National Cancer Institute • **Division of Cancer Prevention**

The Early Detection Research Network

Translational Research to Identify Early Cancer and Cancer Risk

Initial Report • October 2000

Contents

4 Foreword

6 Introduction

8 Conceptualization of the Early Detection Research Network

16 Scientific Direction of Individual Network Grantees

- Biomarkers Developmental Laboratories
- Biomarkers Validation Laboratories
- Clinical and Epidemiologic Centers
- Data Management and Coordinating Center

35 Guiding Principles for Biomarker Validation

37 Key Challenges to the Network

40 Invitation to Continuing Collaborative Opportunities

42 National Cancer Institute Components

Foreword

The National Cancer Institute is dedicated to defeating cancer. To achieve that goal, the Institute continually explores new fields of research, expands ongoing areas of research, exploits all available resources, and creates innovative ways of bringing promising research findings into clinical practice for the benefit of all. The transition of new research findings from the laboratory into medical practice often requires as much imagination and effort as the original investigation.

The National Cancer Institute is pleased to issue this initial report on the Early Detection Research Network, a program of the Division of Cancer Prevention. The Network is one of the Institute's premier enterprises for translational research on earlier cancer detection and risk assessment. The concept behind the Network, as described in this report, is straightforward: For most cancers, successful treatment depends on early detection, and successful prevention depends on the accurate evaluation of risk. The Early Detection Research Network seeks to give treatments the opportunity to work and to make prevention possible.

Many of the clinical tests currently in use are not sufficiently sensitive or specific to detect all cancers at a curable stage or to evaluate risk accurately enough to guide effective prevention interventions. Therefore, to find cancer at an earlier stage, the National Cancer Institute is committed to identifying the initial changes that occur in malignant cells. Cutting-edge technology coming from the fields of molecular and cellular biology can now identify the early genetic as well as antigenic changes that occur during the first stages of malignant transformation. These genetic and antigenic changes will soon serve as biomarkers for early cancer detection and for risk assessment.

The routine clinical application of these new technologies is only a matter of time. The purpose of the Early Detection Research Network is to shorten this time by coordinating the development, testing, and application of new biomarkers for early detection and risk assessment.

Richard D. Klausner, M.D.
Director
National Cancer Institute

Introduction

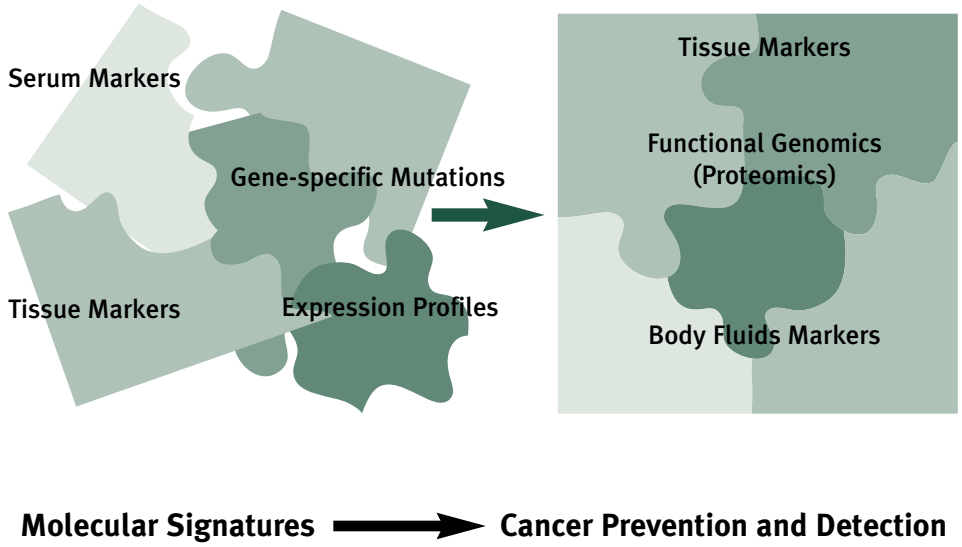
Cancer is a fearsome disease, but research brings hope that it will be conquered.

As the 30th anniversary of the National Cancer Act approaches, many pieces of the puzzle of cancer are falling into place. Research into the inner workings of the cancer cell proceeds at a rapid pace. The technologies to decipher and understand the unique molecular characteristics of cells are emerging. Hopefully, the expansion of molecular knowledge will lead to more effective treatments, better diagnostic tests, better detection tests, and, ideally, to practical ways to prevent a devastating disease.

More than 1.2 million people are diagnosed with cancer each year in the United States and more than half a million people die. More than 8 million people are living with the diagnosis of cancer, and many of them will be diagnosed with the disease a second time. The dazzling discoveries of the molecular world have yet to reach common medical practice in any significant way. The National Cancer Institute is working to bridge that gap—to bring the wonders of the laboratory into clinical use.

NCI's Division of Cancer Prevention created the Early Detection Research Network with the goal of translating this newly emerging molecular knowledge into practical clinical tests. Regular use of early detection and risk assessment biomarkers will meet pressing needs: detection of cancer at its earliest stages and identification of people at risk for cancer before they develop the disease. By identifying people at high risk for developing cancer, intervention efforts can be focused on prevention rather than treatment. This endeavor, one of unprecedented charge and scope, could profoundly impact medical practice.

The Early Detection Research Network supports a comprehensive approach to molecular-based prevention and detection research



The Network is harnessing scientific expertise from leading national and international institutions to identify and validate molecular markers for the detection of precancerous and cancerous cells and to assess risk for developing cancer. The Network is an investigator-initiated consortium for collaborative research to link the discovery of biomarkers directly to the next steps in the process of developing early detection tests and subsequent clinical assessment.

The Network is an opportunity and a challenge for the scientific community—an opportunity to make science work for people and a challenge to make this new found model of collaboration and cooperation a productive scientific construct that other scientists will emulate.

This Initial Report was assembled to document the birth and inauguration of the Early Detection Research Network and to describe the structure of the program. Further reports of the likely successes will follow. Ultimately, the hope is that the Network will create a legacy that speaks for itself.

Conceptualization of the Early Detection Research Network

In early 1996, the National Cancer Institute's Board of Scientific Advisors assembled a series of Review Groups to make a thorough evaluation of the programs of the Institute. One of these groups was charged with examining the Cancer Prevention Program.

The 20-member Cancer Prevention Program Review Group outlined a number of specific recommendations to revitalize NCI's Cancer Prevention Program in June 1997.[1] Of those recommendations, presented to both NCI's Board of Scientific Advisors and to the National Cancer Advisory Board, the following four were relevant to the creation of the Early Detection Research Network:

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

A separate working group, the Early Detection Implementation Group, was created to address these recommendations. This 24-member group, which included both scientific and consumer viewpoints, met four times and suggested 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.[2]

The Early Detection Implementation Group brought the concept for the Early Detection Research Network to the Board of Scientific Advisors on November 13, 1998, giving the following description:

"The initiative will support the creation of a multi-center 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, colorectal, and upper aerodigestive tract, and for the assessment of risk. Specifically, the objectives of the Network will include:

1 The full report of the Cancer Prevention Program Review Group and list of members is available on NCI's Web site at: http://deainfo.nci.nih.gov/advisory/bsa/bsa_program/bsacaprevnt.htm

2 The report of the Early Detection Implementation Group is available on NCI's Division of Cancer Prevention Web site at: http://dcp.nci.nih.gov

- 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 accuracy, sensitivity, specificity, and, whenever possible, medical benefits, 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 and risk assessment viewpoint;
- conducting early phases of clinical/epidemiological studies, e.g. cross-sectional, retrospective, to evaluate predictive value of biomarkers; and
- encourage collaboration and rapid dissemination of information among awardees to ensure progress and avoid fragmentation of effort.

The ultimate impact of the new technology on reducing mortality will not be felt until highly predictive biomarkers are developed for earlier cancer detection or for 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 preinvasive 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."

The concept was approved, and the Early Detection Research Network was begun.

A full description of the Early Detection Research Network concept was published in the journal *Disease Markers*, Volume 15, No. 4, December 1999, pages 213-219.

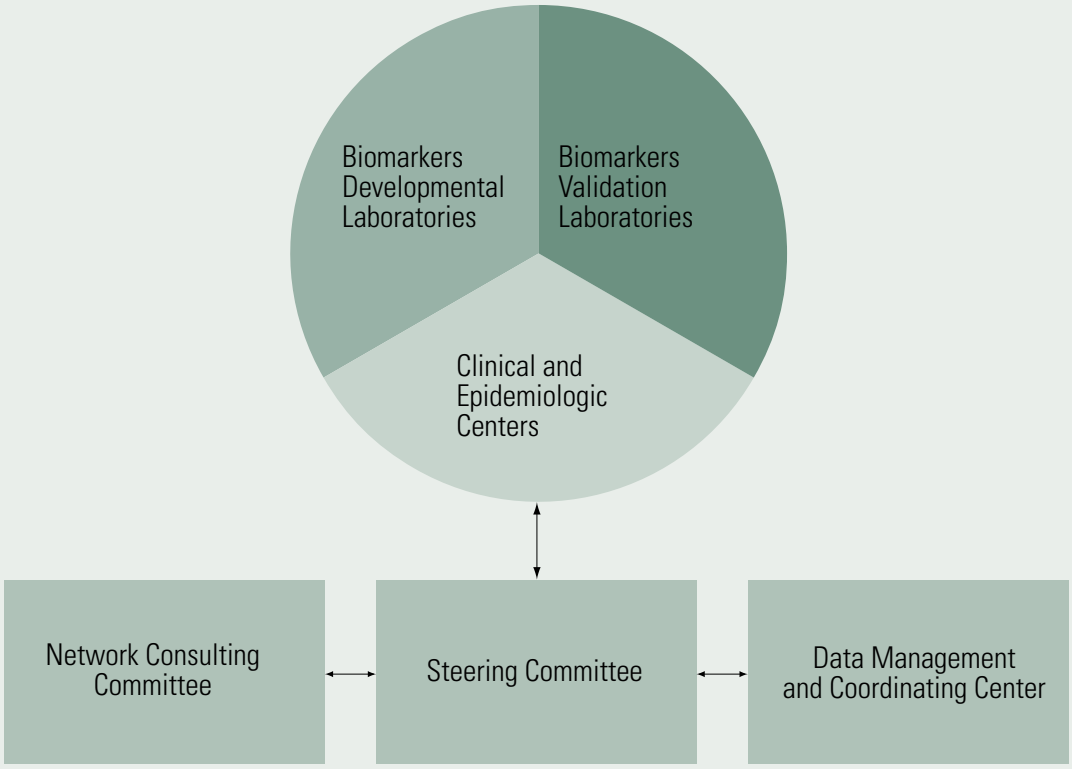
The Early Detection Research Network Web site can be found at http://cancer.gov/edrn.

