Request for Application for Biomarker Reference Laboratories

This is the Request for Application (RFA) issued by the Division of Cancer Prevention (DCP) for EDRN Biomarker Reference Laboratories.

THE EARLY DETECTION RESEARCH NETWORK: BIOMARKER REFERENCE LABORATORIES

RELEASE DATE: April 9, 2004

RFA Number: RFA-CA-05-009

EXPIRATION DATE: August 17, 2004

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:
National Institutes of Health (NIH)
(http://www.nih.gov)

COMPONENT OF PARTICIPATING ORGANIZATION:
National Cancer Institute (NCI)
(http://www.nci.nih.gov/)

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.394

LETTER OF INTENT RECEIPT DATE: July 16, 2004
APPLICATION RECEIPT DATE: August 16, 2004

This RFA is a reissue of RFA CA-99-008, which was published in the NIH Guide on March 16, 1999.

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PURPOSE OF THIS RFA

The Division of Cancer Prevention (DCP), National Cancer Institute (NCI), invites new and competing renewal cooperative agreement applications to continue the national Network that has the responsibility for the development, evaluation, and validation of biomarkers for earlier cancer detection and risk assessment. Biomarkers are defined as cellular, biochemical, and molecular (genetic and epigenetic) alterations by which a normal or abnormal biologic process can be recognized or monitored. Biomarkers are measurable in biological media, such as in tissues, cells, or fluids. The Network has four main components: Biomarker Developmental Laboratories (BDLs), Biomarker Reference

Laboratories (BRLs) (formerly known as Biomarker Validation Laboratories), Clinical Epidemiology and Validation Centers (CECs)(formerly known as Clinical and Epidemiologic Centers), and a Data Management and Coordinating Center (DMCC). The BDLs have responsibility for the development and characterization of new or the refinement of existing biomarkers and assays. The BRLs serve as a Network resource for clinical and laboratory validation of biomarkers, which include technological development and refinement. The CECs collaboratively conduct clinical and epidemiological research on the Network-wide clinical validation of biomarkers. The DMCC supports statistical and computational analysis and informatics infrastructure and coordinates network-wide meetings and conferences. For further details, see http://www.cancer.gov/edrn.

The Early Detection Research Network (EDRN) Steering Committee (SC) is composed of the Principal Investigators (PIs) in the Network and appropriate NCI staff to coordinate the work of the Network.

The purpose of this Request for Applications (RFA) (CA-05-009) is to invite new and competing renewal applications for the BRLs. An RFA (CA-04-006) for the BDLs was previously published in the NIH guide, September 26, 2003. This RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-006.html. The RFA for the CEC (CA-05-005) was published in the NIH Guide on January 14, 2004, and is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-005.html. The RFA for the DMCC is being issued at a later date. Applicants are encouraged to seek funding to participate in more than one component, because it is recognized that collaborations already exist in individual institutions for clinical testing and validation of biomarkers and reagents.

RESEARCH OBJECTIVES

A. Background

The Network has a straightforward mission, which is to translate newly emerging molecular knowledge into practical clinical tests to detect cancer and cancer risk. For most cancers, successful treatment depends on early detection, and successful prevention depends on the accurate evaluation of risk. The EDRN seeks to give treatments a greater opportunity to work and to make prevention more possible.

The Network is using cutting-edge technologies to identify the changes that occur in the earliest stages of a cell's transformation onto the road of cancer. Scientific expertise from leading national and international institutions has been harnessed to identify and validate crucial molecular markers to detect cancer and to assess cancer risk. The Network is an investigator-initiated Network for collaborative research to link the discovery of biologic markers directly to the next steps in the process of developing early detection tests. The power of bioinformatics and computer-assisted programs are being put to full use to analyze Network data and to facilitate faster answers to key questions. New technologies, such as genomics, epigenomics, and proteomics, are able to identify genetic as well as antigenic changes during the early stages of malignant progression. Some of these changes show promise as biomarkers for preneoplastic development or for early malignant transformation. The use of these emerging technologies in the field of early detection and risk assessment is a high priority in the NCI's strategy for reducing mortality from cancer. Detection of early cancer has been identified as an area of extraordinary opportunity for research investment in the NCI 2004 Bypass Budget (http://plan.cancer.gov/).

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 a productive scientific construct. Collaborations and partnerships that are necessary for the ultimate success of this project have been put into place. The acceleration of scientific progress through the Network is faster than it has ever been; consequently, the need to translate

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

Since its inception in 1999, the EDRN has followed a "vertical" approach to biomarker research that is an established, integrated, multidisciplinary environment that would facilitate collaboration among technology developers, basic scientists, clinicians, epidemiologists, biostatisticians, and other health professionals. Such an environment would expedite efficacious clinical applications of the molecular knowledge that has burgeoned in recent years (Srivastava, 1999). The Network has produced a system for evaluating biomarkers as tools to clinically detect cancer before symptoms appear and to identify people at risk (http://www.cancer.gov/edrn). A five-phase approach has been established as a standard and guidelines for successfully translating research on biomarker applications from the laboratory to the bedside (Pepe, M.S., Etzioni, R., Feng, Z., Potter, J., et al.;. Phases of biomarker development for early detection of cancer; J Natl Cancer Inst 2001; 93: 1054-1061). The phases are as follows:

Phase I: exploratory studies to identify potentially useful biomarkers, i.e., the "discovery" phase;
Phase II: studies to determine the capacity of biomarkers for distinguishing between people with cancer and those without, i.e., the validation phase;
Phase III: studies to assess the capacity of a biomarker to detect preclinical disease by testing the marker against tissues collected longitudinally from research cohorts;
Phase IV: prospective screening studies; and
Phase V: definitive large-scale population studies to the overall impact of screening on health outcomes in the target population.

Significant progress has been made by the EDRN investigators from discovery to development, to validation, and application. The pace of identification of molecular signatures (e.g., those that are identified by proteomics and/or genomics technologies) that are associated with causal pathways and processes is accelerating. However, the major challenges remain in integrating these discoveries and developments into clinical practice. The Network stimulates collaborative research to meet this challenge by supporting translational research. For further research activities across the Network, see http://www.cancer.gov/edrn. Applicants are encouraged to see the EDRN's second progress report at http://www3.cancer.gov/prevention/cbrg/edrn/edrn_report2002.pdf.

Applicants are strongly encouraged to forge partnerships with industry (including biotechnology firms), and to develop biomarkers, reagents, technologies, and assays. The Network continues to serve as an attractive source of collaborations for industry, since it will provide clinical opportunities for the evaluation of new technologies. The Network will encourage collaborations with industry in order to leverage funds awarded under this RFA. NCI funds will be used to support the underlying infrastructure and the cost of studies not having direct implications for a company's product development or marketing strategy. NCI views partnerships with industry as an

important component of the EDRN mission. However, with respect to new technologies and/or reagents provided by such participants that are part of development or product plans, the individual companies will be responsible for costs in such areas as technology standardization and quality assurance as well as scale-up of laboratory techniques, collection and formatting of specialized data required by regulatory agencies for device approvals, preparation of registration documents, and supporting a portion of the accrual to studies pivotal for registration.

