distributed to committee members in advance of the August meeting.

Cancer Genetics - Dr. James Hanson

Dr. Kramer reminded other committee members that at an earlier meeting they had wondered how an early detection consortium would link to the cancer genetics network (CGN) consortium of the Division of Cancer Control and Population Sciences (DCCPS). He introduced Dr. Hanson, a medical geneticist, to tell the Committee about the Network and the Consortium. Dr. Hanson defined the CGN as an infrastructure for collaborative research on the genetic basis of human cancer susceptibility. Several individuals from DCP are working with DCCPS on this project, including Dr. Robert Hiatt and Dr. Susan Nayfield. The aim is to foster the understanding of genetic risk factors and their interactions with each other and the environment and to ascertain how to apply such knowledge to public health.

Previously, NCI focused on gene discovery in high-penetrance families. The CGN will include high-risk individuals and population subgroups. The goals of the network are to recruit a large number of participants through the collaborating groups, foster collaborative research, explore ways to integrate the knowledge gained into medical practice, and identify ways to address psychosocial, ethical, and legal issues within the human cancer genetics field (working in parallel with the National Human Genome Research Institute [NHGRI] on such issues).

The network structure involves multiple centers serviced by an informatics group. The informatics & information technology group includes three sites, Yale University, Massachusetts General Hospital, and the University of California at Irvine (UCI). UCI will handle the central database and extract files (e.g., for genetic analysis, statistics, and identification of eligible participants). Massachusetts General can help on statistics and research design. Yale will assist with the databases for special studies.

Each center is expected to carry out education and outreach, recruit families for its resource pool, implement protocols, and conduct genetic testing and counseling in a research setting. The central database will collect core data from the centers, correlate registration follow-up, and provide general information for planning.

The members and users of the CGN will need to define what high risk means within the context of the Network. Once core data are obtained on enrollees, there will be annual follow-up. Participants will receive periodic updates and invitations to participate in research projects. Investigators will need to consult with the CGN while designing their studies and conducting their research. They will compete in the usual peer-reviewed arenas for funding, then work through the centers to recruit for their studies. The informatics Center will be available to them to assist in data analysis.

Several committees will have key roles in the administration of the Consortium: (1) The CGN Steering Committee (two-thirds principal investigators [PIs] and one-third NCI representatives, external scientists, an ethicist, and a consumer representative), (2) the Informatics Steering Committee (the informatics PIs, a specialist in computer security policy, and a representative of the centers), (3) an independent Advisory Committee to carry out scientific review of research proposals (NCI welcomes suggestions for individuals to serve on this committee), and (4) the NIH CGN committee, an NIH-based management group that will be set up to evaluate the Networks progress (Dr. Barbara Rimer, the DCCPS Director, is leading the effort to establish this committee.)

The following components lead to the CGN research agenda translation of genetics into medical practice (establishment of genetic public health policies, evaluation of efficacy of specific interventions, the benefits of screening for genetic risk, genetic influence on the response to treatments, and a genotype-based prevention and therapeutics approach), public health issues concerning genetic susceptibility (including ethical and psychosocial issues, informed decision making for genetic testing, effective and responsible communications, and a healthcare infrastructure that can deliver genetic testing services), and the genetics of cancer susceptibility (prevalence of mutations in different populations, penetrance, variability in phenotypes, risks of lower penetrance genes, gene-gene interactions, and gene-environment interactions).

Other NCI-supported projects with which the CGN will interact include the Cancer Genetics Study Consortium (developed in 1994, about 15 members, supported by four NIIH Institutes), the Family Registries (e.g., on breast and colon cancer), and genetic epidemiologic consortia (e.g., on prostate cancer). Dr. Hanson provided the following comparison of the family registries and the CGN.[1]

[1] The diagrams that Dr. Hanson used to illustrate his presentation were developed by Dr. Nayfield. A CGN factsheet was distributed.

Family registries	High-penetrance families	Lower volume, higher data intensity	Detailed data collection, DNA samples	Broad informed consent
CGN	high-risk individuals[2]	higher volume, lower data intensity	probably no biologic samples collected	staged informed consent

Discussion of Dr. Hanson's presentation

Dr. Hanson was asked if he could provide copies of the DCCPS slides that illustrated his presentation on the CGN. He said he would do so. Another query concerned storage, linkage, and availability of the biologic specimens to be collected. Dr. Hanson observed that the policy would probably evolve within the context of the types of research proposals that ask to draw on the resources of the collection. The question of whether the data include patient identifiers complicates public policy. Dr. Sheila Taube mentioned that her program at NCI has a branch that tracks specimens at various institutions. It is useful to know where everything is. Dr. Hanson indicated that he welcomes collaboration. The default position is that the specimens remain at the centers that collected them.

The CGN centers are being funded through cooperative agreements. Dr. David Longfellow asked about the conditions to be met in linking individual investigators with the centers. Dr. Hanson said that the protocol for this is being worked on. It will include encouraging investigators to consult with the operations center and database staff. Probably, both the Steering Committee and Advisory Committee will be involved in reviewing research proposals and setting priorities for the use of resources. CGN support for a proposal may be useful when it is submitted for NIH-R01 or other funding. Dr. Hanson indicated that NCI is aware of the need to prevent this from becoming a cumbersome process. The draft protocol for research applications and review should be ready by next fall or winter.

Dr. Longfellow suggested that, to keep up momentum, each proposal be judged when submitted rather than in batch processing. He also said that it might not be necessary to develop a set of priorities for resource utilization in advance. Dr. Hanson noted that one goal should be a balance of research activities. Dr. Taube observed that, in her experience, it takes time to get the decision making process worked out. Dr. Hanson explained that once the Advisory Committee is established, general guidance will be prepared first before the development of specific and explicit prioritization criteria.

Dr. Hanson also reported that a website is planned providing access to the extramural community. The CGN is seeking broad community input. From previous experience with a birth defects registry, he is aware that it can take a long time to get a system established. Dr. Taube suggested that good publicity could accelerate the process.

[2] Dr. Hanson later indicated that the level of risk is defined by self-perception.

Dr. Kramer asked about any plans to link with industry and managed care organizations. He noted that industry could provide an ideal laboratory for considering environmental versus genetic risk. Dr. Hiatt mentioned having some experience working with managed care organizations. Dr. Hanson said that no plans had yet been developed for working with these sectors. However, CGN staff are aware that managed care is a major force in some areas where the CGN centers are sited. Dr. Kramer urged early planning for such linkages. He also inquired about linking the CGN to Dr. Martin Brown's consortium and to a health maintenance organization (HMO) network, particularly as industry often uses HMOs. Dr. Hanson replied that he does see the potential for interactions and would seek guidance from other NCI staff who have more experience in this arena.

Dr. Kramer next inquired about specific criteria for success. Dr. Hanson agreed that a method to measure progress is needed. He suggested obtaining input from Dr. Richard Klausner, the NCI Director, and from external sources. Dr. Hiatt said that different criteria may be needed for different phases of the project.

Dr. Sudhir Srivastava asked how basic science proposals would fit in with the CGN. Dr. Hanson observed that two likely areas for interfacing with specimen collection are biomarkers and gene mechanisms. Investigators will be advised to confer with potential collaborators at the centers and with the Advisory Committee in preparing their R01 submissions and their CGN applications.

When Dr. Sally Vernon inquired about tracking the reasons individuals might refuse to enroll in the CGN registry, Dr. Hanson said that he is not aware of any plans to analyze refusals although there are plans to encourage registration. Dr. Vernon then commented that examining recruitment problems may become important if registration lags among special populations for example, Native Americans.

Dr. Brown wondered whether the power analysis shows that the goals can be achieved for low penetrance genes. Dr. Hanson said that examinations of low penetrance genes need to be postponed until sufficient numbers have been recruited by the CGN.

Dr. Kramer noted that one opportunity for collaborative research would be a before-and-after study of individuals who decide on prophylactic surgery because of concerns about the level of cancer risk in their families. Such research would focus particularly on their biomarkers and any chemoprevention.

Dr. Richard Hayes asked about obtaining biospecimens on everyone at the time of recruitment; however, during the planning process a decision was made not to do this, and no funds have been budgeted for such a collection.

The discussion ended with an invitation from Dr. Hanson to contact him with any additional comments and suggestions.

Microsimulation Cost-Effectiveness Analyses in Screening (MISCAN) - Martin Brown

Dr. Brown initiated his presentation by citing four reasons for developing models: (1) surveillance work (e.g., to detect if screening affects mortality or morbidity), (2) extending and elaborating on the results of randomized screening trials (e.g., effectiveness of annual versus biennial mammography), (3) evaluation of screening policies and programs implemented without trial data (e.g., the congressional vote requiring Medicare coverage of colorectal cancer (CRC) screening), and (4) assistance in selecting the best design for a screening trial.

Dr. Brown mentioned several other screening models that the Applied Research Branch is working on besides the MISCAN model, which he is applying to CRC screening. Dr. Nicole Urban is a member of a peer group that supports model studies. Dr. David Eddy presented the first model in 1980; it was later reprogrammed by NCI. The work on screening models evolved when understanding the effects of screening turned out to be the weakest point in a generic simulation model of cancer interventions.

MISCAN is a class of models developed through U.S.-Netherlands collaboration. The first models in the class were for breast and cervical cancer. The same group developed a model for prostate cancer in parallel with the European screening trials for prostate-specific antigen (PSA). The literature on MISCAN includes articles published in the *Journal of the National Cancer Institute.* Dr. Brown and colleagues chose to apply MISCAN to CRC screening in anticipation of an U.S. CRC screening trial. Dr. Brown said that a few previous CRC models exist, and two models were described recently in *Health Economics.*

The reasons for developing the MISCAN CRC model include that the other models have been difficult to validate, this model is better for comparing with actual clinical trials data, and only the microsimulation models can include a wide range of individual characteristics. The model deals with a hypothetical population in which the individuals have been randomly assigned unique life experiences. Five types of data are needed: epidemiologic data (e.g., birth and death dates, survival, cancer incidence, and polyp incidence and prevalence), information on disease processes (e.g., the natural history of adenomas before they become cancerous), the operating characteristics of the screening test, the screening program (e.g., values, intervals for screening, follow-up procedures, compliance), and economic parameters for cost-effectiveness analyses (e.g., the cost of follow-up and the cost of treatment at different stages).

The MISCAN CRC project was funded as a contract. It has an informal advisory committee. In determining what the model should look like, decisions had to be made about which life experiences to include. A literature review and access to some unpublished information were used to help determine whether to specify the regions of the colon in which polyps are located, their characteristic size and histology, and race and gender within the population.

The next step was to make initial estimates of all relevant parameters for example, the percentage of polyps that would become cancerous. Autopsy and colonoscopy data were examined in making these estimates. To do the financial manipulations, a figure was needed for the cost of a colonoscopy. The data available showed a threefold range. It was also necessary to distinguish cost from charge. Another parameter was the compliance within the community in obtaining a

colonoscopy after a positive fecal occult blood test. Unfortunately, such compliance is typically low.

The third step in developing the model involved running the model with plausible data to conduct a sensitivity analysis. One question is whether some parameters matter a lot more than others do. Validation is the final step that is, using new data and examining how well the simulation agrees with the initial assumptions and parameters.

The MISCAN CRC model has been through the first three steps and now is in the middle of validation exercises. The data being used for validation come from the Minnesota fecal occult blood test (FOBT) trial, the national polyp cohort series, and the Kaiser Permanente sigmoidoscopy-screening program. Dr. Brown is also in touch with the Lieberman/V.A. colonoscopy cohort study and the European FOBT studies. He expects to interact with the prostate, lung, colon, and ovarian (PLCO) cancer screening trial later on. Within 1 to 2 years, the model should provide insight on its parameters, on extending natural history data, and on the usefulness of a new approach to uncertainty analysis.

MISCAN Discussion

When Ms. Mary Ann Napoli asked if the calculation of cost-effectiveness includes the cost of selling the idea of being screened, Dr. Brown replied that while that is factored in, it probably is not given enough emphasis. Europeans are more accustomed than researchers here to do such cost accounting. Dr. Brown noted that while only minimal work has been done on this subject, Dr. Urban has done cost-effectiveness analyses of such programs independent of any models. It is likely that such programs are cost-effective only for a few individuals. Compliance is notoriously low.

Ms. Napoli reported that Dr. Eddy was quoted in a newspaper article as saying that mammography screening, even if limited to women aged 50 to 69, was never cost-effective. Dr. Brown explained that cost-savings are different from cost-effectiveness. The former is rarely achieved in screening programs. The latter means that the monies spent per life-year attained are economically reasonable expenditures versus other ways those resources could have been spent.

Dr. Hiatt asked whether the MISCAN model could handle differences among health systems. It might be possible to calculate the cost of health education activities within a specific health plan, and, yet, be difficult to do a similar calculation for society as a whole. Dr. Brown said that the life-history factors could include any events chosen for entry. In addition, it is possible to reprogram later.

Dr. Srivastava inquired about any follow-up with the MISCAN model after the July 1998 strategy meeting on the cost-effectiveness analysis of genetic screening for cases of hereditary nonpolyposis colon cancer (HNPCC). Dr. Brown indicated that some of the individuals who attended had gotten in touch with MISCAN project staff to follow up.

Dr. Urban urged collaboration with the PLCO trial. PLCO data can be valuable in validating ovarian, prostate, and colorectal cancer models. (There is no model, as yet, for lung cancer.) She

also suggested that modeling can be a powerful tool for looking at biomarkers. The variability in marker data is enormous; applying models and statistical analysis could help. Dr. Brown commented that it would be useful if a marker for CRC could be developed that would predict which polyps lead to cancer. Dr. Longfellow suggested that multiple markers would be needed, possibly correlating with multiple pathways. He also commented that polyps are likely to be too late a marker to be useful for prevention.

Dr. Urban then noted that including the natural history of the disease in the models helps alert researchers to the areas that are not understood. She said that she had requested a presentation on models because of questions about whether a model could predict outcomes in the PLCO trial and whether a model could help with decisions about when to embark on a trial. Dr. Brown responded that the model was not predictive for PLCO but would be helpful with the interim results of the trial.

Dr. Brown reported that funding for the Cancer Research Network is expected in December 1998. The network will include infrastructure projects that deal with early detection and other research projects related to screening. Advisors, like the members of the Committee meeting here, will be needed.

In further discussion, the group generally agreed that models are unlikely to replace screening trials. They are probably most useful to help with trial design. Sometimes, they might be able to replace a trial for lower priority issues. Dr. Brown noted that because trials tend to be simplistic, screening programs rarely replicate the trial setting. A model might be able to predict the situation in the real world based on trial results. Dr. Urban provided, as an example, that if the PLCO trial were to show that yearly screening for ovarian cancer is effective, a model might be able to determine whether screening every 2 years would be sufficient and cost-effective. Dr. Kramer pointed out that a model might also be useful to evaluate how much improvement in a screening process is needed to make it cost-effective.

Some Statistical Issues in Early Detection of Cancer - Dr. Stuart Baker

Dr. Baker indicated that he would talk about three subjects evaluating biomarkers, evaluating periodic cancer screening without randomized controls, and prioritizing randomized trials.

Evaluating biomarkers

His current interest in marker evaluation concerns how to combine information from multiple markers and look for correlation with cancer prevalence. In a future Phase II study, such markers could be used to indicate when to apply an early intervention. He worked first with data from an alpha-tocopherol/beta-carotene study in Finland, in which 130 prostate cancer cases and 227 age-matched controls were identified, and their sera were tested for free and total PSA. When he used a logistic regression, the two most important predictors were the log total PSA ($p<.00001$) and the ratio of log free PSA to total PSA ($p=.02$).

Dr. Baker then plotted, the logic showing the distribution of logic number for cases versus controls and combining numbers from totals and ratios. He also plotted the true positive ratio

(TPR) versus the false positive ratio (FPR) to obtain the receiver operating characteristic (ROC) curve for different regression values.

Next, Dr. Baker wanted to include a factor for the prevalence of screening for a particular type of cancer. He therefore used a utility function that subtracted a term for the cost (in which C = the number of unnecessary biopsies performed while preventing one premature cancer death) from a term for the benefit (reduction in mortality). (Both of these terms factor in prevalence.) Adjusting the ROC curve with the utility function, he plotted TPR versus C for ages 50 and 60 for the PSA test and similarly for breast cancer screening.

The aim of these manipulations is to identify combinations of biomarkers that make a good trigger for early intervention and to use information about cancer prevalence.

Discussion

When Mr. Wesley Sholes inquired about the cost-benefit ratio used in the model, Dr. Baker explained that the model uses a ratio of 100 for the PSA screening. The number for breast cancer screening would be much less that is, 11. Mr. Shoals also asked if an individual's wish could take precedence over policy. Dr. Baker said that this would affect the C value. Ms. Napoli commented on the likely discomfort of individuals when the term false positive is applied to them. Dr. Baker acknowledged that there are other costs that were not applied in this model, such as anxiety and the time off from work needed to get screened.

Dr. Hayes asked whether the value for a maximum odds ratio for PSA is indicative of a strong marker. He also expressed concern about potential overlap in markers between cases and non-cases. Dr. Baker noted that to achieve the same low false positive rate as for breast cancer screening (i.e., 0.014), the odds ratio for prostate cancer would need to be 140. The screens in use that have become accepted all have small false-positive rates. However, PSA screening also has to be considered acceptable because it is so widely used. For PSA, he has seen odds ratios of 1.3 to 1.7, which corresponds to a high false-positive rate. This involves a cutoff of 4. If the binary cutoff is set at 20, the odds ratio jumps to the 5 to 10 range, and most cases are metastatic.

When Dr. Srivastava inquired whether low prevalence and high utilization would affect the model, Dr. Baker replied that they would.

Periodic cancer screening without randomized controls

Dr. Baker noted that while randomized teals provide the best protection against random risk factors affecting results, they are expensive and, for cancer interventions, require a long time for follow-up. Alternatives include meta-analysis of previous trials, natural history models like MISCAN with their many assumptions, and periodic screening evaluation without randomized controls. The latter permits a decrease in selection bias with regard to the concern that individuals who obtain screening may differ from those who do not.

Besides the non-randomization, the basic design for periodic screening evaluation includes tracking individuals who are positive on either a first or later screening and those whose signs of

cancer are detected between the regular screenings. Dr. Baker developed a formula to calculate the incident rate without screening and in the absence of controls. The next question he posed was how to calculate the decrease in mortality resulting from screening. He compared for two different ages (40 and 50 years old) the sum of the age-specific incidence multiplied by the mortality at that age. Assumptions for this comparison included that individuals positive on the first screen would remain positive, age would not be affected by the year of birth, and, without screening, survival rates after cancer diagnosis would remain the same. He considers the latter a weak assumption.

To validate his design, Dr. Baker used data from both compliers and noncompliers in the HIP breast cancer study.

Overall, the periodic evaluation approach seems to be useful for comparing different ages at which one could start periodic cancer screening and, by using data only from screened subjects, in reducing selection bias in estimating the age-specific incidence if there were no screening.

Discussion

When Mr. Sholes asked whether the data conflict with discussion at an earlier Committee meeting about lowering the age for prostate cancer screening, Dr. Baker explained that, to date, he has analyzed only breast cancer screening data. He does not know if the assumptions will also apply to prostate cancer. Dr. Kramer added that the minimum age for the PLCO trial was lowered to 55 from 60 not because of any screening information but because the urologic consultants judged that there was a health benefit to detecting prostate cancer further earlier.

Dr. Barbara Tilley inquired about the impact of sample size and the applicability to the real world. Dr. Baker replied that the formula he had worked out results in a size calculation similar to that needed for randomized trials. He considers the first formula applicable to real data. He has discussed the subject in greater depth in his chapter in a new book on cancer screening.

Prioritizing randomized trials

The method to choose among potential trials that Dr. Baker described is based on ranking the trials for cost-effectiveness using a ratio of the yearly deaths prevented per trial (benefit, B) to the cost of the trial to the agency (C). Other scientific and political issues are not weighed in this calculation. The goal is to achieve the maximum benefit within the limits of available funding.

Dr. Baker explained the following formula for calculating benefit:

$$B = \text{prior} \times \text{power} \times (f-g) \times r \times M.$$

Prior is the probability that an alternative hypothesis is true; power is the probability of a statistically significant result; f is the fraction that would adopt the intervention if a trial showed statistical significance; g is the fraction that would adopt the practice without a trial; r is the reduction in cancer mortality under the alternative hypothesis; and M is the yearly cancer mortality in the population.

Dr. Baker specified how several criteria discussed by the Early Detection Implementation Committee at its March 10, 1998, meeting could influence the various terms in the formula. Portfolio balance could affect g; strength of hypothesis could affect prior, power, and r; strength of design could affect f; and burden of disease could affect M. Using hypothetical values, he then demonstrated the effects on B and B/C of different interventions.

Dr. Baker anticipates that this cost-effectiveness approach, except for identifying the fraction of the intervention that is statistically significant, should be easy to implement. It provides a formal method for combining criteria, including criteria that the Committee considers important.

Discussion

Dr. Hayes commented that the power term in the formula is the percent chance of detecting, not of having, cancer. Dr. Baker agreed and said that if detection is increased, then it is likely that the number of individuals using an intervention will also increase, thereby causing a greater decrease in mortality. Responding to a question, Dr. Baker also clarified that power is a purely statistical term indicating the likelihood of statistical significance.

Dr. Hiatt suggested that it might be possible to conduct a quantitative assessment such as Dr. Baker described and then overlay strategic and political factors to obtain the priority for a particular trial. Dr. Baker suggested that if the two approaches yield different results, it is necessary to determine why. Other committee members noted that in the formula, different weights can be given to the multipliers. For example, if a professional society were to promote a particular health message, this could change the number of individuals seeking screening. If no mortality reduction can be achieved, this would imply an effect on one or more of the terms used to calculate B. Dr. Baker said that, for this brief presentation, he had not factored in the null hypothesis as true times the probability it would be true, which also affects the value of B.

Dr. Hiatt pointed out that whether using Dr. Baker's formulae or a set of bulleted statements for priorities, subjective factors influence their application. Dr. Kramer said that bulleted recommendations are therefore preferable because more individuals will be comfortable using such a list than applying a formula.

General Discussion: Implementation Strategies

The Committee reviewed the list of 10 questions addressed in the draft committee report along with the proposed responses provided in the second draft, dated July 15, 1998. Dr. Kramer asked other committee members to comment on whether the responses properly reflect the Committee's series of discussions since March 1998.

Question 1 (readiness for screening trials)

1. What should be the criteria for starting clinical trials in cancer screening?

The Committee held an extensive discussion on the list of criteria proposed in the draft, considering both the order of presentation and proposals of other criteria to be added. Committee

members identified as illustrated below where certain factors fit within the listed criteria. They also discussed whether to indicate that the order of presentation was equivalent to an order of priorities.

Eventually the Committee decided not to prioritize except for a consensus on the final priority (i.e., portfolio balance) being rated below all the others. The items on the list are therefore bulleted rather than numbered. While agreeing with the use of bullets, Dr. Urban pointed out that, inevitably, this leads to different views of the weights to be assigned to each factor. Based on experience with reviews of grant applications, Dr. Leslie Ford was optimistic on achieving an informal consensus about the value of each criterion.

The final order of criteria selected by the Committee was the following:

Strength of hypothesis
Impact on public health
Impact on scientific paradigm
Strength of study design
Feasibility/efficiency
Window of opportunity
Portfolio balance "strategic"

Congressional interest and public interest were mentioned as secondary criteria and were not listed. Members said that equipoise is a part of the strength of the hypothesis. Equipoise considers the amount of information available and whether undertaking a new effort to learn more is worthwhile.

It was decided to split the impact of the program (into scientific and public health impacts] to indicate that there are different kinds of impacts. (Burden of disease became impact on public health during this discussion.) For example, a useful discovery about cell biology could be made without affecting disease outcome. Consideration was given to omitting the importance of the scientific question being asked (also called scientific opportunity, but then changed to impact on scientific are criteria for prioritizing clinical trials. However, a consensus was reached that, within that context, this is still a worthwhile criterion. Dr. Hiatt commented, for example, on advice from the Institute of Medicine to extend the focus. Dr. Ford added that number of deaths is an oversimplification regarding the extent of impact. Eventually, the group decided to list impact on public health before impact on scientific paradigm because the former has a more wide-ranging effect.

In addition, the Committee decided to drop the word "positive" in describing results and substitute indefinite results since negative results can be useful too. To clarify, it was suggested that a statement be included specifying that Phase III trials are the type of study referred to in Question 1 and that it is important to encourage such trials. Dr. Gohagan asked how to include the point that one has to consider the cost of carrying out an activity that is not really effective if there is no trial to prove effectiveness. While this concept fits under impact on public health, Dr. Gohagan recommended explicitly addressing it in the discussion section under Question 1. One appropriate phrase (that Dr. Kramer used in a previous report provided earlier to the Committee

as background) was, “The economic and human costs of simply disseminating a practice can far outweigh the costs of doing a trial”.

The group also noted that sometimes there is a window of opportunity for conducting a trial; if a practice becomes too widespread, it becomes much more difficult to do the trial. The group therefore added “window of opportunity” to the list of criteria, deciding that this is a separate strategic issue, not a part of “feasibility”. The suggestion to change feasibility to “tools” was rejected.

Dr. Urban suggested including the “opportunity cost” of conducting a particular trial and therefore not being able to conduct certain other trials at the same time. Consideration must be given to ensure that the questions addressed by the chosen trial are complete. Once the group decided that this topic is part of efficiency and design of trials, the term “efficiency” was added to the feasibility category. (“Strength of study design” was already on the list of criteria.) The example cited of a lost opportunity in study design was the failure to include collection of blood specimens from the controls in the PLCO trial. (Dr. Gohagan indicated that Dr. Prorok could explain the PLCO planning process to whoever is interested.) The group chose not to make feasibility and efficiency part of “strength of study design”.

Mr. Sholes requested that the group review who the intended audience is for the Committee’s report. Dr. Kramer replied that the audience would include staff within the NCI and external advisors. He anticipates that the report will become a tool to objectify decisions about which initiatives to fund. Currently, there are no criteria, and Dr. Kramer views the decision making process as highly subjective. Dr. Hiatt noted that NCI also can make the report available to external research and lay communities and inform them of how NCI plans to implement the recommendations.

Dr. McKenna asked where test parameters would fit among the criteria. Besides sensitivity and specificity issues for tests, there are public health issues about effectiveness and costs. The consensus was that test parameters are part of the “strength of study design” category.

Question 2 (funding decisions)

2. What should be the process for funding decisions on large investigator-initiated cancer screening trials?

Dr. Kramer asked committee members if an additional process is needed, such as an ad hoc committee of intramural and extramural representatives to prioritize trial proposals based on agreed-upon criteria and to determine how best to spend the available budget. This approach is not practical unless sufficient monies have been set aside specifically for screening trials. If Congress designates a specific funding category for new initiations, monies are sometimes available through the request for applications (RFA) process. Prioritizing is useful only if there is a budget. For special programs like the Small Business Innovation Research (SBIR) program, there usually seems to be more available money than can be spent; this is another situation in which prioritizing is not useful. Authority for multi-million dollar projects, such as screening trials, lies with Congress.

Dr. Longfellow doubted the utility of adding another committee layer to the present peer-review system. Dr. Urban noted that, currently, when a grant application requests more than $500,000 per year, the appropriate NCI division must clear the request before the application is reviewed. Dr. Ford indicated that once the peer review committee assigns priority scores, there is little flexibility because of the pressure to fund all applications with scores above the cutoff. She also suggested that the only way to deal with large trials is to have a committee specifically assigned to review applications for screening trials. Dr. Kramer said that it is essential that the reviewers have guidelines. Dr. Urban added that it would be an asset to have the NCI program staff collaborate on trial design.

Recognizing that the National Heart, Lung, and Blood Institute (NHLBI) administers some large trials, the group inquired about the funding source. Dr. Kramer indicated that NHLBI has a budget specifically for large trials. One question is whether the Early Detection Implementation Committee wishes to recommend a separate budget for NCI screening trials. Another is whether any existing study sections have experience reviewing large projects. Dr. Kramer said that the NCI Division of Extramural Affairs (DEA) handles RFAs, cancer centers, and cooperative agreements. Dr. Taube suggested that the issues involved in reviewing screening trials are sufficiently different (from both basic research and clinical trials to designate a different review method. In further discussion, however, DEA was viewed as the likely potential review administrator.

Dr. Urban noted that the Department of Defense and the Agency for Health Care Policy and Research (AHCPR) set programmatic goals instead of relying on priority scores. Other group members observed that disapproval of the AHCPR approach had jeopardized that agency's funding and that there are other approaches not involving percentile scoring. Dr. Gohagan added that contracts are outside the peer review system.