Timeline

June 1997	Cancer Prevention Program Review Group report recommends expanded research into molecular markers.
November 13, 1998	Early Detection Implementation Group proposes concept for Early Detection Research Network to NCI Board of Scientific Advisors. Concept is approved.
January 20, 1999	Request for Applications for Biomarkers Developmental Laboratories is released.
March 16, 1999	Request for Applications for Biomarkers Validation Laboratories and Clinical and Epidemiologic Centers is released.
April 6, 1999	Request for Applications for Data Management and Coordinating Center is released.
June 14-16, 1999	Request for Applications for Biomarkers Developmental Laboratories reviewed.
July 30, 1999	Funding Plan for Biomarkers Developmental Laboratories presented to NCI leadership.
October 6, 1999	Eighteen Biomarkers Developmental Laboratories funds awarded.
November 10-12, 1999	Request for Applications for Biomarkers Validation Laboratories and Clinical and Epidemiologic Centers reviewed.
November 18, 1999	Request for Applications for Data Management and Coordinating Center reviewed.
January 17, 2000	Funding Plan for Biomarkers Validation Laboratories, Clinical and Epidemiologic Centers, and Data Management and Coordinating Center presented to NCI leadership.
April 2000	Early Detection Research Network fully funded
April 12-14, 2000	First Steering Committee meeting, St. Petersburg, Fla.
May 2000	Three Biomarkers Validation Laboratories, 9 Clinical and Epidemiologic Centers, and the Data Management and Coordinating Center funds awarded.
May 2000	Collaborative opportunities announced on Network Web site, http://cancer.gov/edrn
June 2000	Task Force for molecular taxonomy of preneoplasia convened.
August 2000	Manual of Operations completed.
September 2000	First round of proposals for collaborative studies approved.
September 25-27, 2000	Second Steering Committee meeting and first Scientific Conference, Chicago, Ill.
October 2000	Initial Report of Early Detection Research Network published.
January 2001	Second round of proposals for collaborative studies approved.
January 2001	Third Steering Committee meeting, San Antonio, Texas.
May 2001	Third round of proposals for collaborative studies approved.

Components of the Early Detection Research Network

The Early Detection Research Network is organized into four working and two oversight components. The working components are the Biomarkers Developmental Laboratories, the Biomarkers Validation Laboratories, the Clinical and Epidemiologic Centers, and the Data Management and Coordinating Center. The oversight components are the Network Consulting Committee and the Steering Committee.



Working Components

Biomarkers Developmental Laboratories

The Biomarkers Developmental Laboratories are one of the four working components of the Early Detection Research Network and serve to identify, develop, and characterize new biomarkers or refine existing biomarkers.

These laboratories conduct translational research in the biology of cancer formation. Translational research in this context is defined both as the movement of discoveries from the laboratory into patient or population research settings and as the movement of observations from patient settings back to the laboratory.

Biological, morphological, and clinical alterations found in premalignant and malignant lesions offer the opportunity to detail the early stages of tumor progressions, providing a wider window of opportunity for intervention. High-priority research opportunities in early detection and risk assessment include determining which secreted proteins correlate with the presence of precancerous and cancerous lesions and developing highly sensitive and specific assays to detect cancer-related proteins or tumor cells in body fluids. The emphasis is on identifying risk factors in accessible surrogate anatomic sites for the less accessible major cancer sites, such as a blood marker that detects disease in the lung or pancreas.

Wilbur Franklin, M.D.
University of Colorado Health Science Center, Denver, Colo.

Jose Costa, M.D.
Yale University, New Haven, Conn.

Bruce Trock, Ph.D.
Johns Hopkins University, Baltimore, Md.

Melvin Tockman, M.D., Ph.D.
University of South Florida, Tampa, Fla.

David Fishman, M.D.
Northwestern University, Evanston, Ill.

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

Edward Highsmith, Jr., Ph.D.
University of Maryland, Baltimore, Md.

Stephen Meltzer, M.D.
University of Maryland, Baltimore, Md.

David Beach, Ph.D.
Genetica, Inc., Cambridge, Mass.

Samir Hanash, M.D., Ph.D.
University of Michigan, Ann Arbor, Mich.

Yingming Zhao, Ph.D.
University of Texas, Southwestern Medical Center, Dallas, Texas

Jeffery Marks, Ph.D.
Duke University Medical Center, Durham, N.C.

Timothy Block, Ph.D.
Thomas Jefferson University, Doylestown, Pa.

William L. Bigbee, Ph.D.
University of Pittsburgh, Pittsburgh, Pa.

George Wright, Jr., Ph.D.
Eastern Virginia Medical School, Norfolk, Va.

Adi Gazdar, M.D.
University of Texas-Southwestern Medical Center, Dallas, Texas

Bogdan Czerniak, M.D., Ph.D.
University of Texas-M.D. Anderson Cancer Center, Houston, Texas

Nancy Kiviat, M.D.
University of Washington, Seattle, Wash.

Biomarkers Validation Laboratories

The Biomarkers Validation Laboratories are the second of the four working components of the Early Detection Research Network. In order to develop accurate early detection screening tests, it is crucial to develop high-throughput assays/technologies that are reproducible and cost effective. The Biomarkers Validation Laboratories serve as the Network's resource for laboratory validation of biomarkers, including technology development, quality control, refinement, and high-throughput operations.

These laboratories are responsible for standardizing laboratory assays and methods, and for instituting quality control for reagents and technologies for collaborative Network-directed studies. They have knowledge and practical experience with Standard Operating Procedures and in the evaluation of accuracy, precision, reproducibility, and performance characteristics of tests in multicenter settings, including sensitivity, specificity, and positive and negative predictive values.

William E. Grizzle, M.D., Ph.D.
University of Alabama at Birmingham, Birmingham, Ala.

David Chia, Ph.D.
University of California-Los Angeles, Los Angeles, Calif.

Peter E. Barker, Ph.D.
National Institute of Standards and Technology, Gaithersburg, Md.

Clinical and Epidemiologic Centers

The Clinical and Epidemiologic Centers are the third of the four working components of the Early Detection Research Network. The centers are tasked with conducting clinical and epidemiologic research on the clinical application of biomarkers and with providing resources such as tissue specimens for Network-directed validation studies.

The focus of the research done by the Clinical and Epidemiologic Centers includes, but is not limited to, preliminary studies establishing and comparing sensitivity, specificity, and predictive accuracy of biomarkers in a clinical context; relating biomarker expression to clinical outcome; and evaluating computational methods for combining multiple biomarkers for earlier detection and risk assessment.

As a resource, the centers expedite the clinical validation and application of biomarkers through participating in multi-institutional studies, providing the clinical expertise for conducting trials, and in collecting and distributing tissue specimens.

Elizabeth R. Unger, M.D., Ph.D.
Centers for Disease Control and Prevention, Atlanta, Ga.

Kathy Helzlsouer, M.D.
Johns Hopkins University, Baltimore, Md.

Alan Partin, M.D., Ph.D.
Johns Hopkins University, Baltimore, Md.

Daniel W. Cramer, M.D.
Brigham and Women's Hospital, Boston, Mass.

Dean E. Brenner, M.D.
University of Michigan, Ann Arbor, Mich.

Henry T. Lynch, M.D.
Creighton University, Omaha, Neb.

William N. Rom, M.D.
New York University School of Medicine, New York, N.Y.

Margaret R. Spitz, M.D., M.P.H.
University of Texas-M. D. Anderson Cancer Center, Houston, Texas

Ian M. Thompson, M.D.
University of Texas Health Sciences Center, San Antonio, Texas

Data Management and Coordinating Center

The Data Management and Coordinating Center provides statistical, computational, and logistical support to the entire Early Detection Research Network, including study design consultation, data analysis and meeting coordination. The center manages the flow of information across the Network and is establishing a biomarkers database and developing new statistical and analytical techniques in the emerging field of biomarkers research. The center is the fourth and final working component of the Network.

Ziding Feng, Ph.D.
Fred Hutchinson Cancer Research Center, Seattle, Wash.

Oversight Components

Steering Committee

The Steering Committee provides major scientific management oversight to the Network, with the responsibility for developing and implementing protocols, designs, and operations. Steering Committee members are Principal Investigators from the laboratories and centers, National Cancer Institute program staff, and other ad hoc members as invited by the Steering Committee. Five subcommittees and one working group report to the Steering Committee. An Executive Committee of the Steering Committee meets monthly to perform management and oversight tasks. The Executive Committee is made up of chairs for the subcommittees, the NCI program director, and the Steering Committee chair and co-chair.

Collaboration and Publication Subcommittee defines procedures and conditions for formal collaborations within the Network and with investigators outside the Network, and defines publication policies.

Technology and Resource Sharing Subcommittee establishes the rationale and conditions for sharing technology and other resources among investigators within the Network.

Communications and Workshop Subcommittee defines formats for exchange of scientific findings, such as workshops, seminars, and electronic information resources that serve to inform the research communities of scientific advances. A Task Force on Molecular Taxonomy has been formed out of this subcommittee.

Prioritization Subcommittee establishes procedures for prioritizing and allocating research resources within the Network, including defining the decision criteria needed for the evaluation of biomarkers beyond the discovery stage and setting up a review process for implementing these criteria. The Review Group for collaborations is part of this subcommittee.

Data Sharing and Informatics Subcommittee develops processes and mechanisms compatible with the NCI Informatics Enterprise system for sharing and reporting results of research with Network members.

Clinical/Epidemiological and Ethical Working Group develops processes and mechanisms for the clinical and epidemiological studies and for ethical issues within the Network.

In addition to these existing subcommitees, the Steering committee will form various working groups, task forces, and ad hoc committees as needed to assist with issues that arise. Task forces on intellectual property rights and informatics are being formed.

Network Consulting Committee

The Network Consulting Committee reviews the progress of the Network, recommends new research initiatives, and ensures that the Network is responsive to promising opportunities in early detection research and risk assessment. Network Consulting Committee members are not investigators in the Early Detection Research Network.

Current Advisory Committee Members:

Chair:
Bernard Levin, M.D.
University of Texas-M. D. Anderson Cancer Center, Houston, Texas

Mary Daly, M.D.
Division of Population Science
Fox Chase Cancer Center, Cheltenham, Pa.

Heidi Malm, Ph.D.
Loyola University, Chicago, Ill.

Jane Beth William
Houston, Texas

Larry Norton, M.D.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.

David Johnson, M.D.
Vanderbilt Medical School, Nashville, Tenn.

Peter Jones, Ph.D.
Univerisity of Southern California/Norris Comprehensive Cancer Center
Los Angeles, Calif.

Dave Parkinson, M.D.
Novartis Pharmaceuticals, East Hanover, N.J.

Hoda Anton-Culver, Ph.D
University of California-Irvine
Irvine, Calif.

Richard Pazdur, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, Md.

Judy Ellen Garber, M.D.
Dana-Farber Cancer Institute, Boston, Mass.

Robert Jaffe, M.D.
University of California-San Francisco, San Francisco, Calif.