B. Network Administrative Structures

Network Organization: The Network is structured around four main components, and currently includes eighteen BDLs, three BVLs, nine CECs, and a DMCC. See the Early Detection Research Network: Translational Research to Identify Early Cancer Risk; NCI Publication No. 01-4852, August 2001).

o The BDLs develop and characterize new biomarkers, or refine existing biomarkers (Phase I and Phase II). Current RFA for BDL can be found at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-006.html.

o The BRLs (which replace the Biomarker Validation Laboratories in this reissuance) serve as a resource for the clinical and analytical validation of biomarkers, including development of technology, standardization of assay methods, and refinement of existing methods. (See previous RFA BVL: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-008.html.)

o The CECS conduct or participate in early phases (Phase II and Phase III) of clinical validation and epidemiological research into the application of biomarkers. (See the current CEC RFA: CA-05-005.)

o The DMCC provides statistical, logistic, and informatics support and develops the theoretical and statistical approaches to the simultaneous pattern analysis of multiple markers (see the previous RFA for the DMCC at http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-99-011.html).

Four federal agencies participate in the EDRN through interagency agreements: the National Institute of Standards and Technology (NIST), which serves as a validation laboratory; the Centers for Disease Control and Prevention (CDC), which serves as a Clinical and Epidemiologic Center; the Food and Drug Administration (FDA), which serves on the Network Consulting Committee; and the Jet Propulsion Laboratory (JPL), NASA, which provides informatics support.

Each component is funded through a separate RFA. An applicant, however, may seek funding to participate in more than one component. Each awardee will conduct independent and/or collaborative research using their U01 or U24 funds, respectively, collaborative research using the Core Funds from the Headquarters (see definition of the Headquarters below), and from the set-aside funds in their U01, pending approval by the EDRN Steering Committee and release by the NCI, respectively.

Each laboratory/center will be managed by a PI and may include academic and industrial biotechnology investigators who are involved in cancer detection and diagnostic research. In order to expedite the translational research, the Network will be supplemented by the ad hoc participation of additional (academic or community-based) investigators who are able to validate the results of laboratory studies.

Currently, the Network consists of experts in basic molecular science, laboratory technology, clinical studies, biometry, and epidemiology. The expertise in laboratory science includes conducting research on the biology of incipient neoplasia encompassing the development, characterization and testing of biomarkers of early cancer and risk, development of relevant technologies for biomarker detection, and analytical tools for the evaluation of biomarkers for detection and risk assessment. The expertise in laboratory validation

includes knowledge and practice of Standard Operating Procedures (SOPs), and experience in the statistical evaluation of accuracy, precision, reproducibility, and performance characteristics of tests in multi-center settings. Expertise in patient accrual and associated clinical issues for studies will be needed to apply basic science discoveries to clinical settings. Computational and informatics needs of the Network are provided by a Data Management and Coordinating Center and the JPL.

Steering Committee (SC): The SC has responsibility for scientific management and oversight, including monitoring the activities of the DMCC. For administrative structure and responsibilities of the SC see "Collaborative Responsibilities."

Network Consulting Committee (NCC): A separate advisory committee has been established by the NCI to ensure that the overall Network is adequately responsive to promising opportunities, exhibits the desired degree of flexibility in composition and decision-making and makes prioritization decisions free from conflicts of interest. For further details, see "Collaborative Responsibilities."

Data Management and Coordinating Center (DMCC): The DMCC provides logistic support for the conduct of the SC and NCC meetings, provides statistical and data management support for protocol development, and conducts analyses of clinical data and informatics. It studies applied and theoretical approaches to the simultaneous analysis of multiple markers. In addition, the DMCC, in collaboration with JPL and EDRN investigators, has developed common informatics, Common Data Elements (CDEs), and analytical tools for the interpretation of data, as well as instruments for checking uniformity, consistency, accuracy, timeliness, reproducibility, and privacy of the data.

Headquarters: The institution of the Chair of the SC serves as the Headquarters of the Network. The Chair of the SC can be any PI involved in the Network. The Chair serves as the PI of the Headquarters and awards and implements the scientific, operational, and organizational policies of the Network. The headquarters provides the executive leadership, scientific direction, and management for the Network. It serves as a center for information dissemination to investigators and institutions in the Network as well as to others outside the Network.

Funds: Funds will reside with 1) the individually funded U01/U24 awardees in the Network and 2) the Headquarters.

The PIs with U24 awards will have funds available to cover applicable administrative costs, and conduct developmental studies. The BRL will be provided support for the collaborative validation studies from the Core Fund (see below) on an as needed basis.

Core Funds for the Headquarters: Core Funds will be available to the Chair of the SC. Applicants under this RFA should not apply for the Core Funds in their U24 applications. Core Funds are reserved for post-award collaborative research and for a variety of other functions:

1. Core Funds are used to expand participation within the Network through supplemental funding to an investigator who is not part of the Network. However, receipt of these supplemental funds does not, in and of itself, imply membership on the SC.

2. Core Funds can also be used to move a new marker test to the point at which it can be validated at multiple centers and in larger populations. Test reagents will require scale-up at this point, and the SC will require sufficient funding to contract with commercial laboratories or companies that can scale up production and maintain quality of the reagents (e.g., monoclonal antibodies, labels, etc.) and to fund CEC for subject accrual. Funds will also be required for data management, travel, meetings, and other collaborative

activities of the Network. However, Core funds should not be used to pay for activities that have direct implication for a company's product development or marketing strategy.

Supplements from the Core Funds may provide direct costs and appropriate facilities and administrative costs. The following example illustrates the functions of the Network and the support it offers for moving basic research findings into clinical practice.

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

There is also flexibility so that investigators outside the Network could form collaboration(s) with one of the existing centers, or directly bring their discoveries to the SC (e.g., Letter-of-Intent). To support such efforts, the SC is able to use core funds to supplement the investigator's ongoing research. The investigator, in turn, must agree to share his research findings and become part of the Network as an associate member.

Recipients of core funds, such as commercial laboratories or manufacturing companies and institutions of outside investigators, participating for example in validation studies, will be subject to the plans applicant submits and are accepted that address the sharing of research resources and intellectual property as noted in Section 6 of the Supplementary Instructions of this RFA. Awardees must advise core funds recipients and outside investigators of these terms and conditions of the award.