Dr. Taube pointed out as another model that the National Institute of Allergy and Infectious Diseases will accept large projects only through RFAs. However, Dr. Kramer was concerned that RFAs and requests for proposals (RFPs) for contracts are not readily approved by NIH outside advisory boards and councils. When program announcements (PAs) were proposed as an alternative, Dr. Kramer said that they are meaningless because no monies are reserved specifically for PAs. In later discussion, Dr. Srivastava pointed out that another problem is that PIs do not like the idea that PAs specify the kind of research that must be done.

Dr. Urban suggested that a consortium (such as the Committee plans to discuss during the second meeting day) could provide a useful forum for communications among investigators to help avoid inappropriate proposals. Dr. Longfellow said that he agreed with Dr. Gohagan on the concept of a hybrid review, in which ideas would first be presented, and the overall package then negotiated. NCI would be available to provide technical advice to the reviewers. Dr. Kramer stressed the importance of having a majority of extramural members on the review committee. Later, however, the Committee determined that it is likely that the requirement is that all members of the review committee must be extramural, so that intramural staff normally cannot serve. However, a program director can be assigned an informational role, providing objective information to the reviewers and answering their questions.

Dr. Gohagan recommended that both the review process and the budget need to be designated as specific to large trials. Other committee members added that clearly more expertise in this area is needed and that the expertise of the current Executive Committee and of the Board of Scientific Advisors is too limited. Additional expertise beyond chemoprevention, screening, control, and trials expertise (that the regular review committee should have) could be provided by ad hoc members. Different advocates could be asked to serve as well, depending on the subject.

Dr. Kramer predicted an increasing need for chemoprevention trials, mentioning selenium and retinoids as likely subjects. As a previous trial with selenium was not definitive, no public health recommendation can be made as to whether selenium prevents cancer. Criteria for judging are needed both for this element and for other potential chemopreventives, including vitamin E.

Dr. Urban inquired about the source of funds if a screening trial budget could be established. Dr. Kramer explained that NHLBI sets aside a certain percentage of its RPG allotment, the rest of which is used for regular R0l research grants. Dr. Tilley commented that everyone has become accustomed now to this division of the NHLBI budget and that the NHLBI trials review committee conducted a strong review and ensured that projects were strengthened. The Specialized Programs of Research Excellence (SPORE) were cited as another project that evolved because translational research was not faring well in regular peer review committees. Dr. Tilley suggested exploring more than one process before specifying how best to handle the large screening trials. Other funding information provided during discussion in included the fact that P01 grants and cooperative agreements as well as R01 grants derive from the NCI RPG and funding of U01 grants for clinical trials and of genetics consortia are through separate, protected budgets.

Dr. Kramer then polled the group, determining that there was support for a separate trials budget and even more support for a separate screening trials review process. Dr. Kramer proposed evaluating the NHLBI Process. The immediate source of funding would be the RPG, although there is always the possibility that Congress could sometime allocate specific funding. Dr. Tilley commented that the proposed changes in the review committee and budget are timely. Dr. Taube described the plan as setting a cap or spending limit for large trials rather than creating a set-aside fund.

One suggestion was to do a PAR, but this would need to be set up again each year and only can extend for 3 years. Dr. Longfellow proposed doing a policy announcement instead.

Dr. Kramer then proposed emphasizing a pre-review step with triage, advising investigators to rework their proposals to strengthen them. This step could be carried out by the NCI program when letters of intent are submitted. Dr. Urban said that there are three possible review outcomes: a recommendation not to do the trial, a recommendation for NCI to fund the trial, and an approval with a priority too low for NCI funding.

Question 3 (validating markers)

3. What is the critical pathway to be followed in validating early detection molecular or secreted protein markers?

The group decided that discussion of this question would fit with the agenda of the second meeting day.

Question 4 (surrogate endpoints)

4. Can surrogate endpoints replace cause-specific mortality in definitive screening trials? How would such endpoints be validated?

Dr. Kramer indicated that this subject also relates to the August 14 agenda. He proposed that a scientific committee be established to discuss the use of surrogate endpoints.

Question 5 (long-range follow-up)

5. How can the Institute plan for long-range follow-up in screening trials to detect benefits and risks for screening and treatment?

Dr. Kramer noted that it would be useful to have a stable funding mechanism for long-term projects. Whenever there are budget constraints, it becomes necessary to measure the costs and investment in follow-up versus costs of new projects. Dr. Taube said that as a result of the Committee's deliberations, she believes this group reached a consensus on the need to make a commitment to finish trials. Dr. Kramer expressed concern about the discontinuity in such decisionmaking when a new review group examines the record at the 5-year renewal point.

Drs. Taube and Gohagan proposed that criteria be established for trial continuation. Dr. Gohagan would link this to planning for a trial's progress review. He said that an independent review group should decide if the trial endpoints have been reached.

The group approved the record submitted (in the July draft) of their discussion of Question 5, with the addition of the context of a network and review.

Question 6 (biorepositries)

6. How should the Institute prioritize resources for biorepositories attached to screening trials?

Dr. Kramer noted that Question 6, like Question 5, involves a prioritization of resources. Work is in progress to set up a committee to deal with repository issues. Dr. Kramer suggested that the Early Detection Implementation Committee defer to the new committee for establishing objective criteria and developing a repository proposal. Such a proposal could then be brought back to this Committee to review.

Question 7 (informed consent for biorepositories)

7. What is the appropriate informed consent for future tests on collected materials in biorepositories?

Dr. Kramer reminded the group that Dr. Ford is leading an internal NCI process on improving informed consent.

Question 8 (behavioral, systems, and minority approaches)

8. What are the behavioral and systems approaches that can be studied to improve dissemination of screening practices that have been proven to decrease mortality? What special approaches are directed at minority populations?

Dr. Kramer reported that the NCI program proposes that DCCPS take the lead since it has a mission to conduct behavioral studies. DCCPS could review the behavioral projects that are proposed as part of trials. Behavioral scientists should be part of the review group. The review group should also take the initiative to suggest projects to investigators, not just evaluate submissions. If a consortium is developed, it also should have a behavioral component.

Dr. Vernon noted that the CGN requires multidisciplinary cooperation. She suggested preparation of a programmatic statement that behavioral scientists should be included on research teams conducting clinical trials. Dr. Kramer stated that CGN reviews also need to include behavioral factors. Dr. Hiatt noted that there are two approaches: either one should require behavior-based studies after a test has been proven efficacious, or one should integrate behavioral questions into the design and application in trials.

Question 9 (organizational structure)

9. Is the organizational structure of the early detection effort ideally configured for early phase (or preclinical) and clinical screening studies?

Dr. Kramer noted that this question, which was omitted in the July 15 draft version under discussion, could be addressed through the organizational restructuring of DCP. Dr. Greenwald, DCP Director, should be available to discuss this on August 14. One recommendation is that DCP establish a unit devoted to molecular markers and basic studies. This unit would serve as a foundation for other areas.

Dr. Kramer invited other committee members to provide suggestions for the reorganization. He noted that across the division more integration is needed for such subjects as nutrition and utilization of various markers.

Question 10 (role of industry)

10. What is the role of industry in development of biomarkers and tools for early detection? How can NCI work with industry?

Dr. Kramer said that industry needs to be involved in the proposed consortium. Even before a procedure is ready for scale-up, participation by industrial representatives could be valuable. When Dr. Napoli commented on a potential conflict of interest, Dr. Kramer acknowledged this possibility. He said, however, that it is important to familiarize industrial representatives with the validation process and to make them aware that scientists will speak up if a process is promoted without such validation. He hopes that such a cadre of opinion leaders can serve as a brake, preventing sales directly to the public (of tests for unapproved uses).

Dr. Taube recalled that the PSA test was approved by FDA only for monitoring but was promptly marketed for other uses. At least, laboratories holding Clinical Laboratories Improvement Act (CLIA) certification will conduct no tests lacking any type of FDA approval. Dr. Kramer pointed out that Medicare permits billing for PSA kits (that are being used for unapproved uses).

Dr. Kramer proposed scheduling further discussion of the potential problems of involving industry in development for the following day.

Introduction to the August 14 Agenda

Dr. Levin served as chair for the second day of the meeting. Discussion centered on the organizational structure of DCP and the proposal to establish a prevention research network.

Proposed Organizational Structure Dr. Peter Greenwald

In response to Question 9, concerning the organizational alignment of divisional programs, Dr. Greenwald described a draft model for a restructured Division of Cancer Prevention. Committee members were encouraged to respond to the proposed reorganization.

Dr. Greenwald explained that NCI has a traditional vertical structure with programs and branches. He proposed a new structure to increase the interactions among divisional programs and branches. The objectives of restructuring are (1) strengthening ties to intramural and extramural basic research related to cancer prevention and early detection (avoiding duplication of activities by the Division of Cancer Biology), (2) broadening ties to the extramural research community to develop translational research in cancer prevention, (3) fostering career development, and (4) implementing a matrix organization, as used in corporations with a translational thrust.

Dr. Greenwald described a draft divisional structure based on a matrix organization. The matrix relies on the interaction between programs and organ-oriented branches. The programs (seen as the foundation for prevention resources) would include chemopreventive activities (e.g., Community Clinical Oncology Program [CCOP]), nutritional science, basic prevention science

(e.g., infectious agents, and genetic factors), early detection activities (e.g., biorepositories, PLCO trial), and biometry. The organ-oriented branches would include gynecological cancers, prostate and genitourinary cancers, lung and upper aerodigestive cancers, and gastrointestinal cancers. The matrix would be managed by the Coordinating Unit for Prevention, Biomarkers, and Early Detection Research. In addition, a training program would support 12 to 20 preventive oncology fellows annually. The fellows would serve an apprenticeship in biometry, epidemiology, nutritional science, basic science, or clinical studies. Sabbatical activities also were suggested; divisional personnel could work in extramural labs, and extramural personnel could join NCI laboratories.

Programs and branches would collaborate and would form task groups for specific studies. For example, the chemoprevention program and prostate-genitourinary branch might support studies examining the effect of vitamins or minerals on prostate cancer. A recent study by Larry Clark and colleagues examined the effect of selenium dietary supplements on the incidence of cancer. More than 1,000 patients with a history of basal or squamous cell skin carcinoma received a selenium-enriched yeast supplement or placebo in a double-blind fashion. While the selenium did not significantly affect the incidence of recurrent skin carcinomas, a 60% reduction in prostate cancer was observed. The results warrant further evaluation in well-controlled clinical intervention trials. Such a study is a perfect candidate for collaborative efforts enhanced by a matrix structure.

Organizational Structure Discussion

Dr. Taube asked what type of research would be conducted in the program for basic prevention science. Dr. Greenwald explained that the structural design is still incomplete, but biomarker research might fall under this program. A planning workshop is being arranged to discuss these issues.

Dr. Levin questioned if the branches would interact with other NIH institutes. Dr. Greenwald strongly endorsed inter-institute collaboration. He noted that nutritional studies are perfect candidates for a multidisciplinary approach, perhaps with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and NHLBI. Rough estimates suggest that one-third of all cancers have dietary determinants. Dietary factors also affect the risks for diabetes and heart disease. Identification of dietary risk factors or ameliorative nutritional supplements would have powerful societal implications.

Dr. Hiatt noted that the Hewlett-Packard Company pioneered the matrix organizational structure, which met with great success. He inquired how this structure would handle accountability.

Dr. Greenwald said that resource allocations should reward translational research tied to public benefit.

Dr. Levin asked how the draft model would accommodate the close link between cancer control and prevention. Dr. Greenwald explained that task groups would support collaboration between DCP and DCCPS. Dr. Kramer inquired if other divisions would be required to have a similar

matrix structure. Dr. Greenwald said he believed that such a structure would not be necessary in other divisions.

Dr. Hiatt wondered if the reorganized division would support a finite or an open-ended number of projects. Dr. Greenwald stated that projects would be prioritized. The main objective is to support studies with the strongest likelihood of public benefit.

Dr. Taube inquired about the progress of the human papilloma virus (HPV) vaccine. Dr. Greenwald reported that three companies are working on HPV vaccines. Two approaches are used: (1) prevent infection and the introduction of oncogenic DNA and (2) prevent infected cells from progressing to cancer. The first approach fits a more traditional public health vaccination effort. Efforts to prevent infection in cow and cottontail rabbit models have met with success. Nearly 70 HPVs have been identified, but four types account for 80% to 90% of cervical cancer. Important questions remain concerning safe vaccine delivery, selection of appropriate adjuvants, and the use of multivalent vaccines. Intramural groups can perform the early work in vaccine development, but an infrastructure is needed to support collaboration with clinicians and experts in clinical trials.

Mr. Sholes asked for an explanation of the Coordinating Unit. Dr. Greenwald explained that it would be administered by an assistant director. The heads of programs and branches would participate, along with some external experts. The Coordinating Unit would manage and promote collaborative efforts for specific tasks.

Dr. Hiatt inquired how the matrix structure would accommodate research projects initiated by extramural investigators. Dr. Greenwald replied that many trials are run by cooperative agreements, but the matrix could also accommodate R0l grants.

General Discussion - Prevention Research Network

Referring to the draft version of the proposal for a consortium provided in the meeting packet ("Prevention Research Network for Studies in Cancer Detection and Risk Assessment"), Dr. Kramer explained that the Network's goal is to promote the development of biomarkers from the discovery phase through validation studies. The proposed initiative would support the creation of a multi-center network with resources for translational research. Participating disciplines would include basic sciences, clinical sciences, public health, biostatistics, informatics, and computer sciences.

Currently, investigators work individually on specific biomarkers or specific points in the molecular carcinogenesis pathway but do not have access to mechanisms for validation or clinical application. The result is a plethora of unconfirmed biomarkers. The Network would offer investigators a road map for biomarker development. The Network scientific advisory committee would establish criteria for prioritizing biomarkers for technical development and initial phases of clinical study. Preset development criteria would serve as an incentive for industry involvement by enabling selection of the most promising biomarkers and clearly outlining the steps leading to validation.

Dr. Kramer described a preliminary organizational structure for the Network. (A copy of the organizational structure was provided in the meeting packet.) The heart of the proposed organization would be the Centers for Biomarkers in Prevention Research (CBPR), consisting of the laboratories and academic centers that generate new biomarkers. A steering committee would act as the Network's governing body, responsive to a scientific advisory group. Membership in the scientific advisory group could be structured in one of three ways: (1) combined membership with the steering committee, (2) limited cross-membership with the steering committee, or (3) all advisory group members being external to the Network. An Accrual and Validation Study Group would provide access to patient populations and manage validation steps involving patients or biorepository material.

Other Network functions involve a data management center and informatics group responsible for the collection, management, and analysis of data. A production and application group, with no NCI involvement, would provide an opportunity for private industry involvement in biomarker production. Several committees with representatives from basic science, clinical study, prevention study, data management, and quality assurance would assist in the validation process. For example, the quality assurance group would coordinate small initial studies to determine the inter-laboratory variance of particular biomarker assays.

Dr. Hiatt questioned how the Network would avoid the appearance of exclusivity. Dr. Kramer replied that the Network would consist of a core membership that meets regularly but would include temporary members, as needed, for specific projects, studies, or tasks. The core membership would provide structural stability and consistency, and temporary members would contribute flexibility.

After discussion of the scientific advisory group structure, the Committee recommended a limited cross-membership with the steering committee, that is, the chair of the advisory group should be a member of the steering committee, and the chair of the steering committee should participate in the advisory group. Remaining members of the scientific advisory group would come from outside the Network and represent multiple disciplines.

Mr. Sholes asked where the organizational structure would incorporate input from the public health sector. Dr. Kramer explained that public health professionals could participate in the steering committee, scientific advisory group, and accrual and validation study group. Public health advocacy representatives (laypersons) could participate in the steering committee, clinical study group, and accrual and validation study group.

Dr. Ford indicated that the validation process should pass to existing networks when it reached a Phase-III level. Dr. Kramer agreed, stating that the proposed network would coordinate only the initial steps of validation, and it was not intended to validate biomarkers for public use. Dr. Tilley asked if the proposed network were analogous to Phase II of treatment studies. Dr. Kramer said this is an excellent analogy. Network activities would include defining appropriate study populations, providing access to those populations, determining specificity and sensitivity of the biomarker, and defining the ROC curve.

In response to Dr. Urban's question on the criteria for positivity, a decision flow chart for biomarker development designed by Dr. Srivastava was distributed. The basic steps following biomarker discovery involve (1) proof of principle strength of the association of the biomarker with risk, existence of disease, or prognosis; (2) demonstration multi-center cross checks and quality assurance studies; (3) prioritization—generalizability of the test, accuracy and frequency of positive tests, and cost; (4) validation of clinical use- decision criteria, population selection, and establishment of protocols.

Dr. David Sidransky questioned what laboratories would participate in quality assurance testing. He noted that laboratories focused on basic research would not want to perform quality assurance tests. Dr. Kramer replied that laboratories within the Network, with the appropriate expertise, would conduct quality assurance tests. Basic research laboratories that focus on the discovery of new markers would not necessarily participate in the quality assurance phase. Different laboratories have different expertise, but the aggregate of Network laboratories would cover the full array of validation activities. Dr. Taube added that laboratories within the Network should contribute to collaborative activities. For example, basic research laboratories could participate in training programs, while clinical groups could provide access to patient groups. The steering committee would assist in coordinating Network activities.

In a discussion of network funding, Dr. Dan Sullivan was asked how the Diagnostic Imaging Network handles this issue. He explained that the Diagnostic Imaging Network is structured as a committee of experts, not institutions. After selecting a study or trial, the committee contacts appropriate institutions for the project from letters of agreements and applications kept on file. This arrangement maximizes flexibility. Funding is awarded to an organization (not a singular hospital or medical center). The PI pulls together project committees, defined by the application. The committees bring together various institutions based on the protocols and expertise required.

Dr. Taube suggested a funding scheme analogous to SPORE, in which a central developmental fund is used to aid specific projects. Dr. Tilley proposed funding a core set of laboratories and compiling a list of qualified laboratories for validation and quality assurance testing. Dr. Kramer envisioned that a core group of centers for prevention research and initial validation testing would form a consortium. Dr. Taube mentioned a cross-divisional model that funds individual laboratories forming a cooperative network. Within the network, one organization functions as a central administration. Developmental funds—dispersed through the advice of a steering or advisory committee—can supplement individual laboratories for unanticipated projects or staffing needs.

Dr. Sidransky inquired about the issue of technical development. He commented that few basic research laboratories have developed bioassays sufficiently for cross-validation tests. Dr. Levin suggested that biotechnology laboratories might be interested in this step. Dr. Sidransky asked whether such laboratories would be part of the Network, or whether the responsibility for finding an appropriate development laboratory would fall to the investigator. Dr. Kramer recommended that the Network core select a laboratory with the required expertise. Funding would come from a core Network budget. Dr. Taube proposed advertising for technical development laboratories and establishing intellectual property rights. Dr. Greenwald remarked that a contract mechanism

could be used for supplemental laboratory work to assist with bottleneck steps in the development process.

Dr. Urban stated that criteria for biomarker validation must encompass evaluating performance over time and the combined use of multiple markers. Dr. Kramer noted that some biorepositories have serially acquired specimens from retrospective cohorts. Mathematic modelers and informatics specialists could assist with criteria for multiple markers.

Committee discussion led to a revised Network design. The heart of the Network would be the Centers for Clinical Biomarker Research, comprised of the basic research or discovery laboratories, validation laboratories, clinical representatives (clinicians, clinical trialists), and epidemiologists. Discovery, validation, and clinical groups would form an equal partnership, represented as overlapping circles in an organizational diagram. As in the original design, the steering committee—consisting of PIs, public health representatives, and ethicists—would serve as the governing body, interacting with the Centers for Clinical Biomarker Research, scientific advisory committee, and data management center. The steering committee would determine research priorities and select biomarkers for continued development. Specific subcommittees would evolve as the steering committee selects and develops projects. A funding mechanism would allow the Network to contract with biotechnology companies or development laboratories for explicit steps in the validation process. A peer-review evaluation process should take place periodically, perhaps every 3 to 5 years, followed by necessary modifications.

Dr. Martin Oken inquired about the formation of a cooperative group for cancer detection research. A clinical trial mechanism would be used, with healthy individuals screened by detection centers or primary care physicians. Dr. Greenwald explained that a recommendation was made for a prevention review group, but it was not pursued. Hopefully, the divisional restructure will address this issue through organ-specific branch development. Additionally, CCOP proved that large prevention trials could be done successfully, and a new structure was deemed unwarranted. If the CCOP structure is inadequate for subsequent trials, the formation of a new cooperative group will be addressed.

Dr. Levin asked about the cost of implementing the Prevention Research Network. Dr. Greenwald stated that the bypass budget process might serve as a funding source. Through this process, major initiatives are introduced every 3 years. The intervening years are used to refine the initiatives.

On a separate issue, Dr. Greenwald reported that he proposed initiating a large trial budget to the executive committee. The budget structure would provide a systematic process for funding large prevention and early detection trials and would improve prioritization of projects. NHLBI has implemented a large trial budget with great success. Dr. Greenwald noted two important differences between NHLBI and NCI that must be considered. NCI carries out more basic research than NHLBI, and cancer involves more organ systems than do heart and respiratory disorders. An ad hoc committee in DEA could annually review proposals for large trials for initial or continued funding. A consensus statement from the Committee would add leverage in favor of such a budget process. Dr. Portnoy volunteered to contact NHLBI for information concerning the categorization and budget process for large trials.

Committee logistics

Committee members were requested to contact Ms. Cindy Rooney regarding (1) any reimbursement issues and (2) any changes to the May 11, 1998, minutes.

The revised draft committee report will be sent to the members for review and comment. Dr. Kramer said he viewed the report as a brief review that would include a preamble, an introduction to the proposed network, the list of questions, a brief background for each, and the Committee's recommended solutions. The preamble will describe the committee process. The report will also include a diagram for the Prevention Research Network for Studies in Cancer Detection and Risk Assessment and the Committee's response to the 10 implementation-related questions. Appendices will provide appropriate supplementary information, such as the minutes of each meeting. The appendices might also include (1) an approach for the consortium to use to solve questions assigned to it, (2) development of informed consent, and (3) the developmental process for biomarkers. Dr. Hiatt commented on the difference between this report and another one dealing with tobacco that will provide extensive background. He said that it would be interesting to see which report is used more.

Dr. Kramer announced that the Committee would not meet again formally. Teleconferences will be arranged as necessary to finalize the Committee's report. Ms. Wanda Davis will be asked to contact committee members to coordinate schedules for the teleconferences.

Drs. Kramer and Levin thanked the other committee members and the support staff. Each recognized the Committee's work as a successful example of intramural-extramural cooperation.

The final session was adjourned at 12:00 noon.

Participants

Stuart Baker, Sc.D., Division of Cancer Prevention
Michael Birrer, M.D., Division of Cancer Prevention
Martin Brown, Ph.D., Division of Cancer Control and Population Sciences
Leslie Ford, M.D., Division of Cancer Prevention
John Gohagan, Ph.D., Division of Cancer Prevention
Peter Greenwald, M.D., Division of Cancer Prevention
James Hanson, M. D., Division of Cancer Control and Population Sciences
Richard Hayes, Ph.D., Division of Cancer Epidemiology and Genetics
Robert Hiatt, M.D., Division of Cancer Prevention
Rick Kaplan, M.D., Division of Cancer Treatment and Diagnosis
Barnett Kramer, M.D., Co-Chair, Division of Cancer Prevention
Bernard Levin, M.D., Co-Chair, University of Texas, M.D. Anderson Cancer Center, Houston
David Longfellow, Ph.D., Division of Cancer Biology
Matthew McKenna, M.D., Centers for Disease Control and Prevention, Division of Cancer Prevention and Control
Mary Ann Napoli, Center for Medical Consumers, New York
Martin Oken, M.D., University of Minnesota
Barry Portnoy, Ph.D., Division of Cancer Prevention
Philip Prorok, Ph.D., Division of Cancer Prevention
Wesley Sholes, Cancer Survivor, Santa Monica, California
David Sidransky, M.D., Johns Hopkins University, Baltimore
Sudhir Srivastava, Ph.D., Division of Cancer Prevention
Dan Sullivan, M.D., Division of Cancer Treatment and Diagnosis
Sheila Taube**,** Ph.D., Division of Cancer Treatment and Diagnosis
Barbara Tilley, Ph.D., Henry Ford Health Sciences Center, Detroit
Nicole Urban, Sc.D., University of Washington at Seattle
Sally Vernon, Ph.D., University of Texas School of Public Health, Houston

Meeting Support Staff

Wanda Davis, Secretary, Division of Cancer Prevention
Cathy Fomous, Ph.D., Rapporteur, TASCON, Inc., Rockville, Maryland
Cindy Rooney, Executive Secretary, Division of Cancer Prevention
Linda Silversmith, Ph.D., Rapporteur, TASCON, Inc., Rockville, Maryland

Concept

Early Detection Research Network

INTRODUCTION:
Over the past year, two review groups of outside experts (the Cancer Prevention Program Review Group and the Cancer Control Program Review Group) met to give advice to the National Cancer Institute (NCI). After the review groups had submitted their reports to the NCI and to the Board of Scientific Advisors, a number of implementation working groups were established. One of the working groups, the Early Detection Implementation Group (EDIG), was created to address the major recommendations made by the Cancer Prevention Program Review Group (CPPRG) in early cancer detection. Only relevant conclusions from the CPPRG report are presented here:

- develop new molecular markers for the early detection of cancer
- expand identification of high risk healthy populations based on genetic predisposition and the development of new molecular markers
- develop and improve new high through-put technologies for implementation of promising molecular diagnostic approaches in clinical and population-based trials
- develop and expand existing biorepositories and provide new access with appropriate consent to such materials for the testing of new molecular detection strategies.

The EDIG met four times to review all early detection-related recommendations made by the CPPRG in order to propose strategies for their implementation (the meeting dates and members of the EDIG are included in attachment). The EDIG endorsed the formation of a consortium to accelerate the progress made in the area of molecular and genetic markers toward application in cancer prevention, earlier detection and risk assessment. This concept represents one of the major recommendations made by the EDIG. The Chemoprevention Implementation Group, the Breast Cancer Progress Review Group and the Prostate Cancer Progress Review Group independently made similar recommendations.

BACKGROUND: Although the primary tumor can usually be controlled by local therapy, most cancer deaths are caused by metastatic disease. The goal of early detection and screening is therefore the diagnosis and treatment of cancer before it spreads beyond the organ of origin, perhaps even in its pre-invasive state. Unfortunately, available early detection and screening techniques pick up many tumors at a relatively late stage in their natural history. As a result, decrements in mortality even with the best available detection modalities are likely to be modest. On the other hand, some early detection and screening techniques identify changes with a low probability of progression to life-threatening cancer, thereby resulting in unnecessary diagnosis and over-treatment. New technologies coming from the field of molecular and cellular biology are able to identify genetic as well as antigenic changes during the early stages of malignant progression. Some of these changes show promise as biomarkers for preneoplastic development or for early malignant transformation. The application of these emerging technologies in the field of early detection and risk assessment is a high priority in the National Cancer Institute's strategy for reducing mortality from cancer. Detection of early cancer has been identified as an area of extraordinary opportunity for investment in the NCI 1999 Bypass Budget.

Data show that detection and treatment of pre-malignant or early lesions can reduce mortality, for instance, mammography and Pap screening. Although clinically proven, both technologies have problems with sensitivity, specificity as well as predictive value. Therefore, it seems reasonable to explore the application of the new molecular-based technologies for earlier and more specific detection and even for risk assessment, that is, before the cancer physically develops in order to institute chemoprevention. These are the overarching goals of the proposed research network.

Early detection technologies are rapidly evolving while existing technologies are undergoing progressive refinement in their sensitivity, specificity, and throughput. Improved analytic tools have allowed more detailed examination of the molecular basis of carcinogenesis and provided the ability to identify the molecular and cellular signatures of cancer and explore gene-environment interaction relevant to early detection. To fully explore the application of molecular profiles for earlier detection, it is essential to understand the molecular pathogenesis of cancer, that is, the natural history of tumor progression at the molecular level, so that the biological behavior of an evolving lesion (for example, dysplasia or field change) can be predicted with greater accuracy. Current observations indicate that cancers usually evolve through many complex cellular processes, pathways, and networks. A better understanding of the circuits in these pathways is critical if we are to successfully apply these molecular-based technologies to earlier detection.

Research in molecular genetics, cell biology, protein chemistry, and immunology has found that cells undergo many changes during neoplastic progression. Often occurring early in the malignant process, these changes include, for example, production of novel proteins, growth factors, cytokines, etc., in addition to multiple genetic alterations. Because these changes have been consistently associated with malignant transformation, they are now recognized as biomarkers for cancer, but are not always predictive. Such biomarkers, whether present in serum, urine, etc., could serve as indicators of early cancer or as markers of risk for impending cancer.