Scientific Direction of Individual Network Grantees

Biomarkers Developmental Laboratories

Biomarkers in Lung Carcinoma and Premalignancy
1U01CA085070-01
Wilbur Franklin, M.D.
University of Colorado Health Science Center
Department of Pathology
Box B216 4200 East Ninth Avenue
Denver, CO 80262

With a focus on lung cancer, the group is interested in identifying biomarkers for lung carcinoma and premalignancy. Investigators have focused on assessing chromosome copy number and/or region-specific instability in malignant and premalignant airway epithelial cells by using spectral imaging technology; confirming the specificity of alternative mRNA splicing in lung tumors and developing antibody reagents for improved detection; evaluating differentially expressed WNT and HOX loci, along with SEMA3F, hDEF-3, and HuD proteins for use as biomarkers; and identifying more differentially expressed genes during the disease development. Approaches such as differential gene expression techniques (cDNA arrays, differential display restriction fragment-PCR) and in situ technologies (spectral imaging, fluorescence in situ hybridization, and immunohistochemistry) will be applied to lung specimens derived from tumors, biopsies, or primary cultures of normal and preneoplastic epithelium and possibly abnormal cells derived from sputum or blood. Patterns of gene expression likely represent the most detailed molecular characterization of tumors and preneoplastic cells currently possible and should provide a host of new biomarkers for evaluation. It has been proposed that a specimen processing facility for the preparation of cells from sputum and blood will distribute specimens to testing laboratories. This facility will employ new flow cytometry centrifugation and immunomagnetic fractionation procedures for bronchial washings and lavage fluid, sputum, and peripheral blood. Investigators at the University of Colorado Cancer Center and the Colorado Lung Cancer SPORE (Specialized Program of Research Excellence) project will provide facilities and expertise to this group.

Cancer Risk Detection by Mutational Load Distribution
1U01CA085065-01
Jose Costa, M.D.
Yale University
Department of Pathology
P.O. Box 208203, 310 Cedar Street
New Haven, CT 06520-8023

The Biomarkers Developmental Laboratory at Yale University focuses on identifying patients at risk during early phases of neoplasia in pancreatic, breast, and colon tumors. Surrogate samples for the analysis of these tissues provide an opportunity for the development of novel biomarkers whose status can be assessed through noninvasive or minimally invasive procedures. Investigators propose that quantitating the proportion of mutated cancer alleles in a population of somatic cells and measuring the degree of diversity at specific gene loci will accurately reflect the risk for cancer and is likely to emerge as a biomarker that can be validated prospectively and applied widely. This analysis is referred to as mutational load distribution analysis. Surrogate tissue samples containing a sufficiently small number of cells will enable us to to perform mutational load distribution analysis during the preneoplastic stages of tumor development. After somatic genotyping, the tissue samples will be further analyzed by a newly developed technology, which has the power to detect and quantify point mutations at the cytological level. This analysis will serve to corroborate, at the cellular level, the presence of previously detected mutations and will also permit the colocalization of specific mutations with immunohistochemistry-based biomarkers developed by other investigators in the Early Detection Research Network.

Detecting Breast Cancer Protein Signatures in Body Fluid
1U01CA085082-01
Bruce Trock, Ph.D.
Johns Hopkins University
600 N. Wolfe Street, Jefferson Street Building
Baltimore, MD 21287-8915

This Biomarkers Developmental Laboratory plans to develop a new approach to early detection of breast cancer, based on the identification of protein expression patterns associated with acquisition of the malignant phenotype. This approach is derived from the premise that the malignant phenotype is driven by functional abnormalities in protein expression, and that these abnormal expression patterns can be detected prior to the development of a detectable mass lesion. Such altered protein expression patterns or "signatures" should be detectable among secreted proteins shed into biologically relevant body fluids such as nipple aspirate fluid (NAF) or serum. The study will first identify a breast cancer-specific protein signature by analysis of protein expression profiles in normal breast tissue, ductal carcinoma in situ, and early invasive breast cancer. Once a candidate protein signature associated with the invasive phenotype has been identified in tumor material, the feasibility of detecting it in body fluids will be evaluated. In this validation phase, investigators will determine whether the protein signature developed on tissue can discriminate NAF and serum samples from women without breast disease, with ductal carcinoma in situ, and with early invasive cancer.

The tissue-based phase of the study will use laser capture microdissection (LCM) to sample pure cell subpopulations of normal breast tissue, ductal carcinoma in situ and invasive breast cancer. Proteomic expression in these cells will be analyzed using surface enhanced laser desorption ionization (SELDI) spectroscopy Protein Chip™ systems and arrays (Ciphergen Biosystems, Inc.), permitting high-throughput detection of intact proteins within a molecular weight detection range of 1,000 to 60,000 D. Because it can work with complex mixtures without requiring a purification step, SELDI will also be used to analyze unprocessed NAF and serum samples. This powerful detection capability will allow investigators to detect small proteins that may pass through cell membranes and be secreted into body fluids but may be too small to be detected with more traditional proteomic methods.

The Biomarker Development Laboratory at Moffitt (BEDLAM)
1U01CA084973-01
Melvin Tockman, M.D., Ph.D.
University of South Florida
H.L. Moffitt Cancer Center, Department of Internal Medicine
12902 Magnolia Drive
OSWFBB MDC 44 Dialysis Center, 2nd Floor
Tampa, FL 33612-9497

A group of ten investigators makes up the Biomarkers Developmental Laboratory at H.L. Moffitt Cancer Center and focuses on developing assays to detect preclinical lung cancer proteins and altered DNA in body fluids. They have already identified one potential biomarker, expression of hnRNP A2/B1 in exfoliated airway epithelial cells, which is currently in clinical trials. New markers from collaborating laboratories at Moffitt are being developed, refined, and compared on common paired tumor and normal specimens from the Moffitt core tissue bank. These biomarkers include a difucosylated ceramide, lacto-N-fucopentose III; markers of the TGF-beta signaling pathway, TGF-beta receptor Type II, SMAD 2, SMAD 4, and SMAD 7; and markers of tumor suppressor genes silenced by promoter methylation and by allelic loss. Technical approaches include enzyme-linked immunosorbent assays, western blot analysis, methylation specific PCR, immunostaining, thin-layer chromatography, automated DNA sequencing, and laser-scanning immunofluorescence. These panels of assays are being developed as complementary technologies to helical CT detection of preclinical lung cancer. Promising biomarker assays from this project will be applied to archived sputum specimens collected during the ongoing Moffitt helical CT lung cancer screening trial, "Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers." This archive will provide preclinical material with subsequent known cancer outcome for final biomarker case-control assay. The final assay will be conducted on a high-throughput screening platform currently under development by a Collaborative Research and Development Agreement industrial partner. Comparisons of additional biomarkers on these specimens will be facilitated through interactions with the Lung Cancer SPORE programs at Johns Hopkins University, the University of Colorado, and the University of Texas-M.D. Anderson Cancer Center.

The National Ovarian Cancer Early Detection Program
1U01CA085133-01
David Fishman, M.D.
Northwestern University
333 East Superior Street, Prentice-Suite 420
Chicago, IL 60611

The National Ovarian Cancer Early Detection Program clinically applies the biochemical, genetic, and molecular basis of ovarian carcinogenesis, invasion, and metastasis to address the problem of early detection. The metastatic cascade of cellular adhesion, migration, extracellular matrix degradation, invasion, proliferation, and neovascularization are influenced by numerous regulators, such as epidermal growth factor, urinary-type plasminogen activator, matrix metalloproteinases, telomerase and lysophospholipids, such as LPA. Therefore, specific genetic, molecular, and serum biomarkers identified in women with ovarian cancer may have clinical utility in the evaluation of asymptomatic women deemed at increased risk for the development of this disease. Increased risk is assigned to those with either a personal history of breast cancer (4x increase), a family history of affected first-degree relatives (2-7x increase), membership within a recognized inherited malignancy syndrome (40-60% increase), or the presence of an inherited BRCA mutation (16-100% increase). Additionally, the newly developed ovarian Pap test will provide cytological samples for molecular, genetic, and biochemical analysis. It is anticipated that the clinical application of these newly developed molecular, genetic, and biochemical assays will result in the accurate detection of early rather than late-stage ovarian cancer.

Integrated Development of Novel Markers
1U01CA084986-01
David Sidransky, M.D.
Johns Hopkins University
Otolaryngology-Head/Neck Surgery
720 Rutland Avenue
818 Ross Building
Baltimore, MD 21205-2196

The Biomarkers Developmental Laboratory at the Johns Hopkins University has assembled a team of scientists to identify new biomarkers for non-small-cell lung cancer. The identified markers will then be tested on a unique set of paired bronchioalveolar lavage and serum samples from lung cancer patients. This laboratory will also take advantage of the Lung SPORE at Hopkins and its available tissue resources and cores for additional support. These critical resources will allow the team to characterize newly developed markers for rapid translation in the clinical setting through the extended components of the early detection research network. The technology applied for the identification of biomarkers will be serial analysis of gene expression, PCR-based detection of hypermethylated gene promoter regions, a novel method of nucleic acid-based detection for identification of hypermutable sequences in mitochondrial DNA. Several critical issues pertaining to mitochondrial DNA, such as the difficulty in identifying mitochondrial mutations despite exhaustive searches, characterizing clustered mutations, or identifying mutations that are not concentrated in one region or considered to be hot spots or hypervariable regions, are being addressed by this group. Depending on the nature of the mutations, the group will

develop a robust assay to detect a large number of individual mutations or proceed with high-throughput chip technology. Since surgical resection remains the only curative therapy for patients with non-small-cell lung cancer, improvements in early detection are essential for improving the survival in patients. Based on the preliminary data and the past experience of the investigators in this project, it is expected that useful biomarkers will be identified. Furthermore, the genetic alterations identified in primary tumors and paired samples during the tenure of the project will be a useful resource for other Network investigators.

Plasma Telomerase as a Cancer Biomarker
1U01CA084988-01
Edward Highsmith, Jr., Ph.D.
University of Maryland
Department of Pathology
10 South Pine Street
Baltimore, MD 21201-1192

This Biomarkers Developmental Laboratory plans to evaluate the utility of plasma telomerase as a clinical tool for diagnosing malignancies, monitoring therapeutic response, and predicting patient relapse. All measurements of telomerase activity to date have used cellular material, so the work of this laboratory represents a pioneering endeavor to identify fluid-based assays for cancer detection. By measuring the activity of telomerase in the noncellular fluids from a large group of patients, the team will reveal a clearer understanding of the biological impact of telomerase, an enzyme found to be at elevated levels in malignant cells that allows cells to proliferate indefinitely. Because telomerase has been detected in nearly 90% of all tumors types tested to date, this laboratory plans to use a variety of cancers, including lung, esophageal, and gastrointestinal tract cancer, to evaluate plasma telomerase measurements. The primary focus of the project, however, will be on lung cancer. Automated telomeric repeat amplification protocol (TRAP) assay using capillary electrophoresis with laser-induced fluorescence (CE-LIF) detection, quantitative RT-PCR and other molecular and biochemical techniques will be applied in the project. All of these procedures are user friendly, robust, and highly sensitive. The objective, to develop sensitive assays to detect cancer in body fluids, is complementary to the mission of the Early Detection Research Network.