C. Objectives (applicable to Network as a Whole)

The goals of the Network are to discover, develop, evaluate, and validate biomarkers/reagents (Phase I-III) for the earlier detection of cancer and for the assessment of risk for developing cancer. The intent of this RFA is to continue to foster research investigations, technological innovations, and collaborations to accelerate the development and validation of biomarkers and tools that have the potential of rapidly moving to Phase II and Phase III. Specifically, the objectives of the Network include:

o the development and testing of promising biomarkers or technologies at institutions with the necessary scientific and clinical expertise, with the goal being to obtain preliminary information to guide further testing;

o the timely and early phase evaluation of promising, analytically-validated biomarkers or technologies. These evaluations would include measures of diagnostic predictive accuracy, sensitivity, specificity, and, whenever possible, medical benefits, such as predictors of clinical outcome or surrogate endpoints for early detection and for prevention intervention clinical trials;

o the timely development of biomarker expression patterns, sometimes of multiple markers simultaneously, that can serve as background information for subsequent large definitive validation studies in the field of cancer detection and screening;

o collaboration among academic and industrial leaders in molecular biology,

molecular genetics, proteomics, clinical oncology, computer science, public health, and other areas to facilitate the development of high-throughput, sensitive assay methods to identify biomarkers that are useful in detecting cancer in its early stages and in assessing cancer risk;

o conducting early phases of clinical/epidemiological studies (e.g., cross-sectional, retrospective, Phase I-III studies as described above), to evaluate predictive value of biomarkers; and

o encouragement of collaboration and rapid dissemination of information among awardees to ensure progress and avoid fragmentation of effort; management of intellectual property rights in ways that do not restrict the ability to share research materials or impede products being brought to market to benefit the public.

Because early detection and treatment issues are often related, the Network seeks meaningful participation from various medical organizations. In some of its activities, the Network may need to relate programmatically to research infrastructures supported by NCI. The NCI anticipates that augmenting the EDRN expertise with a broad base of clinical and public health perspectives will enable the Network to apply existing methods and newly discovered technologies toward clinical application.

For some activities, the Centers may need to relate programmatically to other research infrastructures supported by the NCI (for example, Specialized Programs of Research Excellence [SPOREs](http://spores.nci.nih.gov/), Cancer Genetics Network [CGN] (http://epi.grants.cancer.gov/CGN/), Breast and Colon Cancer Family Registries (http://epi.grants.cancer.gov/CCFR/index.html; http://epi.grants.cancer.gov/BCFR/index.html), Cooperative Human Tissue Network (http://www-chtn.ims.nci.nih.gov/), Cancer Genome Anatomy Project (http://cgap.nci.nih.gov/), with ongoing NCI clinical research programs/trials (e.g., Clinical Community Oncology Program [CCOP](http://www3.cancer.gov/prevention/ccop/), Prostate, Lung, Colon, and Ovarian Trial PLCO)(http://www3.cancer.gov/prevention/plco/index.html); or with other health agencies, such as the Food and Drug Administration (FDA), the Department of Defense (DOD), and the Veteran's administration (VA). Certain types of trials in earlier detection, especially those involving treatment, may best be conducted as inter-group studies with treatment-oriented cooperative groups, such as the NCI Clinical Cooperative Groups, NCI designated Cancer Centers, international collaborators, clinical epidemiologists, and health maintenance organizations. The need for such cooperation should be anticipated and provided by the center leadership. Awardees must advise prospective collaborators, that with respect to these collaborations, their institutions will be subject to the plans applicant submits and are accepted that address the sharing of research resources and intellectual property as noted in Section 6 of the Supplemental Instructions of this RFA.

D: Scope (applies to this RFA)

A BRL provides resources for analytical and clinical validation of biomarkers, including development of technology, standardization of assay methods, and refinement of existing methods. The primary responsibility of the BRL is to participate in and perform Network collaborative studies approved by the EDRN SC. The secondary responsibility of the BRL is to develop an individual developmental study that is directly relevant to the goals of the EDRN. The funded BRLs will work in close collaboration with EDRN investigators under the direction of the EDRN SC.

BRL's Network Collaborative and Individual Developmental Studies:

1. BRL's Network collaborative Studies:

The BRLs are responsible for standardizing laboratory assays and methodologies, instituting quality control for reagents and technologies for collaborative

Network-directed studies, and collaborating in other studies as directed by the SC. The Laboratory should have knowledge and practical experience with Standard Operating Procedures (SOPs) and in the evaluation of the accuracy, precision, reproducibility, and performance characteristics, for example, sensitivity, specificity, and positive and negative predictive values, of tests in multi-center settings. These characteristics are important when sampling body fluids or mixed cell types where only a very small percentage of cells may exhibit the specific genetic or molecular changes. The BRL may be asked to conduct studies on a variety of assays in order to improve their performance characteristics. Studies may include, but are not limited to:

Methodology/Assay Refinement and Technology Optimization:

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 BRL are expected to plan, design, and conduct analytic validation studies, as directed by the SC, for assay procedures, protocols, sample collection, etc. Some sample validation issues are provided below to describe the anticipated lines of research that the laboratories will be expected to address.

Methodologies:

- determining measures of diagnostic discrimination, e.g., sensitivity, specificity, and predictive accuracy, as appropriate for clinical applications;
- determining the range of normal values and reproducibility for various tests, as appropriate;
- determining that data and specimens are collected under uniform investigative protocols; and
- determining that data are collected to determine the benefits and risks that follow from positive or negative test results.

Assay Design:

- optimizing the selection of target sequence, primer, and probe sequences;
- single versus multiple targets;
- selecting specimen types;
- handling problematic specimens; and
- designing internal controls, controls for contamination, reagent and instrument standards and well characterized panels of reference reagents.

Assay Optimization:

- optimizing extraction methods, sampling, internal controls, specimen storage, and processing conditions;
- optimizing length, sequence, efficiency, and specificity of primers, probes, enzymes;
- optimizing configuration and performance of controls, calibrators, capture probes, detectors, etc.;
- optimizing independent reproducibility for example, do multiple independent repetitions of the test under the same conditions produce nearly identical results?;
- optimizing technical reproducibility for example, are there technical factors in the performance of the test that lead to inconsistent results?;
- optimizing assay conditions, including time, temperature, storage, and transport stability;
- conducting precision testing, including multiple sites, different days, operators, kit lots; and
- conducting proficiency testing, including single operator, multiple days, kit lots.

Assay Validation:

o conducting analytical validation of each assay developed within the Network;
o developing scaled-up, automated methods for high volume throughputs;
o conducting multi-center cross-checks for pooled specimens, and other inter- and intra-laboratory interfering factors;
o developing additional formats and systems (paper or electronic) for reporting test results; and
o developing kits for rapid, inexpensive testing.