Progress in the field, however, is currently impeded by some practical hurdles. The systematic application of biomarkers for earlier cancer detection or even for risk assessment is fragmented and not well coordinated. For many years, the National Cancer Institute has sponsored research in genetic and molecular biomarkers through traditional funding mechanisms, such as R01s and P01s. While studies conducted through these mechanisms have been useful in advancing our understanding of carcinogenesis, there has been a lack of research emphasis on the continuum of preclinical tumor development, early evaluation of new techniques and their clinical application. In many of these reported studies the investigators did not fully explore the biological implications or systematically test the clinical application of these molecular markers. This has resulted, in part, from the lack of a stable connection between basic laboratory research and the opportunity for rapid clinical evaluation. Other factors contributing to the lack of systematic evaluation include the non-availability of high quality matched specimens from normal, suspicious, preneoplastic and multistage neoplastic lesions. In addition, the lack of large uniform collections of well-defined preneoplastic and neoplastic lesions, collected with ancillary demographic and follow-up clinical data, has also limited progress in the development and application of these biomarkers. As a consequence, much work in this area is fragmented into

numerous small and disconnected studies without complete evaluation. Usually, the results of these studies cannot even be generalized to the population as a whole. In many instances, the population of inference cannot be defined.

GOALS AND MAJOR OBJECTIVES: The initiative will support the creation of a multicenter network with resources for translational research that will include the laboratory sciences, clinical sciences, public health, biostatistics, informatics, and computer sciences. The initial goals of the network will be to discover and to coordinate the evaluation of biomarkers/reagents for the earlier detection of epithelial cancers, such as prostate, breast, lung, colo-rectal and upper aerodigestive tract, and for the assessment of risk. Specifically, the objectives of the network will include:

- the development and testing of promising biomarkers or technologies in institutions having the scientific and clinical expertise, in order to obtain preliminary information that will guide further testing;

- the timely and early phase evaluation of promising, analytically proven biomarkers or technologies. Evaluation will include measures of diagnostic predictive value, sensitivity, specificity, and whenever possible, medical benefits, risk, and harms, such as predictors of clinical outcome or as surrogate endpoints for early detection and for prevention intervention clinical trials;

- the timely development of biomarkers and expression patterns, sometimes of multiple markers simultaneously, which will serve as background information for subsequent large definitive validation studies in the field of cancer detection and screening;

- collaboration among academic and industrial leaders in molecular biology, molecular genetics, clinical oncology, computer science, public health, etc., for the development of high throughput, sensitive assay methods for biomarkers from an early detection viewpoint;

- conducting early phases of clinical epidemiological studies, e.g., cross-sectional, retrospective, to evaluate predictive value of biomarkers; and

- encouraging collaboration and rapid dissemination of information among awardees to ensure progress and avoid fragmentation of effort.

The ultimate impact of new technology on prolonging survival and reducing mortality will not be felt until highly predictive biomarkers are developed for earlier cancer detection or risk assessment. The success of this effort depends in large measure on exploring the concordance between genetic or molecular markers and the morphologic changes associated with premalignant and pre-invasive lesions that have life-threatening potential. In other words, we need to identify biomarkers that are predictive of clinical outcomes. Surrogate endpoint biomarkers could provide biologic insights in the short-term, and eventually provide a rationale for changes in the design of clinical trials.

ORGANIZATIONAL STRUCTURE

Definitions:

Network: This refers to a web of different intercommunicating components with defined functions and responsibilities in an overall organization. In this case, it refers to the overall organizational structure of the research proposal.

Consortium: This refers to a group of institutions conducting research in various scientific disciplines within the Network. In this proposal, it refers to the group of individual institutions in the network (i.e., the circle in the attached figure)

Network: The Network will consist of four components: (1) Consortium for Biomarkers in Early Detection Research (CBEDR), (2) a Steering Committee (SC), (3) an Advisory Committee (AC), and (4) a Data Management and Coordinating Center (DMCC) (Figure 1).

Consortium for Biomarkers in Early Detection Research: The CBEDR will consist of three main scientific components: (i) Biomarker Developmental Laboratories (BDL), (ii) Biomarker Validation Laboratories (BVL), and (iii) Clinical and Epidemiologic Centers (CEC). Each laboratory/center, which will be managed by a Principal Investigator, will include academic and industrial biotechnology investigators who are involved in cancer detection and diagnostic research. In order to expedite the translational research, the Consortium will be supplemented by the ad hoc participation of additional institutions (academic or community-based) that are able to validate the results of laboratory studies through patient accrual. The work of the Consortium will be coordinated by the Steering Committee (Figure 1).

It is anticipated that the CBEDR will consist of experts in basic molecular science, laboratory technology, clinical studies, biometry, and epidemiology. The expertise in laboratory science should include conducting research in the basic biology of preneoplasia encompassing the development and testing of biomarkers of early cancer, development of relevant technologies for biomarker detection, and analytical tools for the evaluation of biomarkers for risk assessment. The expertise in laboratory validation should include knowledge and practice of Standard Operating Procedures (SOPs), and experience in statistical evaluation methodologies for checking accuracy, precision, reproducibility and performance characteristics of tests in multicenter settings. Expertise in patient accrual and associated clinical issues for pilot studies will be needed to apply basic science discoveries to clinical settings. Computational and informatic needs of the Consortium will be supported by the Data Management and Coordinating Center. Experts in informatics will include database developers, combinatorial data analysts, and computer application program developers/specialists.

Research Member in the Consortium: Participation in the Consortium will require expertise in one or more of its scientific components. An applicant may seek funding to participate in more than one component. They will conduct research of the consortium using their core funds supplemented in some cases, as noted below.

Steering Committee: The SC will be composed of the Principal Investigators and Co-Principal Investigators from each member of the Consortium, the director of the Data Management and Coordinating Center, NCI program staff, and the chairperson of the Advisory Committee. The chair of the Steering Committee will be elected by the members of the Consortium. The Committee will decide on the frequency and content of meetings.

The Steering Committee will have major scientific management oversight, including monitoring the activities of the DMCC. Specifically, it will develop uniform criteria for the collection of clinical data, collection of tissue and blood specimens, and for instituting laboratory quality assurance. In addition, the Committee will develop common informatic and analytical tools for the interpretation of data and instruments for checking uniformity, consistency, accuracy and reproducibility of the data. It will study applied and theoretical approaches to the simultaneous analysis of multiple markers. The informatics support will be provided by the DMCC.

Advisory Committee: The AC will include members who are not participating in the Consortium. Each Principal Investigator in the consortium will be asked to nominate members for the AC. The membership to the Committee and duration will be decided by the NCI in consultation with the Steering Committee. The AC will include basic scientists, clinicians, prevention scientists, epidemiologists, ethicists, statisticians, and members from relevant advocacy groups. Scientific experts will be drawn from various disciplines relevant to multi-center detection research and experts in data management, biostatistics, and clinical study design. The Chair of the AC will be elected by its members. The Chairperson of the Steering Committee will also serve as a member of the Advisory Committee. The NCI will be represented by the relevant program staff.

The AC will independently advise the Steering Committee on relevant scientific issues, including study design, prioritization of biomarker development, development of study protocols, including decision criteria for clinical applications, e.g., early detection, prognosis, etc. The AC will also advise the Steering Committee when to move discoveries from the laboratory into clinical testing using appropriate patient groups, and evaluate the progress and success of the Network. Prospective evaluation criteria for the success of the Network will be developed.

Data Management and Coordinating Center
The DMCC will provide logistic support for the conduct of the Steering and Advisory Committee meetings, provide statistical and data management support for protocol development, conduct analysis, and informatics. It will study applied and theoretical approaches to the simultaneous analysis of multiple markers.

Funds: Operating funds will reside with (1) the Consortium For Biomarkers in Early Detection Research, (2) the Data Management and Coordinating Center, and (3) the Steering Committee.

Consortium for Biomarkers in Early Detection Research
The Principal Investigators will have funds available to support the development of the scientific program and clinical protocols. Collaborations will also be extended to investigators who are engaged in translational research on biomarkers, but are not funded through the consortium. It is

expected that the Steering Committee will establish guidelines for including such investigators. Core funds will be made available for such investigators in order to include valuable clinical collaborators who may come from outside the core group as well as from industry. All investigators will be encouraged to seek supplemental funding through SBIR/STTR, R21/R33, and other research mechanisms.

Data Management and Coordinating Center
The DMCC will be funded through a separate RFA. While the NCI plans to proceed with the funding request, its publication and timing will depend on the establishment of the Consortium and the Steering Committee first.

Core Funds for the Steering Committee
Discretionary funds will be available to the Steering Committee. Core funds can be used for a variety of functions:

1. Core funds would be used to expand the membership of the consortium through supplemental funding to an investigator's current funded grants.

2. Funds will often be needed in moving a new marker test to the point at which it can be validated at multiple centers and in larger populations. Test reagents will require scale-up at this point, and the Steering Committee will require sufficient funding to contract to laboratories or companies that can scale up production and maintain quality of the reagents (e.g., monoclonal antibodies, labels, etc.) Funds will also be required for data management, travel, group meetings, and other core activities of the group.

INTERACTION WITH THE CLINICAL TRIAL/TREATMENT COMMUNITY: Plans will include collaboration with other NIH Institutes and government agencies or departments (e.g., FDA, DOD, VA), with other NCI programs (e.g., SPOREs, Cancer Genetics Network, Breast and Colon Cancer Family Registries, Cooperative Human Tissue Network), with ongoing NCI clinical research programs (e.g., CCOP, PLCO), and with active research groups with ongoing trial core functions and laboratory support such as the Cooperative Groups, NCI designated cancer centers, international collaborators, clinical epidemiologists, and health maintenance organizations interested in early detection research. Collaboration with the DOD and VA may be expedited by the Agreement that NCI has signed, which calls for joint research in cancer prevention and early detection.

INTERACTION WITH INDUSTRY: A major difficulty facing industry is the lack of access to clinical environments for technology assessment. Creation of the Network will serve as an attractive collaborator for industry, since it will provide clinical opportunities for the evaluation of new technologies. The Network will encourage collaboration with industry on a substantial cost-sharing basis. NCI funds will be used to support the underlying infrastructure and the cost of studies not having direct implications for a company's product development or marketing strategy. However, for new technologies that are part of a company's development or product plans, the individual companies will be responsible for costs in such areas as technology standardization and quality assurance as well as scale-up of laboratory techniques, in collection and formatting of specialized data required by regulatory agencies for device approvals, in the

preparation of registration documents, and in supporting a portion of the accrual to studies pivotal for registration. It is anticipated that industry participating in the Network will not charge investigators or NCI for technologies/reagents that will be evaluated in collaborative studies. NCI views the partnership with industry as an important component without resorting to the subsidization of private companies.

Governance: The Principal Investigator will be responsible for administering and supervising research personnel, and for conducting research. The Principal Investigator will also be responsible for the expenditure of the annual budgets.

The Steering Committee will be responsible for coordinating the research effort across the Consortium, including the Data Management and Coordinating Center, and may formulate directives that will govern the operations of the Consortium. A simplified example is provided that illustrates the functions of the Consortium and the support it offers for moving basic research findings into clinical practice.

An investigator within the Consortium identifies a putative biomarker through original laboratory research. Based on the pilot research findings, the putative marker seems to be useful for early cancer detection. The investigator can then approach the Steering Committee for additional evaluation of the marker and possible support for further testing. The Steering Committee then has the responsibility to review the data on the potential marker using its standing formal criteria as a guide. The Steering Committee can consult the Advisory Committee to obtain information on the requirements and need for additional research on the marker. It also can consult the Biomarker Validation Laboratories and the Clinical Centers regarding requirements for laboratory tests, needs for quality assurance, and the availability of patient groups for clinical validation. If necessary, resources from other Centers can be pooled to conduct studies. Concurrently, the informatics team in Data Management can develop tools for the analysis of results.

There will also be flexibility so that investigators outside the Consortium could form collaboration with one of the existing centers, or directly bring their discoveries to the Steering Committee (e.g., by Letter of Intent). To support such efforts, the Steering Committee will be able to use core funds to supplement the investigator's ongoing research. The investigator, in turn, will agree to share his research findings and become part of the Consortium.

JUSTIFICATION FOR COOPERATIVE AGREEMENT: The mechanism of support will be the Cooperative Agreement. This mechanism is appropriate because the participating organizations will have the responsibility for defining the scientific objectives and approaches needed. The purpose of this RFA is to encourage and to facilitate interdisciplinary collaboration among organizations (institutes and/or consortia) toward a common coordinated national effort in research in early cancer detection. Substantial NCI involvement is anticipated in order to: (1) facilitate interaction among the centers, (2) coordinate their efforts with other ongoing NCI and non-NCI initiatives, (3) promote the use of this resource among the scientific and medical communities, and (4) solicit the presentation of research proposal's requesting the utilization of the laboratory science discoveries, epidemiologic data and biologic specimens. It is anticipated that prioritization of proposals requesting access to technologies/reagents developed through the

Consortium for Biomarkers in Early Detection Research will be made by the Steering Committee in consultation with the Advisory Committee.

CURRENT PORTFOLIO ANALYSIS: There are no standing activities supported by NCI that have as the goal the "vertical," sequential development of biomarkers for early detection, beginning with basic discovery, to translational research, and to clinical validation. Also, there is no existing NIH mechanism to expedite technology transfer across a broad spectrum of sciences applicable to technology development from laboratory to clinical application. Portfolio analysis suggests that developmental studies in biomarker research that originate in academic centers have nowhere to go for definitive comparative testing or for validation, because there is little formal connection between biomarker laboratory research and clinical application. Microsatellite analysis, for example, has been rigorously tested for its analytical accuracy and found to be associated with the early phases of tumor development. However, its value in screening is yet to be determined. Hereditary cancer markers, such as APC, hMSH2, hMLH1, hMLH2, and other serum-based markers, such as PSA, and CA-125, are being widely used without having undergone validation and knowing if there is net benefit or harm as a result of their application. A gap exists between basic research in preclinical early detection and the means for clinical testing. At present, investigators develop molecular and genetic markers, and then move on to new markers without validating the utility of previous ones. Validation studies do not often fare well within the present peer-review system, because these studies are not necessarily considered innovative, and they are also considered expensive.

PROGRAM EXPECTATION/EVALUATION: The establishment of improved strategies for the identification of individuals with small neoplastic or preneoplastic lesions with reasonable probability of progression (and that are amenable to cure) is the primary goal of this research program. It is anticipated that the research will develop and evaluate an ensemble of biological markers that will indicate the presence of early cancer or preneoplastic events. An ensemble of markers is likely to be more useful and a better predictor of disease status than a single marker or a narrow range of markers that might focus only on one or two pathways in carcinogenesis. Such a strategy will require a multidisciplinary, mufti-institutional approach, such as the Network presented here.

There is no precedent for this model. However, the present concept has been inspired by the successful launching of *The Cooperative Trials in Diagnostic Imaging* by the Diagnostic Imaging Program (DIP). The Early Detection Research Network will closely interact with DIP and learn from its experience to periodically evaluate the success of this model. It will involve the members of the various advisory groups, such as the Board of Scientific Advisors and the National Cancer Advisory Board, to help evaluate the program against the criteria established by the Advisory Committee.

PROMOTION: A critical element for success will be promotion of the Program. Editorials and commentaries describing the objectives of the Program will be prepared and submitted to major medical journals. Professional organizations will be specifically requested to publicize the Program through their newsletters and to provide time for NCI presentations at their annual meetings. Program plans to work with the Office of Cancer Communication in disseminating information about the Program, especially through the press. Various industrial related

organizations will be contacted about the Program and scientific directors invited to NCI. Periodic workshops and symposia will be held on the research progress of the Consortium, which will be published. An interactive Web page will be created to announce the availability and receive input from investigators at large. Letters of Intent to collaborate will be encouraged. In addition, members of the Consortium and other committees will be asked to publicize the Program.

BUDGET: The Network will be funded through a Cooperative Agreement. $3.0 million dollars for the first year, $10 million in the second year, and $12 million dollars each year after for a total of six years are requested. The total cost is split into the following components: $4.6 million to Biomarker Developmental Laboratories (10-12 awards); $2.0 million for Biomarkers Validation Laboratories (2-3 awards); $3 million to Clinical/Epidemiology Centers (3-4 awards) which includes $2 million for patient accrual (2000 patients @ $1000/case) which will not start until year 2 and reimbursement will be based on per case basis; $400K for Data Management and Coordinating Center (one award), and $2 million as Core Funds to the Steering Committee to support collaborations with investigators within and outside the network on a competitive basis. This core fund will reside with the Steering Committee. The yearly budget is shown below:

Fiscal Year	Budget (in million dollars)
1999	03
2000	10
2001	12
2002	12
2003	12
2004	12

Note: The first year budget will be used as startup fund for planning, coordination, and initial round of funding to Biomarker Developmental Laboratories.

Attachment

EARLY DETECTION IMPLEMENTATION GROUP

Meeting Dates and Roster

Meeting Dates:

March 10, 1998
April 6, 1998
May 11, 1998
August 13-14, 1998

Roster:

NON-NCI

Pelayao Correa, M.D., Louisiana State University Medical Center
Virginia L. Ernster, Ph.D., University of California at San Francisco
Alfred Knudson, M.D., Institute for Cancer Research, Fox Chase Cancer Center
Nancy C. Lee, M.D., Center for Disease Control and Prevention
Bernard Levin M.D., UT M D Anderson Cancer Center
John D. Minna, M.D., UT Southwestern Medical Center
Mary Ann Napoli, Center for Medical Consumers
Martin M. Oken, M.D., Virginia Piper Cancer Institute, Minneapolis
Wesley Scholes, M.P.A., Scholes & Associates Consulting Firm
Susan L. Scherr, Director, Community/Strategic Alliances
David Sidransky, M.D., Johns Hopkins University
Barbara Tilley, Ph.D., Henri Ford Health Sciences Center
Nicole D. Urban, Sc. D., Fred Hutchinson Cancer Center
Sally W. Vernon, Ph.D., University of Texas, School of Public Health

NCI

Michael Birrer, M.D., National Cancer Institute
Leslie G. Ford, M.D., National Cancer Institute
John K. Gohagan Ph.D., National Cancer Institute
Richard B. Hayes, Ph.D., National Cancer Institute
Robert A. Hiatt, M.D., Ph.D., National Cancer Institute
Barry S. Kramer, M.D., M.P.H., National Cancer Institute
David G. Longfellow, Ph.D., National Cancer Institute
Arnold Potosky, Ph.D., National Cancer Institute
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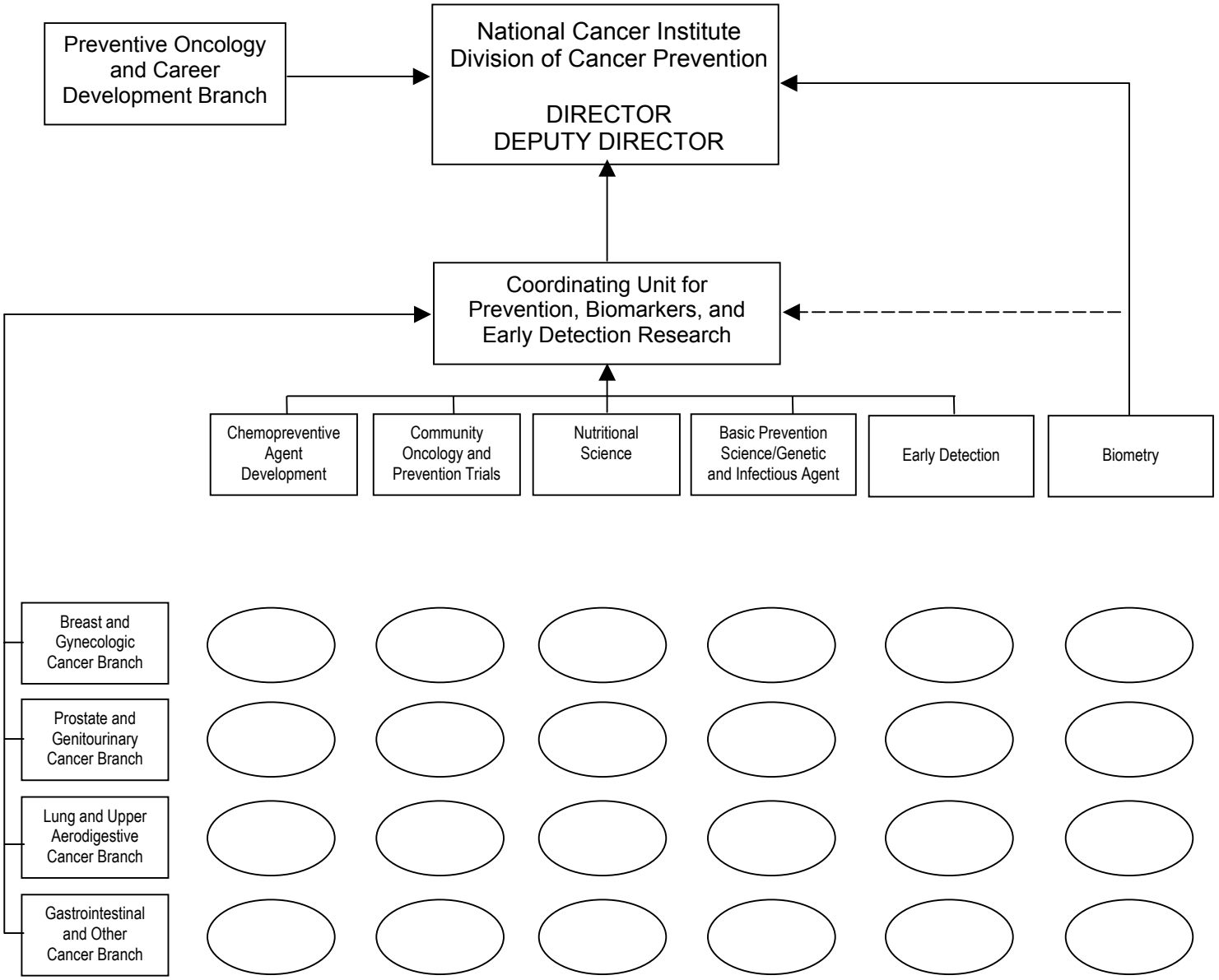
WORKING DRAFT



National Cancer Institute (NCI)/Division of Cancer Prevention (DCP)
EARLY DETECTION IMPLEMENTATION COMMITTEE MEETING

May 11, 1998

MEETING REPORT

Introduction and Welcome

Dr. Barnett Kramer welcomed the members and speakers to the third meeting of the Early Detection Implementation Committee. To ensure that everyone had a copy of the 10 questions on which the Committee is focusing, he arranged for these to be copied and handed out. Following a round of introductions—during which new members were particularly welcomed—Dr. Bernard Levin, Co-Chair, read through the 10 questions, noting that some are also being addressed by various NCI offices. (For ease of reference, the list of questions is appended to this report as Appendix A.)

The meeting packet—containing the agenda, a list of planned meetings (dates and locations), the draft April committee action report and meeting report, a set of NCI function statements, a recent article on intraepithelial neoplasia and surrogate endpoints, and the Report of the Cancer Prevention Working Group—was distributed in advance of May 11 to committee members.

Dr. Kramer noted that the second meeting had featured discussion of behavioral and risk prevention subjects as well as a briefing on related activities of the new NCI Division of Cancer Control and Population Sciences and that this third meeting will focus on biological approaches—including (1) evaluation of biomarkers and (2) early detection technology.[1]

Strategies on How to Develop a Biomarker

Dr. Sheila Taube

Dr. Taube provided hard copies of her slides and entitled her talk as "Why don't we have more markers that are reliable?" She then reviewed the marker development process, pointing out complexities, pitfalls, and the high dropout rate of promising markers. Her broad definition of the term marker was "a characteristic of a cell or tumor that provides information to the physician to aid clinical decisionmaking." Examples ranged from the type of genome to RNA, secreted protein, and even the status of lymph nodes as an indicator of the ability of a primary tumor to spread.

The potential uses of markers during screening are to identify risk and to detect early lesions. During an office visit, markers could aid in differential diagnosis, helping to determine the next tests to be performed, to predict outcomes, to guide therapeutic choices, and to evaluate response to therapy or detect recurrences.

Marker development can start with the identification of a clinical need and the identification of a characteristic potentially useful as a marker. Such a characteristic may be identified while studying

[1] The presentation of Family Registries/Cancer Genetics Network by Dr. Susan Nayfield that was scheduled for May 11 has been deferred until after the announcement of the grant awards for the new network.

tumor biology. In early clinical studies, a researcher looks for a correlation with a parameter of interest—such as tumor stage or grade. A method of assay must then be developed. Eventually, the first crude assay must be turned into a standardized assay system with reproducible results. In choosing between alternative assays, the evaluation takes into consideration not just sensitivity, specificity, and laboratory performance but the context of clinical usefulness. For screening, the least invasive test is desirable as well.

Screening for early lesions is more straightforward than identifying risks, which can be complicated by environmental interactions and the degree of genetic penetrance. To study markers of risk can require large populations and a long time. A study, whether large or small, must be designed with sufficient statistical power to test the hypothesis. If disease prevalence is not known, the sensitivity and specificity characteristics cannot be determined. Until all the comparisons to be included in a study have been identified, sample size cannot be calculated.

To validate a marker, it must be tested with a fresh set of samples or patients to determine if the behavior is the same as in earlier studies. It must also be tested in the same format as the clinical samples that will be run. In addition, the test needs to be run in such a way that the evaluators are "blinded" to clinical information about the samples.

Dr. Taube described prostate-specific antigen (PSA) as an example of a marker that is in use despite not yet having been properly validated as a screening tool for prostate disorders. The Food and Drug Administration (FDA) approval was granted for use of PSA in monitoring, not for early detection. As discussed at an earlier committee meeting, the PLCO (prostate, lung, colon, ovarian) screening trial may provide the data to prove whether PSA is useful for screening.

Dr. Taube noted that for in vitro devices, FDA regulates labeling, not clinical usefulness. If a device can perform a certain measurement, it is not necessary for that measurement to have proven clinical utility. In addition, under new regulations for tests that are not invasive, FDA is not required to ask an advisory panel to review the results of studies—although the agency may ask a panel to advise in advance on the study design.

Discussion of Dr. Taube's presentation

Dr. Minna, who reminded the group that this is his first meeting, asked about the types of early detection under discussion. Dr. Kramer indicated that the DCP focus is on screening to identify risk and detect early lesions (the first two indications for markers on Dr. Taube's slide 3)—that is, detection that has a chance of changing the outcome. Dr. Minna suggested it might be possible to conduct a quantitative assessment, setting a particular value for the odds ratio. However, Dr. Kramer replied that the situation is more complex for several reasons—including the uncertainty in the relative risk when, for example, the value keeps decreasing with each additional study of the breast cancer genes BRCA 1 and BRCA2. Dr. Taube commented that Dr. Minna is speaking about defining useful characteristics for a marker while Dr. Kramer is addressing what the relative risk must reach to make it possible to study a genetic marker. Translating to the general population can be challenging after working with families that have high penetrance. Dr. Minna then asked if behavior that puts an individual at risk could be a marker. Dr. Kramer indicated that behavioral markers are not currently included; the group is focusing on the assessment of technology. Using cervical cancer as an example, Dr. Kramer mentioned that smoking and sexual behavior are not

markers, but the human papilloma virus (HPV) is. Dr. Kramer also verified that inherited risk factors are included.

Dr. Taube inquired why Dr. Kramer had not cited the third item on her third slide— "at time of office visit to aid in differential diagnosis"—when specifying situations in which markers can help. She commented that markers can receive faster and better evaluations in that context. Dr. Minna suggested that this approach is useful for identifying whether prostate cancer has a benign course versus neoplastic lesions and for using mammography to categorize women as having no problem versus DCIS (ductal carcinoma in situ) versus a neoplastic condition. Dr. Kramer said that DCP considers screening to be a process applied to "subjects" who are asymptomatic individuals who may have self-referred but who have no a priori reason for having a malignancy. In contrast, "patients" have disorders requiring problemsolving. Dr. Urban added that even for an asymptomatic individual, a marker can help determine whether to go beyond a routine physical examination to do a test, such as a biopsy. Dr. Kramer then noted that exceptions tend to be made to rigorous definitions when we want to help individuals suffering from disease and that it would be helpful to have a group like this one develop objective criteria. The criteria might spell out what information is needed before going to the next step.

Dr. Levin suggested that while the current focus is on early detection, Dr. Taube's other uses for markers could be incorporated later. Dr. Taube remarked that the hypotheses and endpoints are different for the two types of studies. She mentioned that mammography is useful at identifying risk but is not really diagnostic. Yet, Dr. Kramer commented, the Health Care Financing Administration (HCFA) requires the funding of mammography for cancer testing.