Comprehensive Biomarker Development in Early Esophagus Cancer
1U01CA085069-01
Stephen Meltzer, M.D.
University of Maryland at Baltimore
Department of Medicine, Gastroenterology
N3W62 22 South Greene Street
Baltimore, MD 21201

The Biomarkers Developmental Laboratory at the University of Maryland at Baltimore is focusing their efforts on identifying promising biomarkers for adenocarcinoma of the esophagus and gastroesophageal junction, a disease whose incidence is rising faster than that of any other cancer in the United States. Due to the limitation of current detection, diagnostic, and prognostic tests, improved approaches for the early detection of esophageal-related cancers are needed. This group proposes to improve upon existing knowledge by identifying unique molecular alterations that are acquired during the neoplastic progression of esophageal and gastric epithelia. These alterations, once identified, would serve as biomarkers for earlier diagnosis and improved prognosis and would help direct screening, prevention, and treatment efforts. Further, new markers would serve as a template for the development of more specific and sensitive assays for early detection of esophageal cancers. The group will employ a number of technologies in their project, including laser-capture microdissection (LCM), cDNA microarrays, serial analysis of gene expression, microsatellite instability analysis, loss of heterozygosity analysis, and other mutation detection techniques.

Early Diagnosis of Cancer: The CANFIND Consortium
1U01CA084976-01
David Beach, Ph.D.
Genetica, Inc.
1 Kendall Square, Building 600
Cambridge, MA 02139

A major effort in applied cancer research in the coming years will be a search for improved diagnostic methodologies, and the aim of the Biomarkers Developmental Laboratory at Genetica, Inc. is to identify secreted and cell surface markers that are diagnostic of early stage cancers of the colon and breast. The investigators of this Laboratory will begin by distilling sequences that represent secreted and cell surface proteins from a highly complex cDNA library by use of a powerful biological selection technique. Tumor and normal cells will be purified by laser-capture microdissection and will subsequently be used for the preparation of specific probes for differential expression analysis of DNA microarrays. When coupled with sequence information, differential expression data will contribute to a database of expression patterns for secreted and cell surface proteins in early stage lesions of the colon and breast. The investigators' focus on developing gene expression profiles in cancers of the colon and breast corresponds well with the objectives of the Early Detection Research Network.

Proteomics Biomarker Development Laboratory
1U01CA08482-01
Samir Hanash, M.D.
University of Michigan
1150 West Medical Center Drive
R4451 Kresge I, Box 0510
Ann Arbor, MI 48109-0510

The Biomarkers Developmental Laboratory at the University of Michigan focuses on identifying tumor antigens and tumor-secreted proteins that induce a humoral response and on developing assays to validate the potential utility of such markers for early cancer detection. Initially, the group will focus on potential biomarkers for colon, esophageal, and lung cancer. Progress in the area of humoral response against tumor antigens relates well to potential screening and diagnostic utility of antibodies and their corresponding antigens. Additionally, antigens that induce a humoral response may have clinical utility in immunotherapy directed against tumors. The group's interest in secreted proteins stems from preliminary assays developed for serum and other bilogical fluids. Two-dimensional gel electrophoresis and mass spectroscopy, western analysis, and other biochemical methods will be used for proteome analysis.

Identification of Prostate and Ovarian Cancer Markers
1U01CA085146-01
Yingming Zhao, Ph.D.
Department of Biochemistry
UT Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75390-9038

The focus of this biomarker development project is on the identification of protein biomarkers for early diagnosis, risk assessment, and anticancer drug evaluation in prostate and ovarian cancer. Laser-capture microdissection, mass spectrometry, and two-dimensional gel electrophoresis technologies will be utilized for the screening of prostate and ovarian cancer samples. The initial utility of these studies will be to aid clinicians in the diagnosis of prostate and ovarian cancer in patients bearing an early stage of disease. These studies will also provide a modality to accurately predict prognosis and help clinicians recommend the most appropriate treatment and follow-up strategies. Thus, this research will contribute to prolonging patients' survival and reducing mortality of prostate and ovarian cancer, an objective of the Early Detection Research Network.

Expression-Based Markers for Breast Cancer Detection
1U01CA084955-01
Jeffrey Marks, Ph.D.
Duke University Medical Center
Department of Surgery
Box 3873
Durham, NC 27710

The Biomarkers Developmental Laboratory at Duke University is engaged in research to identify expression-based markers for breast cancer and develop sensitive assays to detect circulating breast cancer cells. Serial analysis of gene expression libraries of breast cancer and normal epithelium are being constructed, and high-density Affymetrix chips (30,000 genes/ESTs) will be utilized for screening. After the in silico analysis, the lead markers will be subjected to a validation algorithm that includes northern analysis, RT-PCR, and in situ hybridization. Antibodies to the most promising candidates will be developed, particularly for gene products that may be secreted or presented on the cell surface. The project is a collaborative effort between the Duke Breast Cancer Program and Abbott Diagnostic Breast Cancer Venture Group. This laboratory will also collect whole blood and serum from women newly diagnosed with breast cancer at the Duke University Medical Center and will develop a specimen repository as a primary validation set for markers.

Early Detection of Liver Cancer and Hepatitis
1U01CA084951-01
Timothy Block, Ph.D.
Thomas Jefferson University
Delaware Valley College
700 East Butler Avenue, Suite 238
Doylestown, PA 18901-2697

Focusing on biomarkers for hepatocellular carcinoma, the Biomarkers Developmental Laboratory of Thomas Jefferson University plans to identify novel biomarkers that aid in the diagnosis and prediction of liver disease in hepatocellular carcinoma (HCC). It has previously been determined that individuals who are chronically infected with hepatitis B or C virus (HBV or HCV) are at a high risk for developing hepatitis and eventually HCC, a disease that progressively develops after many years. HCC is among the world's most common cancers and is responsible for between 250,000 and 800,000 deaths annually. Given the limitations of current clinical tools and the growing hepatitis population, advances in detection, diagnostic, and predictive modalities for HCC would have substantial public health benefits. This group intends to investigate serum polypeptides from individuals at different stages in the disease continuum, using two-dimensional gel electrophoresis. Polypeptides that correlate by their appearance, disappearance, or post-translational modification with disease status will be identified and developed into highly specific and sensitive tests for assaying specific polypeptide profiles. After developing biomarkers for HCC and associated liver disease, this laboratory will identify promising markers for validation at collaborating Network centers and laboratories.

Early Cancer Detection and Susceptibility Biomarkers
1U01CA084968-01
William L. Bigbee, Ph.D.
University of Pittsburgh Cancer Institute
305 Iroquois Building, 200 Lothrop Street
Pittsburgh, PA 15213

The University of Pittsburgh Cancer Institute Biomarkers Developmental Laboratory is an integrated multidisciplinary project bringing together researchers with expertise in colorectal, lung and aerodigestive tract, and ovarian cancer. For the colorectal cancer project, laser-capture microdissection is being applied to biopsy specimens to identify genetic alterations and changes in gene expression in adenomatous polyps as early detection markers of colorectal carcinoma. For the lung and aerodigestive tract cancer project, the quantitation of gene expression coding for cell-surface receptors of the growth modulating molecules, epidermal growth factor, and gastrin-releasing peptide in buccal mucosa and peripheral blood are being evaluated as early detection biomarkers of head and neck squamous cell carcinoma and non-small-cell lung carcinoma. To identify and further characterize these genetic components of cancer susceptibility, particularly with respect to tobacco smoke exposure which is a major risk factor for lung and aerodigestive cancer, this group is applying genotyping assays for polymorphic genes (CYP1A1, GSTM1, GSTT1, MPO, and NAT2) involved in carcinogen activation and detoxification to the development and validation of new assays for the recently described polymorphisms in the DNA nucleotide excision repair genes, XPD and XPF. In the ovarian cancer project, serial analysis of gene expression of ovarian tumors is being used to characterize and identify altered patterns of gene expression for discovery of peripheral blood-based tumor-specific protein markers. All of these research activities are being conducted in an active University of Pittsburgh Cancer Institute translational molecular epidemiological research environment focused on a collaborative process of cancer biomarkers discovery, evaluation, and validation to support the broader research and clinical goals of the Early Detection Research Network.

Early Detection of Cancer by Affinity Mass Spectrometry
1U01CA085067-01
George Wright, Jr., Ph.D.
Eastern Virginia Medical School
Microbiology and Immunology
700 West Olney Road
Norfolk, VA 23507-1696

The research objective of the Biomarkers Developmental Laboratory at Eastern Virginia Medical School is to identify unique cancer protein fingerprints that can be used to improve the early detection of prostate and breast cancer. The novel protein biochip mass spectrometry technology developed by Ciphergen Biosystems, Inc., surface enhanced laser desorption ionization (SELDI) time of flight mass spectrometry, will be used to meet this

goal. The initial focus of this project is to discover the pre-cancerous and cancerous signature proteins in microdissected cancer cells. Lysates from all developmental stages will be analyzed to identify the unique cancer protein fingerprints. From these fingerprints, researchers will identify which unique cancer-associated proteins are secreted or shed into body fluids and determine the potential clinical use of SELDI protein profiling for early cancer detection. Particularly, the researchers propose to identify proteins that correlate with pre-cancerous and cancerous lesions via sequence analyses. Antibodies to the unique proteins will be used to develop SELDI immunoassays for quantitation of the cancer-associated proteins in body fluids. Since the same platform is used for discovery, identification, characterization, and diagnostic assay development, it is anticipated that a rapid high-throughput SELDI phenomic fingerprint profiling or SELDI multiplex immunoassay will be developed to improve the early detection of prostate and breast cancer.

Markers for Risk Assessment/Early Detection of Lung and Breast Cancer
1U01CA084971-01
Adi Gazdar, M.D.
University of Texas Southwestern Medical Center
Hamon Center for Therapeutic Oncology Research
5323 Harry Hines Boulevard
Dallas, TX 75235-8593

The Biomarkers Developmental Laboratory at the University of Texas Southwestern Medical Center brings to the Network an expertise in mutations that contribute to lung and breast cancers. Realizing that much of the upper aerodigestive tract is mutagenized and at an increased risk for cancer in patients with lung neoplasia, the group has focused their study on the marked progression of preneoplastic lung and airway disease development. It has been established that tumor DNA is often shed or released into the circulation of a patient with invasive cancer. If isolated and tested, these exfoliated cells express molecular and genetic changes that are representative of the molecular circuitry of the actual tumor. The non-invasive isolation of these cells and detection of molecular changes is expected to aid in early detection, diagnosis, and monitoring of tumor course and response to therapy. Markers to be studied for risk assessment include onset of clonality, allelic losses at multiple regions, microsatellite alterations using multiple polymorphic markers, and presence of aberrantly methylated genes. The group is using specialized software, PANORAMA, to identify approriate primer sequences suitable for methylation specific PCR. A major application of PANORAMA is the discovery of CpG islands associated with the genes in the aberrantly methylated region. After determining the presence of a CpG island in the 5'-promoter region and lack of expression of a specific genetic region, investigators will determine if the gene is silenced via aberrant methylation. This information can also be combined with allelic loss and mutational data to give a more comprehensive picture of preneoplastic and neoplastic contributors. Microarray chip technology will be used to detect aberrantly methylated genes. Along with identifying genetic mutations, the group will collect specimens from surrogate organ, sputum, bronchial biopsies/brushes, and bronchioalveolar lavage fluids to assist the specimen resources need by the Early Detection Research Network. Fine-needle aspirates of periareolar tissues from women at increased risk for the development of breast cancer will be obtained and analyzed to determine whether molecular markers can aid in risk assessment and histopathological/cytological examination.