Quality Control Program: Although each of the BDLs and CECs will take primary responsibility for its on-site quality control and quality assurance activities, the BRL may be asked to advise the SC on quality control issues and to implement them in the collaborative Network-directed studies. Quality control at a minimum should consist of:

o device and instrument calibration, precision, and reproducibility;
o quality control of data. The BRL will follow the Network procedures for data quality and laboratory quality control in accordance with the Network guidelines and policies; and
o interim evaluation and consideration of assays/reagents developed by the Network scientific components for tests/reagent scale-up for multi-center studies per direction of the SC.

Reference Materials: With the rapid advances in molecular, genomic, and proteomics-based diagnostic technologies, reference materials for controls in molecular assays/technologies, such as Polymerase Chain Reaction (PCR), Comparative Genomic Hybridization (CGH), gene and nucleotide microarrays, etc., and for proficiency testing are needed. The BRL will work with the SC to:

o refine and develop guidelines for using references, establish criteria for the storage, preservation, and transportation of specimens; and
o assist the DMCC continuous effort in developing computer-based catalogues of published data on biomarkers for Network investigators with the format and design of the database to be determined by the SC.

Study Organization:

Capability and Characteristics of the BRL: This is an important requirement of the BRL and is critical in support of their participation as a BRL. The expertise of the BRL must encompass broad subject areas within the clinical diagnostic field. As the Network gains experience and its responsibilities shift and expand, the number and expertise of the investigators should change in response to the scientific opportunities. Qualified investigators in laboratory technology should be invited to assume responsibility in a flexible manner as the need arises.

Scientific Agenda:

In support of their applications, applicants for the BRL must develop and articulate a plan that summarizes their views and their anticipated lines of laboratory support for each issue discussed above on which they choose to focus. The applicants must describe both short-term and long-term goals in the plan demonstrating their knowledge and practice of a typical reference laboratory. The applicants must also describe the experience, expertise, and resources of the laboratory, all of which will be a consideration in peer-review.

2. BRL's Individual (Developmental) Studies:

The BRL may seek developmental funds (see section on Instructions for Application Preparation) for conducting pilot studies on reagents and/or technology development and refinement that will have a broad impact in cancer detection and risk assessment. Applicants should clearly define the research objective for the first year, which will be peer-reviewed by the scientific review committee. Support for subsequent years will be reviewed by the EDRN SC,

which will make recommendations to the NCI. Prior to proposing the developmental study, applicants are encouraged to contact the program officials listed on this RFA to discuss the needs of EDRN in the area of technology and assay refinement.

All funded BRLs will be encouraged to develop validation studies with other EDRN investigators and seek funding from the Core Fund. Applicants are encouraged to review research activities across the Network and develop collaborations by visiting the following website http://www.cancer.gov/edrn and by reading the EDRN second progress report at http://www3.cancer.gov/prevention/cbrg/edrn/edrn_report2002.pdf.

MECHANISM OF SUPPORT

This RFA will use the NIH Cooperative Agreement (U24) award mechanism. As an applicant, you will be primarily responsible for planning, directing, and executing the proposed project. The anticipated award date is July 2005. The RFA may be reissued in the future, contingent upon the availability of funds.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Follow the instructions for non-modular budget research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIH (U24) is a cooperative agreement award mechanism. In the cooperative agreement mechanism, the PI retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH Program Coordinator being substantially involved as a partner with the PI, as described under the section "Cooperative Agreement Terms and Conditions of Award." At this time, the NCI anticipates that there will be a renewed competition after 5 years. If the NCI does not continue the program, awardees may submit grant applications through the usual investigator-initiated grants program. However, before submitting such an application, applicants are advised to contact Program Coordinator listed under the INQUIRIES section listed below.

FUNDS AVAILABLE

The NCI intends to commit approximately $2 million in FY 2005 to fund up to four new and/or competitive continuation grants in response to this RFA. An applicant should request support for 5 years. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the NCI provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic institutions
o Foreign institutions are not eligible to apply
o Faith-based or community-based organizations.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

Definitions

Awardee: The institution to which a cooperative agreement (U24) is awarded.

Principal Investigator (PI): The investigator who is designated by the applicant organization to direct the project that is supported by the U24 award in response to this RFA. The PI will assume the responsibility and accountability to the applicant organization officials and to the NCI for the performance and the proper conduct of the research supported by the U24 mechanism in accordance with the terms and conditions that are stated in this RFA. The PI will be a voting member of the SC and will attend two SC meetings in the first year and two SC meetings and a workshop a year in subsequent years. Attendance at these meetings are required as part of this cooperative agreement.

NCI Program Coordinator: A scientist administrator from the NCI extramural staff, the Program Coordinator will be substantially involved in the scientific coordination and collaboration within the Network, will have responsibilities in broad scientific and programmatic issues, and will serve as a voting member of the SC, as defined under the "Cooperative Agreement Terms and Conditions of Award."

NCI Program Director: A Health Scientific Administrator from the NCI extramural staff will provide normal stewardship for U24 grant awardees.

Cooperative Agreement Terms and Conditions of Award

These special Terms of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Parts 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements. (Part 92 applies when state and local governments are eligible to apply as a "domestic organization.")

Under the cooperative agreement, the NCI purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and the NCI Program Coordinator.

In addition, the following terms and conditions will be incorporated into the U24 award statement, and will be provided to the PI and to the institutional official at the time of award.

A. Rights and Responsibilities of BRL Awardees

BRL Individual (Developmental) Study:

The PI of a BRL will have the primary authority and responsibility to plan, design, and execute the research objective of the developmental project. The PI will also be responsible for laboratory service, standards for reagents, quality control, safety monitoring, conduct, data collection and analysis, and publication of results.

The PI of a BRL will assume responsibility and accountability to the applicant organization officials and to the NCI for the performance and proper conduct of the research supported by the U24 in accordance with the terms and conditions of the award.

BRL Network Collaborative Studies:

The PI of a BRL will be responsible for collaborating on common research designs and protocols, including methods, handling of data, appropriate sharing of methods and data among Network investigators and collaborating organizations as directed by the EDRN SC.

The PI of a BRL will assume responsibilities for laboratory support of individual protocols/research and collaborative projects that were approved by the EDRN SC.

The PI of a BRL will attend two SC meetings and any other meeting required for the conduct of the collaborative study.

The PI of a BRL will be responsible for accepting and implementing the goals, priorities, common protocols, procedures, and policies agreed upon by the SC.

B. NCI Extramural Staff Responsibilities

There will be one primary NCI Program Coordinator for the Network. However, the Program Coordinator may be assisted by other NCI staff (Program Director/s) on specific scientific or programmatic issues as needed.

The NCI Program Coordinator will have substantial scientific programmatic involvement during conduct of this activity, through technical assistance, advice and coordination above and beyond normal program stewardship for grants as described below.