Dr. David Sidransky

Dr. Sidransky identified his topic under the general subject of biomarkers as "From the bench to the bedside: Designing a molecular diagnostic test." He listed the basic steps in marker research and development as (1) the concept—that is, a new idea (for a marker), (2) a new approach (assay), (3) proof of the principle (does it have value?), (4) revising or improving the approach, (5) pilot feasibility studies (in paired samples), (6) technology enablement (ensuring that more than one laboratory can apply the approach), (7) prospective monitoring trials, and (8) a prospective screening trial. In discussing each of these steps, Dr. Sidransky stressed the factors needed to accomplish the goal and the pitfalls that might interfere.

Using a colon progression model, Dr. Sidransky said that it would be useful to be able to identify markers (e.g., histopathologic changes) that indicate when to expect progression to the next stage, such as... normal epitheliumohyperprolific epitheliumoearly adenomaointermediate adenomaolate adenomaoneoplasia. This is an example of the first step in marker development—coming up with a new idea or new approach. Ideas can flourish in a rich environment, with access to experimental tools, dedicated scientists, and sufficient funding and recognition. Poor funding mechanisms, a lack of commitment, and insufficient research tools are among the pitfalls.

Dr. Sidransky reported that development of the ability to identify a *ras* mutation in urine, tumor, and stool led to molecular screening studies in bladder, colon, pancreas, and lung cancer situations. One different approach is based on the concept that some cancers are clonal. His laboratory made an observation related to microsatellite instability (MSI), compared markers, and sought funding

from a biotechnology company after failure to obtain R0l grant funding from NIH. The behavior of the markers appeared to be clonal.

To prove the original hypothesis, Dr. Sidransky indicated that the research group needed molecular competence, access to a cancer panel, clinical samples, and application of a critical interpretation to the results. He expressed particular concern about the deficit in critical interpretation that he has observed in publications in this field. For the pilot testing that rechecks the hypothesis, access to samples as well as establishment of boundaries and application of critical interpretation is again needed. Potential pitfalls include a poor assay, poor sample collection, and poor interpretation.

The Hopkins group decided to develop a panel of 10 to 15 markers to test in a blinded fashion with bladder cancer. New alleles were observed in tumor and in urine. There were chromosome deletions and loss of heterozygosity. In the pilot study, the assay detected 19 of 20 cancer cases and 2 of 5 reinflammations and was negative for all 5 of the controls. However, as the number of markers could not define all patients, the researchers decided to expand the number of markers to 20 in the next study, which was a small monitoring trial (i.e., the subjects have the disease, so this is not a screening). A better assay was developed. It was also time to consider statistical analysis. In this trial, the assay identified all cases of invasive (10) and high-grade (14) disease as well as 10 of 11 recurrences (91% sensitivity). The identification of recurrences was far better than that possible using cytology. Both urine and cancer tissue were tested at 0, 9, and 13 months.

The next step scheduled was a larger, multisite trial in which individuals were followed at 6month intervals. This study is ongoing but hampered by the fact that the industry partner is currently under financial stress. A new collaboration with Rich Mathes using a capillary system will permit 96 markers to be tested simultaneously. Other collaborators and funding for technological development are needed. If this trial can be completed, screening trials could be conducted next with a robust assay and a continuing low false positive rate, but a very large study population would be needed.

Dr. Sidransky made the following recommendations: (1) Establish centers of molecular diagnosis making available a wide range of expertise and ability. (2) Increase R01 funding for biomarker research. (3) Encourage collaborations with industry. (4) Develop a national diagnostic trials group with national cohorts and biorepositories.

Discussion of Dr. Sidransky's presentation

One committee member offered the interpretation that Dr. Sidransky's group had conducted observational studies, not trials. However, Dr. Sidransky said that the studies fit his definition of trials. Dr. Minna stressed the importance of conducting prospective blinded studies and obtaining informed consent to use samples.

Dr. Taube suggested that the hypothesis one is trying to prove can affect study design. Dr. Minna described Dr. Sidransky's first hypothesis as whether one could use genetic abnormalities to detect bladder cancer in cells shed into urine by individuals with clinical cases. A second hypothesis would be that asymptomatic individuals can be screened to predict who will have bladder cancer. However, Dr. Ernster pointed out that this second hypothesis was not examined by the Hopkins group. The group did examine whether the test could predict or detect recurrence. Dr. Ernster also

offered the opinion that the term "false positive" should not be used with the study of recurrence since all subjects have had the disease.

Dr. Knudson asked whether it is possible to predict the number of cells in a tumor from the number detected in urine. Dr. Sidransky said that about 50 cells are needed for detection in urine. It is possible to use the urine test to identify tumors of less than 5 mm in diameter and about 1 to 10 million cells. Dr. Knudson also inquired about the ability to use blood samples. Dr. Sidransky noted that this depends on the type of cancer; he has observed low detection for bladder cancer but higher for kidney cancer.

Dr. Taube raised two questions—whether screening should be done for every disease and what the criteria for screening should be. Dr. Kramer pointed out that there are not enough resources to screen for everything. One criterion beyond incidence should be prevalence. Dr. Taube asked about screening populations that are at relatively high risk. Dr. Kramer liked the idea of establishing criteria for developing screening tests and said that the impact of the disease would be another criterion. He suggested a gathering of public health consultants and scientists to work on the criteria. Dr. Ernster proposed three criteria: (1) a certain percentage decrease in mortality for a particular cancer (e.g., 33% for colon cancer); (2) the number of subjects to be treated or screened in order to extend life (saving one life or avoiding an event or saving from premature death); and (3) the extent of unwanted consequences of screening (e.g., the false positives). Dr. Kramer noted that these three criteria are applicable only after a marker has been developed and undergone a trial. One concern is whether the trial is conducted using populations that reflect the actual eventual use of the marker.

Dr. Srivastava noted that no one had addressed yet how long it takes to develop a marker. For hereditary nonpolyposis colon cancer (HNPCC), 60 years were needed, and for BRCA1, 20 years. Dr. Hayes suggested a backward view from the cancer to assess adenomal stages, localized disease, and pre- or asymptomatic conditions even though this requires much work. Dr. Kramer commented that applying this approach could prevent premature broad application of still-unproven technology. Dr. Taube added that if a test is useful for detecting recurrence, it still has to be evaluated for ability to detect early stage initial lesions. She agreed with Dr. Hayes that screening for different stages is usually inadequate. Dr. Sidransky said that the performance of TAG1 is fairly good with an 80% identification rate. Dr. Minna recommended concentrating on genetic changes for which there is strong biological evidence of a connection to tumorigenesis.

Cancer Genome Anatomy Protect (CGAP)—Dr. Robert Strausberg

Dr. Strausberg explained that CGAP, which is now 1 year old, aims to carry out a comprehensive molecular characterization of malignant cancerous and precancerous cells. After an overview, the plan calls for narrowing to the most informative markers. This molecular approach might include modulators of carcinogenesis, hormones, and host factors. Alterations in DNA, expression, and proteins can be examined—looking, for example, for protein interactions and communications. To be successful, CGAP wants to involve the technology and cancer communities to achieve an integrated system of molecular analysis.

The timeliness of this project devolves from the accumulated evidence for molecular bases for cancer, the new high-throughput technologies for molecular analyses, and the information base

that is developing from the Human Genome Project. An early step is to establish an index of genes that are expressed in tumor cells, along with their normal counterparts. One approach to gene discovery is to identify tissue types in which a high rate of gene discovery can be expected. Another approach is to look for genes that are uniquely expressed during progression to and in cancer. The tool of laser capture microdissection, developed at NCI by Lance Liotta and colleagues, can be applied to obtain very small sections and even individual cells. cDNA libraries are then established for sequencing genes of normal and precancerous tissue as well as different stages of cancerous tissue. Each library is derived from a single tissue sample or occasionally from pooled samples. The libraries derive from both microdissected and nonmicrodissected tissues. The initial focus in implementing CGAP is on five types of cancers—breast, prostate, lung, colon, and ovarian.

Dr. Strausberg invited committee members to visit the CGAP website (updated weekly at *www.ncbi.nlm.nih.gov/ncicgap*) and provide him with feedback (301-496-1550). CGAP plans to conduct some analyses itself but encourages others to access its libraries and conduct their own studies. Dr. Strausberg showed a sample visit to the site using the prostate library and categorizing genes as tissue unique, tissue specific, or highly regulated. Initially, the site did not include precancerous tissue but that will be added shortly. Histology is provided for a range of tissues—for example, normal prostate tissue, low-grade prostatic interstitial neoplasia (PIN), high-grade PIN, and prostate cancer. When nothing else is known yet about a gene, it can still be categorized by an expressed sequence tag (EST) of about 300 nucleotide pairs. Data on the website are also provided to GenBank.

Currently, CGAP has about 22,000 sequences, and more than 5,170 new genes detected. Dr. Strausberg illustrated this graphically, showing the CGAP discoveries as part of some 400,000 genes that have been detected. As an example of a discovery that might have immediate benefits, Dr. Strausberg mentioned the identification—using a CGAP EST and cloning a full-length gene—of a gene for a catalytic subunit of telomerase by Tom Cech and colleagues. CGAP has begun to apply electronic analysis to examine the uniqueness of expression of genes. A discovery by Ira Pastan's lab at NCI of three genes unique to prostate tissue (out of seven selected by ESTs) was reported in a January 1998 research paper.

The current focus on gene discovery includes positionally cloned genes, oncogenes, and tumor suppressors. The EST database is searched for matches (to date, 90.5% for positionally cloned and 95% for oncogenes and tumor suppressors). Dr. Strausberg indicated that CGAP is examining whether the project can maintain records of these matches and is assessing the informatics resources that would be needed to do this. The intent is to share everything of value with the research community.

CGAP goals for 1998 include continuing sequencing, mapping ESTs, full-length sequencing of selected materials, identifying nucleotide polymorphisms, interfacing with gene expression technologies, and starting up a mouse tumor gene index. The mouse CGAP model would permit some kinds of testing and other research that cannot be done in humans but that can be used to draw parallels with human cancers.

The range of participants in the NCI tumor gene index project includes collaborators at NIH (both within NCI and at other NIH Institutes) and extramurally. For example, one group of collaborators

is involved in library preparation, another in library arraying, and still others in DNA work and clone distribution. The overall aim of CGAP is to find out at what stage of a cancer an impact can be made.

CGAP Discussion

Dr. Knudson inquired about finding that a gene is overexpressed in a number of different cancers. Dr. Hayes suggested that—for screening—the subsequent step might be to look for message transcripts in the sera of prediagnostic samples. Dr. Kelloff asked about the availability of tissue resources. Dr. Strausberg said that CGAP is interacting with the community to expand its sources. There are groups who want to contribute. However, pediatric samples are not yet available. For high-quality libraries and sequences, the CGAP group wants to confirm the analyses of other groups.

CGAP does have a steering committee to help guide the project. One criterion in selecting genes to examine is their patterns of expression. The steering committee is focused on getting the current project accomplished; it has not discussed what the next stage should be. Dr. Taube commented that she agrees with Dr. Sidransky on the need for biorepositories. She is on the steering committee and views CGAP as a database that researchers will use as a resource in their initiatives.

Dr. Levin asked how preneoplastic tissue is identified. Dr. Strausberg noted that microdissection is used to obtain different cell types. Usually, the preneoplastic tissue is adjacent to a tumor. Tissue labeled as normal showed no pathology near a tumor section when obtained by microdissection. Bulk normal tissue is not checked in this way. No clinical follow-up is linked to the tissue collection. Dr. Sidransky commented that it would help investigators to know the genetic status. Dr. Strausberg said that this information is obtained more reliably with a larger number of samples and correlation with expression. (Dr. Sidransky indicated an interest in lowexpression genes and whether they might be below p53 in a pathway; he and Dr. Strausberg agreed to confer later on this subject.)

Drs. Lee and Ernster raised a question about whether tissue adjacent to an invasive cancer is truly representative of the preneoplastic state. The genetic makeup of the two adjacent tissues is also relevant. Drs. Hayes and Minna expressed concern about localized tissue samples being too narrow. For example, a lung cancer can affect epithelia quite distant from the lung, presumably by clonal genetic changes.

Dr. Strausberg reported that clones will be discussed at a meeting in early June. Dr. Minna suggested that the Early Detection Planning Committee might be able to provide input. One issue will be the size to require for clones—possibly 2 kb or longer. The difficulty of obtaining a full-length sequence could be assessed. The Office of the NIH Director is providing $2.5 million this year to initiate full-length sequencing. Dr. Minna commented that an early detection trial would cost much more than $2.5 million.

Dr. Strausberg also asked the planning committee for suggestions on how to make CGAP more useful. Citing the $20 cost per clone, Dr. Minna said that it would be valuable to know the expression patterns of preneoplastic lesions. He suggested that the expression data obtained by

users of CGAP samples should be reported back to CGAP and shared. Dr. Longfellow indicated that it should be possible to link the biology with the molecular status; he is therefore concerned about the "pure normal" tissue being a random grab. Dr. Sullivan said that this is particularly important if we are relying on one or two samples—not a larger number, such as 20.

Dr. Minna added that information on alterations and loss of heterozygosity is also missing from CGAP. Dr. Strausberg then asked committee members to think about how they could use comprehensive molecular analyses. He invited everyone to contact him later with their additional comments and questions.

General Discussion

Dr. Levin proposed focusing first on the third of the 10 questions, discussing possible mechanisms and the advice to give NCI. Later, the Committee addressed some of the other questions and made plans to consider still others at future meetings.

Question 3

3. What is the critical pathway to be followed in validating early detection molecular or secreted protein markers?

Dr. Levin posted a copy of Dr. Ernster's three criteria (from the morning discussion) and asked committee members to share their ideas on the best structure to set up. [The three criteria were (1) a certain percentage decrease in mortality for a particular cancer (e.g., 32% for colon cancer); (2) the number of subjects to be treated or screened in order to extend life (saving one life or avoiding an event or saving from premature death); and (3) the extent of unwanted consequences of screening (e.g., the false positives).] One committee member raised an additional question to think about— "validating for what?"

Dr. Urban asked whether the search is for a marker specific to a particular organ or sensitive to cancer but not necessarily specific to an organ site. She views the earliest possible detection as the ideal. Possibly, what is needed is a group of markers. But what criteria should we use in choosing markers? Examples are extreme over- or underexpression or presence in a large proportion of cancers. Dr. Urban added that part of the validation process is verification. She suggested a nested case-control design to check for a marker prior to diagnosis and proposed focusing on markers for cancers that would cause death if not detected and treated. However, Dr. Lee pointed out that some cancers—for example, cervical and colon cancer—no longer kill in all cases; for these, the aim is to reduce morbidity. Dr. Taube stressed that this is why it is important to define the endpoint. In later discussion, she pointed out that a marker present in all cancers would be impractical as screening would then have to be applied to every organ. Nevertheless, one has to pursue markers that are not specific for only one organ.

Ms. Napoli expressed concern about how to be sure that the surrogate pathway is correct when trying to separate out preneoplastic conditions. Dr. Kramer said that one advantage of studying cervical cancer is the 50 years of information about a marker. For other situations, it may be necessary to apply various technologies. For example, traditional mammography and magnetic resonance imaging (MRI) may turn out to identify different types or aspects of breast lesions.

Dr. Minna proposed listing general classes of markers. He cited (1) acquired genetic changes in cancer (e.g., mutations, loss of heterozygosity, microsatellite alterations, amplifications, and methylations); (2) cancer-cell-specific changes in marker expression (with or without a somatic genetic basis); (3) changes induced in the host (e.g., antibody or T-cell changes); and (4) genetic eidemiology (markers for which the DNA can be genotyped to see if there is a heritable basis for increased risk). For all of these, a first test is the presence of the marker in the patient with early-stage cancer detectable by clinical instruments or tests but absent in individuals without cancer. The next step would be a test involving individuals with high-grade preneoplastic regions versus individuals without cancer. Dr. Kramer expressed concern that broad screening approaches would mean having to test one-third of the population periodically since the rate of having a cancer is 1 in 3 in a lifetime.

Dr. Tilley commented that she liked the differentiation in Dr. Taube's handout between outcome and endpoint of the marker of interest. She views the endpoint as what one is trying to prevent and the outcome as what to measure. Dr. Kramer noted that FDA focuses on technical outcomes. As a member of FDA panels, Dr. Taube reported that FDA staff have advised her panels that their interest in clinical decisions is not relevant to their business.

Dr. Vernon suggested that the process of developing and evaluating markers needs to include cross-validation all along the pathway using independent samples. Another methodology issue involves looking for opportunities to use multiple methods to measure a potential outcome and identifying the overlap between different tests and their reliability.

Dr. Ernster developed a flow chart of basic science steps leading to clinical trials of markers ("biological footprints") and decreases in cancer mortality and morbidity (a version of the chart is provided as Appendix B). She said that the key question is how to get from the basic research steps to clinical effect. One starts by comparing abnormalities in tumors with normal tissue from the same patient. Sometimes a marker can be compared in tissue from the same patient for precancerous and invasive conditions. Sometimes the tissue must be compared from two different individuals. Sometimes individuals with invasive cancer must be compared with individuals without cancer. It is important to determine if and how a marker varies in distribution across the range of precancerous to cancerous conditions. A mix of these comparisons may be better than choosing one as a priority and might provide some cross-validation. Factors for which measurements should be built into the clinical trials design include false positives, number needed to treat, relative risk, and absolute risk.

Dr. Ernster also offered two caveats: (1) to try to find the cancer early enough to make a difference but not necessarily as early as possible and (2) to be aware that if preneoplastic tissue is surgically removed—as is frequent in the United States—then there is no way to follow up marker changes using it. She also noted that conducting studies of markers over time, comparing individuals who are tested with others who are not, can require 10,000 to 100,000 subjects. Justifying the expense is difficult. She recommended setting up nested cohort/biorepository studies.

Dr. Knudson commented that validation issues apply even to the discovery stage. For example, overexpression can include some housekeeping genes. Dr. Strausberg recommends setting a cutoff—such as a minimum overexpression level of tenfold (to avoid "noise"). Then one might be dealing with a manageable number of genes, perhaps 10 to 100. The field of prostate cancer may

be ready now for such a study. Overexpression is easier to detect than underexpression. An alternative to the overexpression approach is the approach of finding genetic abnormalities in tumor cells, as described earlier in the meeting by Dr. Sidransky.

Dr. Knudson said that another question is whether early tumors show changes. For example, can adenomas that never progress be distinguished from adenomas that are precancerous? A related question is where to look for early tumors. Presumably, this would be in individuals with high early risk because of risky behaviors or known genetic factors. Working with high-risk individuals shortens the time and the number of subjects needed to obtain answers. (Dr. Knudson also noted that the pathways tend to be similar for hereditary and nonhereditary situations.)

Dr. Kramer commented that we need to know the natural history but are too impatient and perturb it—that is, remove preneoplastic tissue that may not need to be removed. Dr. Knudson mentioned the wide range of natural history with regard to mortality. For some cancers, 10 million cells lead to 90% mortality. For others—for example, Burkitt's lymphoma—despite 100 billion cancer cells, the cure rate is 90%. Dr. Kramer suggested that in a randomized prospective trial detecting lesions and then treating them, it should be possible to learn more about the natural history.

Question 9

Dr. Levin then introduced a discussion of Question 9 and asked other meeting participants to comment.

9. Is the organizational structure of the early detection effort ideally configured for early phase (or preclinical) and clinical screening studies?

Dr. Kramer observed that if trials of 10 to 15 years are needed, the R01 mechanism of funding by NIH would not be practical. When asked about the current structure at DCP, Dr. Kramer explained that the Early Detection Branch focuses on screening of asymptomatic individuals, Dr. Taube is involved with a cancer diagnosis program addressing established disease, and Dr. Sullivan's program deals with diagnostic imaging. The Early Detection Branch tries to cover the whole range from preclinical validation to trials.

Extramurally, there are various possible approaches. For both the PLCO screening trial and the American Cancer Society (ACS), a design was built up and then the project was contracted out. Another approach is the cooperative group structure, of which the Community Clinical Oncology Programs (CCOPs) is an example. This is the mechanism for running the breast cancer prevention trial and the prostate cancer prevention trial.

Dr. Kramer commented that it is cumbersome to build a mechanism each time; an existing vertical structure would be helpful. Dr. Lee said that a vertical structure would be appropriate for early phases, but she wondered how to maintain interest and participation at the trial stage. Dr. Kramer suggested then going to a horizontal design like the cooperative groups and CCOPs.

Dr. Lee then raised another problem—that of having enough subjects for definitive screening studies. Dr. Kramer indicated once again that once a vertical structure carried through the early studies, he hopes that CCOPs could handle the large-scale trials. The vertical structure would need

to include a range of individuals with different expertise. A committee could decide which markers to develop and who should participate in trials. Dr. Tilley noted that besides CCOPs, there is a large primary care network with access to patients. She suggested not always "looking in the same place." Dr. Taube recalled that in studying TAT1 bladder cancer, the primary care patients with low-grade tumors tended to have physicians who were not at the teaching centers where the researchers were. Dr. Tilley suggested that links can be established. Dr. Oken agreed with the idea of bringing in primary care and public health professionals as well as individuals in diagnostic specialties, such as diagnostic radiology. He also proposed clearly defined links to biorepositories. Dr. Kramer emphasized that access to a sufficient number of subjects is critical (as was illustrated in Dr. Sidransky's talk earlier in the day). Dr. Oken added that the structure must include evaluation of testing and screening.

Dr. Kramer also mentioned one model that is being set up now—a diagnostic imaging network. Participants will not all have the same capabilities and assignments. Dr. Tilley said that this might work with flexibility, but she would prefer a structure in which an announcement (RFA) was done for each level—not all of them together—and with specifications that links must be made. Dr. Kramer did not agree with this approach. Dr. Tilley described it as setting up an announcement to establish a network that requires links through all levels from basic science to general patient population studies but allows potentially different institutional/scientific membership at the different levels.

Dr. Ford suggested that an HMO-network that awaits funding might be able to provide subjects for early detection and screening trials. She also hopes that businesses will become involved as they begin to recognize that early detection is better for their "bottom lines."

Dr. Minna remarked that the major oncology cooperative groups seem to be reorganizing to aim for prevention funding. In his opinion, this is not the best approach. Dr. Ford commented that the cooperative groups are not all equal in ability; some can change their "corporate culture" more readily than others. However, none have experience yet with screening, early detection, and molecular markers.

Dr. Minna recommended a setup involving centers and a cooperative network, bringing in imaging, primary care, and public health as well as surgeons and pathologists. Another committee member stressed the importance of facilitating communication between basic scientists and epidemi-ologists. Dr. Kramer suggested that the structure would also need common ground rules as well as statisticians. Dr. Oken said that this needs to be a dedicated structure. Dr. Tilley reminded the group that Dr. Sidransky was concerned about the lack of funding for hypothesis generation. Dr. Ford said that there is a recently published program announcement for early phase, exploratory studies. She noted that reviewers have frequently called the design of such studies poor. Dr. Tilley suggested that this provides another good reason for supporting a structured designated group.

Dr. Levin inquired whether the Centers for Disease Control and Prevention have any involvement in the types of work being discussed. Dr. Lee said that the Center for Environmental Health and some other parts of CDC are doing some biological and molecular studies; her own division is not involved.

Dr. Urban asked if the proposed network would be organ specific or one big network. Dr. Kramer indicated that many issues will be similar regarding early detection and specificity, so the network as a whole would not be organ specific; however, access will be needed to organ system information. Dr. Urban commented that sometimes collaborations are easier to arrange around a specific organ.

Dr. Kramer proposed that a center of molecular diagnosis as well as basic laboratories should be part of the network. Some research in picking up markers could be done through CGAP or elsewhere.

Dr. Kaplan recalled that originally the cooperative treatment groups generated ideas leading to trials. This is no longer the case although CCOPs still does this to some extent. In a new network, he anticipates that the earliest studies could be conducted with a modest number of centers and patients. There would then be a transition to larger scale studies and the participation of primary care patients. One structural element that has helped the treatment trials is an organization that sits in the middle. It is important to anticipate future needs—such as the bladder cancer marker study needing many urologists as the study proceeded even though they were not needed at the start. Dr. Kaplan suggested that the chosen structure will need to separate out systems for generating ideas and for executing large trials. Dr. Ford agreed that the group active in the earliest phases would be different from the group conducting large-scale trials. The latter might even revert to CCOPs and a public health setting.

The other questions

In the remaining time, the planning committee discussed the disposition of the other eight questions.

Question 1

1. What should be the criteria for starting clinical trials in cancer screening?

Dr. Kramer remarked that the first question had been touched on from time to time during the first three meeting sessions. Developing such criteria for markers could be quite helpful. Dr. Lee commented that the PSA situation provides a lesson—we do not know whether PSA is a bad test but it has not shown that treatment works. Another committee member suggested that one criterion could be whether treating early cancer prevents death.

Dr. Longfellow envisioned a clearance step before clinical trials. All participating researchers would discuss what is satisfactory and what needs quality control, balancing these needs against the urgency to move forward. He reminded other meeting participants that at the previous meeting, one subject had been involvement of toxicology in screening and how to validate screening using animals.

Dr. Kramer predicted that many markers will be dropped in the second phase. It should be possible to have more confidence in those that reach the third phase.

Question 2 (funding decisions)

Question 2 was deferred to a future meeting.

Question 4 (surrogate endpoints)

Dr. Kramer noted that there are few surrogate endpoints at present. Potentially, markers could serve as such. One possible surrogate in colon cancer is large polyps. Knowing the natural history helps to validate surrogate endpoints. For long-range follow-up, trials are needed.

Question 5 (long-range follow-up)

Question 5 was mentioned briefly at the March meeting. Dr. Kramer pointed out that at the time that trials reach endpoints, it may be too soon to know about adverse experiences that do not show up until much later.

Question 6 (biorepositories)

Biorepositories were suggested as a subject for the next meeting.

Question 7 (informed consent for biorepositories)

The planning committee made a prior decision to defer this subject. NCI is working internally on drafting a model informed consent document.

Question 8 (behavioral, systems, and minority approaches)

Dr. Hiatt's presentation at the April meeting addressed NCI research plans regarding behavioral issues. Planning committee members were asked to consider whether the research he described is sufficient and to offer any additional suggestions.

Question 9 (organizational structure)

Besides the committee's discussion of this subject at this meeting, NCI has an internal dialog in process about whether preclinical and clinical units need to be established.

Question 10 (role of industry)

Dr. Kramer noted that the planning committee has previously addressed this subject briefly. The organizational structure described during today's discussion of Question 9 would need to include interactions with various types of industry, including biotechnology companies. Dr. Levin mentioned an industry speaker at a recent workshop as someone the planning committee might like to hear. Dr. Srivastava was asked if he could arrange for an industry speaker for an upcoming planning committee meeting.

Committee Logistics

Dr. Levin indicated that he and Dr. Kramer would work on arrangements for speakers and resource persons to assist with the committee's discussion of the remaining questions. Dr. Ford asked for a focus on structure and on "who does what." Dr. Nayfield's talk will be rescheduled for the next meeting if she is available then.

Dr. Kramer explained that in order for Dr. Levin to be able to attend, the next meeting date has to be rescheduled from the previously planned date of June 29. As committee members were unable to agree at this time on either of the two suggested alternate dates (June 8 or July 6) for the next meeting, Dr. Kramer asked Ms. Rooney to circulate calendars to the members to determine whether a new date can be identified. If this cannot be done, another alternative would be to extend the length of next scheduled meeting to 1 or 2 days. Dr. Kramer then thanked the speakers and other meeting participants, and the meeting was adjourned at 3:25 p.m.