Early Detection of Urinary Bladder Cancer
1U01CA085078-01
Bogdan Czerniak, M.D., Ph.D.
University of Texas-M.D. Anderson Cancer Center
Department of Pathology
Box 085
1515 Holcombe Boulevard
Houston, TX 77030

The Biomarkers Developmental Laboratory at M.D. Anderson Cancer Center aims to develop markers for early detection of occult urinary bladder neoplasia and its progression to invasive, clinically aggressive urinary bladder cancer. Altogether, seven investigators will be involved in the project. Fluorescent in situ hybridization, PCR, loss of heterozygosity analysis, and standard biochemical and genetic techniques will be utilized. The group will construct and screen YAC and BAC libraries for the identification of tumor suppressor gene loci involved in several stages of urothelial neoplasia, particularly for in situ preneoplastic lesions through invasive disease. After completion of this project, a diagnostically relevant panel of probes for the detection of preneoplastic changes and aggressive variants with potential to progress to invasive bladder disease may be available for the early diagnosis of bladder cancer. Furthermore, a repository of shared data on all tested markers and their performance as diagnostic probes will be available to the Early Detection Research Network. This repository will serve as a resource on potential diagnostic markers and target genes that may be useful in cancer types other than that of the urinary bladder. The project will also contribute to the identification of regulatory pathways mediated by oncogenic kinase STK15.

Biomarkers Development Laboratory
1U01CA085050-01
Nancy Kiviat, M.D.
University of Washington
Department of Pathology
HPV Research Group
Box 359933
Seattle, WA 98195

The Seattle Consortium for Identification and Development of Biomarkers of Early Neoplasia has established a Biomarkers Developmental Laboratory. The researchers will employ a variety of approaches to develop molecular cancer screening assays. Such assays include genomics-based programs for detection and/or quantification of cancer-associated or cancer-specific proteins, oxidative DNA damage, abnormal DNA methylation sequences, serum antibodies elicited by tumor antigens, novel monoclonal antibodies for detection of ovarian cancer, and development of high-throughput proteome analysis

technology. A number of putative cancer biomarkers are currently awaiting evaluation, and others will become available for testing over the next five years. This developmental laboratory will combine scientific expertise with assay development and early phase "proof of principle" testing to determine the clinical applicability of the novel technologies and candidate biomarkers that are identified. Access to a large number of well-characterized benign and malignant tissues, blood and other body fluids, and corresponding information regarding demographic characteristics, treatment, and risk factors will be available. This group has extensive experience in tissue banking for molecular studies and has the proven ability to develop and validate the required clinical assays and to perform the early phase testing.

Biomarkers Validation Laboratories

The Early Detection Research Network: Biomarker Validation Laboratories
1U24CA086359-01
William E. Grizzle, M.D., Ph.D.
University of Alabama at Birmingham
Department of Pathology
703 S. 19th St.
Zeigler Bldg 422
Birmingham, AL 35294-0007

The Biomarkers Validation Laboratory at the University of Alabama at Birmingham has assembled a group of investigators with extensive experience in biomarker research to offer a broad range of validation systems and research expertise to the Early Detection Research Network. The group has tissue collections from various organ systems, including prostate, colorectum, lung, head and neck, and gynecologic organs. The availability of well-characterized tissue resources, including urine and serum, which have been uniformly collected and stored at the university according to standard procedures, will serve as a major resource for Network validation studies. Special expertise includes tissue matrix preparation, enzyme-linked immunosorbent assay, protein purification, immunohistochemistry, and mRNA isolation. The Core Facilities of the University's Comprehensive Cancer Center, together with other Centers of Excellence at the University, further enhance the resources that will be available to Network investigators. The existing collaborations among the investigators in this group, their associated institutions, and their prior participation in national networks (e.g., the Cooperative Human Tissue Network and SPOREs) will ensure rapid and effective responses to the needs of the Early Detection Research Network.

Biomarkers Validation Laboratories
1U24CA086366-01
David Chia, Ph.D.
University of California-Los Angeles
Department of Surgery
Tissue Typing Lab
950 Veterans Avenue
Los Angeles, CA 90095-1654

The University of California at Los Angeles is serving as a validation laboratory for the Early Detection Research Network, and it has several operational laboratories for the evaluation and analysis of tumor markers using a variety of molecular assays. These laboratories include the Human Tissue Research Center (tissue procurement, sectioning, and histology), Tissue Analysis Laboratories (conventional immunohistochemistry, in situ hybridization, high-throughput tissue microarray), Molecular Pathology Laboratories (gene expression, chromosomal abnormalities, polymorphism, high-throughput array-based mutation analysis), Immunoassay Laboratory (radioimmunoassays, enzyme-linked immunosorbent assays, western blot analysis), and Cellular Analysis Laboratories (flow cytometry, cytology, chromosomal analysis, cytogenetics). These laboratories are located in the School of Medicine (the Department of Pathology and Laboratory Medicine, the Department of Human Genetics, and the Jonsson Comprehensive Cancer Center) at UCLA. Distinguished faculty and Core Facilities support these laboratories. The Core Laboratory Directors and the internal Advisory Board are committed to assisting with project design and strategic planning. A Bioinformatics Core has combined expertise in biostatistics, bioinformatics, and data analysis and mining. The Pathology Consultation Core specializes in correlation of pathological diagnosis with marker expression. The goal for the laboratory is to adapt to the needs of Network analytical validation studies.

EDRN/NIST Biomarkers Validation Laboratory
Peter E. Barker, Ph.D.
Research Chemist
Biotechnology Division
National Institute of Standards and Technology
100 Bureau Drive, MS 8311
Gaithersburg, MD 20899-8311

The National Institute of Standards and Technology (NIST) is involved in biomarker validation for the Early Detection Research Network and will primarily focus on nucleic acid characterization and cytogenetics technologies. Their focus will include the validation of molecular cytogenetic and automated cytometry assays involving slide-based analysis of chromosome spreads by classical and molecular methods. Expertise at NIST in fluorescence intensity standards and molecular cytogenetics will be an asset for the Network's validation studies, and where practicable, NIST can assist in high-throughput platform design for these assays. In addition, a number of validation projects involve genotyping

(for loss of heterozygosity or susceptibility analysis) and sequence analysis of DNA from mitochondrial or genomic sources. For these, NIST's databases, technology, and experience in developing the database on short tandem repeats, standard reference materials for mitochondrial DNA and the p53 gene, and high-throughput forensic DNA analysis with mass absorption laser desorption ionization time of flight (MALDI-TOF) will be applied to validation of a series of loci of importance in classifying and diagnosing cancers at early stages of disease. For biomarkers that prove especially promising, NIST will collaborate on scale-up and implementation of high-throughput analytical platforms to apply biomarker detection to large population samples.

Clinical and Epidemiologic Centers

Clinical Validation of Molecular Signatures of Cervical Cancer
Y1-CN-0101-01
Elizabeth R. Unger, M.D., Ph.D.
Acting Chief, Human Papilloma Virus Section
Centers for Disease Control and Prevention
1600 Clifton Road, MSG18
Atlanta, GA 30333

The focus of the Clinical and Epidemiologic Center at the Centers for Disease Control and Prevention is to define molecular signatures that are predictive of neoplastic progression in cervical lesions. Human papillomavirus (HPV), a highly prevalent viral infection of the genital tract, has been epidemiologically linked to cervical cancer. However, the usefulness of HPV DNA detection as an early detection marker for cervical cancer is limited. Because HPV has been shown to alter the genetic stability of infected cells, it is believed that the accumulated genetic damage subsequently leads to neoplasia. The aim of this study is to detect cellular expression changes that correlate with cervical lesion status and to use these changes as novel markers for early detection of cervical cancer. This center proposes to conduct a case-control study of preinvasive cervical lesions in a high-risk urban population of 1,067 subjects with any grade of cervical dysplasia paired with 1,067 age- and race-matched cervical disease-free control subjects. The group will collect epidemiologic and clinical data through interviews and chart-reviews as well as determine cervical lesion status from cytology, colposcopy, and biopsy results. Investigators will evaluate several molecular features of the subjects, including host immune factors such as serum and mucosal antibodies to HPV-16 VLPs, mucosal cytokine profiles, and cellular gene expression profiles derived from high-density filter arrays. The center also plans to elucidate and control for numerous viral factors known to be potentially important in pathogenesis, including HPV type, type-variant sequencing, viral quantity, integration status, and level of E6/E7 transcription. Confirmation of differentially expressed genes will be performed through reverse transcriptase-PCR and in situ analyses in biopsies to assess viral and cellular gene expression. While the initial focus of study will be HPV-16-associated lesions, because that is the type most frequently associated with cervical neoplasia, investigators will later extend their analyses to other HPV types and combine results with other Network studies for further validation of the biomarkers.

CLUE Studies: Evaluating Biomarkers of Carcinogenesis
1U01CA086308-01
Kathy Helzlsouer, M.D.
Johns Hopkins University
School of Public Health
615 North Wolfe Street
Baltimore, MD 21205

To address the need for resources and methods for rapid clinical evaluation of risk and disease biomarkers, the Clinical and Epidemiologic Center at the Johns Hopkins University will use an existing community-based cohort that is currently under follow-up for cancer outcomes. This group plans to demonstrate the rapid and efficient evaluation of multiple biomarkers for early cancer detection or risk assessment by studying fatty acid synthase concentrations as a potential marker of aggressive forms of breast cancer. Having adquate numbers of specimens is necessary for determining and assessing the validity of biomarkers, their change over time, their association with early and late stages of carcinogenesis, and their latency periods. While the preliminary assessment of promising serologic and genetic markers will be performed using available specimen banks, this center will establish additional resources among screening cohorts. The resources of the CLUE study, a community-based cohort study, will also be used. The CLUE study cohorts will provide a mechanism to rapidly assess potential biomarkers and aid in their transition from the laboratory to the clinical setting.