Because of the Network's diverse scientific agenda and the number of tasks that have to be accomplished to achieve its goals, a number of NCI staff members may interact with the Network as needed. The NCI Program Coordinator (a staff member in the Division of Cancer Prevention) will assist the Network on scientific and programmatic issues and advise the Network on the availability of other resources.

The NCI Program Coordinator will convene the initial meeting of the SC, have voting membership on the SC, and, as determined by the Committee, its subcommittees.

Although the PI will have lead responsibilities in all collaborative tasks and research activities, it is anticipated that the NCI Program Director will have lead responsibilities in sharing broad programmatic issues among awardees.

An NCI Program Director designated in the Notice of Grant Award will be responsible for normal programmatic stewardship and monitoring of the awards. The NCI Program Coordinator will identify other participating NCI staff. The NCI Program Coordinator may also serve as the NCI Program Director.

The NCI reserves the right to adjust funding, withhold support, suspend, terminate, or curtail the study or an individual award in the event of a failure to comply with the Terms and Conditions of Award, data reporting, quality control, or other major breach of the protocol, or human subject ethical issues, whenever applicable.

C. Collaborative Responsibilities

1. Steering Committee (SC): The SC will have major scientific management oversight and responsibility for developing collaborative research designs,

protocols and manuals, facilitating the conduct and monitoring of studies, and reporting study results. The SC will be composed of the PIs from each member organization in the Network, the PI of the Data Management and Coordinating Center, and the NCI Program Coordinator. Each member will have one vote. The Chair (non-NIH person) will be selected by the SC. The institution of the Chair of the SC will serve as the Headquarters (for definition see Network Organization). Subcommittees, including the existing ones, will be established/maintained by the SC, as it deems appropriate; the NCI Program Coordinator will serve on subcommittees as he/she deems appropriate.

After all the Network components have been funded, the SC will convene. Responsibilities of the SC include, but are not limited to, the following activities (investigators are encouraged to review the EDRN Manual of Operation) (http://www3.cancer.gov/prevention/cbrg/edrn/organization.html#manual):

o updating and refining established Network policies and procedures;

o updating and refining established policies and procedures for collaborative projects, protocols, and Network-defined projects;

o updating and refining established policies and procedures for reviewing changes in projects not showing translational significance at the request of the laboratories/centers, and making recommendations to the NCI for replacing the project with more promising ones with revised scope and adjusted budget (increase in the budget will not be permitted);

o updating and refining established standards or "decision criteria" for validating biomarkers/reagents for further clinical studies, such as testing early detection strategies, or as risk factors; and

o updating and refining established policies and procedures for accepting, reviewing, and recommending proposals from investigators outside the Network for supplemental funding and expanding the Network participation.

2. The SC will establish Data and Safety Monitoring Committee (DSMC) for clinical trials as appropriate to ensure protection of human subjects.

3. The SC will review patient accrual, follow-up, protocol compliance, results of audits, and regulatory requirements at the participating Centers and formally report the results of its reviews to the NCI.

4. The SC will promote and foster the inclusion of women and ethnic minorities in clinical studies and assure the completeness of informed consent.

5. The Committee will track the Network research progress and assure that the results of laboratory research and clinical studies are published in peer-reviewed journals in a timely manner and in accordance with the publication policies of the Network. At any time during a Network project, the SC may ask BDL or CEC to serve as a Biomarker Reference Laboratory on an as needed basis. The SC may also examine the validation data for biomarkers/reagents developed by the Network, and decide when a biomarker is sufficiently validated, or recommend when to stop non-productive experiments relating to biomarkers validation.

6. The SC will discuss collaborative projects to be pursued jointly with the funds set aside from the Headquarters and from individual U01 awardees.

7. Collaborative studies/protocols will be approved by the SC. Data will be submitted centrally to the DMCC. The SC will define the rules regarding access to data and publications consistent with NCI policies.

8. The SC will plan one of several Workshops during the network project period to inform the scientific community and relevant advocacy groups of the progress

made toward development and clinical application of biomarkers developed through the Network. The NCI Program Coordinator, the NCC, and other NCI staff will provide the SC with advice on participants for the workshops and symposia. The DMCC will manage the logistics for these meetings.

9. The SC or its Executive Committee (EC) in consultation with the NCI will determine the PI of the Network-wide validation study.

Network Consulting Committee (NCC):

1. A Network Consulting Committee (NCC) was established by the NCI. The NCC advises the SC through the NCI on relevant scientific issues, including study design, prioritization of biomarker development, development of collaborative study protocols, including decision criteria for clinical applications, e.g., early detection, prognosis, etc.

2. The membership to the Committee and duration of service was established by the NCI in consultation with the SC. The membership includes members/institutions not participating in the Network. The NCC includes basic scientists, clinicians, prevention scientists, epidemiologists, ethicists, statisticians, and members from relevant advocacy groups. Scientific experts were drawn from various disciplines relevant to multi-center detection research and experts in data management, biostatistics, and clinical study design.

3. The Chair of the NCC is elected by its members. The Chair of the SC also serves as a member of the advisory committee. The NCI is represented by relevant program staff.

4. The NCC evaluates the progress and success of the Network against the criteria developed by the SC.

5. The NCC helps the NCI in site visits to the participating institutions, as necessary.

6. The NCC collaborates with the SC to suggest participants for and to assist in the implementation of the workshops and symposia and to provide liaison between the cancer research community and the Network.

Data Safety and Monitoring Committee (DSMC):

The DSMC will be appointed by and report to the SC in consultation with the NCI Program Coordinator who will also be the member of this committee. The DSMC will be composed of external, non-participating scientists appointed by the SC to monitor patient safety, conduct data audits, and document progress to the NCI Program Director and the NCC.

D. Arbitration

A panel will be formed to review any scientific or programmatic disagreement (within the scope of the U24 award) between U24 awardees and the NCI. The panel will be composed of three members: one selected by the SC (with the NCI Program Coordinator not voting), or by an individual U24 or U01 awardee in the event of an individual disagreement; a second member selected by the NCI; and, the third member selected by the two prior selected members. Any disagreement that may arise on scientific/programmatic matters (within the scope of the award) between award recipients and the NCI may be brought to arbitration.