Participants

Iris Obrams, M.D., Division of Cancer Control and Population Sciences, Epidemiology and Genetics Program

Michael Birrer, M.D., Division of Cancer Prevention

Virginia Ernster, Ph.D., University of California at San Francisco

Leslie Ford, M.D., Division of Cancer Prevention

Richard Hayes, Ph.D., Division of Cancer Epidemiology and Genetics

Rick Kaplan, M.D., Division of Cancer Treatment and Diagnosis

Gary Kelloff, M.D., Division of Cancer Prevention

Al Knudson, M.D., Fox Chase Cancer Center, Philadelphia

Barnett Kramer, M.D., Co-Chair, Division of Cancer Prevention

Nancy Lee, M.D., Centers for Disease Control and Prevention, Division of Cancer Prevention and Control

Bernard Levin, M.D., Co-Chair, M.D. Anderson Cancer Center, Houston

David Longfellow, Ph.D., Division of Cancer Biology

John Minna, M.D., University of Texas Southwestern Medical School, M.D. Anderson Cancer Center

Mary Ann Napoli, Center for Medical Consumers, New York

Martin Oken, M.D., University of Minnesota

Wesley Sholes, Cancer Survivor, Santa Monica, California

David Sidransky, M.D., Johns Hopkins University, Baltimore

Sudhir Srivastava, Ph.D., Division of Cancer Prevention

Dan Sullivan, M.D., Division of Cancer Treatment and Diagnosis

Sheila Taube, Ph.D., Division of Cancer Treatment and Diagnosis

Barbara Tilley, Ph.D., Henry Ford Health Sciences Center, Detroit

Nicole Urban, Sc.D., University of Washington at Seattle

Sally Vernon, Ph.D., University of Texas School of Public Health, Houston

Meeting Support Staff

Wanda Davis, Secretary, Division of Cancer Prevention

Linda Silversmith, Ph.D., Rapporteur, TASCON, Inc., Rockville, Maryland

Cindy Rooney, Executive Secretary, Division of Cancer Prevention

Appendix A: Questions for the Early Detection Implementation Group

1. What should be the criteria for starting clinical trials in cancer screening?
2. What should be the process for funding decisions on large investigator-initiated cancer screening trials?
3. What is the critical pathway to be followed in validating early detection molecular or secreted protein markers?
4. Can surrogate endpoints replace cause-specific mortality in definitive screening trials? How would such endpoints be validated?
5. How can the Institute plan for long-range follow-up in screening trials to detect benefits and risks for screening and treatment?
6. How should the Institute prioritize resources for biorepositones attached to screening trials?
7. What is the appropriate informed consent for future tests on collected material in biorepositories?
8. What are the behavioral and systems approaches that can be studied to improve dissemination of screening practices that have been proven to decrease mortality? What special approaches are directed at minority populations?
9. Is the organizational structure of the early detection effort ideally configured for early phase (or preclinical) and clinical screening studies?
10. What is the role of industry in development of biomarkers and tools for early detection? How can NCI work with industry?

Appendix B: Flip Charts

I. Three Simple Criteria

1. the % decrease in mortality (for a particular cancer) (e.g., 33%)
2. the number needed to screen to save a life (e.g., 1 in 3,000)
3. unwanted consequences of screening—for example, false positives

II. What are we trying to detect

What are we trying to detect?
- cancer?
- specific cancers?
- preneoplasia?

Endpoints to avoid
- mortality
- invasive cancer
- established surrogate marker

III. General classes of marker

General classes of markers –
- acquired in cancer (genetics)
- expression changes
- host changes
- genotye/inheritable

Strategies to evaluate makers (in individuals with...)
- cancer vs. no cancer
- high-grade neoplasia vs. no cancer
- active vs. inactive cancer

III. Defining Endpoints

* Defining endpoints
- technical endpoints
- clinical decisions
- mortality/morbidity

Cross-validation through the entire pathogenesis pathway
- compare to other tests

* know the natural history

V. Flow Chart

Conduct research to identify a biomarker for early detection of cancer

The research can involve:

- Comparing preneoplastic and adjacent cancer tissue from the same patients
- Comparing individuals with pure preneoplasia and others with invasive cancer
- Comparing individuals with and without cancer
- Comparing individuals' specimens with cancer recurrence and those who do not recur (e.g., nested case control studies using specimen biorepositories from cohort studies)

Implement screening trials using identified biomarkers

Outcome measures to be used in evaluation of clinical trials

- Mortality reduction (in terms of both relative risk and absolute risk reduction)
- Decrease in late stage invasive cancer incidence rates (not relative proportion)
- Positive predictive value
- NNT (number needed to "treat" [screen] to prevent one death)
- Cost effectiveness

VI. Role of Government

Discovery phase: Where to focus efforts:

- 10x expression vs. normal state
- Do early lesions express the gene? Precursor lesions?
- In whom do you look? Elevated risk people?

VII. Role of Government

- Cooperative network for early detection/marker validation ("vertical model")
  - incorporating diversity of expertise (including ability to interface with industry)
- Center(s) for molecular diagnosis
- Link to repositories

[1]National Cancer Institute/Division of Cancer Prevention
EARLY DETECTION IMPLEMENTATION COMMITTEE MEETING

April 6, 1998

MEETING REPORT

Introduction and Welcome

Dr. Barnett Kramer welcomed the members and speakers to the second meeting of the Early Detection Implementation Committee. He explained that several members were absent due to their participation in a press conference announcing the results of the Breast Cancer Prevention Trial. The participants were reminded that the closed proceedings are confidential and that the discussion should not leave the room. An apology was made for the lengthy turnaround time (30 working days) for travel reimbursement.

Following a round of introductions, Dr. Bernard Levin, Co-Chair, welcomed the members and thanked the speakers for accepting the invitation to address the Committee. He encouraged the members to work between meetings to further the objectives of the Committee by sending their comments or concerns to Dr. Kramer or him.

The meeting packet—containing the agenda, dates and location of future meetings, committee action report, meeting report, and the Cancer Control Review Group Report—was distributed to the members. Dr. Kramer stated that calendars will be mailed to schedule meetings subsequent to July 27, 1998. He also asked the members to review the March 10, 1998 meeting report and send any amendments or objections to Ms. Cindy Rooney.

Dr. Kramer noted that behavioral and systems approaches to early detection and screening were the focus of the second meeting. Ample time was scheduled for discussion, during which the Committee should focus on specific strategies that address the concerns of the Cancer Control Review Group.

Division of Cancer Control and Population Science (DCCPS) Activities in Behavioral and Systems Approaches, Cost, and Cost Effectiveness—Dr. Robert Hiatt

Dr. Hiatt first explained the organizational structure of DCCPS, established as part of the 1997 reorganization of NCI. The division consists of three programs—epidemiology and genetics research, behavioral research, and surveillance research. The structure of the surveillance research program was not discussed further as another committee will address this topic. The components of the remaining programs are planned but do not yet exist. Epidemiology and genetics research will have two subdivisions—genetic epidemiology and environmental epidemiology. Behavioral research will support six areas—basic behavior, applied socio-cultural, health communications and informatics, tobacco control, health promotion sciences, and applied cancer screening. Additionally, the Office of Cancer Survivorship falls under the purview of the Division Director.

The research path in early detection involves four major activities—(1) basic science, exploring the use of biomarkers, genes, and imaging; (2) epidemiology, providing methods, validation, and population tests; (3) prevention, examining efficacy and effectiveness; and (4) control, responsible for adoption, adherence, and surveillance. The pathway emphasizes the multidisciplinary approach necessary for the successful implementation of early detection strategies.

Dr. Hiatt continued by reviewing the recommendations of the Cancer Control Review Group, a group convened in 1996 by the NCI Director and the Chair of the NCI Board of Scientific Advisors. The Review Group identified several research areas critical to the early detection of cancer. Dissemination research is needed to establish mechanisms that provide populations with information concerning the effectiveness and limitations of screening procedures. This ties directly with information technology research. Innovative methods, tailored to specific populations, would enhance the communication of screening activities and interventions. Analysis of the barriers to adoption of early detection procedures and issues in underserved populations is also essential. While studies in the last decade highlight an increase in cancer screening, maintaining appropriate behaviors and adherence to screening schedules must be examined separately from behaviors leading to the initial screening test. The role of health providers, in recommending or ordering screening procedures, should be explored. Concerns about adequate cross-cultural and gender communication have arisen. The negative consequences of screening must also be addressed. False positive or false negative test results, ethical concerns of genetic testing, and false information transmitted to individuals or populations are all at issue. Finally, with the rapid growth of managed care, cost-effectiveness and outcomes research are necessary. To be promoted in an organized healthcare system, effective interventions must be delivered in a cost-effective manner.

Dr. Hiatt reiterated the pertinent discussion from the first meeting. One focus question asked "What are the behavior and system approaches that can be studied to improve dissemination of screening practices that have been proven to decrease mortality?" The related topics suggested for presentation and discussion were (1) genetic epidemiology and the genetics consortium, (2) assessing communities and facilitating early detection systems, (3) microsimulation screening analysis (MISCAN), (4) the impact of early detection on underserved communities, and (5) cost and cost-effectiveness. A review of DCCPS program activities followed (as summarized below), demonstrating their relevance to prior discussions.

The epidemiology and genetics program supports 14 studies related to early detection, with a total funding of $3.7 million. The areas of research include the development of biomarkers (four ongoing studies), the relationship of screening patterns to incidence and mortality (three ongoing studies), human papilloma virus (HPV) natural history (two ongoing studies), screening efficacy (three ongoing studies), and statistical methods in screening (two ongoing studies). Examples of specific studies in these areas were described. Dr. D. J. Hunter (Harvard) is using genetic markers—such as n-acetyltransferase 1 and 2, glutathione-s-transferase mu-1 (GSTM-1), and Sip 1A—in a cohort study of colon cancer. Dr. E. W. Flagg (Emory) is examining racial differences in breast cancer. The study is related to an earlier one on black/white differences in breast cancer survival. Screening is a key aspect in the series of studies. Dr. E. L. Franco (McGill) is

investigating the molecular epidemiology of persistent HPV infection. The project evaluates the natural history of HPV as it relates to cervical cancer screening. Dr. N. Weiss (University of Washington) is exploring methods for case-control studies in cancer epidemiology research. In addition to its research activities, the epidemiology and genetics program supports the Cancer Family Registries in Breast and Colon Cancer and the Cancer Genetic Network.

The behavioral sciences program sponsors breast, colon, prostate, and cervical cancer studies in three areas—(1) interventions directed at individuals, providers, or both; (2) health settings such as clinics, organized health systems, communities, and community organizations; (3) psychosocial and potential negative aspects of screening. Research related to breast cancer has the largest program funding, with $53 million. Cervical cancer studies have been awarded $6 million, prostate cancer research $2 million, and colon cancer investigations $1 million. Three behavioral science studies were described. Dr. J. S. Slater (University of Minnesota) is following the adoption of a successful community-based mammography intervention program. The study examines the adoption of mammography intervention and involves 41 public housing units in underserved white and African-American communities in Minnesota. The project engages friend-to-friend intervention or lay health workers—women from the public housing unit and the American Cancer Society (ACS). The lay health workers provide information and support for early detection practices. The study has revealed an increased participation in recommended behaviors. The project has been adopted by the community and the ACS in Minnesota. It represents a successful translation from an NCI-funded activity to a community-sponsored program.

Another behavioral science program study analyzes the cost-effectiveness of breast cancer screening promotion programs, investigated by J. K. Worden and R. H. Secker-Walker (University of Vermont). The investigators are working with populations in Florida to study breast cancer promotion practices and their cost-effectiveness in the community setting. A second project, in San Francisco, examines cost-effectiveness in a public health setting. Dr. C. McBride (Duke) is using biomarkers to motivate smoking cessation. Serum biomarkers and expired carbon monoxide are tracked. The project explores the possibility of using biomarkers in a population setting to motivate screening behavior.

The surveillance program sponsors studies that include breast, colon, and prostate cancers. Research activities for the three types of cancer are similar and involve the self-reported use of screening for the National Health Interview Survey (NHIS) and statistical or mathematical modeling. Breast cancer research also involves the National Survey of Mammography Screening and the Breast Cancer Surveillance Consortium. The Consortium is a nationwide multicenter program examining mammography performance and the operational characteristics of breast cancer in defined populations. Prostate cancer studies include data from Medicare claims, prostate-specific antigen (PSA) testing, and incidence. Both prostate and colon cancer projects employ physician and health system factors in screening to learn more about provider screening activities.

Initiatives for fiscal year (FY) 1999 reflect a multidisciplinary approach to early detection of cancer. A cooperative agreement (U01) will investigate interdisciplinary collaborative studies of gene-gene and gene-environment interactions. An exploratory/developmental grant (R21) will

support basic behavioral research of cancer-related behaviors. A research project grant (R01) will fund health communications in cancer control. The project is designed to elicit studies in cultural tailoring and the use of technology to promote early cancer screening. Small grants (R03) will encourage research in multiple areas, including screening.

Dr. Hiatt concluded with DCCPS challenges in early detection. While survey data support an impressive use of first-time mammography and Pap smear, an increase in maintenance screening behavior for breast and cervical cancers—particularly in underserved groups—must be established. An increased use of colorectal cancer screening must be promoted. Given the current insecurity of PSA values, the appropriate use of prostate cancer screening should be studied. The application of new biomarkers and genetic susceptibility testing in screening procedures needs encouragement. With the latter challenge, the psychosocial effects of genetic susceptibility testing and early detection procedures must be evaluated. Lastly, the use of cancer screening in large organized systems of healthcare delivery, related health outcomes, and cost-effectiveness should be explored.

DCCPS Activities Discussion

Dr. Kramer commented that a maldistribution of behavior is often observed, even with screening tests of proven efficacy. To counterbalance large underserved populations, other populations are overscreened. For example, tests that are effectively employed every 3 years may be promoted as annual procedures. He asked if any studies have examined the overuse of effective tests.

Dr. Hiatt explained that research in underserved populations revealed differences in screening rates among various communities. Additionally, several projects explore the psychosocial impacts of screening procedures. As more sensitive tests become available, abnormalities are found at earlier stages, and subsequent overtreatment becomes a potential problem.

Dr. Kramer noted that screening procedures can be effective tools for one particular disease endpoint, whereas—in contrast—primary prevention can avert a spectrum of diseases. Screening tests will reach a practical limitation as patients and physicians become unwilling to submit to a myriad of procedures. Data for dietary intervention or exercise indicate effectiveness as strong as or stronger than screening tests; yet, primary prevention is rarely part of the dialog in the health profession. Dr. Kramer inquired if the behavioral aspects of primary prevention—on the user level and physician level—are a proposed area of study. Dr. Hiatt replied that tobacco studies may investigate this behavioral aspect. He offered that economic aspects may explain the difference between the two strategies.

Dr. Levin asked if the Breast Cancer Surveillance Consortium presents an opportunity to collect biological material for subsequent analysis. Dr. Urban responded that while the Consortium was not originally designed for this purpose, the concept had been discussed in recent meetings. The collected information includes family history of breast cancer and mammography results. Individuals could be identified and invited to participate in future studies. Dr. Hiatt added that as part of the BCSC (Breast Cancer Surveillance Consortium), Dr. Virginia Ernster collects mammography information on thousands of women per week. In this case, modest data are

compiled for a large group—as opposed to extensive information from a small group. Studies may be possible from this assemblage of data.

Dr. Levin then inquired about the opportunities for dialog between DCCPS and the Centers for Disease Control and Prevention (CDC). Dr. Hiatt recognized the mutual interests of the two groups and the importance of dialog. While there are no formal activities with CDC, informal meetings do take place. Dr. Kramer added that NCI representatives attend regular CDC committee meetings. For example, he participates in the Colorectal Cancer Roundtable and the National Breast and Cervical Cancer Early Detection Program.

Referring to the research pathway, Dr. David Longfellow noted the need for enhanced communication between the activity groups. For example, promising biomarkers are infrequently moved from animal studies to human pilot trials. A better mechanism and collaborative effort are needed to push early detection research along the pathway.

Mr. Wesley Sholes asked if consumers participate in the early stages of screening discussions and if studies examine effective methods of communication that would allow consumers to make more informed decisions. Dr. Hiatt replied that research in patient decisionmaking included an analysis of interactive videos. The videos can be tailored to the patient's questions, or they can follow a stream of questions and answers. He also acknowledged the need for further evaluation of barriers to screening and the application of interventions at the provider, community, and population levels.

Returning to the research pathway. Dr. Barbara Tilley asked if the Committee's charge were to examine the continuum—with the exception of surveillance—or more specifically to bridge the prevention and control activities. Dr. Kramer replied that the Committee should address all the activities in the pathway, except surveillance.

Assessing Communities, and Facilitating and Disseminating Early Detection Tests of Proven Efficacy—Ms. Nelvis Castro and Ms. Melissa Taylor

Ms. Castro explained that the NCI mammography education campaign would be used to demonstrate the process of planning. implementing, and evaluating a communication program. When NCI revised its mammography screening recommendations in 1997, the Office of Cancer Communications (OCC) was charged with publicizing the new guidelines. OCC began by putting together a communication plan.

Identifying the overall goal of the mammography education campaign was the first step in the communication plan. The guiding principle of the program is "to contribute to the reduction of breast cancer mortality and morbidity through translation and communication of breast cancer research findings to facilitate medical and lifestyle decisionmaking." The communication objective was "to increase the percentage of women in their 40s and older who understand the risk factors for breast cancer and the importance of regular mammography, including its benefits and limitations, with particular emphasis on women ages 50 and older."

The mammography education campaign targets two groups. The first group includes women 40 to 49 years old and women 50 years or older, with a special emphasis on minority and underserved women. The second group consists of physicians, healthcare providers, payers, and health professional organizations. Audience research techniques involved focus groups, indepth interviews, central location intercept interviews, and quantitative surveys.

Ms. Taylor continued with a description of the various audience research techniques. She emphasized the importance of informative research in the development and implementation of an effective campaign. To gain insight into the knowledge, attitudes, and opinions regarding mammography issues and to gauge reaction to NCI's revised mammography recommendations, focus groups and indepth interviews were conducted in June 1997.

Six focus groups were formed from 55 women (45% Caucasian and 55% minority) divided by age—40 to 49 years, 50 to 64 years, and 65 to 75 years. Two focus sessions were conducted with each age group, with each session lasting 2 hours. The focus groups were somewhat homogeneous with respect to education level and income. Most women had completed high school or some college education, and all household incomes were less than $60,000. Indepth interviews with 30 women (50% Caucasian and 50% minority) explored the women's thoughts about breast cancer risk and mammography screening on an individual level, without the group interaction. Some interviewed women had less than a high school education and a lower social economic status (SES) compared to the focus groups. The one-on-one interviews lasted 45 minutes and included a younger group of women. The three age categories were 30 to 39 years, 40 to 49 years, and 50 to 75 years.

The focus groups and indepth interviews revealed that most women consider family history as the main risk factor for breast cancer. The relationship of age to increased risk was not well understood. The emphasis on family history may stem from media attention to younger women diagnosed with breast cancer. Premenopausal cases of breast cancer are often associated with a family history of the disease. Additionally, health professionals question patients about the family incidence of cancer, giving the impression that it is a critical risk factor. Ms. Taylor circulated a chart used in the audience research and subsequent education campaign publications, illustrating the increased risk of breast cancer with age. It is a simple but powerful tool to communicate age-associated risk.

The women in the interview and focus groups were asked to read the new NCI recommendations and were offered the opportunity to suggest modifications. The new recommendations state the following: (1) All women age 50 and older should have screening mammograms every 1 to 2 years. (2) Women in their 40s who are at average risk for breast cancer should have screening mammograms every 1 to 2 years. (3) Women who are at higher risk of breast cancer should seek expert medical advice about whether to begin screening mammography before age 40 and to plan personal mammography schedules. One proposed modification called for the proper perspective of risk factors. The majority of women with breast cancer do not have a significant family history of the disease. Instead, the age-related risk should be emphasized. Additionally, confusing and technical language should be removed, and the concept of regular mammograms should be stressed.

Central location intercept interviews were conducted to collect impressions of the publications' design and appeal. Quick interviews in a central location, such as a shopping mall, targeted a mixed audience. Two hundred women (50% Caucasian and 50% minority), over 40 years old, were questioned. A kit containing various publications, cover designs, and theme lines was circulated among the committee members. The surveyed women preferred illustrative artwork representing different ethnic groups over more abstract drawings. The three theme lines that were tested found equal appeal among the women. The theme lines were (1) Mammograms: They're worth repeating, (2) Mammograms: Not just once, but for a lifetime, and (3) Mammograms: A healthy habit for life. All three theme lines emphasize the repeated use of mammography; the second choice was selected for the education campaign.
For quantified observations, an omnibus survey was conducted weekly through a vendor. Three waves of the survey were administered during summer 1997, soon after the release of the revised NCI recommendations. One thousand women, 18 years or older, were questioned. The survey revealed the following impressions: (1) more than one-third were confused about the age to begin regular mammograms, (2) less than half believed that consensus on mammography recommendations now exists among national organizations, (3) more than half believed that most breast cancer patients have a family history of the disease, and (4) women 65 years and older were more likely to believe the risk of breast cancer declines with age. The survey findings were consistent with the focus group reports.

From the audience research, three primary messages were incorporated in the education campaign. The messages state that (1) women in their 40s and older should have regular mammograms, (2) just being a woman and getting older puts you at risk, and (3) national groups agree on the importance of regular mammograms for women 40 and older.

The importance of including health professionals in the education campaign was also recognized. Prior research revealed that the oft-cited reason eligible women had not begun mammography screening was that their physician had not recommended the procedure. Two focus groups with doctors and two focus groups with nurses were conducted to learn how they discussed breast cancer risk and mammography with their patients. Their impressions of what patients know and what patients should know were also of interest. The focus group research found the following: (1) doctors and nurses reacted similarly to the revised NCI recommendations, (2) the 1- to 2-year screening interval was considered ambiguous but allowing flexibility to use professional judgment about the frequency of mammography, (3) the age/risk chart was well received and regarded as an effective communication tool with patients, and (4) use of the term "average risk" was questioned.

The focus group findings were applied to the development of resources for health professionals. A physician fact sheet pad was created, allowing physicians to share important information on breast cancer and mammography in a short time. The back of the pad provided more detailed information for physician use. Mammography kits that included ordering information for NCI publications were distributed through a mailing list. Lastly, resources were provided to health professionals at national conferences. A summary of the findings from focus groups and indepth interviews with women and health professionals is available upon request from OCC.

Ms. Castro continued the presentation with strategies for the mammography education campaign. The campaign adopted four tactics involving a national media campaign. collaboration with appropriate NCI divisions, outreach to health professionals, and partnership with other federal agencies and relevant organizations.

The national media campaign was officially launched by President Clinton during a radio address in October 1997. The timing also coincided with National Breast Cancer Awareness Month (NBCAM). Press releases and mammography kits were sent to consumer media outlets, including minority media. Consumer magazines featured mammography articles during NBCAM, and a mammography section appeared on NCI's website.

The collaboration with NCI divisions and programs involved several services. The Cancer Information Service (CIS) distributed new mammography materials to partners during NBCAM and throughout the year. CIS also worked closely with the CDC National Breast and Cervical Cancer Early Detection Program. The CIS telephone service provided information on the new mammography recommendations to callers. The Office of Liaison Activities (OLA) distributed new materials to advocacy groups. Resource materials were also provided to the Public Affairs Network (PAN) and the Patient Education Network (PEN).

Outreach to health professionals included the creation of new education materials, mailings, and resources distributed through NCI's exhibit program. The new education materials consisted of a physician fact pad, bookmarks appealing to different ethnic groups, and posters for use in clinics, doctors' offices, or hospitals. OCC is currently working with an urban group in Seattle to translate some of the resources into Chinese, Korean, and Vietnamese.

Ms. Castro provided a long list of agencies and organizations working with OCC in the mammography education campaign. A few examples are CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Health Care Financing Administration (HCFA). HCFA has expressed an interest in using OCC materials, tailored at the regional level, in their outreach programs.

The presentation concluded with a description of campaign feedback and plans for continued evaluation. Tracking and feedback were based on the first 2 months of the campaign. The CIS publication ordering service tracking system was used to track the number of publications distributed. The feedback has been consistently positive. Users of the materials agree that the "booklets put all the medical professional lingo into an easy-to-understand form." Resource materials have been used in many settings—health fairs, newsletters, payroll stuffers, libraries, employee break rooms and peer counselors' training—and in developing mammography screening initiatives. Continued evaluation will be provided through analysis of bounceback cards found in kits or booklets, CIS contacts, and follow-up omnibus surveys.

Facilitating and Disseminating Early Detection Tests Discussion

Ms. Mary Ann Napoli raised several concerns related to the lack of detail in the NCI recommendations. For example, the distinction between family members with premenopausal breast cancer versus postmenopausal incidence was not made clear. She also stated that not all

national organizations agree with the revised NCI recommendations. Ms. Taylor explained that, due to time restraints, not all the campaign resources were reviewed during the presentation. The mammography kit, circulated among the members, contains a booklet entitled "Understanding Breast Changes." The booklet offers comprehensive information and addresses each of Ms. Napoli's concerns.

Ms. Napoli questioned the use of younger women in the graphics. If the campaign wished to stress age-associated risk of breast cancer, then older women should be pictured. Dr. Kramer pointed out that the graphics depicted women of different ethnic groups and ages. Ms. Castro added that the publications received positive feedback, particularly from agencies working with older populations—such as HCFA.

Dr. Kramer inquired if the focus groups raised the issue of mammography limitations. Ms. Taylor replied that the group sessions did explore this topic. The women understood that mammography may not detect all cancers or may find an abnormality that is not cancerous. For the most part, the participants viewed mammography as a lifesaving test.

Several members mentioned the ambiguous phrasing of the recommendations calling for mammograms every 1 to 2 years. Ms. Taylor commented that a similar concern arose after a presentation to a group of communicators. They asked why the recommendations did not simply endorse annual mammograms. She stressed the need to balance easily understood language with accuracy.

Referring to the chart illustrating age-related risk of breast cancer, Dr. Nicole Urban noted that statistics can be misinterpreted easily. She suggested that annual screening visits should be promoted instead. During this time, a physician would review and recommend appropriate screening tests for any cancer. Promotion of screening visits might be easier than trying to educate consumers about the benefits and limitations of each cancer screening test. Ms. Taylor acknowledged the merit of such a system. Consumers receive many independent messages on cancer, in addition to recommendations for other health concerns, such as heart disease, diabetes, obesity, and osteoporosis. However, many people are not directly connected to a healthcare system. Consumer education efforts must continue to reach all groups. This includes the communication of complex messages, such as the interpretation of statistical data.

A discussion of statistical presentation ensued. Dr. Al Knudson proposed that the message of age-related risk should be communicated in different ways. A more positive approach would emphasize that cancer is not going to "consume everyone." Stating that 90% of women will reach age 80 without breast cancer is more hopeful than declaring that by age 80 a woman's risk of breast cancer is 1 in 10. Dr. Richard Hayes suggested that the statistics should tie into the screening tests. For example, if a woman's mammography detects no abnormalities, then her risk should be calculated with that result. Dr. Kramer added that risk could be presented as two numbers—with the screening test and without it. He acknowledged that this system is more complex but also more sobering.

CDC Cancer Screening Activities—Mr. Kevin Brady and Dr. Lisa Richardson

Mr. Brady provided committee members with a CDC information packet containing background materials and an address list for the Breast and Cervical Cancer Early Detection Program contact person in each state, territory, and tribal organization. CDC is a cornerstone of the public health system and strives to attain its mission of "healthy people in a healthy world." CDC works with national, state, and local partners to detect and investigate health problems, conduct prevention research, and implement prevention strategies. Current cancer program areas include cancer registries, skin cancer, prostate cancer, breast and cervical cancer, and colorectal cancer. An overview of the activities in the CDC Division of Cancer Prevention and Control was then presented.

In 1992, Congress established the National Program of Cancer Registries (NPCR) by enacting the Cancer Registries Amendment Act. The legislation authorized CDC to provide funds to states and territories to improve existing cancer registries and implement registries where they do not exist. In FY 97, CDC supported 45 states, 3 territories, and the District of Columbia. With an appropriation of $24.2 million for FY 98, CDC will provide resources to equip states to meet CDC standards of timeliness, completeness, and quality of registry data. Improvements will advance state cancer registries as critical components of a national cancer prevention and control strategy.

NPCR enables reporting of cancer data by age, sex, ethnicity, and geographic region—within a state, between states, and between regions. States are expected to collect information on at least 95% of cancer cases diagnosed or treated each year. Comprehensive, timely, and accurate data about cancer incidence, stage at diagnosis, first course of treatment, and death provide useful feedback for evaluating progress toward cancer control in all 50 states and territories. Priority is also placed on tracing cancer information on residents who travel to other states for diagnosis or treatment.

CDC developed partnerships with other organizations that led to the creation of the National Skin Cancer Prevention Education Program. The Program's aim is to increase public awareness about primary prevention of skin cancer by adopting sun-safe behaviors. Program efforts have been conducted within divisions or through cooperative agreements and contracts. With a FY 98 appropriation of $1.7 million, activities include (1) building partnerships with professional societies, academic institutions, and government agencies, (2) developing public awareness of skin cancer risk factors and appropriate protective behaviors, (3) assisting with school and community guidelines for skin cancer prevention, (4) evaluating the ultraviolet (UV) index program and UV index worksite demonstration project, (5) providing skin cancer prevention education to health professionals, and (6) determining baseline rates and future trends of human cancer prevention knowledge and behavior.

The National Skin Cancer Prevention Roundtable, with a $1.8 million fund, works with national organizations to promote skin cancer prevention education activities. Preliminary objectives are to raise awareness of skin cancer and skin cancer prevention behaviors in all populations, with special programs for high-risk populations. High-risk populations include children, young adults, outdoor workers, and athletes. In a nationwide effort, the Roundtable—in partnership with other organizations—hopes to promote behavior change; stimulate and support national, state, and local initiatives; and coordinate a public health response.