Clinical and Epidemiological Center: Prostate Cancer
1U01CA086323-01
Alan Partin, M.D., Ph.D.
Johns Hopkins University
Department of Urology
600 North Wolfe Street, Marburg 205A
Baltimore, MD 21287-2101

The Clinical and Epidemiologic Center at the Johns Hopkins University was established to evaluate the clinical utility of previously characterized and newly discovered biomarkers for cancer of the prostate. The investigators are conducting a series of studies to refine data concerning the relevance of prostate-specific antigen, kallikrein-2, B23, p27, and Ki67 for early detection of prostate cancer. In order to analyze multifactorial clinical information, the center will utilize artificial neural networks. This study could lead to the development of new methods for analyzing and managing vast amounts of new clinical information associated with multiple biomarkers. A remarkable contribution that this group brings to the Early Detection Research Network is a large number of specimen resources, well-established connections with industry, and a unique expertise in neural network-based analysis.

Proteomic/Epidemiologic Paths to Ovarian Cancer Screening
1U01CA086381-01
Daniel W. Cramer, M.D., Sc.D.
Brigham and Women's Hospital
Department of Obstetrics and Gynecology
221 Longwood Avenue
Boston, MA 02115

Investigators at Brigham and Women's and Massachusetts General Hospital in Boston and St. Bartholomew's Hospital in London have the long-standing experience and abundant resources necessary to conduct epidemiologic and laboratory studies on normal, high-risk, and ovarian cancer populations. The investigators currently maintain and will further develop repositories of epidemiologic data and biological specimens that will be available for center- and Network-directed studies with the goal of identifying new screening markers for ovarian cancer. These banks include epidemiological data associated with plasma, buffy coat, and red blood cells from population-based case-control studies of women with newly diagnosed ovarian cancer; fresh-frozen tissues from patients with early stage and advanced ovarian cancer; and blood and tissue specimens from women who undergo prophylactic oophorectomy because of their increased risk for ovarian cancer. Using these specimens and employing recent technological advances, the group aims to identify new biomarkers to distinguish between women with ovarian cancer and those without the disease. One of these technologies is surface enhanced laser desorption/ionization (SELDI), which is a technique for performing protein mass spectrometry. As part of the effort to identify new biomarkers, the team is also interested in developing new statistical methods to identify panels of biomarkers with better performance characteristics than any single biomarker. It is believed that these efforts will lead to the application of a promising set of screening biomarkers developed through the Early Detection Research Network in longitudinally collected specimens from a prospective study of ovarian cancer screening conducted in England.

Great Lakes-New England Clinical and Epidemiology Center
1U01CA086400-01
Dean E. Brenner, M.D.
University of Michigan
Internal Medicine
1500 Medical Center Drive
3215 Cancer Geriatrics Center
Ann Arbor, MI 48109-0934

The Great Lakes-New England Clinical and Epidemiologic Center is composed of a multidisciplinary team of investigators with long-standing experience in recruitment of subjects for cancer prevention trials. This consortium of seven institutions includes the University of Michigan, Henry Ford Medical Center, Dartmouth University, Brigham and Women's Hospital, University of Toronto-Wellesely Hospital, Ohio State University, and Clallit Health System/Technion in Israel. By using colorectal cancer and Barrett's esophagus as a paradigm for biomarker research and development, the team will conduct studies in the etiology of cancer, genetic epidemiology, biomarker development, and statistical analysis of clinical data. Initially, five potential serum markers (S-1000 proteins, Galectin-3, MUC5AC) will be clinically validated. This study will refine statistical criteria for clinical

biomarkers validation and explore a novel organizational structure for clinical studies on new biomarkers. Additionally, this center has an excellent data management system and can provide extensive and diverse human populations for the validation of biomarkers, which will be a precious resource for the Early Detection Research Network.

The Hereditary Cancer Clinical Center
1U01CA086389-01
Henry T. Lynch, M.D.
Creighton University School of Medicine
Department of Preventive Medicine
2500 California Plaza
Omaha, NE 68178

In three decades of study of hereditary cancer syndromes, Creighton University's Hereditary Cancer Institute has amassed a large database of information and biological samples on hereditary cancer families. The principal investigator and colleagues will recruit members of these families for biomarker research as a Clinical and Epidemiologic Center of the Early Detection Research Network. Their objectives will be to focus on developing and maintaining a registry of individuals harboring germline mutations for hereditary cancer syndromes who are willing to participate in biomarker studies. Registrants in such studies are considered to be at high risk for developing specific types of cancer and will contribute as a resource on hereditary cancer syndromes for the Early Detection Research Network. The group, in consultation with other Clinical and Epidemiologic Centers, will share methods for identifying cancer-prone families, protocols for records and specimen retrieval, and database software on hereditary cancer syndrome diagnosis. This center will carry out a pilot study of potential biomarkers of colorectal cancer in fecal specimens in collaboration with an industrial partner, EXACT Laboratories, Inc.

NYU Biomarker Clinical and Epidemiologic Center
1U01CA086137-01
William N. Rom, M.D.
New York University School of Medicine
Department of Medicine
550 First Avenue
New York, NY 10016

The objective of the New York University Biomarker Clinical and Epidemiologic Center is to identify preneoplastic lesions and early cancer in populations of former and active union members who vary in their risk for cancer due to enviromental exposure. The center has developed and maintained a close working relationship with union members and will invite a large number of high-risk individuals to participate in studies within the Early Detection Research Network. The group has also proposed to assemble and prospectively follow a cohort of approximately 2,500 individuals at-risk for the development of lung cancer. The global hypothesis of this project is that bioassays for BPDE-DNA adducts, p53 and K-ras genes, cyclin-cyclin-dependent kinase deregulation and signaling, Rb pathways, oncogenes, and tumor suppressor genes will detect preneoplastic conditions or cancer in its earliest stages. Initially, the study will focus on lung cancer, the leading cause of death due to cancer for both men and women in the United States. The center also proposes to perform lung cancer screening on 1,500 smokers who have been working more than 30 years

in construction trades and have been smoking more than 30 pack-years. The screening will consist of clinical examinations and tests, including spiral CT scan of the chest, spirometry, and the analysis of sputum and blood. In addition, 1,000 Pantex Nuclear Weapons plant workers who have been exposed to ionizing radiation will be prospectively screened for the presence of antibodies to cell-cycle gene abnormalities.

Clinical and Epidemiologic Center for Biomarkers of Upper Aerodigestive Tract Lesions

1U01CA086390-01
Margaret R. Spitz, M.D., M.P.H.
University of Texas-M.D. Anderson Cancer Center
Department of Epidemiology
1515 Holcombe Boulevard
Houston, TX 77030

The Clinical and Epidemiologic Center at M.D. Anderson Cancer Center is focused on expanding ongoing research in upper aerodigestive tract lesions. From early and advanced premalignant lesions, through early stage cancers, and to second primary tumors, this group will conduct research that spans the continuum of disease. Their scientific agenda comprises three interrelated projects to evaluate promising new candidate genetic and phenotypic cellular and molecular biomarkers for assessment of risk, early detection, and therapeutic response in premalignant lesions and cancers of the upper aerodigestive tract. The investigators will apply statistical methodologies for combining biomarker data and for assessing genotype/phenotype and surrogate/target tissue marker correlations, and will support developmental projects for the Network. In collaboration with their industry partner, Genometrix, Inc., the group will validate microarray technology for large-scale metabolic polymorphism genotyping. The resources at this center include intergroup chemopreventive trials and epidemiologic research as well as a multidisciplinary team of investigators, including oncologists, epidemiologists, molecular biologists, pathologists, and biostatisticians. The center's clinical resources also include a comprehensive database that stores clinical information on over 1,000 subjects enrolled in chemopreventive and epidemiologic studies, with approved protocols, and specimen repositories with substantial preliminary data. This resource can also expand to the diverse patient population of the M.D. Anderson Cancer Center and their participation in the Cancer Genetics Network. The biomarker resource at this center integrates a comprehensive panel of biomarkers of risk and early detection, expressed in germline DNA, premalignant lesions, adjacent normal epithelium, and invasive cancer.

San Antonio Center of Biomarkers of Risk for Prostate Cancer

1U01CA086402-01
Ian M. Thompson, M.D.
University of Texas Health Sciences Center
Department of Surgery
7703 Floyd Curl Drive
San Antonio, TX 78284-7845

The San Antonio Center of Biomarkers of Risk for Prostate Cancer is an innovative, prospective study of a multiethnic population of San Antonio to determine the use of novel prostate cancer biomarkers in prostate cancer. The unique contribution of military,

Veterans Affairs, and university health systems, as well as the large number of Hispanic, African-American, and white men who will participate, will provide a powerful foundation to evaluate both new methods to predict prostate cancer risk but also to assess outcomes. A major focus of the program will be to leverage the diverse sites within metropolitan San Antonio to include both minority as well as underserved populations. Additionally, several of the elements of this Clinical and Epidemiologic Center will evaluate new clues to prostate cancer prevention, including dietary and micronutrient contributions to prostate cancer risk. Two important biomarkers to be tested include insulin-like growth factor I as well as genetic polymorphisms of the androgen receptor. A total of 10,000 men will participate in the program.

Data Management and Coordinating Center

Data Management and Coordinating Center
1U01CA086368-01
Ziding Feng, Ph.D.
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-859
P.O. Box 19024
Seattle, WA 98109-1024

The Data Management and Coordinating Center at Fred Hutchinson Cancer Research Center is responsible for three distinct activities to support the Early Detection Research Network: coordination/logistical support, data management for collaborative studies, and development of new statistical methodology for biomarker evaluation and interpretation. Network coordination/logistical support includes activities such as providing logistical and administrative support for all Network meetings, developing and maintaining a secure Network Web site, providing listserves for various Network committees, promoting interactions between the Network and other relevant networks and consortia, assisting with the development and implementation of collaborative study research protocols, analyzing data from collaborative studies, and providing statistical consultation for center-specific studies in the Network. Data management support for Network collaborative studies includes activities such as developing data collection protocols and monitoring their adherence, developing and maintaining collaborative study databases, and providing reports or study data as needed. Statistical methodology development will focus on development of flexible descriptive statistical methods for 1) assessing the reliability and reproducibility of biomarkers and identifying factors that contribute to reduced reliability; 2) assessing the accuracy of biomarkers for cancer detection or cancer risk assessment, and factors influencing their diagnostic potential both when a gold standard exists and when it does not exist; 3) combining multiple biomarkers; 4) identifying cancer heterogeneity by biomarkers; and 5) identifying biomarkers from microarray expression data.

Guiding Principles for Biomarkers Validation

Pathways to biomarker development and validation studies should be critically evaluated for general concept, uniqueness of approach, whether there is proof of principle, whether the path is revising or improving a known approach, if there are pilot feasibility studies, how well technology is used, plans for prospective monitoring trials, and plans for prospective screening trials. These studies should lead to "biological foot prints" in biomarkers research — a designated path for research to proceed from basic science to clinical trials. The fundamental basis for validation studies must be that they operate generically in order to avoid creating a customized structure for each biomarker.