This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appeal able in accordance with the PHS regulations at 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into four areas: scientific/programmatic, intellectual property and technology licensing, peer review, and financial or grants management issues:

o Direct your scientific/programmatic questions for this RFA to:

Sudhir Srivastava, Ph.D., M.P.H.
Program Coordinator
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3142
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 435-1594
FAX: (301)402-8990
E-mail: srivasts@mail.nih.gov

Jacob Kagan, M.Sc., Ph.D.
Program Director
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3140
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-8397
FAX: (301) 402-8990
E-mail: kaganj@mail.nih.gov

o Direct questions about intellectual property, technology licensing, data sharing, and research tools issues for this RFA to:

Wendy E. Patterson, Esq.
National Cancer Institute
Technology Transfer Branch
6120 Executive Blvd., EPS Suite 450
Bethesda, MD 20892-7182
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 435-3110
FAX: (301) 402-2117
E-mail: wp23x@nih.gov

o Direct questions about peer review issues for this RFA to:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041
Bethesda, MD 20892-8329
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: ncirefof@dea.nci.nih.gov

o Direct questions about financial or grants management matters for this RFA to:

Karen Chuang
Grants Administration Branch
National Cancer Institute
6120 Executive Blvd., EPS Room 243
Bethesda, MD 20892
Telephone: (301) 496-2784
FAX: (301) 496-8601
E-mail: chuangk@mail.nih.gov

LETTERS OF INTENT

Prospective applicants are asked to submit by July 16, 2004, a letter-of-intent that includes the following information:

o Descriptive title of the proposed services and research;
o Name, address, and telephone number of the PI;
o Names of other key personnel;
o Participating institutions; and
o Number and title of this RFA.

Although a letter-of-intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NCI staff to estimate the potential review workload and plan the review.

The letter-of-intent is to be sent by the date listed at the beginning of this document. The letter-of-intent should be sent to:

Sudhir Srivastava, Ph.D., MPH
Program Coordinator
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3142
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 435-1594
FAX: (301)402-8990
E-mail: srivasts@mail.nih.gov

PRE-SUBMISSION MEETING

It is also the intent of the program to hold a pre-submission meeting on about May 27, 2004 in Bethesda, MD, with the potential applicants prior to deadline for submission of Letters-of-Intent. Updated information on the pre-submission meeting will be posted on the website, http://www.cancer/gov.edrn.

SUBMITTING AN APPLICATION

Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance, contact GrantsInfo; Telephone: (301) 435-0714; and/or E-mail: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS:

Special Instructions for Preparation of the Application

For this RFA, the format for the "Research Plan" of the PHS 398 grant application is changed. "The Research Plan" section is not subject to the page limitations stated in the PHS 398. Sections a. through d. of the "Research Plan" should be replaced with the following sections: 1) Organizational Structure; 2) Personnel; 3) Experience with Laboratory Test Validation, Scale-up, and Refinement; 4) Environment; 5) Developmental Studies; and 6) Compliance with terms of EDRN Cooperative Agreement. The remainder of the "Research Plan," sections e. through i., remains the same. However, the suggested format and page recommendations should be noted. Indicate the sections in the Table of Contents using the following titles:

1. Organizational Structure (maximum 10 pages, including organizational chart): This should include a description of the laboratory's organizational structure, including lines of authority, with particular attention to its qualifications for validation studies (see "Scope"), service resources, and the Network's major objectives (see "Objectives"). Describe any certification(s), from laboratory accrediting agencies/organizations, for example from CLIA, College of American Pathologists. Describe plans for interaction among laboratory staff and with the various Network components. Describe any ongoing grant-supported, institutional, or private sector resources that augment or complement resources for which funding from this RFA is sought

2. Personnel (maximum 10 pages): Applicants should concisely describe what expertise the group encompasses, that are available to support their participation in EDRN collaborative validation studies. The roles of all key personnel, collaborators, and consultants who are associated with the application may be described, including those with no requested salary support. Applicants should list and summarize each of the agreements with individual collaborators, including a description of the materials, technologies, and expertise to be provided by such collaborators.

3. Experience with Laboratory Test Validation, Scale-up, and Refinement (maximum 10 pages): Summarize experience in each of chosen areas (see "Scope"). Briefly describe previous and current research experience and accomplishments in dealing with validation studies, quality control and excellence in assay development and refinement.
Applicants should also describe the experience of their group in collaborative programs and activities with partners in academia and industry. Some examples of collaborations that may be provided in support of the application are listed below, but are not limited to:

- Demonstrated evidence of collaborative projects and publications;
- demonstrated evidence of collaborative funding; and
- sharing of data and resources, e.g., specimens, technology, research protocols.

For competing renewal applications, applicants should use the Metrics for Programmatic Evaluation that can be found in the EDRN Second Report, http://www3.cancer.gov/prevention/cbrg/edrn/edrn_report2002.pdf. In brief, they should provide:

Documented evidence of:
- participation on ongoing collaborative projects and publications; and
- sharing of data and resources, e.g., specimens, technology, research protocols.

4. Environment (maximum 5 pages): Briefly describe how the facilities and equipment for experimentation are appropriate to support the Network's endeavor and the scientific environment in which the work will be done. Describe the institutional support for computer services, including Internet access, and conference calls. Describe how the proposed environment contributes to the research and encourages collaborative and service arrangements. Provide health and safety plans.

5. Developmental Studies (maximum 15 pages): Justification and plans for the use of developmental funds (see Budget section below) should be carefully described, including specific aims to address the research questions, background and significance, preliminary results/progress report, study design and methods, anticipated outcome, and the overall impact on furthering the Network's objectives. The studies may include, but are not limited to, refinement, automation, analytical validation of reagents, biomarker assays, development of integrated technology platforms in support of ongoing studies within EDRN and other studies conducted elsewhere for the identification of risk and early cancer. The applicant may submit a research proposal for a developmental study for year one; this proposal will be peer reviewed by the

scientific review committee. The budget for this one year developmental study may not exceed $200,000 in direct costs. For each of the subsequent years, the PI should submit an application for the set aside funds ($200,000 in direct costs, see Budget section below) for developmental projects/collaborative studies, even if the applicant did not request this fund for developmental study in year 1. The use of the set-aside fund will be reviewed by the EDRN Executive Committee and approved by the NCI.

6. Compliance with terms of EDRN Cooperative Agreement (maximum 10 pages): Specific issues related to cooperative agreements must be addressed in this section.

Applicants must include their specific plans for responding to the "Cooperative Agreement Terms and Conditions of Award" section. Applicants should state their willingness to collaborate and share data freely with the other EDRN components, to participate in planning and attending workshops and symposia, to serve on the SC and be bound by its decisions, and to be able and willing to share data and research resources with each other and the NCI. Successful applicants will be expected to adapt information on specimen collections to the Network's Common Data Elements (CDEs) and register their protocols with the Network's DMCC.

At the end of this section, applicants must append a letter from the applicant institution describing how that institution intends to address the NIH policies for sharing of data or why data sharing is not possible. In this regard, attention is drawn to the NIH Final Statement on Sharing Research Data (http://grants.nih.gov/grants/policy/data_sharing/index.htm and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html), which was published in the NIH Guide on February 26, 2003. This is an extension of NIH policy on sharing research resources, and reaffirms NIH support for the concept of data sharing.