The promotion of widespread screening for prostate cancer is controversial, and professional medical organizations remain divided on this practice. CDC recognizes that continued behavioral, epidemiological, and clinical research are important to understand prostate screening issues. FY 98 funding for CDC prostate cancer initiatives is $3.9 million. Since 1993, CDC has been authorized to work with existing cancer control efforts in state health departments to develop state-based demonstration projects for prostate cancer. The funded projects—in central Harlem in New York City and in rural northwest Louisiana—assess the knowledge, attitudes, and practices of men and their physicians that are crucial for designing early detection programs. Both projects have focused on the population with the highest risk—African-American men. Research studies designed to evaluate the relationship between prostate cancer and coexisting health conditions are also supported. These studies will help determine how coexisting conditions affect the risk of death among men diagnosed with prostate cancer. Lastly, CDC supports efforts concerning informed decisionmaking.

CDC is collaborating with the ACS in establishing a national coalition of public, private, and voluntary organizations to educate healthcare providers and the public about the importance of colorectal cancer screening. Partners include state health departments, professional digestive disease organizations, medical societies, federal agencies, consumers, cancer survivors, managed care organizations, and health educators. State health departments have a leadership role in the development of colorectal cancer initiatives. In the last year, CDC hosted two meetings for CDC staff and state health department representatives to share current and future plans for initiatives and to identify challenges and opportunities in developing state-based colorectal cancer efforts.

CDC and the ACS hosted two National Colorectal Cancer Roundtables in 1997 to discuss strategies for identifying barriers to screening, assessing current public awareness of screening, and developing health messages to promote screening. Additionally, CDC has developed a National Colorectal Cancer Program as an internal mechanism to work with state health departments in establishing the groundwork for a fully national colorectal cancer screening program. The public health infrastructure is a critical component in overcoming barriers to screening. The goal is to build a multiphase program to help state health departments reach 50% of the uninsured low-income men and women 50 to 64 years old.

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) was initiated by the Breast and Cervical Cancer Mortality Prevention Act of 1990. NBCCEDP has grown with its funding—beginning with $29 million at its inception to $145 million for FY 98. NBCCEDP currently supports comprehensive screening programs in all 50 states, 5 territories, the District of Columbia, and 15 tribal organizations. Mr. Brady explained that Dr. Richardson would discuss the program in greater detail.

Five components were identified for a successful early detection program: (1) public education; (2) surveillance, tracking, and follow-up to recall women for routine screening at appropriate intervals, ensure that women with abnormal screening results receive timely diagnosis and treatment services, and ensure appropriate collection of data for analysis; (3) service delivery and quality assurance; (4) professional education; (5) traditional and nontraditional coalitions and partnerships. In implementing a nationwide screening program to support clinical prevention services, a number of building blocks must be in place. Clinic facilities, public and professional

education efforts, partnership development, and community outreach strategies must be established. Billing and reimbursements systems coordinated with third-party payers, such as Medicaid and Medicare, must be developed. An analysis of appropriations reveals that 73% of program funding is spent on screening, diagnostic, and follow-up activities, while the remaining 27% is available for public and professional education, quality assurance, and surveillance.

Dr. Richardson continued the presentation with a detailed explanation of NBCCEDP screening results. CDC, in collaboration with its state partners, developed a set of standardized minimum data elements (MDEs) to monitor NBCCEDP's screening, diagnostic, and follow-up activities. For each woman enrolled in the program, information is collected about demographic characteristics, self-reported screening history, self-reported breast symptoms, screening results, diagnostic procedures and outcome, and initiation of treatment. The information is sent to CDC in a computerized format twice a year.

NBCCEDP data have been used in several reports and publications. A report on the first 4 years of program mammography data appears in the January 1998 issue of the *American Journal of Roentgenology* (a copy of the article was included in the CDC packet distributed to the Committee). Additionally, several planned projects will use NBCCEDP findings. For example, program data will be analyzed to describe detection rates of cancerous and precancerous lesions by race. This project grew out of the observation that Native-American women appear to have a lower incidence of breast cancer. Another study, currently being designed, will determine and evaluate predictors of rescreening for Pap smears and mammograms.

Through March 1997, more than 1.3 million screening tests were provided by NBCCEDP. Of the 576,408 mammograms provided, 6.8% were abnormal; and 3,409 breast cancers were diagnosed. Of the 732,754 Pap tests provided, 3% were abnormal. A total of 23,782 cases of cervical intraepithelial neoplasia (CIN) I, II, or III and 303 cases of invasive cervical cancer were diagnosed. The program was charged with bringing cancer screening services to underserved women, including older women, women with low income, and women of racial and ethnic minority groups. From 1991-1997, approximately 46% of Pap tests and mammograms were provided to women of ethnic minority group, 55% of women 50 years or older received mammograms, and 55% of women 40 years or older received Pap tests.

The published report on the first 4 years of NBCCEDP-provided mammography to medically underserved women characterizes the state of breast cancer screening practices in the 1990s. The results—obtained through hundreds of diverse facilities—should be useful to clinicians, researchers, and public health personnel in counseling patients, planning new studies, and improving efforts to control breast cancer. From July 1, 1991, to June 30, 1995, 230,143 women 40 years or older underwent a total of 284,503 mammographic examinations. Mammograms with abnormal findings constituted 6.5% of all results; however, 4.1% of the abnormal results were classified as "assessment incomplete." Approximately 2% of the abnormal findings were classified as "suspicious" and 0.3% were judged "highly suggestive of malignancy." The proportion of abnormal findings was higher for first-time mammography than for subsequent mammography—a relationship consistent for all age groups. The proportion of cancers diagnosed in early stages (Stages 0 and 1) increased from the first round (54%) to subsequent rounds (81%). The proportion of cancers diagnosed in more advanced stages (II, III, IV)

decreased from the first round of mammography to subsequent rounds; more late-stage cancers are detected in the initial mammogram. The results offer encouragement that NBCCEDP can reduce mortality from breast cancer among medically underserved women.

Pap test results from the same 4-year period (1991-1995) are also available. A total of 312,858 women had 401,136 Pap tests. Approximately 1.0% of the results were judged unsatisfactory, and 3.8% were classified as abnormal. A diagnosis of low-grade squamous intraepithelial lesion (LSIL) constituted 3% of the total findings. Atypical squamous cells of unknown significance (ASCUS) results were not included. The Pap smear findings were dependent upon the examining facility. For example, results from clinics with a focus on sexually transmitted disease (STD) were inconsistent with results from a long-term care facility. An analysis of women with abnormal results by age group revealed that younger women have more abnormal results, but they tend to be a lower grade (e.g., LSIL). A larger proportion of high-grade squamous intraepithelial lesions (HSIL) is more likely to be detected in older women. A positive predictive value (PPV) of 56% was found among women with HSIL. The value was consistent across all age groups. Based on 150 cases, a stage-distribution analysis revealed that 54.0% of cancers were local, 23.9% regional, 6.0% distant, and 16.0% unknown.

The Cancer Surveillance Branch, within the Division of Cancer Prevention and Control, funded four states—New Mexico, North Carolina, Minnesota, and Michigan—to assess mammography performance in state-based breast and cervical cancer control programs by linkage to cancer registries. The objectives of the research were to (1) examine performance characteristics of screening mammography in state-based breast and cervical cancer control programs (BCCCP) and (2) compare performance measures with published standards (e.g., Agency for Health Care Policy and Research (AHCPR) Quality Determinants of Mammography). All women screened during the 1992-1994 period were matched to the cancer registry based on social security number, date of birth, and last name. All in situ and invasive cancers that occurred up to 12 months from the date of screening were identified.

The mammography results were reported using the standard breast imaging reporting and data system (BIRADS) classification. The research revealed that 360 breast cancers were diagnosed in 55,720 screening cycles. A comparison of performance measures with AHCPR standards was encouraging. Detection rate, specificity, and positive predictive value fell within the accepted standards. Sensitivity was somewhat lower than desired (i.e., accepted value is greater than 85%, average observed value was 81%). The multistate case study revealed that state-based cancer control programs are finding diagnostic and treatment resources for women, but the time and energy investment are tremendous. Community partnerships were shown to be critical to the success of the program.

CDC Activities Discussion

Dr. Hiatt inquired if the positive predictive value of mammography were known for different ethnic groups. Dr. Richardson replied that analysis by ethnic group was ongoing.

Referring to the pie-chart illustration of Pap tests by race and ethnicity, Dr. Longfellow asked if any data revealed the penetrance of the procedure in different populations. Dr. Richardson

answered that the Surveillance, Epidemiology, and End Result (SEER) program has data on the local level. For example, a SEER analysis of screening usage in New Mexico for a 5-year period before NBCCEDP and 5 years after its initiation (1991 to 1996), showed a significant increase in screening of Native-American women.

Dr. Longfellow suggested a collaboration with the American Red Cross and the lifesaving training program with skin cancer prevention activities. Mr. Brady explained that a collaborative effort was established with the American Academy of Dermatology targeting lifeguard training programs. Dr. Richardson added that the University of Hawaii has initiated a sun protection education program at swimming sites. The program objective is to increase skills, intentions, and practices for skin cancer prevention among parents, lifeguards, pool managers, and children.

Ms. Napoli inquired if studies have revealed consistency in the treatment of LSIL and ASCUS. Dr. Richardson replied that one goal of NBCCEDP is to identify ASCUS and LSIL lesions that will regress. Treatment is decided at the local level, between the patient and physician. Most often a colposcopically-directed biopsy is performed. Among women with low-grade lesions, 41% of the biopsies found no malignancy. Ms. Napoli asked if infertility caused by overtreatment was part of the program study. Dr. Richardson explained that the national program does not follow women after treatment initiation.
With the increased use of managed care plans, Dr. Hayes asked about the impact of this change in the healthcare delivery on screening behavior. Dr. Richardson responded that providers have found it difficult to offer gratis services with capitated care. Mr. Brady added that Oregon and Washington have demonstration projects trying to involve managed care organizations in screening uninsured and underinsured women. The projects revealed many barriers hindering the inclusion of this population in the managed care system.

Dr. Levin commented that an uneven standard of knowledge and screening practice existed among managed care organizations. He inquired about available resources to coordinate opportunities for research and interpret current practices in cancer. Dr. Arnie Potosky replied that the Breast Cancer Surveillance Consortium includes selected health maintenance organizations (HMOs). A systematic examination of knowledge and beliefs in different managed care organizations has not been done; however, a survey of health plans for colorectal cancer screening is in the nascent planning stage. The plan calls for a collaborative effort with the American Association of Health Plans. Dr. Kramer inquired if the survey would determine what type of health professional carries out screening procedures. Dr. Potosky explained that in connection with the health plan survey, a complementary survey of physicians is under consideration. CDC and ACS are working together on similar initiatives, and a collaboration is being discussed. Dr. Hiatt pointed out that managed care organizations form a heterogeneous group—some serve well-defined populations, and many have overlapping responsibilities. Assessment of screening practices must allow for this. Mr. Sholes added that in California the indigent populations, by mandate, are treated under managed care. Great disparity among those organizations results.

Addressing Mr. Brady, Ms. Napoli stated that the CDC promotes colorectal cancer screening to the public, but its effectiveness is uncertain. The results of the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) trial will not be known for several years. Mr. Brady invited Dr. Kramer

to reply from his perspective as a member of the National Colorectal Cancer Roundtable. Dr. Kramer explained that screening tests are presented on the strength of the evidence. The strength of evidence for fecal occult blood testing (FOBT) is the strongest as it is based on three prospective randomized trials that examined risks and benefits. The trials showed a 33% reduction in colorectal cancer mortality with an annual FOBT screen. Weaker inferential evidence supports sigmoidoscopy. The recommendation for sigmoidoscopy rests on case-controlled observational studies, not prospective randomized trials. However, sigmoidoscopy should be considered due to its associated decrease in mortality and the strong hypothesis that polyps progress to cancer. On the other hand, case-controlled studies with sunscreens suggest an associated increase in mortality from melanoma with sunscreen use. The result leads one to conclude that by not using sunscreen one can avoid dying from melanoma. The conclusion is obviously wrong. The same strength of evidence can signify a different message for sunscreen than endoscopy based on supplementary observations. Public messages on screening and prevention activities must be carefully constructed.

Returning to the issue of HMOs, Dr. David Sidransky explained a Kaiser Permanente prospective study of Pap tests. Their study revealed that 15% to 20% of Pap tests showed a diagnosis of ASCUS. Women over 45 years old were prospectively triaged on the basis of HPV testing. The HPV-positive women accounted for 95% of the cases of HSIL and cervical cancer. The current practice, upon ASCUS diagnosis, is to perform colposcopy or serial Pap smears. Dr. Sidransky questioned how the Kaiser study could be integrated into treatment practices. Dr. Richardson noted that the HPV test is still controversial as it is not specific enough. Dr. Sidransky responded that the HPV test had been used with 20,000 women in the Kaiser study, and it appeared specific. Well-designed studies by HMOs could help save money if fewer colposcopies were performed. He stressed that this resource of information should not be ignored. Dr. Kramer asked if HPV testing were used as the initial screening tool or as an adjunct to the Pap test. Dr. Sidransky replied that HPV testing was used only in the case of ASCUS diagnosis in women over 45 years old. Dr. Kramer stated that HPV testing as a triage technique, adjunct to abnormal Pap smears, was the objective of the ASCUS-LSIL Triage Study (ALTS). The sensitivity and specificity of HPV testing are not well defined. The study will also investigate the natural histories of LSIL and ASCUS. Dr. Sidransky responded that the Kaiser study used HPV testing in older women (over 45 years old) and only to triage for colposcopy.

Mr. Brady commented that CDC will fund comprehensive cancer planning efforts in states with existing comprehensive cancer plans. Currently, 20 states have established comprehensive cancer plans. Funding is available for three cooperative agreements. Implementation of the project is being considered.

General Discussion—Morning Session

Referring to Dr. Urban's comment on the potential misinterpretation of statistics, Dr. Tilley stated that she disagreed with the solution to focus education efforts on health professionals. A distrust of healthcare providers exists in some communities, so education campaigns targeting health professionals would be ineffective. Additionally, the managed care environment is uneven in its willingness to participate in prevention programs. The effort to educate patients should not be abandoned. Healthcare providers work most effectively with well-informed consumers. Dr.

Urban agreed that the patient education component should not be discontinued. However, the promotion of screening needs to be simplified as more procedures are recommended. She proposed a screening schedule similar to a vaccination schedule—at certain ages, certain screening tests are performed. Dr. Otis Brawley commented that Dr. Urban's suggestion was similar to the National Cancer Society recommendation to healthcare providers regarding the content of screening physical examinations.

Dr. Kramer offered a middle ground in screening strategy. He envisioned a systems approach with health centers devoted to screening. Through an educational process, with a trained health professional, individuals would select screening tests from a menu of effective procedures. The process of screening involves two separate questions—(1) Is the procedure effective? (2) Is it appropriate for each individual? Clinical trials can answer the first question, but only the consumer can answer the second question.

Dr. Hiatt remarked that physicians were not trained in screening procedures in one setting. Breast cancer screening practices are learned in oncology or gynecology; colorectal cancer tests are taught along with digestive diseases. As a result, physicians may not think in terms of prevention practices. Computer-based reminders could alert physicians when patients should have a variety of screening tests—for cancer, diabetes, or heart disease. Research efforts should examine mechanisms that will effectively handle a cornucopia of screening procedures. Information technology is a critical area of study. Dr. Kramer agreed that piecemeal screening efforts will not work.

Dr. Sheila Taube questioned what Dr. Kramer meant by piecemeal screening. He replied that it is dependent upon physicians bearing the responsibilities for screening procedures—as opposed to a systems approach using screening or prevention centers that cut across many organ systems. Dr. Taube remarked that with a growing number of validated tests, attention must be given to a system of identifying groups at increased risk. Dr. Hiatt suggested a mechanism to gather pertinent medical information on each patient—such as risk factors and genetic susceptibility to disease. Based on this information, each patient would receive a customized screening schedule for all diseases, not just cancer. Ms. Napoli asked if the U.S. Preventive Services Task Force were identifying at-risk groups through evidence-based reviews grouped by age. Dr. Hiatt responded that the Task Force issues recommendations but not the process to implement the recommendations.

Dr. Urban stated that in designing an implementation mechanism, one should consider the goals of screening tests—to decrease mortality and improve the quality of life. She questioned whether the promotion of screening tests causes increased worry of cancer and a degradation of quality of life. Systems-level changes may be necessary to overhaul incentives for behavioral change and compliance with screening procedures. Dr. Kramer agreed and added that system approaches could remove impediments to screening—such as when patients must travel to one site for mammography and to a different site for endoscopy or a heart scan.

Dr. Levin remarked that a systematic analysis of the behavior of managed care organizations is critical. Impediments are related to the lack of perception that preventive measures provide long-term benefits to that particular organization. In an average HMO, with rapid subscriber turnover, the benefit is passed along, and the organization may perceive prevention measures

negatively. Impediments will continue until there is a uniform mechanism to carry the benefit from one provider to the next. Dr. Kramer noted that many of these problems could be solved with a research model for a prevention center. Such a center would be less susceptible to the motives of organ-specific professional groups.

Dr. Hiatt commented that substantial changes in smoking behavior had come through legislative action. Perhaps the same type of action must be taken in terms of responsibilities of healthcare providers to patients in terms of providing recommended cancer screening tests. He then asked if the Committee were to make specific recommendations. Dr. Kramer replied that recommendations could be as simple as a program announcement or as complex as the infrastructure to support a prevention group responsible for multiple endpoints.

Dr. Taube requested that Dr. Kramer clarify the questions the Committee should address. Dr. Kramer explained that the Committee was to recommend specific strategies to implement early detection research. The strategies could take the form of program announcements, requests for applications (RFAs), and organizational or structural recommendations. The intent is to prove the utility and efficacy of screening technologies and implement those technologies. For example, the Committee could propose that cooperative groups use a vertical approach in the development of biomarkers—from the laboratory through implementation, efficacy testing, and application in a defined population.

Dr. Hiatt remarked that the infrastructure for disseminating screening tests of proven efficacy is good. The focus of system research should be on the dissemination of new tests. Another issue involves the use of informed decisionmaking for tests with insufficient evidence. Ms. Napoli warned that screening procedures are often promoted before supporting evidence is available. A more honest approach should be taken with the public when the value of a test is uncertain. Dr. Hiatt stated that health education is required to teach the public the pros and cons of screening tests. Dr. Kramer added that health education could take place in prevention centers with trained staff assisting individuals to weigh the evidence and work through the medical options.

Dr. Longfellow noted the need to research how best to translate basic research to application of new technologies. Dr. Kramer responded that a mechanism must be designed to operate in generic fashion to avoid creating a customized structure for each issue.

Returning to the topic of informed decisionmaking, Dr. Sally Vernon questioned what outcome measures would be applied to evaluate patient education efforts. She also suggested that future screening initiatives cut across NCI divisions and involve organizations such as CDC and ACS. Dr. Kramer agreed and noted that cooperative groups would cut across divisions and organizational lines.

Continuing with the concept of centralized prevention centers, Drs. Tilley and Levin discussed potential logistical problems, such as revenue and use of nonphysician staff (e.g., nurse practitioners). Dr. Hiatt noted that one recommendation from the Cancer Control Review Group stated the need to "support research on large-scale interventions within healthcare systems to introduce or improve the delivery of cancer prevention in general, and cancer prevention and control services in particular, not only for those who seek medical care, but to the broader

insured population for which they are responsible." The proposals for prevention centers or cooperative groups address this recommendation. Dr. Kramer recognized the logistical problems with each approach but noted that they are worthy of discussion.

General Discussion—Afternoon Session

Dr. Hiatt remarked that emerging screening tests—such as those using biomarkers or identifying genetic mutations—detect risk, not early cancer. Epidemiology and behavioral science research are necessary to prepare health professionals and consumers for the increasing use of these tests. Education efforts must communicate that a positive test result does not identify the disease itself but an increased risk for the disease. Similar to a questionable mammogram, a positive biomarker result would necessitate further tests, generate additional cost, and perhaps increase anxiety. The issues of uncertainty and psychosocial consequences of receiving positive test results must be examined. Dr. Kramer added that PSA and CA125 markers were examples of tests detecting risk and that much could be learned from their introduction and use. In response to Dr. Levin's question on research strategies, Dr. Hiatt replied that in addition to program announcements and RFAs, models from the Human Genome Project should be considered.

Speaking from his experience with a large public health agency, Mr. Sholes commented that the people affected by public policy are rarely engaged in the policy process. He proposed that consumers play a role in risk perception research—as early in the process as possible. Dr. Taube suggested that risk research could be integrated into ongoing screening studies.

Ms. Napoli noted that risk factors are often equated with disease. For example, decreased bone density is treated as if a hip fracture will definitely occur. Pharmaceutical advertising campaigns lead women to believe that old age is unattainable without long-term drug therapy. She proposed that consumers have access to an information resource free of bias. Dr. Kramer stated that the U.S. Preventive Services Task Force issues a formal level of evidence rankings. The physician data query (PDQ) also states levels of evidence for screening, treatment, and primary prevention. Even with these attempts to provide unbiased information, pressure mounts for testing recommendations.

Ms. Susan Scherr inquired about the interpretation of ductal carcinoma in situ (DCIS) when discovered in breast cancer screening. Dr. Kramer responded that DCIS should not be equated with cancer. PDQ has been modified to separate the term DCIS from invasive cancer. He mentioned that Edward Golub, in his book *Limits of Medicine: How Science Shapes Our Hope for the Cure,* explains how technology drives medicine. In the past, diagnosis of disease involved growing a culture, identifying the pathogenic organism, and defining the disease. Today, medical tests are drastically different. The tests do not define the disease, but the relative risk for disease. However, patients and health professionals remained conditioned to equating positive test results with disease. For example, a positive CA125 test is equated to ovarian cancer until additional procedures prove otherwise. Research is needed to effectuate the disengagement of risk and disease.

Ms. Napoli stated that patients should not learn about the uncertainty of a diagnosis (e.g., DCIS) after the procedure is performed. Uncertainty should be explained before examinations. Dr. Hiatt

mentioned that informed consent research has been implemented by Dr. Virginia Ernster at the University of California at San Francisco. One issue worth exploring is the effect of informed consent on screening rates. Dr. Taube noted the importance of this issue as an increasing number of tests identify risk and not disease. Dr. Brawley remarked that when the risks and benefits of PSA testing are explained, many men view the test as controversial and do not opt for screening. Dr. Hiatt replied that poorly-executed informed consent becomes a scare tactic. Every effort must be made to use informed consent as an educational tool. Dr. Sidransky emphasized the need to understand potential outcomes if patients are not screened or reject follow-up procedures.

Ms. Napoli observed that many health professionals equate success with the number of people screened. Rejection of a medical procedure, following informed consent, is a valid decision and should be accepted. Whether an increased education effort to explain risks and benefits of screening tests will affect mortality is unknown. Information cannot be held back simply because it may lead to the rejection of a test.

Dr. Tilley commented that the Committee should use the recommendations from the Cancer Control Review Group and the Cancer Prevention Program Group as a foundation for discussing strategies for implementation. The first step should be prioritizing the recommendations. Dr. Kramer stated that the members already had a copy of the full report from the Cancer Control Review Group and that he would mail the full text of the Cancer Prevention Program Group report for the next meeting. He requested that the members read and prioritize the recommendations in both reports for the May meeting.

Referring to the PLCO study, Mr. Sholes asked if the eligible age range could be modified for special populations. Dr. Kramer explained that the parameters for the PLCO trial were based on the median age at which the four cancers are diagnosed. The size of the trial also depends on the number of anticipated endpoints. The Monitoring Advisory Panel asked for a reduction in the age of eligibility from 60 years to 55 years. The lower age is 17 years below the median age of prostate cancer, but the modification might allow detection of the earliest lesions. If the age were dropped below 55 years, the size of the trial would become unmanageable as disease events would be rare. After the trial results are available, the efficacy of a lower age for screening can be determined.

Dr. Sidransky inquired if representatives from all divisions could list the objectives of their divisions and the strategies to implement those objectives. The information could be used to identify gaps in the early detection mission. Dr. Kramer stated that the information could be collated and mailed to the members for the next meeting.

Dr. Longfellow spoke of his experience on a committee for the validation of alternative methodologies. The committee compiled generic aspects for determining the strength of an alternative procedure or treatment. For early detection tests, a generic process should be created for indicating relative risk and benefit. Committee members could contribute components to the process from their own perspectives. Dr. Taube suggested that the Food and Drug Administration (FDA) perspective should also be added.

Dr. Urban asked if a comprehensive list of biomarkers were available—including those rejected for application or used for a purpose other than early detection. She proposed using such a list to identify possible combinations of markers for further study. Dr. Taube commented that a list could be compiled from recent grant applications and offered to search for a list of currently used biomarkers. She added that many markers are evaluated for diagnostic or prognostic use. Reevaluation of independent markers for screening use or in combination with other markers may be valid. Dr. Kramer added that a compendium of biomarkers existed at one time, but it demanded an enormous effort to maintain and did not prove useful. Dr. Taube responded that new technologies allow efficient pattern analysis of large databases.

Addressing Dr. Dan Sullivan, Dr. Levin asked about barriers to imaging studies. Dr. Sullivan replied that the issues of when large studies should be done and how that decision should be made are viable topics of discussion. For example, virtual colonoscopy has shown promising results in initial studies at five sites. A larger study, with 2000 patients, will examine sensitivity and specificity of the procedure. Upon success of the larger study, the next step must be decided. The process of making that decision should be discussed.

Before the next meeting, Dr. Kramer requested committee members examine the prioritization criteria listed under tab 1 (page 3) of the meeting notebook and determine their usefulness in identifying projects for large trials. He explained that the criteria encompass two sets of guidelines. The primary guidelines address (1) the strength of the hypothesis engendered in the project, (2) strength of the study design and the trials necessary to answer the hypothesis, (3) importance of the scientific question being asked, and (4) impact on public health. The secondary guidelines include (1) uniqueness of the problem being addressed, (2) congressional interest in the issue, and (3) public interest in the issue. A Likert scale, ranking each guideline, could be used to prioritize research projects. The development of a practical prioritization scheme for large trials was recommended by the Cancer Control Program Review Group.

Dr. Taube suggested the need for research equating intermediate markers to disease outcome and not risk for disease and asked if any validation research for intermediate endpoints were ongoing. Dr. Kramer replied that the PLCO trial offers an opportunity to examine markers that might track with cancer mortality endpoints. Dr. Taube inquired if the methodology to address intermediate endpoints is being developed. Dr. Kramer responded that the objective response rate was used as a surrogate endpoint for cancer therapy. To achieve longer survival, the patient must respond to cancer therapy. While the endpoint was simple and obvious, the response rate did not always support the mortality outcomes. As a result, it was not embraced as an intermediate measure. Dr. Urban asked for a definition of the objective response rate. Dr. Kramer explained that a complete response indicated no detectable disease, and a partial response meant a greater than 50% decrease in the sums of the perpendicular diameters of sentinel lesions. Dr. Levin noted that with increasingly sensitive technology, residual cancer will always be detected, and no response will be judged complete.

Dr. Sidransky commented that the concept of cancer had changed. For a long period, cancer was defined by gross morphological criteria. Cancer is now viewed along a continuum—a process beginning with a single cell to a cluster of cells that are morphologically and clinically identified as cancer. In considering intermediate endpoints, knowing where they function along the

continuum is important. A biomarker may identify clonal lesions or genetic change, but not the likelihood of progression to cancer.

Returning to the topic of cooperative groups, Dr. Kramer proposed a vertical approach to research studies. In the past, cooperative groups were based on a horizontal design; the same approach was used across many diseases. This approach did not reveal an understanding of the disease mechanism. In a vertical design, basic science techniques (e.g., biomarkers) would be followed though validation and large-scale studies. Various aspects of the technique could be studied—such as modulation by primary chemopreventive agents or dietary micronutrients. Dr. Taube commented that this approach had been taken with a network of investigators interested in different organ sites. The design had worked very well and allowed more flexibility, incorporation of new technologies, and progression of the research to large-scale studies. Dr. Urban asked if cooperative groups were defined by funding mechanism. Dr. Kramer explained that the groups are formed by cooperative agreement. He suggested that a protected consortium could address research questions along a linear pathway, much like the Eastern Cooperative Oncology Group (ECOG) model. ECOG has a budget and, within its committee structure, research questions are prioritized for development of therapeutic strategies.

Dr. Sidransky noted that one recommendation from the Cancer Prevention Working Group alluded to "forming an extramural multimodality prevention trials group, patterned after the Oncology Therapy Trials Group, which would set guidelines, make funding recommendations, and monitor the progress of prevention trials." The multimodality approach was emphasized as existing cooperative groups have little interest in early detection or prevention studies.