The Early Detection Research Network has adopted seven formal criteria that will be used to assess the readibility of biomarkers for analytical and clinical validation:

1. Biologic rationale/strength of hypothesis: The strength of the science is of paramount importance. Several basic criteria must be met before potential markers could serve as adequate surrogate endpoints either for risk or clinical outcome: 1) Is the biomarker differentially expressed in normal and high-risk or tumor tissue? 2) At what stage of carcinogenesis does the marker appear? 3) Do the marker and its assay provide acceptable sensitivity, specificity, and accuracy? 4) How easily can the marker be measured? Biologic rationale based on one or more of these criteria must be tested prior to any large studies.

2. Strength-of-design issues include whether the preliminary study is subject to "spectrum bias," i.e., bias that occurs when biomarker studies are restricted to individuals with late or symptomatic disease versus normal individuals with no confounders. Another design issue will concern the prospective or retrospective nature of the study, with size and confidence intervals also being important. Strength of design can also be judged based on the phase of development of the marker. For example, if a prospective cohort study is proposed when a cross-sectional study has never even been done, then the marker is too early in its development to jump to a prospective design. However, as another example, a preliminary study will not be considered flawed because it looks at cancer patients and controls only.

3. Technical parameters will include reproducibility, sensitivity, specificity, and definitions of each. The magnitude of differences in the biomarker between normal, benign ("confounders"), and precancer, as well as cancer in its early stages, will be considered. Finally, throughput, automation, and cost issues will also be considered under this category. This is not to imply that cost-effectiveness would be evaluated at this stage, since it will be very difficult to know cost-effectiveness at a population level this early. Finally, all of these parameters are also issues for Validation Laboratories, but to some extent must be considered even at this stage of development.

4. Clinical or scientific impact issues favor biomarkers devoted to decreasing mortality in a common cancer with a wide burden of disease in the public. Rare diseases, however, offer opportunities for scientific insights resulting in paradigm shifts; such proposals may also receive high priority for their impact on fundamental scientific understanding. Finally, the relative impact on each specific cancer is considered: A biomarker approach that would reduce mortality by 90% in a less common cancer would receive equal or greater priority than one that would reduce mortality by 1% in a common cancer.

5. Portfolio balance refers to the intention not to put all the eggs in one basket, e.g., not to prioritize five projects in the same disease site or five gene-array projects to the exclusion of other disease sites or other technologies. The Network will strive for a portfolio of projects to include various organ sites in order of their contributions to cancer incidence and mortality.

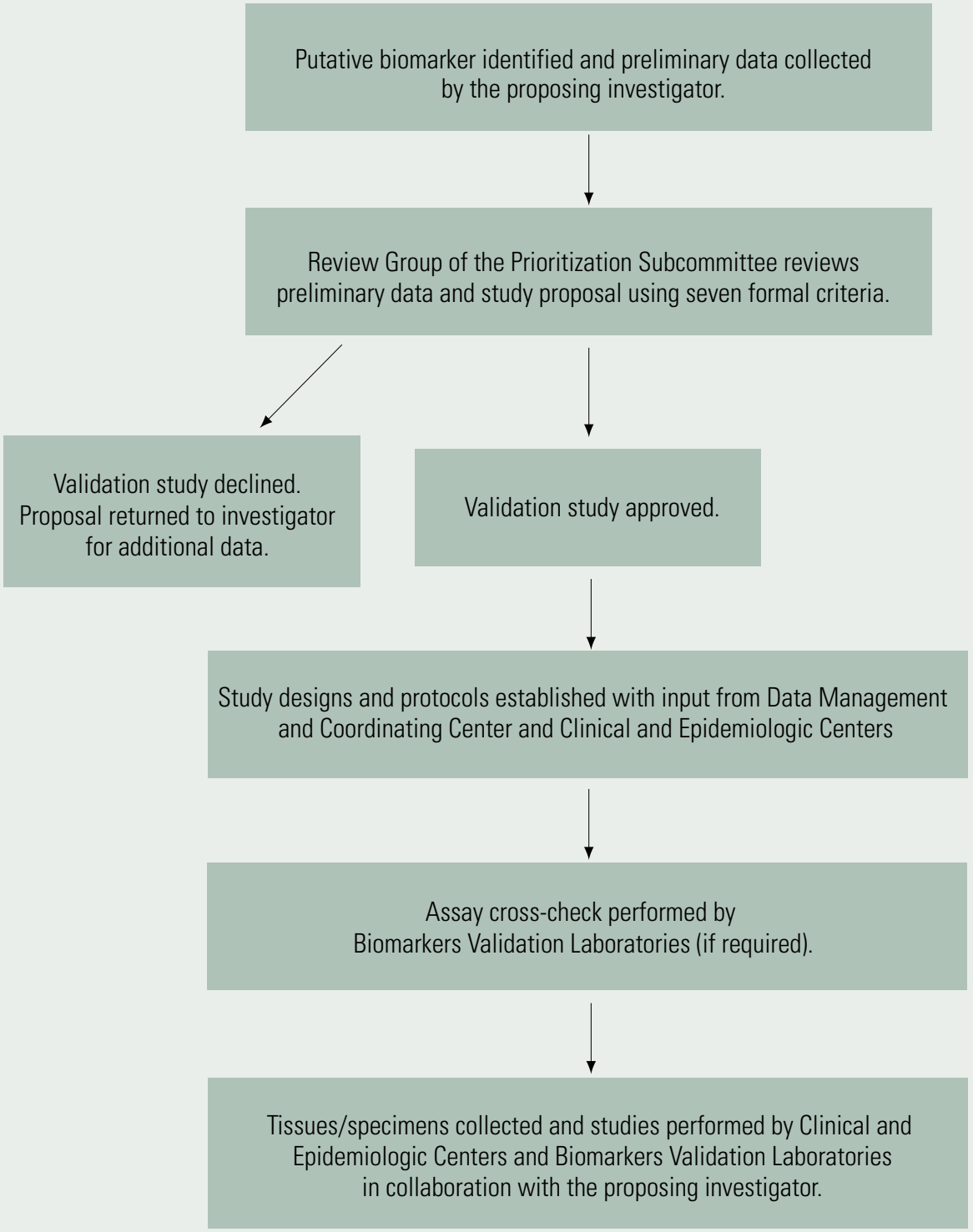
6. Practicality (e.g., sample size, or how many specimens it would take, scores or thousands; how much tissue, a nanogram versus a gram of material). Diagnostic testing is a sometimes a low-margin, low-profit business, and the market size may be relatively small under some circumstances. Practical limitations 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 Early Detection Research 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 misdevelopment results from a lack of expertise at the early stages of innovation.

7. Collaborative strength/team effort: The Early Detection Research Network promotes a "vertical approach" to biomarker research, i.e., a seamless division of labors among participating institutions in regard to biomarkers development, biomarkers validation, and clinical assessment. This 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 many patients, including those with premalignant lesions. New tests can be evaluated in all groups. The Network is establishing a stable and reliable connection between basic laboratory research and clinical testing as well as industry, a need that was considered by the Early Detection Implementation Group.

These seven criteria are being used by the Network's Review Group to evaluate both internal proposals and proposals for collaboration. The Review Group, which has a rotating membership, consists of one Principal Investigator from the Biomarkers Developmental Laboratories, one Principal Investigator from the Biomarkers Validation Laboratories, one Principal Investigator from the Clinical and Epidemiologic Centers, one Principal Investigator from the Data Management and Coordinating Center, and two members of the Prioritization Subcommittee. Additional consultants can be added at the discretion of the Executive Committee.

Finally, the proposed research within the Early Detection Research Network is also evaluated in light of its relevance to the "extraordinary opportunities" identified in the National Cancer Institute's Bypass Budget, which has staff input from NCI, and which may be important for individual proposals.

Early Detection Research Network Process for Supporting Systematic Validation of Biomarkers



Key Challenges to the Network

In academic research, researchers often compete rather than collaborate. This competition can create redundancy in research projects and reduce potential syngergies among researchers. This, in turn, may impede "vertical" integration and development of new biomarkers along the path to clinical application. "Horizontal" research results in rapid discoveries of many individual biomarkers, but does not delineate the roles and clinical significance of each newly discovered biomarker or judge biomarkers in relation to one another.

The Early Detection Research Network is promoting a "vertical" approach for biomarker research in an integrated, multidisciplinary environment that facilitates collaboration among technology developers, basic scientists, clinicians, epidemiologists, biostatisticians, and other health professionals. The Network's structure and charter encourage researchers to collaborate as a team rather than compete as individuals. In addition, a smooth flow between laboratory discoveries and clinical translation of biomarkers must be ensured to provide clinical tests for early detection of cancer and identification of high-risk individuals.

To respond to these challenges, the Network will:

Create Novel Approaches to Validation Studies

Evidence-based medicine requires randomized trials of new early detection tests to prove their clinical efficacy, but conducting such large-scale trials with a mortality endpoint would severely limit the number of biomarkers to be tested. Validation of each new biomarker by traditional randomized trials will not be possible because of cost, time required for follow-up, rapidly changing technologies, variations in treatment, and the sheer number of new biomarkers likely to be discovered. Methods other than randomized trials must be found within the Network to evaluate and validate biomarkers for clinical application during the early stages of investigation. These methods could include novel study designs and more effective recruitment strategies.

Improve Informatics and Information Flow

Several factors hamper the efficient flow of scientific information for translating new technologies and strategies to improve public health. Information about biomarkers is not well organized, is often difficult to find, and is published in a large variety of

Network Response to Challenges in Biomarker Research

- Create novel approaches to validation studies
- Improve informatics and information flow
- Standardize data reporting
- Generate statistical and computational tools
- Standardize reagents and assays

journals and databases. For the purposes of mining data, designing studies, and testing hypotheses, data need to be organized in a consistent and accurate manner. Among institutions, there are no uniform information storage schemes, complicating literature searches and data queries for biomarker information.

The Early Detection Research Network is working with NCI's informatics infrastructure to accelerate broad access to data. Two systems, a biomarkers informatics system and a biomarkers knowledge base, are being developed by the Network to facilitate the storage and use of data. The informatics system will enhance information exchange and be compatible with ongoing NCI efforts to ensure compatibility and widespread access to cancer information. Ultimately, the Network's biomarkers informatics system is expected to provide tools to facilitate data organization and sharing.

In addition, the Network is creating a Web-based biomarkers knowledge center that will facilitate the organization of resource-related information generated by research. While highly integrated systems have evolved to link publications about genes and proteins through a variety of biomedical informatics sources, such a system has not yet emerged in linking biomarkers to disease processes. The knowledge center would enable users to search through multiple sources (publications, databases, etc.) to identify and organize biomarker information. New systems will establish unique identifiers for publications that will enable data mining and organizational strategies. The Early Detection Research Network has established the Data Sharing and Informatics Subcommittee, a group comprising bioinformatics staff, pathologists, and participants from NCI's Informatics Enterprise, to address the complicated issues of scientific information storage and exchange.