To address the interest in assuring that research resources are accessible, NIH also requires applicants who respond to this RFA to submit plans (1) for sharing the unique research resources, e.g., human biospecimens and novel cancer biomarkers, generated through the grant; and (2) for addressing how they will exercise intellectual property rights, should any be generated through this grant, while making such research resources available to the broader scientific community. Dissemination of research resources and management of intellectual property in accordance with these plans are consistent with NCI's programmatic objectives for the EDRN.

GUIDANCE FOR PREPARATION OF RESEARCH TOOLS SHARING PLAN AND INTELLECTUAL PROPERTY MANAGEMENT PLAN

The EDRN is premised on the belief that an established integrated, multi-disciplinary environment will expedite clinical applications of biomarker research. From the outset, the NCI anticipated that EDRN members would collaborate with industry both to develop biomarkers and/or reagents and to provide a clinical environment for the evaluation of new technologies. Early interactions with industry are expected to permit research collaborations likely to benefit both EDRN grantees and industry partners. It is hoped that validated biomarkers may ultimately be commercialized into diagnostic products for early detection of cancer and cancer risk. Many of the EDRN investigators have had active collaborations with industry. While the one-university/one-company collaborations have worked well, there is general agreement that successful multi-institution/multi-company collaborations have been harder to implement.

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. The NIH is interested in ensuring that the research resources developed through this grant also become readily available to the broader research community in a timely manner for further research, development, and application, in the expectation

that this will lead to products and knowledge of benefit to the public health.

Investigators conducting biomedical research frequently develop unique research resources. The policy of the NIH is to make available to the public the results and accomplishments of the activities that it funds. To address this interest in assuring that research resources are accessible, NIH requires applicants who respond to this RFA to submit a plan for sharing the research resources generated through the grant (e.g., human biospecimens and novel cancer biomarkers) and for addressing how they will exercise intellectual property rights, should any be generated through this grant, while making such research resources available to the broader scientific community consistent with this initiative. Therefore, the research resources tools sharing plan and intellectual property management plan must make unique research resources readily available for research purposes to qualified individuals within the scientific community in accordance with the NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps/) and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, December 1999 (http://ott.od.nih.gov/RTguide_final.html and http://ott.od.nih.gov/NewPages/64FR72090.pdf)("NIH Research Tools Policy"). These documents define terms, parties, and responsibilities prescribe the order of disposition of rights, and a chronology of reporting requirements; and delineate the basis for and extent of government actions to retain rights. Patent rights clauses may be found at 37 CFR Part 401.14 and are accessible from the Interagency Edison web page, (http://www.iedison.gov); see also, 35 USC SS 210(c); Executive Order 12591, 52 FR 13414 (Apr. 10, 1987); and Memorandum on Government Patent Policy (Feb. 18, 1983). If applicant investigators plan to collaborate with third parties, the sharing plan must address how such collaborations will not restrict their ability to share research materials produced with NIH funding.

Reviewers will comment, as appropriate, on the adequacy and feasibility of the sharing of research resources plan and the intellectual property plan. Comments on the plans and any concerns will be presented in an administrative note in the Summary Statement. These comments will not affect the priority score of the proposal. NIH program staff will consider the adequacy of the plans in determining whether to recommend an application for award. The approved plans will become a condition of the grant award and Progress Reports must contain information on activities for the sharing of research resources and intellectual property.

It is essential that applicants provide plans to address further development of technologies consistent with the goals of this RFA in a manner that does not restrict research use by the scientific community, both nonprofit and for profit. NCI has not requested a Determination of Exceptional Circumstances (DEC) in accordance with 35 USC SS 202(a) (ii) to effectuate the collaborative mission of the EDRN as set forth in this RFA. However, the success of the entire enterprise will depend on the successful collective management of intellectual property arising out of Network activities.

Where it is anticipated that there will be an exchange of collections of human tissues, consideration should also be given to obtaining the appropriate assurances from the DHHS Office of Human Subject Protections (http://www.hhs.gov/ohrp/assurances/assurances_index.html) and necessary IRB approvals and/or exemptions. In addition, issues pertaining to the protection of patient identifiable information under the Privacy Rule of the Health Insurance Portability and Accountability Act of 1976 (HIPAA) should be addressed. For more information concerning the HIPAA Privacy Rule, see http://www.hhs.gov/ocr/hipaa.

In the development of the research resource sharing and intellectual property management plans, applicants should confer with their institutions' office(s) responsible for handling technology transfer-related matters and/or sponsored research. If applicants or their representatives require additional guidance

in preparing these plans, they are encouraged to make further inquiries to the appropriate contacts listed above for such matters. Furthermore, applicants may wish to independently research and review examples of approaches considered by other institutions such as those described on the NCI Technology Transfer Branch website (http://ttb.nci.nih.gov/IPPlans.html).

BUDGET:

Applicants should budget for the following three activities:
- Administrative Cost;
- Individual Developmental Study; and
- Collaborative Studies.

Provide the budget for each activity separately.
Administrative Costs: The applicants should request funds to cover applicable administrative and travel costs (only for EDRN activities). Applicants must budget for travel expenses for SC meetings and workshops. Applicants should plan for two investigators, the PI and an additional senior investigator, to attend two SC meetings and an annual Workshop each year. Administrative costs may include salary support for the PI and administrative staff and other expenses required for the applicant to participate in EDRN activities.

Individual Developmental Study:

The budget may include salary for the PI (Laboratory Director) and support staff for the time and effort involved in managing the developmental project. Provide justification for each key personnel. The direct cost must not exceed $200,000 a year. The proposed developmental studies for the first year will be evaluated as part of the peer review of the overall U24 application.

Reasonable consultant cost will be allowed, if the consultant is contributing directly to the conduct or development of laboratory research. Clear and quantifiable justification is required.

Collaborative Studies:

New applicants should budget $200,000 (direct cost) in set-aside funds from the second year onward. The use of these set-aside funds will be restricted to collaborative projects relevant to Network's objectives, and must be reviewed and approved by the EDRN SC and the NCI. For competing renewals, the applicant should budget the actual amount that has been approved by NCI for the duration of the ongoing collaborative studies, otherwise budget as indicated for the new applicant.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number, CA-05-009, on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title, THE EARLY DETECTION RESEARCH NETWORK: BRL, and number, RFA CA-05-009, must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Referral Officer
Division of Extramural Activities
National Cancer Institute
6116 Executive Blvd., Room 8041, MSC-8329
Bethesda MD 20892-8329
Rockville, MD 20852 (express courier)

Appendices should be comprised of single-sided, unbound materials, with separators between documents.