Dr. Tilley addressed the issue of minority patient enrollment. She explained that treatment trials consist of tertiary-care patients; in contrast, prevention trials involve people in the community. The populations are quite different. Centers with good minority enrollment for treatment-oriented, tertiary care studies may have trouble enrolling minority members of the community. Dr. Kramer commented that people with a diagnosis responded differently from people with no diagnosis, who are recruited for screening trials. Dr. Brawley added that prevention trials attract people from higher education and income levels. The problem extends beyond minority enrollment and includes the underrepresentation of lower socioeconomic groups.

Dr. Kaplan remarked that the structure of cooperative groups will probably undergo an evolutionary process. The process will include a national network, with primary care physician and surgeon participation, targeting activities more suitable to early detection and prevention. A new cooperative structure could address the objectives of this Committee.

Dr. Kramer announced that the next meeting will be held on May 11, 1998, beginning at 8:30 a.m. The meeting will be held in Conference Room H of Executive Plaza North, 6130 Executive Boulevard, Rockville, Maryland. He thanked the speakers, and the meeting was adjourned at 2:50 p.m.

Participants

Kevin Brady, Division of Cancer Prevention and Control, CDC
Otis Brawley, M.D., Office of Special Populations
Nelvis Castro, Office of Cancer Communications
Richard Hayes, Ph.D., Division of Cancer Epidemiology and Genetics
Bob Hiatt, M.D., Division of Cancer Control and Population Sciences
Rick Kaplan, M.D., Division of Cancer Treatment, Diagnosis, and Centers
Al Knudson, M.D., Fox Chase Cancer Center, Philadelphia
Barnett Kramer, M.D., Co-Chair, Division of Cancer Prevention
Bernard Levin, M.D., Co-Chair, M.D. Anderson Cancer Center, Houston
David Longfellow, Ph.D., Division of Cancer Biology
Mary Ann Napoli, Center for Medical Consumers, New York
Martin Oken, M.D., University of Minnesota
Barry Portnoy, Ph.D., Division of Cancer Treatment, Diagnosis, and Centers
Arnie Potosky, Ph.D., Division of Cancer Control and Population Sciences
Phil Prorok, Ph.D., Division of Cancer Prevention
Lisa Richardson, M.D., Division of Cancer Prevention and Control, CDC
Susan Scherr, National Coalition for Cancer Survivorship, Silver Spring, Maryland
Wesley Sholes, Cancer Survivor, Santa Monica, California
David Sidransky, M.D., Johns Hopkins University, Baltimore
Sudhir Srivastava, Ph.D., Division of Cancer Prevention
Dan Sullivan, M.D., Division of Cancer Treatment, Diagnosis, and Centers
Sheila Taube, Ph.D., Division of Cancer Treatment, Diagnosis, and Centers
Melissa Taylor, Office of Cancer Communications
Barbara Tilley, Ph.D., Henry Ford Health Sciences Center, Detroit
Nicole Urban, ScD., University of Washington at Seattle
Sally Vernon, Ph.D., University of Texas School of Public Health, Houston

Meeting Support Staff

Wanda Davis, Secretary, Division of Cancer Prevention
Cathy Fomous, Ph.D., Rapporteur, TASCON, Inc., Rockville, Maryland
Cindy Rooney, Executive Secretary, Division of Cancer Prevention

National Cancer Institute / Division of Cancer Prevention

EARLY DETECTION IMPLEMENTATION COMMITTEE MEETING

March 10, 1998

MEETING REPORT

Introduction and Welcome

Dr. Barnett Kramer welcomed the members to the first meeting of the Early Detection Implementation Committee. He noted that the Committee is an ad hoc group that will disband upon completion of its mission and that the Committee will probably hold at least three to four meetings at monthly intervals. Dr. Kramer then briefly reviewed the history of the Committee's formation, referring to information under tab l of the meeting notebook. He explained that two groups of outside experts—the Cancer Prevention Program Review Group and the Cancer Control Program Review Group—made recommendations to the National Cancer Institute (NCI) on cancer prevention and control research. As a result of these recommendations (listed under tab 2 of the meeting notebook), a series of implementation working groups was formed. One such Group, the Early Detection Implementation Committee, was assigned to address the early detection themes of the set of recommendations. Dr. Kramer enthusiastically noted that the Committee reflects a partnership between federal and nonfederal experts.
Continuing with an explanation of the recommendations, Dr. Kramer directed the members' attention to tab 1 (page 2) of the meeting notebook. The specific recommendations from the two Review Groups were placed into the five categories listed below. The Committee will address the first four categories.

I. Advisory processes, resources, and prioritization
II. Screening studies
III. Molecular early detection and exposure/risk markers
IV. Behavioral and systems approaches to implementation of effective screening tests
V. Surveillance of the population for screening behavior

Dr. Kramer then introduced his Co-Chair, Dr. Bernard Levin, Vice-President for Prevention at M.D. Anderson Cancer Center. Dr. Levin acknowledged NCI's flexibility and wisdom in forming a joint intramural and extramural committee and stated that he looks forward to the exciting challenge of the Committee's tasks.

Dr. Kramer distributed an updated meeting agenda, noting that it included a revised membership list. (A list of meeting participants is attached at the end of the meeting report.) He also reminded the nonfederal members to sign their professional service contracts (PSCs). Following a round of introductions, the formal presentations began.

Orientation on Committee Operations – Ms. Sue Feldman

Ms. Feldman addressed the issues of conflict of interest and confidentiality. She asked that the non-NCI members sign the distributed form acknowledging their understanding of the confidential nature of the closed proceedings and the avoidance of actions that may give the appearance of a conflict of interest.

Ms. Feldman stressed the confidential nature of the meeting and that the discussion should not leave the room. One concern is that members might share information or materials to which they are not the sole proprietors. NCI wishes to avoid premature disclosure and an inadvertent use of information that might injure a third party—such as a collaborator or employee. Furthermore, premature disclosure of information might inhibit the final outcomes or subsequent recommendations of the Committee.

Ms. Feldman added that the members should avoid any actions that might give the appearance that a conflict of interest exists or that could reasonably be viewed as affecting their objectivity. Members should not participate in any activities of the Committee in which close associates or family members may have a real or apparent conflict of interest. Ms. Feldman suggested that the member abstain from any related discussions if a conflict of interest exists.

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening and Attached Biorepositories—Dr. John Gohagan

Before the PLCO briefing presentations began, Dr. Kramer noted that the Prevention Review Group made specific recommendations (tab 2 of the meeting notebook) concerning clinical trials. One such recommendation outlined the need for randomized clinical trials (RCTs) in prevention and for a process to decide how, when, with what, and in whom to do them. As background for discussion of this recommendation, Drs. Gohagan and Hayes were asked to review the largest randomized, prospective clinical trial to date—the PLCO cancer screening trial. (An early version of the PLCO protocol is located under tab 7 of the meeting notebook.)

Dr. Gohagan first presented the objectives of the PLCO trial. The primary objective is to determine if mortality is reduced by screening. The secondary objectives include assessing (1) screening variables other than mortality for sensitivity, specificity, and predictive value, (2) survival or stage shift, (3) early markers of cancer, and (4) etiology. Dr. Gohagan explained that prostate, lung, colorectal, and ovarian cancers account for 57% of cancer deaths in men and 39% of cancer deaths in women.

Following a brief history of trial, Dr. Gohagan provided a status report. The trial involves 10 screening centers located at the University of Colorado, Georgetown University (Washington, D.C.), Pacific Health Research Institute (Honolulu), Henry Ford Health System (Detroit), University of Minnesota, Washington University (St. Louis), University of Alabama, University of Pittsburgh, University of Utah, and Marshfield Medical (Wisconsin). The pilot phase was completed in 1994. Following the recommendations of the Monitoring and Advisory Panel, the eligibility age range was expanded from 60-74 years old to 55-74. The current enrollment is approximately 95,000. The trial includes a contamination verification study (to reduce contamination), a review of the prostate-specific antigen (PSA) and CA 125-II assays, international collaborations with European groups, and special activities to enhance minority recruitment.

Dr. Gohagan then reviewed the workshops and conferences that contributed to the evolution of the trial design. The trial concept was initiated in 1988. The most recent change occurred in 1997—with the addition of substantial funds to enhance the biorepository. Dr. Gohagan noted that when the trial began, many people thought that all the answers were known, but that the technology would change dramatically. Five years into the trial, the technology is still the same, and all the answers are not known. For example, it is uncertain if PSA is a good screening test although there is reason to believe that it is. The CA 125 assay does not appear to be an effective screening test, but it is too early to make a judgment. Dr. Gohagan stressed that the trial is working. It is a reproducible and effective study. He credited the trial's ongoing success to the clinics and contractors participating in the trial.

An explanation of the Monitoring and Advisory Panel (MAP) followed. Dr. Gohagan showed a list of the panel membership, reflecting the members' affiliations with external institutes. MAP's purpose is to monitor and provide oversight for the scientific and operational aspects of this study. The panel serves as a liaison between the study, the Project Officer, and the Board of Scientific Counselors of the Division of Cancer Prevention (DCP). The panelists' recommendations have included modifications in the funding structure, a change in the age range for study participation, and contamination monitoring advice.

Dr. Gohagan continued with a diagram of the PLCO trial organization and hierarchy. He reviewed the screening centers and noted that the University of Alabama is a minority center co-funded by the Centers for Disease Control and Prevention (CDC). Ongoing is an effort to add two more screening centers, one focusing on Hispanic populations.

The protocol design involves a control arm and a screened arm. The participants are screened annually for 4 years, T_0 through T_3. Men are screened for prostate, lung, and colorectal cancers. In T_0 through T_3 visits, they undergo a digital rectal exam, PSA screening, and chest X-ray. In T_0 and T_3 visits, they undergo f1exible sigmoidoscopy. Women are screened for lung, colorectal, and ovarian cancers. In T_0 through T_3 visits, they receive CA125 screening, transvaginal ultrasound, ovarian palpation, and chest X-ray. In T_0 and T_3 visits, they undergo flexible sigmoidoscopy. The controls consist of an equal number of men and women who receive routine medical care. A 10-year followup of both screened subjects and controls will determine the effects of screening on cancer-specific mortality.

Dr. Gohagan displayed sample size calculations for the trial. Power calculations assumed a 10-year trial and were presented as percent reduction in mortality. Target mortality reduction is 20% for prostate and colorectal cancers and 10% for lung cancer. The value for ovarian cancer is still in question as not enough is known about the operating characteristics of ovarian screening procedures.

Biorepository data have been improved with additions to the screening arm of the trial. A questionnaire provides information on extended risk factors and diet. Blood collection now includes serum at T_0 through T_2 and plasma, buffy coat, and red blood cells for T_0. The T_3 collection is still in the planning stage. Ancillary studies include prospective etiologic and early marker projects. One study will examine the link between risk factors and molecular events by using the questionnaire, blood samples, and pathology specimens. Other studies will address environmental and behavioral factors, biochemical and DNA components, and protein expression. Cost efficiencies will be analyzed both within the ongoing PLCO screening trial and by using a nested case-control design.

Dr. Gohagan concluded with an outline of the analysis plan. Early in the trial, the following components will be examined: population characteristics, compliance, contamination, diagnostic followup, and etiology hypotheses. Later, the trial will address incidence and prevalence, screen test characteristics, cancer characteristics, stage of disease, case survival, and mortality rates.

Early Marker and Etiologic Studies in the PLCO Trial—Dr. Richard Hayes

Dr. Hayes reviewed the basic elements of the tria1, noting that its unique strength is the ability to follow the cancer's natural history. From an etiologic perspective, cancers (particularly prostate cancer) that develop over a short period are of great interest. The sequential screening over 4 years may allow investigators to determine if or how fast-growing cancers differ from slow-growing cancers.

The trial includes a Biorepository Advisory Committee that gives permission to use samples for proposed studies. The Committee consists of investigators from the Division of Cancer Epidemiology and Genetics (DCEG) and DCP along with individuals from Harvard and Johns Hopkins Universities who have experience in large cohort studies.
The estimated number of cancer cases in the study cohort over a 10-year period was provided. Approximately 3,000 cases of each of the more common cancers—prostate, lung, and colorectal—are expected over 10 years. Ovarian Cancer is less common, with an expected 300 cases.

Dr. Hayes continued by elaborating on the protocol additions. The currently enrolled participants will be asked to reconsent for genetic studies. The original consent form contained a generic statement about participation in medical research that is inadequate for genetic studies. New subjects will sign an updated consent form. The T_3 collection will include plasma, red blood cells, DNA, and viable cells. The participants in the control arm will also answer a dietary questionnaire, and their buccal cells will be collected.

Dr. Hayes concluded with a timeframe for the etiologic studies. Benign conditions—such as adenomatous polyps of the colon—will be studied from 1998 through 2000. The frequently occurring tumors of prostate, lung, and colon cancers will be investigated from 1999 through 2004. As the study moves forward, less frequently occurring tumors will be considered.

PLCO Screening Trial Discussion

Dr. Kramer noted that a similar randomized trial is underway to study cervical cancer. The study stemmed from the need to evaluate the management of mild abnormalities and develop more cost effective triage techniques. Many minor or atypical Pap smear abnormalities fall into two categories—atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSILs). The trial is known as the ASCUS-LSIL Triage Study or ALTS (details of the study are found under tab 8 of the meeting notebook).

The proper evaluation and management of the cervix following an abnormal Pap smear report are controversial. Although most low-grade lesions regress spontaneously, many physicians manage all cases of LSIL and persistent ASCUS with colposcopically-directed biopsy, which is the same management that is used for high-grade lesions. The ALTS trial will examine the use of human papilloma virus (HPV) testing as a means to identify high-risk subtypes requiring treatment. Similar to the PLCO trial, ALTS has an associated biorepository and will explore etiologic hypotheses.

Agreeing with the modified age range for the PLCO study, Mr. Sholes asked if an even lower age should be considered for minority populations. He noted that the incidence of prostate cancer is higher in African Americans. Dr. Gohagan replied that there is no definitive answer as conflicting information exists concerning incidence rates. The urologists on the advisory panel supported the 55-74 age range.

Dr. Correa inquired about minority enrollment, particularly Hispanic participation. Dr. Gohagan acknowledged that the Hispanic trial population is too low—approximately 2% to 3%. The overall minority population in the trial is about 15%, with an estimated 7% African-American participation. Special efforts are underway to enroll more Hispanics—including a request for proposals (RFP) targeting a Hispanic-focused screening center. Each center is responsible for recruiting in proportion to the population makeup in its area. Dr. Kramer added that—as present strategies are ineffective—recent requests for applications (RFAs) focus on innovative methods to improve minority recruitment. It was noted that regardless of race, participants of lower social economic status (SES) are underrepresented. The trial tends to attract the well-educated members of each ethnic group. This discrepancy also needs to be addressed and corrected.

Dr. Ernster inquired about the collection of the preneoplastic pathologic specimens mentioned in protocol additions. Dr. Hayes replied that no samples have been collected yet. A pathology review of the PLCO trial is anticipated that will address the collection of additional specimens for etiologic purposes. Collection of polyps and benign hyperplasias is expected.

Ms. Napoli noted that some screening tests—such as PSA and CA125—are aggressively sold to the public. As a result, the control group may not be that different from the screened group. She asked how this issue is addressed in the trial. Dr. Gohagan explained that some precautions have been implemented. The control group is monitored for examinations by random sampling. Men who have had repeat PSAs are not eligible for the trial. Subjects who have undergone a flexible sigmoidoscopy, barium enema, or colonoscopy in the past 3 years are also ineligible.

Informed Consent—Dr. Leslie Ford

Dr. Ford began by stating that the Early Detection Implementation Committee probably did not need to address informed consent for stored specimens. Many expert panels and state and federal legislatures diligently work on this issue. Her objective was to present information on current trends and provide exemplary models for informed consent.

In the past, the only consent that existed for stored samples was that given by surgical patients. Some of their tissues were saved by pathology departments for diagnosis and subsequent use by researchers and clinicians. The notion of explicit prior consent evolved with the changing medical environment, particularly with advances in molecular biology and genetics. Specimens are no longer examined just for morphological changes but also for genetic changes. The impact of genetic changes can extend beyond the individual patient to family members. These advances—along with heightened patient awareness and the ability to transmit data electronically—have led to the practice of explicit prior consent.

The increasing use of stored specimens for research purposes necessitated a redirected flow of information. Previously, the patient has a two-way flow of information with the clinician, who—in turn—has a two-way flow of information with the pathologist. The introduction of a researcher precipitated development of a mechanism to protect patient confidentiality. The mechanism involved the addition of a tissue bank trustee in the flow of information. The tissue bank trustee can be a person, an institutional review board (IRB), or computer-encrypted

information. With the new model, the patient still maintains a two-way dialog with the clinician, who—in turn—has a two-way dialog with the tissue bank trustee. The subsequent flow of information from the trustee to the researcher is one way. The researcher cannot communicate with the patient. The block on researcher communication means that the subject will not receive any research test results.

A growing trend is the option of recontacting subjects for additional information. The model consent form written by the National Action Plan on Breast Cancer (NAPBC) (under tab 4 of the meeting notebook) lets the subjects decide if they wish to give permission for future contact. (Related information on consent forms is found under tabs 5 and 6 of the meeting notebook.) Assuming that the subject gives permission for further contact, the specimen identification must be encrypted so that additional information can be obtained. Often, however, the specimen is irreversibly delinked between research and clinical settings. As a result, the data bank cannot be replenished with outcome data. Gaining in popularity is an encrypted flow of information that allows for updated information but still no direct contact between the researcher and the subject.

Dr. Ford noted that in the NAPBC model the consent form is user friendly, transforms the tissue donor into an active partner, and establishes standards for specimen use that protect donor privacy while facilitating research. The consent form also specifically mentions the potential use of donor tissue for genetic research. The next step is a field test of the consent form applied in different clinical care settings.

The key features of the PLCO trial consent form were also presented. The form has gone through the NCI IRB and is currently under review by the 10 screening center IRBs. The subject is informed that (1) blood will be stored for future medical research that may include genetic factors, (2) the genetic research may reveal genetic information about the subject and his/her family, but this information will be kept confidential, (3) the subject will not receive research test results, and (4) the future studies will not provide any direct benefits. Dr. Ford diagramed the flow of information between the accrual sites, biorepository, coordinating center, and researcher. The flow design does not allow the researcher to connect the clinical data or specimen to the patient.

Consent Form Discussion

Dr. Urban inquired if research test results come back to the biorepository. Dr. Hayes explained that data from analyzed samples are entered into a central database accessible to other researchers. The data cannot be linked to the patient.

In reply to Dr. Hiatt's question on dissemination and privacy legislation, Dr. Ford stated that NIH has invested a large effort addressing this issue. There is concern that the proposed congressional privacy bills will curtail research as the bills focus on patient confidentiality. Dr. Aamodt noted that Dr. Harold Varmus, Director of NIH, has organized an internal committee to explore these issues and provide analytic information that he can take back to Congress.

Dr. Hiatt asked Dr. Ford to explain the debate concerning permission to recontact subjects. Dr. Ford explained that there was concern of uninformed refusals, particularly among surgical patients. These patients—who frequently want to put the surgical experience behind them—are likely to opt not to be recontacted. They may not fully understand the value of their specimens for future research.

Dr. Ernster questioned the timing or setting for signing the consent form. Dr. Ford replied that the growing trend is to present the consent form at the time of initial evaluation. The subject then has time at home to read and digest the consent form and supplemental information.

Dr. Tilley inquired about the current thinking on stored specimens collected before informed consent. Dr. Ford explained that the presidentially-appointed National Bioethics Advisory Commission will make that decision. It is hoped that the Commission will grandfather existing specimens as it would be unreasonable to get new informed consent. Dr. Aamodt commented that the Commission is advisory and that its recommendations will undergo a series of processes before they are enacted as a regulatory policy or law. The larger risk is that IRBs will follow the Commission's recommendations, despite whether they become encoded as law.

NCI-Supported Biorepositories—Dr. Roger Aamodt

D. Aamodt provided materials on the NCI-NAPBC Breast Cancer Specimen and Data Information System and began with an explanation of available tissue resources. The handout listed the database website and brief information on 14 resource sites. Currently, the database focuses entirely on breast cancer, but there are plans to include other NCI-supported tissue resources. In addition, a list of NCI-supported biorepositories is provided under tab 3 of the meeting notebook.

One of the resource sites listed in the NCI-NAPBC database is the NCI Cooperative Human Tissue Network (CHTN). Operational since 1984, it provides human specimens to researchers who are in the early phases of marker studies. CHTN has distributed over 100,000 specimens to more than 500 researchers. A new project is the NCI Cooperative Breast Cancer Tissue Resource (CBCTR). This pilot resource was set up to determine whether archival specimens (formalin-fixed and paraffin-embedded) could be accessed along with the clinical and outcome data. The specimens will be provided for more advanced validation studies that require outcome data.

Other tissue resource sites include the Gynecologic Oncology Tissue Bank, part of the clinical cooperative groups at NCI, providing ovarian and cervical cancer specimens; the NCI AIDS Malignancy Bank; and the Cooperative Family Registry for Breast Cancer Studies that is a hereditary tissue bank designed for researchers performing family studies. The Specialized Program of Research Excellence (SPORE) in breast, prostate, and lung also provides tissue specimens. A number of tissue resources are also supported by the Cancer Center Program and by program project grants.

Several resources relate to early detection studies. Sites at the University of California at San Francisco (UCSF) and the University of Texas Health Sciences Center (UTHSC) at San Antonio maintain a ductal carcinoma in situ (DCIS) resource. A planned joint breast cancer SPORE and DCIS resource will offer cDNA specimens from patients. Cancer Center and SPORE programs also dispense specimens related to early detection studies.

D. Aamodt continued with an explanation of the newly appointed tissue expediter whose job is to help researchers locate tissue specimens. The expediter is familiar with publicly available resources and those in intramural programs. Investigators' needs can be rapidly matched to appropriate specimens, and collaborations can be established as needed. In conjunction with this new position, an active marketing program was launched. Advertisements will be placed regularly in cancer-related journals announcing publicly available NCI specimen resources.

Turning to the subject of establishing a tissue resource, Dr. Aamodt emphasized the importance of beginning with a clear definition and purpose. The resource should meet a critical research

need: the user group must be identified. In defining the need, one must also address the clinical data requirements—whether limited to demographics and diagnosis or requiring additional information such as outcome and exposure history. Quality control criteria are also important. The specimen should be free of contamination from nonrelated tissue. Finally, cost-effectiveness must be considered.

Providing a handout, Dr. Aamodt explained the recently developed schema for the evaluation of specimen resources. The initiative brought together NCI program directors and the Deputy Director of the National Center for Research Resources. Their charge was "to develop a set of criteria that can be used to evaluate a human specimen resource in order to determine whether it is effectively meeting a critical research need." A critical research need was defined as a resource that facilitates research that contributes to an essential body of knowledge, such as the discovery of new genes, development and testing of technologies, diagnostic assays, or predictors of treatment outcomes.

In general, NCI expects an evaluation to answer the following three critical questions: (1) How effectively has the resource performed? (2) What impact has the resource had on research? (3) Is there a continuing need for the resource? Performance is the easiest item to evaluate by factors such as the number of specimens provided, number of researchers who have obtained specimens, number of different specimen types dispensed, repeat requests, and number of research papers published by resource users. The impact of a resource is the most difficult characteristic to measure—although it becomes easier with time. Time is required not only to establish the resource but also for publication of critical findings resulting from resource use. Impact measure might include the number of citations by other investigators of resource-related papers or the role of the resource in the development of useful technologies or research techniques. In determining continuing need, one can ask if the resource is meeting its objectives and if alternate specimen sources are available to researchers.

Dr. Aamodt concluded by mentioning the development of a task force to address specimen resources. The task force will consist of external academic experts who will advise NCI on a range of topics from the development of tissue resources to legal and ethical issues. NCI is in a position to evaluate tissue resources—what exists, what should exist, and the needs they fill.

Biorepository Discussion

Dr. Longfellow commented that a critical aspect in any type of collection is flexibility. He asked if the tissue expediter's role includes an assessment of needs not currently met. Dr. Aamodt acknowledged that a key role of the tissue expediter is to monitor changes in the science and types of requests. These shifts can then be addressed by modifying existing resources or proposing new resources.

Dr. Sidransky inquired about depletion rates and the kinds of studies that can be supported in terms of statistical power. Dr. Aamodt explained that the depletion issue varies by resource. CHTN collects tissue prospectively. CHTN requests are taken from investigators, and the tissue is located by monitoring surgical schedules at various institutions. CBCTR currently has a large number of specimens—over 5000—and the ability to replenish as it is depleted. Experience with depletion is limited as the demand for large numbers of specimens is somewhat recent. Statisticians do review proposals to determine if the specimen request is appropriate. In larger validation studies, establishing the existence of an adequate statistical population is important.

Dr. Levin asked how investigators gain access to tissue specimens from CBCTR or CHTN. Dr. Aamodt replied that investigators begin with a short letter of intent explaining the study objectives and the number and types of specimens required. If the letter is found feasible when reviewed by the Research Evaluation Panel (REP), a full application is requested. The six to seven-page application is reviewed, and recommendations made to the resource. In response to Dr. Levin's question on funding, Dr. Aamodt explained that NCI funds the tissue resource, but the investigator is charged for preparation and shipment costs.

Dr. Urban inquired if there were any requirement that the research proposal be peer reviewed and funded by NIH. Dr. Aamodt stated that those conditions are not required, but priorities have been established for the resources. For CHTN—for example—peer-review research has the highest priority, followed by new investigators or investigators starting new lines of research where a funding history has not been established. Commercial users have the lowest priority. Dr. Ernster asked about the split among the three categories. Dr. Aamodt answered that an attempt is made meet the needs of all three categories. In severe shortages, the commercial users may be left out. Furthermore, investigators may also (be) asked to reduce the amount of their requests so the specimens can be distributed to more researchers.

Dr. Longfellow questioned the ability to track resource-related publications. He noted that the specimen request may not come directly from the principal investigator. Dr. Aamodt explained that an effort is made to obtain the principal investigator's name along with that of the contact person. Once a year, a literature search is done. The investigator is sent the list of publications and asked to check off the papers related to the resource.

Dr. Levin asked how tests or diagnostics performed by private industry are monitored. Dr. Aamodt responded that requestors from private industry must explain their intent in the review process, and they must agree not to commercialize any product received directly from the specimen resource. Ground rules are agreed to, but they are not policed beyond that.

Dr. Sidransky inquired if the resources had age-matched controls. Dr. Aamodt replied that control tissue consisted of normal tissue surrounding the tumor. He noted that the specimens were not collected for research but for diagnostic purposes.

Dr. Hiatt questioned if the CBCTR identifies the population from which the specimens derive. Dr. Aamodt stated that the ethnicity is known, but no epidemiological information is provided. He added that the hereditary tissue bank, funded by the epidemiology branch, does provide population information.

Biomarker Initiatives—Dr. Sudhir Srivastava

Dr. Srivastava began with the recommendations from the Cancer Prevention Program Review Group—to (1) develop new molecular markers for early cancer detection, (2) develop and expand existing biorepositories for the testing of new molecular detection technologies, and (3) expand identification of high-risk healthy populations based on genetic predisposition and new molecular markers. Dr. Srivastava used the recommendations as an outline for his presentation.

Biomarker studies have not successfully competed for funding as they are not always hypothesis-driven. As a result, the study proposals do not score well in the peer-review process. Recognizing these weaknesses, DCP initiated the Early Detection Research Network (EDRN) in 1990. In its 5-year existence, EDRN promoted three biomarker initiatives— to (1) establish a network of institutions with necessary resources, expertise, and interest in integrated biomarker research in cancer control programs; (2) promote and encourage translational research to bridge gaps

between basic and clinical sciences in the field of early detection and screening related to biomarkers for preneoplastic and neoplastic lesions; and (3) assess emerging trends and results in cancer detection research through sponsoring workshops, conferences, and group discussions.

EDRN was comprised of 14 investigators selected for their expertise and experience in the field of early detection. The EDRN program consisted of two components—the biorepository and molecular studies. The biorepository was responsible for collecting more than 3000 tissue samples using a uniform protocol for processing, storage, and archiving. Additionally, a computerized clinical database was established. The database included medical histories and information on demographics, occupational exposure, diet, tobacco use, and alcohol consumption. The molecular studies addressed three areas—(1) frequency of chromosomal abnormality (loss and/or gains), mutation, and loss of heterozygosity in prospective and cross-sectional specimens; (2) validation (sensitivity, specificity, and positive predictive value) of selected biomarkers; and (3) correlative studies with known risk factors and molecular characteristics.