Standardize Data Reporting

While the development of a biomarker informatics system is an important undertaking for better data management, challenges of data classification also impede the sharing, retrieval, and analysis of data. Data classification—i.e. the way data are described—is lacking a consistency that would enable researchers to query data sets using common terms and generate results that accurately represent the data of interest. With improvements in data classification, scientists will have the capability to use common search criteria and common data elements for the retrieval of information.

In an effort to classify scientific data in a universally useful manner, the Network is organizing a dictionary for the description of neoplastic and preneoplastic events and common data elements for biomarkers. The Network's Task Force on the Molecular Taxonomy of Preneoplasia was established to develop a consistent categorization for processes, events, and histology of precancerous and cancerous lesions. This Task Force is expected to generate standard vocabulary that will feed into an ongoing NCI initiative on describing scientific information through standard data classification terms. Using standard terms to classify data, referred to as common data elements, would assist in describing information with an accurate yet standard vocabulary. This effort is expected to enhance molecular classification schemes and offer a consistent way of finding and retrieving a variety of clearly defined information.

Generate Statistical and Computational Tools

As new biomarkers near clinical testing or use, assessing an individual with multiple tests may become practical and valuable for cancer detection, diagnosis, and prognosis. Data from multiple markers offer an opportunity to augment the performance of medical tests and to enhance clinical decision-making. While a number of factors are considered when diagnosing a patient by use of multiple tests, this compilation may represent an improvement over the conventional, single-marker approach to cancer detection.

However, the statistical comparisons used to assess the accuracy of the multiple markers approach will become more complex. Expertise from statisticians and biomedical mathematicians will be vital, especially when creating statistical algorithms for assessing the accuracy of multiple markers. The Network's Data Management and Coordinating Center plays a key role in this regard. This center is made up of experts in statistical issues surrounding biomarker research and evaluation. Their focus on developing the appropriate algorithms and methodologies to assess biomarker utility will be a critical asset to the Network.

Standardize Reagents and Assays

In order to have accurate early detection screening tests, it is crucial to develop high-throughput assays/technologies that are reproducible and affordable. The Early Detection Research Network Biomarkers Validation Laboratories are expected to plan, design, and conduct analytic validation studies, as directed by the Steering Committee, including assay procedures, protocols, sample collection, and others. The Biomarkers Validation Laboratories will develop and operationalize Network procedures for data quality and laboratory quality control.

With the rapid advances in molecular, genomic, and proteomics-based diagnostic technologies, reference materials for controls in molecular assays/technologies, such as PCR and comparative genomic hybridization, and for proficiency testing are needed. The Biomarkers Validation Laboratories will develop guidelines for using references and establish criteria for the storage, preservation, and transportation of specimens.

Invitation to Continuing Collaborative Opportunities

Collaborations between Network investigators and investigators from U.S. and foreign institutes and industries are encouraged. Associate Membership is designed for investigators who are not affiliated with the Network and who wish to propose collaborative studies within the scope and objectives of the Network. The Associate Members can contribute by sharing available technologies, contributing specimens, making high-risk registries and cohorts available, and providing other resources.

To encourage collaboration, four Collaborative Groups have been organized and chairs named.*

Breast and Gynecologic Cancer

Daniel Cramer, M.D.
Brigham and Women's Hospital
Department of Obstetrics
and Gynecology
OB/GYN Epidemiology Center
221 Longwood Avenue
Boston, MA 02115
Tel: (617) 732-4895
Fax: (617) 732-4899
E-mail: dcramer@partners.org

Gastrointestinal and Other Cancers

Dean E. Brenner, M.D.
University of Michigan
Internal Medicine Center
1500 Medical Center Dr.
Ann Arbor, MI 48109-0934
Tel: (734) 647-1417
Fax: (734) 647-9817
e-mail: dbrenner@umich.edu

Lung and Upper Aerodigestive Tract Cancer

Wilbur Franklin, M.D.
University of Colorado Health
Sciences Center
Dept. of Pathology, Box B216
4200 East Ninth Ave.
Denver, CO 80262
Tel: (303) 315-1807
Fax: (303) 315-1835
e-mail: Wilbur.Franklin@UCHSC.edu

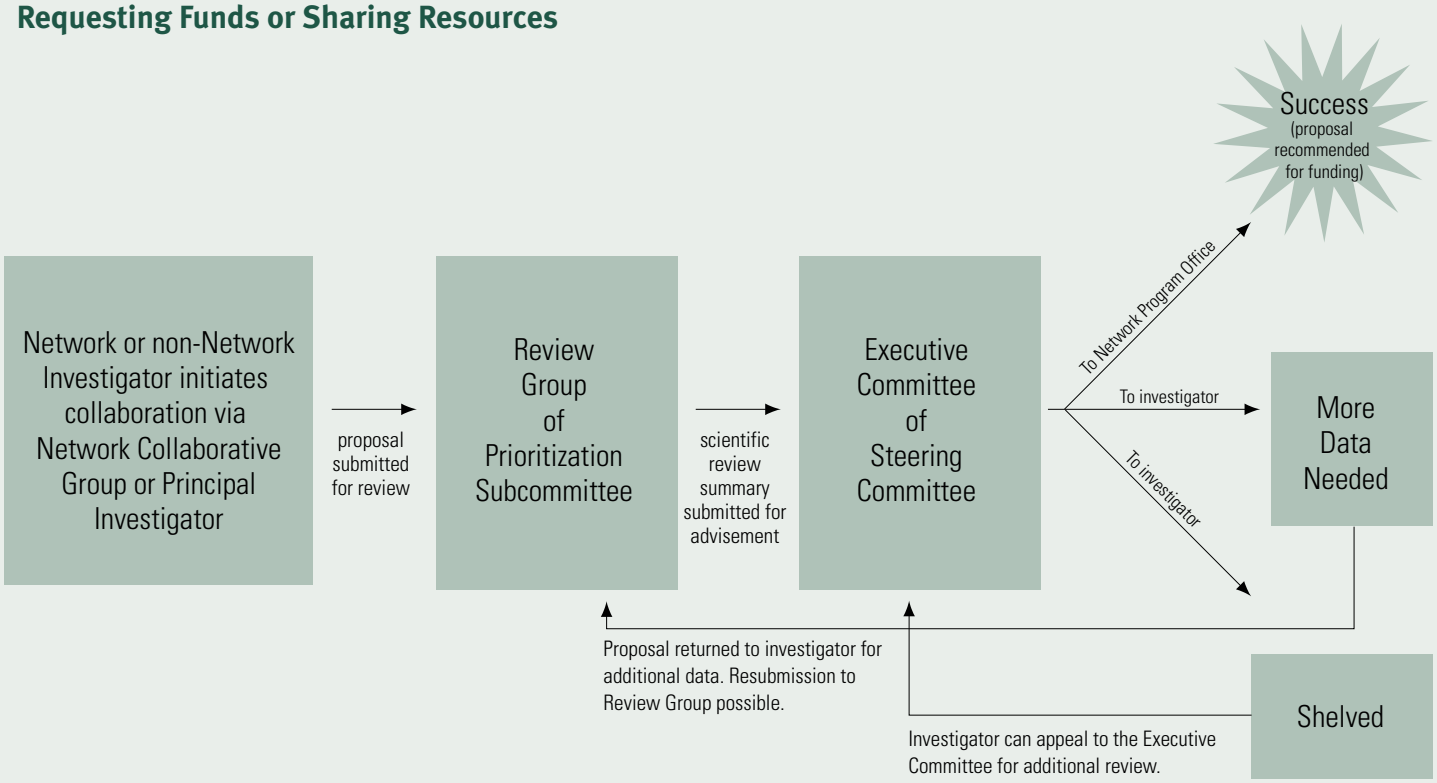
Prostate and Other Urologic Cancers

William E. Grizzle, M.D., Ph.D.
Univ. of Alabama at Birmingham
Dept. of Pathology
703 S. 19th St. Zeigler Building 422
Birmingham, AL 35294-0007
Tel: (205) 934-4214
Fax: (205) 975-7128
e-mail: grizzle@path.uab.edu

Investigators planning to become Associate Members can join a Collaborative Group on the basis of their expertise and interest. The chairs of the Collaborative Groups are Network Principal Investigators who can serve as the primary contact for nonaffiliated investigators interested in Associate Membership. Interested researchers can also contact any Network Principal Investigator about collaboration.

* For the most recent information, see the NCI's Early Detection Research Network Web site at: http://cancer.gov/edrn

Early Detection Research Network Process for Approving Collaborations, Requesting Funds or Sharing Resources



National Cancer Institute Components

Division of Cancer Prevention
http://dcp.nci.nih.gov

The National Cancer Institute's Division of Cancer Prevention has a core mission to conduct and support research to improve the health of the public by decreasing the incidence, mortality, and morbidity of cancer. The division is the primary NCI unit devoted to cancer prevention research and is directed by Peter Greenwald, M.D., Dr. P.H.

More specifically, the Division of Cancer Prevention

- Plans and directs an extramural program of cancer prevention research, including chemoprevention, nutritional science, genetic and infectious agents, biometry, and early detection including biomarker development and validation.
- Develops and supports research training and career development in cancer prevention and early detection.
- Coordinates program activities with other Divisions, Institutes, or federal and state agencies, and establishes liaison with professional and voluntary health agencies, cancer centers, labor organizations, cancer organizations, health care delivery and managed-care organizations, and trade associations.
- Coordinates community-based clinical research in cancer prevention and dissemination of cancer treatment practice through a consortium of community clinical centers.

Cancer Biomarkers Research Group
http://dcp.nci.nih.gov/cbrg

The mission of the Division of Cancer Prevention Cancer Biomarkers Research Group is to engage basic and clinical scientists as well as epidemiologists and statisticians in a search for and validation of promising early cancer biomarkers. To do so, the Cancer Biomarkers Research Group supports and facilitates a broad spectrum of national and international research activities in molecular biology and genetics, particularly for the discovery of biomarkers for risk prediction and early detection of cancer.

The Cancer Biomarkers Research Group also supports the development of databases and informatics systems to optimize tracking and assessment of biomarker utility and expression patterns. By facilitating, promoting, and coordinating cutting edge research with the latest discoveries in technology and molecular circuitry of preneoplastic cells, the Cancer Biomarkers Research Group hopes to provide a mechanistic picture of preneoplastic progression and tools for effective cancer prevention and clinical management. The mission will be accomplished through a mix of program portfolios, including grants, contracts, and program-initiated research.

Sudhir Srivastava, Ph.D., M.P.H., is chief of the Cancer Biomarkers Research Group and program director for the Early Detection Research Network.

Acknowledgements

Dr. Srivastava would like to acknowledge the following individuals for their assistance in the creation of the Network and this Initial Report:

Barry Kramer, M.D.
Director, Office of Medical Applications of Research, National Institutes of Health

Cindy Rooney
Office of Medical Applications of Research, National Institutes of Health

Lora Kutkat
Cancer Biomarkers Research Group, Division of Cancer Prevention, National Cancer Institute

Kara Smigel
Communications Manager, Division of Cancer Prevention, National Cancer Institute