APPLICATIONS HAND-DELIVERED BY INDIVIDUALS TO THE NATIONAL CANCER INSTITUTE WILL NO LONGER BE ACCEPTED. This policy does not apply to courier deliveries (i.e., FEDEX, UPS, DHL, etc.)
(http://grants.nih.gov/grants/guide/notice-files/NOT-CA-02-002.html).
This policy is similar to and consistent with the
policy for applications addressed to Centers for Scientific Review as published in the NIH Guide Notice at
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-012.html.

APPLICATION PROCESSING: Applications must be received on or before the application receipt date, June 25, 2004, listed in the heading of this RFA. If an application is received after that date, it will not be reviewed.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, U24 applications will be reviewed for completeness by the CSR and for responsiveness by NCI program staff. Incomplete and/or nonresponsive applications will not be reviewed.

U24 applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Division of Extramural Activities at the NCI in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a written critique
o Receive a second level review by the National Cancer Advisory Board.

REVIEW CRITERIA

Overall Review

In view of the roles and responsibilities of a BRL, the applications will primarily be reviewed for their presentations of the knowledge and practices of

assay validation and the availabilities of infrastructure, including equipment, to support them. Secondarily, the proposed developmental study will be reviewed in light of its relevance in enhancing the current or future validation study (see below). The scientific review group will consider the following criteria in assigning the application overall score, weighting them as appropriate.

1. Understanding the Scientific Issues: Does the application document evidence that the applicants understand the objectives and the goals of the RFA? Is the study design appropriate? Do the methods and approaches proposed demonstrate understanding of the technical requirements and the technical challenges in biomarkers validation? Are the proposed solutions timely and effective? Applicants for the BRL are encouraged to describe their own ideas about how best to meet the goals of the Network, and are expected to address issues identified under the "SPECIAL REQUIREMENTS" section of the RFA."

2. Personnel: Research experience and qualifications of the PI in managing relevant laboratory studies and multi-institutional collaboration; capabilities, qualifications, and experience of staff to perform tasks of the RFA. Factors considered to be important for review include: demonstrated expertise in laboratory diagnostic research including, but not limited to validation studies of biomarkers; quality control; and adequate experience in molecular genetics, genomics, proteomics, and pathology for early cancer detection to execute the proposed research plans.

3. Equipment and Environment: Adequacy and suitability of facilities and equipment for experimentation to support validation of biomarkers; adequacy of the scientific environment in which the work will be done; commitment and documented evidence of institutional support for BRL; appropriate facilities and infrastructure including equipment for high-throughput testing, computer services including Internet access; unique features for collaborative research; multi-disciplinary team of collaborators; substantial interactions among collaborators.

For competing renewal applications, applicants will be also evaluated on their performance of EDRN validation and developmental studies, and their overall contribution to collaborations within, and outside the Network in meeting the EDRN missions (see EDRN Second Report, http://www3.cancer.gov/prevention/cbrg/edrn/edrn_report2002.pdf, Metrics for Programmatic Evaluation).

Review of Developmental Studies:

For the developmental study, the scientific review group will address and consider each of the following criteria and rate them as "acceptable" or "unacceptable." The reviewer may recommend removing the proposed developmental study without affecting the overall score.

1. Significance. Does the proposed developmental research address an important need for technology and/or reagents development, standardization, quality control, or protocols suitable for earlier cancer detection and risk assessment? What is the immediacy of the research opportunity? Over the project period, is there potential for the applicant to develop technology/reagents other than those specified in the application?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed and appropriate to address the objectives of the RFA? Does the applicant acknowledge potential problem areas and consider alternative strategies? Can the test results be confirmed by an independent method? Can these approaches be used for clinical testing of biomarkers/reagents for a variety of incipient neoplastic lesions? Are the criteria chosen to characterize the biomarkers/reagents sufficient and appropriate? Will the laboratory be able to carry out its planned studies in a reasonable period of time?

3. Innovation. Does the project employ novel concepts, approaches or methods? Is the project original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? Will the approaches advance the field of biomarkers/reagents development in the context of cancer detection and risk assessment? Has the applicant adequately addressed his/her institutional patent policy?

4. Investigators. Are the PI and collaborators appropriately trained and well suited to carry out this work, especially in the area of laboratory quality control and high volume assays? To what extent do these investigators have the necessary complementary skills? Have collaborations been established or consultants identified to provide the appropriate depth and breadth of scientific expertise required for the project? Will this team of investigators contribute unique skills to the overall Network?

ADDITIONAL REVIEW CRITERIA:

In addition to the above criteria, the following item will be considered in the determination of scientific merit and the priority score:

1. Interactions: Are there adequate plans for effective interaction and coordination with the Network components such as the CEC, the BDL, the DMCC, the SC, and the NCI? Do the investigators state their willingness to abide by the priorities and policies agreed upon by the SC for collaborative studies? Have the applicants proposed sound strategies for communication among themselves, with the other Network components, and with the NCI?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below.)

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below.)

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS The following items may be also be considered by reviewers but will not be included in the determination of scientific merit.

Sharing Research Data

Applicants requesting more than $500,000 in direct costs in any year of the proposed research must include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score. (See URL in Federal Citations, below.)

Budget: Does the apportionment of the budget reflect that the applicants understand the requirements of managing a BRL in the Network enterprise? Is the commitment of effort appropriate to the scope of the project, and are the resources and environment adequate to support the project?

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: July 16, 2004
Application Receipt Date: August 16, 2004

Peer Review Date: February/March 2005
Council Review: June 7, 2005
Earliest Anticipated Start Date: July 1, 2005

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. See http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); and efficacy, effectiveness, and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html.)

Clinical trials supported or performed by NCI require special considerations. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the PI/project manager or NCI program staff or a Data and Safety Monitoring Board (DSMB). These monitoring activities are distinct from the requirement for study review and approval by an Institutional review Board (IRB). For details about the Policy for the NCI for Data and Safety Monitoring of Clinical trials, see http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm. For Phase I and II clinical trials, investigators must submit a general description of the data and safety-monitoring plan as part of the research application. See NIH Guide Notice on "Further Guidance on a Data and Safety Monitoring for Phase I and II Trials" for additional information: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html. Information concerning essential elements of data safety monitoring plans for clinical trials funded by the NCI is available at http://www.cancer.gov/clinical_trials/.

SHARING RESEARCH DATA: Starting with the October 1, 2003, receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (see http://grants.nih.gov/grants/policy/data_sharing). Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data-sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials, that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subject research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html. A continuing education program in the protection of human participants in research is available online at http://cme.nci.nih.gov/.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at

http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

References

Early Detection Research Network. Disease Markers. Volume 15, No. 4, December 1999, pages 213-219.

Pepe, M.S., Etzioni, R., Feng, Z., Potter, J., Thompson, M. L., Thornquist, M., Yasui, Y. (2001). Phases of biomarker development for early detection of cancer. J Natl Cancer Inst. 93, 1054-1061.