During its short existence, EDRN activities led to the publication of 25 journal articles, 5 book chapters, 20 abstracts, and several manuscripts pending publication. (Dr. Srivastava provided a publication list.) EDRN also sponsored several workshops. The 1995 workshop on genetic screening for colorectal cancer resulted in three major developments. First, it promoted studies on the population prevalence of hereditary nonpolyposis colorectal cancer (HNPCC)-associated genes. Secondly, an RFA entitled "Cooperative Family Registry for Epidemiological Studies of Colon Cancer" was developed and jointly funded by DCEG and DCP. Lastly, an international collaboration to study HNPCC-associated genes was established. Three sites are involved in the collaboration—Boston, Mayo Clinic, and Finland. A 1996 workshop on telomerase resulted in a collaborative effort with the National Institute on Aging.

Successful genetic screening requires guidelines and standardization. In 1997, an international workshop established the Bethesda Guidelines for microsatellite instability (MSI) testing. The guidelines have been widely accepted by international organizations and are currently undergoing field testing. Also in 1997, a panel of experts convened and recommended a standard nomenclature for MSI. Use of MSI is preferred over MIN, MI, RER, USMs, or MMP. The panel also defined MSI as any length change—whether due to insertion or deletion of repeating units—in a microsatellite within a tumor when compared with normal tissue. MSI was divided into two types—MSI-H and MSI-L. MSI-H tumors are defined as having instability in two or more markers (BAT25, BAT26, D5S346, D2S123, D17S250). MSI-L tumors are defined as having instability in one marker. Dr. Srivastava noted that the guidelines set up for colorectal cancers can be applied to other tumor types. Standardization continues for early detection testing processes.

Planned biomarker initiatives will promote three research areas—(1) proteins secreted from premalignant and tumor cells, (2) sensitive assays for protein detection in blood samples, and (3) tumor cell detection in exfoliated cells and bodily fluids. Most of the studies on secreted proteins remain in the laboratory setting and need to be translated to the clinical setting. Promising markers still in the basic science stage include pancreatic serum protein (PSP) and human epithelial mucin (MUC1). Two markers, CD44 and MUC2, are reported in developmental clinical settings. The only applied clinical markers are PSA and CA125, which have not been validated as cancer detection biomarkers. A similar status exists for exfoliated cell studies. Promising research in the laboratory setting involves detection of genomic instability, loss of

heterozygosity, and detection of mutations. Limited clinical studies use MSI testing in urine samples. Applied clinical use of exfoliated cells is nonexistent.

Dr. Srivastava offered a biological paradigm for biomarker use in cancer detection. The key component is environmental factors that may produce a wide array of genetic changes. These factors include infectious agents, diet, and exposure to radiation and toxins. The sporadic genetic changes may lead to clonal expansion, preneoplastic expression, primary tumor, and then metastasis. Successful biomarkers detect changes early enough to allow intervention before the primary tumor stage. Biomarkers could shorten clinical trials and reduce costs.

Biomarker development can be viewed as a life cycle. Beginning with historical data (based on studies with animal models or tumor cells), a hypothesis is generated. The hypothesis is tested in a clinical setting for confirmation. Clinical testing may involve differential expression or tumor specificity. Assuming confirmation, the cycle proceeds to evaluation using controlled clinical studies to examine sensitivity, specificity, and predictive values. The next step is validation using randomized clinical trials. Success is determined by reduction in morbidity and mortality. A successful biomarker moves into population-based use; an unsuccessful marker begins the cycle anew. Dr. Srivastava concluded by emphasizing the multidisciplinary approach to biomarker development. The development begins with basic scientists and proceeds with contributions from epidemiologists, clinicians, oncologists, and public health professionals.

Biomarker Discussion

Dr. Ernster commented that Dr. Greenwald had reported at the Board of Scientific Advisors (BSA) meeting that, of the 75 identified biomarkers, very few had undergone testing for sensitivity, specificity, or predictive value. These studies should receive high priority. Dr. Srivastava agreed and noted that 5 to 6 biomarkers are ready for this stage of testing.

Dr. Sidransky brought up two important issues. He noted that specimens for biomarker testing have no matched controls. From the available resources, sensitivity can be assessed but not specificity. As a result, investigators with ideal biomarkers must collect their own samples. The second issue involves technology. The technology does not exist to proceed to large population studies. A bottleneck forms in moving from validation to the final stage of testing. Dr. Srivastava stated that an initiative for technology is under consideration. Referring to the first issue, Dr. Kramer added that specificity can be determined by using a standard to which everyone is measured or looking at long-term followup. He conceded that no database exists for a standard and that it is difficult to develop one. However, the 15-year PLCO trials could make specimens potentially available through the biorepository.

In response to Dr. Hiatt's question on biomarkers that can be applied to paraffin blocks, Dr. Srivastava replied that most of the biomarkers can be used. Degradable biomarkers—such as RNA-based markers and telomerase—probably would not work.

Referring to the biomarker development life cycle, Dr. Urban noted that before sensitivity and specificity can be evaluated, the criteria for positivity must be established. Basic scientists tend to use their controls and define positivity with sensitivity that is too low. Change over time, C-curve analysis, and marker combinations are not considered. As a result, useful markers may be ruled out. Dr. Srivastava agreed that criteria for evaluation need attention.

Dr. Longfellow questioned the extent to which the Government should be involved in providing standardization before assays are offered commercially. The Federal Government appears to

favor a multiagency task force and the peer review process before new methodologies enter the marketplace. The issue should be examined by this Committee.

Dr. Ford mentioned two additional tissue resources. Associated with the prostate cancer and breast cancer prevention trials are banks of serums, white blood cells, and —to some extent—tissues from biopsies and clinical specimens.

Physicians Data Query (PDQ) Initiative and Protocol Listing—Dr. Gisele Sarosy

Dr. Sarosy provided handouts on NCI information resources, sample PDQ clinical protocol abstracts, and an outline of the PDQ database. PDQ began in the 1980s as an information source primarily in cancer treatment. It has evolved over time and now comprehensively covers cancer screening, prevention, diagnosis, and treatment (adult and pediatric) and issues of interest to cancer survivors. The PDQ database is updated regularly and currently contains a register of over 1,500 ongoing clinical trials and over 9,500 completed trials. Dissemination services include CancerFax, CancerMail, CancerNet, and a toll-free telephone information service.

PDQ information is provided in two formats—one for health professionals and another for the lay public. Reformatting is under consideration. The new format would provide more flexibility and allow the users to pick the level of information appropriate to their needs and background. PDQ is updated and maintained through an editorial board process. Each month, approximately 100 journals are examined for relevant articles for review. The articles are distributed to the appropriate editorial boards, and information changes are made as necessary.

Approximately 90% of the active clinical trials are treatment trials. NCI sponsors about half the treatment trials, the pharmaceutical industry sponsors less than 10%, and the remaining are funded by other sources. While the screening, prevention, and diagnostic trials are small in number, they are large in terms of the number of people involved. All clinical trials undergo review prior to inclusion in the database. The NCI-sponsored studies undergo review by the Cancer Therapy Evaluation Program, an NCI Cooperative Group, NCI Comprehensive and Clinical Cancer Center, or the NCI grant process. Submissions from other sources are reviewed by the PDQ editorial board or a process approved by the editorial board. For example, trials conducted by some European cooperative groups are included without additional review. Protocols that fulfill the Food and Drug Administration (FDA) criteria for Phase II and Phase III clinical trials are also included without further review.

Dr. Sarosy demonstrated the use of the CancerNet website to obtain information on clinical trials. Important features include optional pathways for information (professional or patient) and the use of pull-down menus for search options. The patient pathway uses less technical language, and the protocol summary is hyperlinked to a glossary. The summary further allows one-click access to the health professional abstract. CancerNet also allows one to search for genetic counselors. Pull-down menus allow the user to select a counselor specializing in a specific area and located in a specific geographic site. The genetic counselor's contact information and board certification are provided.

It is difficult to quantitate the use of PDQ as it is accessed through several mechanisms. The number of hits per month and number of user sessions of the website both indicate a steeply increasing usage. The number of hits per month is now more than 2.5 million compared to 500,000 less than 3 years ago. User session data indicate that the average user looks at 15 pieces of information. People who visit the site stay awhile.

In an effort to improve PDQ, a broad base of users was assembled in February 1998 to compile a list of recommendations. The recommendations will be reviewed and passed to a technical implementation team. The preliminary recommendations offered six suggestions—(1) describe the clinical trial information in the context of general health care, (2) include as many clinical trials as possible with an appropriate review process, (3) provide the information in multiple levels of complexity and detail, (4) customize retrieval to the needs of the user, (5) consider the variations in user demographics, and (6) develop concurrent evaluation and marketing plans.

Members who knew of clinical trials not currently in the PDQ were asked to call Kevin Davis at NCI (301-496-7406) to make the database as comprehensive as possible.

PDQ Discussion

Dr. Hiatt asked if the non-NCI-sponsored clinical trials were primarily supported by pharmaceutical companies. Dr. Sarosy explained that the pharmaceutical industry represents less than 10% of the non-NCI-sponsored trials. The remainder is funded through other sources such as cancer centers or European studies. Dr. Hiatt then asked what criteria are used for including pharmaceutical-sponsored studies in the PDQ. Dr. Sarosy replied that the criteria included either review by the PDQ editorial board or fulfillment of FDA requirements for Phase II and Phase III clinical trials.

Mr. Sholes inquired about the effort to advertise the PDQ service to the general population. Agreeing that a stronger effort is needed, Dr. Sarosy stated that NCI is working on a clinical trials marketing campaign in which the promotion of PDQ will play an integral part. The current promotion effort has targeted the physician community, with presentation at medical meetings over the past several years.

Dr. Levin asked if the PDQ captures alternative medicine trials in place at cancer centers or NCI. Dr. Sarosy replied that a collaborative effort is underway with the NIH Office of Alternative Medicine to determine the best way to disseminate that information.

Dr. Levin questioned how many website hits were from foreign countries. Dr. Sarosy did not have the breakdown on domestic and foreign but stated that quite a few telephone calls and requests for information originate from overseas. Mr. Sholes asked if the website is linked to commercial servers, such as AOL and Compuserve. Dr. Sarosy explained that other health information resources are encouraged to link to the CancerNet site. A review process evaluates the linked resource to ensure that users receive credible and useful information.

General Discussion—Morning Session

Dr. Correa asked about the status of the ALTS trials and the participating centers. Dr. Kramer stated that the four screening centers are in Seattle, Pittsburgh, Oklahoma, and the University of Alabama. The ALTS trial—as with other screening tests that dip below the clinically evident line—dramatically expanded the population with cellular abnormalities. To identify the 14,000 to 15,000 patients facing cervical cancer each year, an estimated 50 million women would have to be screened, and 5 million to 8 million women would have abnormal pap smears. The natural history of cervical lesions is not fully understood but it is accepted that some lesions will progress to cancer while others will regress. In the United States all women with lesions are offered excision. While the strategy is effective, many millions of women may be unnecessarily treated as their lesions would regress. A strategy to triage women for treatment is the central component of the ALTS trial.

The ALTS trial is a three-armed randomized study targeting 7,600 women. The three arms involve (1) definite diagnosis and treatment, (2) an HPV triage arm considered high risk that receives definite treatment, and (3) a purely natural history arm that uses frequent pap smears to track lesion regression.

Addressing Dr. Ernster's question, Dr. Kramer explained that the ALTS trial's outcome measures concern the type of lesion. Since the trial began, there is mounting evidence that most HPV infections are short lived and regress. Most women will clear the infection and not progress to cancer. However, with infection, cervical cell abnormalities are found. The study is built on the characteristics of the virus, but superimposed characteristics of the host (e.g., immunologic response) determine if the virus will continue to reside in cells or be cleared. Immunologic parameters will be examined for use in predicting immunologic response

Mr. Sholes asked what criteria were used in selecting the ALTS screening sites. Dr. Kramer replied that key factors included expertise and ability to perform the tests, along with access to appropriate populations with LISL or ASCUS. Currently, African Americans are oversampled, and Hispanics are undersampled. A strenuous effort is underway to increase Hispanic participation through satellite centers. Mr. Sholes then asked what made the University of Alabama a good minority site. Dr. Gohagan explained that the University of Alabama has a history of African-American recruitment and is organized to carry out the necessary examinations.

In reference to minority samples, Mr. Sholes stressed that financial and sociological variations must be considered. Minority populations should not be viewed as homogeneous. It is important to learn if the variations have an impact on clinical trials. Dr. Levin asked Dr. Brawley to comment on early detection screening in minorities. Dr. Brawley first noted the initiatives to recruit blacks and Hispanics into clinical trials. The importance of communication and an understanding of the trial objectives were stressed. Dr. Brawley also agreed with Mr. Sholes' observation that trial participants tend to be of middle or upper SES. If trials are to be more inclusive, the poor need to be represented—regardless of race or ethnicity.

Ms. Napoli turned to the topic of biomarkers and asked how they are validated. Dr. Kramer began by noting that very few biomarkers are considered validated. There is an ongoing dialog to determine the best approach for biomarker validation. One problem is that the natural history of biomarkers is not understood, making it difficult to identify true perturbations. As a result, investigators are boxed into randomized prospective trials that are large and expensive. Dr. Ernster added that the biomarker evaluation criteria—sensitivity, specificity, and predictive value—are often not revealing. Dr. Longfellow commented that when an at-risk population is defined, improved diagnostic methods involving minimal invasiveness should be available.

Dr. Levin remarked that most health care is delivered through managed care settings with patient capitation. He questioned what mechanisms are in place to examine patient accessibility to early detection screening. Dr. Kramer replied that an RFA devoted to healthcare systems with defined populations and equipped to handle centralized data will target issues surrounding prevention, screening, and behavior. Dr. Hiatt stated that the RFA addresses a spectrum of cancer-related questions—from etiology to heath services. The RFA is completed and awaiting review. Dr. Ernster commented on the usefulness of having a list of NCI-sponsored screening and prevention trials.

Early Detection Imaging Progress Review Committee —Dr. Dan Sullivan

Dr. Sullivan explained that the Early Detection Imaging Progress Review Committee is one of seven subcommittees comprising an imaging working group. To date, the Review Committee has met only once—in January 1998. At the end of the meeting, it was decided to split into 3 subgroups. The objective for each subgroup is to (1) evaluate leading technologies for lung cancer screening, (2) examine risk clarification for lung and colon cancer, and (3) evaluate modeling and the optimal opportunities for screening in the course of the disease. The next committee meeting is scheduled for April 29, 1998.

During the first meeting, the Review Committee discussed issues related to RCTs. For more effective screening, particular factors must be addressed. Better prevalence data—especially for preclinical disease—are essential. This is particularly true if autopsy studies through any given organ do not exist. Improving risk stratification is integral for the application of early detection imaging. Future imaging technologies that are less invasive and meet patient acceptability are also crucial.

Dr. Sullivan discussed three imaging technologies related to lung cancer screening—spiral computed tomography (CT), digital radiography, and PET scanning. Small ongoing trials are examining the use of spiral CT. A group at Memorial-Sloan Kettering Cancer Center has found unsuspected small tumor nodules in about 15% of high-risk patients. Digital radiography coupled with artificial intelligence for automatic target recognition (ATR) is expected to be the next step for chest radiography. PET scanning coupled with radiolabeled antibodies has met with limited success, due partly to antibody specificity problems and partly to the PET scanning technique. Other PET scanning methods are under consideration. If one can successfully identify and label ligands for appropriate biomarkers, then PET scanning may be more successful. In addition to radiolabels, paramagnetic and optically active compounds could be used for labeling (the latter would by useful only for epithelial tumors).

Dr. Sullivan also mentioned that virtual bronchoscopy, which shows some promise for colon cancer screening, is a possibility. Pilot studies focused on a few hundred patients, and NCI is now funding a Mayo Clinic study with 2,000 patients. Virtual colonoscopy is expected to be fairly sensitive in detecting colon lesions. An important issue is how to distinguish benign lesions without an invasive procedure. Tumor markers might be combined with virtual colonoscopy.

Three additional factors related to improving cancer screening were mentioned. Based on experience with mammography screening, standardized terminologies are considered very important. Standardization would also help in combining data from a variety of trials. Central registries and understanding consumer options are also essential.

Dr. Sullivan reported on two other relevant items. First, an RFA, published last year, called for a cooperative national trials group for agency trials. It is hoped that the project will be funded and in operation by fall. Secondly, several trials over the last few years have examined the use of MRI for diagnostic purposes in patients with abnormal mammograms. The trial results are very promising. The sensitivity is high, and the negative predictive value for negative MRI is also very high. As a result, there is much interest in using MRI for high-risk women, particularly younger women who do not fit the guidelines for mammography. MRI is already in clinical use in many places without guidelines or study data. Five sites are presently involved in pilot studies to analyze its effectiveness. Similar trials are also ongoing in Canada, Great Britain, and Germany.

Imaging Discussion

Dr. Longfellow inquired about the use of MRI and changes in breast density associated with women on postmenopausal hormones. Dr. Sullivan explained that density is not a relevant issue in MRI as it is in mammography. It is one of the reasons that MRI is considered slightly more effective.

In response to Dr. Levin's question on the availability of the MRI pilot study data, Dr. Sullivan replied that it would be published in 4 to 5 years. It is possible that the foreign data may be available sooner. Answering Dr. Greenwald's inquiry on age groups, Dr. Sullivan stated that there is no age limit in the domestic pilot studies, but the British study targets women under 60 years old.

Dr. Hiatt asked about the specificity of MRI. Dr. Sullivan responded that it is as good as mammography—and perhaps better. The issue is under investigation through a cooperative trial in 14 sites across the United States and Germany. The largest study so far—from the University of Pennsylvania—reports a specificity of 80% or better. Dr. Kramer noted that this is not as good as mammography. Dr. Sullivan agreed but explained that the study examined diagnostic patients, many of them with multiple lesions.

Dr. Levin inquired about any interest in thermography. Dr. Sullivan replied that thermography had not been advocated for screening, but recently some experimental devices operating on the same principle have been promoted. He did not know of any clinical data.

Dr. Greenwald's question related to DCIS, tools for defining high-risk patients, and identifying patients interested in chemoprevention trials. Dr. Sullivan stated that the patients participating in the trials were diagnostic patients. Additional foci were identified with MRI in 30% of the patients. MRI can detect early DCIS that is mammographically occult. Dr. Greenwald asked about the possibility of serial MRI. Dr. Sullivan explained that not enough is known about sensitivity; significant data are lacking.

Dr. Kramer suggested that there are three categories of imaging tests for breast cancer. The first is screening in which mammography is replaced by another imaging tool, such as PET scans. The second category is for adjunct tests. This would be similar to pap smears that can identify abnormalities missed by a manual exam. The third category is for problemsolving or diagnostic tests. He asked where MRI fits into these categories. Dr. Sullivan answered that MRI is being studied for its use as a screening process for high-risk women. High risk is defined as women positive for the BRCA-1 or BRCA-2 genes or with a strong family history of breast cancer.

Answering Dr. Hiatt's inquiry, Dr. Sullivan stated that the 5 centers involved in the MRI pilot study were part of a larger consortium of 14 institutions. The Universities of Pennsylvania and Alabama are 2 of the 5 sites, but he was unsure of the others.

Dr. Sidransky asked about the study of the gadolinium time course and washout associated with MRI, whether the related studies look promising, and whether the procedure is more complicated than a standard MRI. Dr. Sullivan stated that extramural grants support studies that are examining the time course of uptake and gadolinium washout. It is too early to know if the studies show any promise. The actual data collection is not more complicated than standard MRI, but the analysis is. One way to address this problem is to break the region into pixels, rather than taking a large regional reading.

Dr. Greenwald inquired about the charge for MRI. Dr. Sullivan replied that the charge ranges from $600 to $1,000. If systems dedicated to breast MRI are built, the cost may be reduced to $200.

General Discussion—Afternoon Session

Dr. Correa opened the discussion by stating that the prioritization for screening should be changed. Public health needs more immediate attention. One mission of NCI is to lessen the burden of cancer in the community. The early detection program aims to solve the problem of late detection, and late detection is primarily a problem of lower SES and minorities. The large screening and early detection programs—with 90% participation from upper SES populations—are not doing enough to lower the cancer rate. Statistics show that the stage at diagnosis is much better for the higher SES groups using private hospitals than for the lower SES groups using public hospitals. The mortality rate is higher in the lower SES communities. If the national cancer rate is to be reduced, the populations with the highest mortality due to late diagnosis need to be addressed.

Dr. Greenwald responded by suggesting that the infrastructure of public health centers could be upgraded if they were part of clinical trials. Based on his visit to a Los Angeles health department clinic, he observed that patients may not be offered screening tests and that—in the case of mammography—finding the patient for a followup exam is difficult. Placing a digitization trial that has rapid feedback in a public health clinic would serve those who have the most to gain. If the infrastructure could be upgraded as part of the trial, all segments of the population could be helped. Dr. Ford agreed that one of the biggest problems in breast and cervical cancer screening is following up the positive screens—too many women fall through the cracks.

Dr. Kramer mentioned that he sits on the Breast Cancer and Cervical Cancer Screening Committee at CDC. He explained that, historically, CDC only received money for screening, not followup. More recently, funds have been added for qualifying activities and diagnostic procedures. In most instances, biopsies can be put into a program and be funded. The next phase is to explore timing. An interim delay between abnormality detection and treatment may exist.

Dr. Hiatt commented that it is recognized that infrastructure can be built through research. A lot of activity in urban public health comes from research budgets. He suggested that the report from the Cancer Control Review Group would be a good basis for a discussion of the application of technologies, such as biomarkers.

Ms. Napoli stated that it is assumed that screening is always a good thing but that the existence of a clinical trial is an admission of uncertainty. Lack of access to screening may not always explain why people have a higher rate of diagnosis at late stages; other factors must be considered. Dr. Kramer then offered two contrasting examples of screening studies. Randomized studies in breast cancer screening established that early diagnosis—achieved by screening—leads to decreased mortality. In lung cancer studies where early diagnosis was accomplished—that is, more stage I and stage II surgically-approachable lesions were identified—mortality was not decreased. Survival was better but only because the date of diagnosis was earlier. Screening success needs to be measured disease by disease and strategy by strategy.

Dr. Sidransky opened a discussion on the prioritization of research and clinical studies. He and Dr. Greenwald stated that research money is better spent looking for optimal new technologies

than funding trials with suboptimal tools, such as mammography. Dr. Sidransky also addressed the resources for Phase I, Phase II, and Phase III studies. Acknowledging that Phase III studies require large funds, he suggested tighter competition in this phase so that it frees some resources for Phase I. Dr. Greenwald noted that if the technology is stagnated, little is achieved by doing large and expensive field studies. The better strategy may be to spend more money on developing new tools. NCI should have an explicit approach for prioritization. Dr. Levin noted that one responsibility of the Committee is to provide advice for that approach.

Dr. Urban commented that at the end of randomized trials, not much is known. Expensive trials are not providing useful information. The trials do not reveal the years of life saved or the cost per year of life saved. She proposed an investment in a statistical technology infrastructure so that the results of a trial could be predicted. Statistical methods can be developed so that, in the future, clinical trials will be unnecessary. While there was agreement in the usefulness of this approach, it was acknowledged that it will take many years to develop a successful model.

Dr. Kramer presented the following questions targeting areas for future discussion: (1) What should be the criteria for starting clinical trials in cancer screening? (2) What should be the process for funding decisions on large investigator-initiated cancer screening trials (case by case or with a long-range plan)? (3) What is the critical pathway to be followed in validating early detection molecular or secreted-protein markers? (4) Can surrogate endpoints replace cause-specific mortality in definitive screening trials? How would such endpoints be validated? (5) How can NCI plan for long-range followup in screening trials to detect benefits and risks of screening and treatment? (6) How should NCI prioritize resources for biorepositories attached to screening trials? (7) What is the appropriate informed consent for future tests on collected material in biorepositories? (8) Is the organizational structure of the early detection effort ideally configured for early phase (or preclinical) and clinical screening studies? In the course of discussion, one more question was considered—(9) What are the behavior and system approaches that can be studied to improve dissemination of screening practices that have been proven to decrease mortality?

Dr. Kramer suggested that two topics—databases for prevention trials and informed consent—could be dropped as other groups are successfully addressing these issues. The members agreed with this suggestion.

Dr. Longfellow mentioned two concerns. He noted that many biorepositories and relevant information may not be readily available to those who need them. Barriers to access should be identified and corrected. His second issue involved reaching populations that would benefit most from screening. Factors that facilitate the integration of services and new technologies on the community level must be defined and implemented. A member from the Director's Consumer Liaison Group, such as Eleanor Nealon, was suggested as a possible speaker. Dr. Kramer pointed out that the latter issue echoes Dr. Correa's earlier comments—barriers to delivering community health services must be confronted.

Dr. Levin noted that the first three questions by Dr. Kramer have a similar theme—prioritization. A discussion of successful and failed screening trials may be helpful in tackling the broader issue of establishing criteria for prioritization. Dr. Greenwald stated that NCI lacks an explicit defensible strategy for funding decisionmaking and that this needs to be addressed. Dr. Kaplan commented on the tension between funding large-scale validation trials and promoting new technology. Perhaps the two objectives could be incorporated. For example, biomarker studies

might be carried out in a subpopulation of the larger trial cohort. Smaller novel studies could be built onto the framework of the larger trial that uses mature technologies.

Dr. Correa emphasized the need to examine the impact of early detection and screening in the community. Dr. Kramer agreed and suggested that a speaker from the Division of Cancer Control and Population Sciences (DCCPS) discuss how behavior associated with acceptance and dissemination of screening practices could be improved.

In addressing the recommendation for the development of new biomarkers, Dr. Kramer proposed a presentation by Dr. Sidransky on the evolution of a biomarker—from the laboratory bench to clinical use. One focus of the discussion should be the criteria used for selecting markers with the most potential. Several members agreed, and Dr. Aamodt added that Dr. Sheila Taube should also be an invited speaker on this topic. Dr. Gohagan mentioned that statistical approaches for selecting biomarker development would also be useful.

Dr. Levin asked if any surrogate endpoints have been accepted. Dr. Greenwald answered that some colon polyp types are recognized as surrogate endpoints. Colon cancer, for the most part, comes from polyps. Identifying and removing all polyps effectively removes the risk for cancer. It is not 100% effective as a proportion of polyps may escape detection. Dr. Kramer added that response rate is also considered a surrogate endpoint, but it has not replaced cause-specific mortality in screening trials.

Drs. Levin and Longfellow raised the issue of NCI's strengths and how NCI differs from CDC or other centers. A determination should be made on where NCI is best involved—in running major screening trials as the infrastructure is in place, setting standards or guidelines, or providing a framework for basic innovative research to ride on the coattails of larger trials. This determination would help prioritize funding.

The topic of cooperative groups and their role in clinical trials was considered. Dr. Kaplan commented that the infrastructure to support treatment and prevention trials within the cooperative groups and their satellites will be expanded to better support other categories of trials—such as imaging. Dr. Kramer noted the different models of cooperative groups. Some are horizontal, with many disease categories. Others are vertical—for example, starting with a biomarker and taking its development through clinical use. The two models require different infrastructures. He noted that none of the models involve state health departments, an involvement suggested by Drs. Correa and Greenwald. The participation of health departments would achieve dissemination of technologies while testing hypotheses, much as the Community Clinical Oncology Program (CCOP) was designed to do. Dr. Ford mentioned that previous attempts to use state health departments as CCOP research bases did not succeed. Prior experience with capacity building in the state health departments should be reviewed.

Dr. Levin asked about partnership mechanisms between NCI and CDC. Dr. Greenwald stated that some informal mechanisms exist—some work well and others do not. Dr. Ford commented that on a project-by-project basis some very collegial relationships have developed. Dr. Greenwald noted that CDC has a DCP that should be contacted.

Following further discussion, several topic ideas and speakers were suggested for future presentations, including the following: the Cancer Genome Anatomy Project (CGAP), Dr. Robert Strausborg, speaker; the genetics consortium, Dr. Iris Obrams, speaker; development of biomarkers, Dr. David Sidransky, Dr. Sheila Taube, and Dr. Faye Austin, speakers; statistical approaches to biomarker development, Dr. Stuart Baker, speaker; accessing communities and

facilitating early detection systems, Eleanor Nealon, speaker; National Health and Nutrition Examination Survey (NHANES II), a representative from CDC or DCCPS as speaker; Microsimulation Screening Analysis (MISCAN), Dr. Martin Brown, speaker; and impact of early detection programs, a representative from DCCPS as speaker. Dr. Greenwald proposed that the speakers dedicate a third of their presentations to strategies and recommendations that the Committee could discuss and address.

The meeting adjourned at 3:53 p.m.

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- Expand the SEER program to include additional populations, more data from patient's medical records and patients themselves, and population data from the SEER regions to monitor individual and societal mediators of cancer.
- Use the SEER expanded data and expertise to produce a timely report card on the cancer burden.

Early Detection Implementation Group

Roster

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