

Request for Application for Clinical Epidemiology and Validation Centers

This is the Request for Application (RFA) issued by the Division of Cancer Prevention (DCP) for the EDNRN Clinical Epidemiology and Validation Centers.

THE EARLY DETECTION RESEARCH NETWORK: CLINICAL EPIDEMIOLOGY AND VALIDATION CENTERS

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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 Early Detection Research Network (EDRN) 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, abnormal, or simply 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 (BDL), Biomarker Reference Laboratories (formerly

known as Biomarker Validation Laboratories), Clinical Epidemiology and Validation Centers (formerly known as Clinical and Epidemiologic Centers), and a Data Management and Coordinating Center (DMCC). The Biomarker Developmental Laboratories have responsibility for the development and characterization of new, or the refinement of existing, biomarkers and assays. The Biomarker Reference Laboratories serve as a Network resource for clinical and laboratory validation of biomarkers, which include technological development and refinement. The Clinical Epidemiology and Validation Centers collaboratively conduct clinical and epidemiological research on the Network-wide clinical validation of biomarkers. The Data Management and Coordinating Center 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 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) is to invite new and competing renewal applications for the Clinical Epidemiology and Validation Centers. This RFA will allow the submission of applications involving U01 and U24 Cooperative Agreement award mechanisms. An RFA (CA-04-006) for the Biomarker Developmental Laboratories was previously published in the NIH guide on September 26, 2003. This RFA is available at <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-006.html>. RFAs for the Biomarker Reference Laboratories (CA-05-009) and for the Data Management and Coordinating Center will be issued in the near future. 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 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 a road map 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). These phases are:

Phase I: exploratory studies to identify potentially useful biomarkers- the "discovery" phase.

Phase II: studies to determine the capacity of biomarkers for distinguishing between people with cancer and those without-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.

Phase V: definitive large-scale population studies to determine 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, 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, 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 Biomarker Developmental Laboratories (BDLs), three Biomarker Validation Laboratories (BVLs), nine Clinical and Epidemiologic Centers (CECs), and a Data Management and Coordinating Center (DMCC) (The Early Detection Research Network: Translational Research to Identify Early Cancer Risk; NCI Publication No. 01-4852, August 2001).

o The Biomarker Developmental Laboratories 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 Biomarker Validation Laboratories (to be replaced by Biomarker Reference Laboratories in the reissuance of the RFA) 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 for BVL: <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-008.html>.)

o The Clinical Epidemiology and Validation Centers (which replace the Clinical/Epidemiologic Centers in this reissuance) conduct or participate in early phases (Phase II and Phase III) of clinical validation and epidemiological research into the application of biomarkers. (see previous RFA for CEC: <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-007.html>.)

o The Data Management and Coordinating Center provides statistical, logistics, and informatics support and develops the theoretical and statistical approaches to the simultaneous pattern analysis of multiple markers. (see previous RFA for DMCC: <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 (BDLs, BRLs, CECs and the DMCC) is funded through a separate Request-for-Applications. An applicant, however, may seek funding to participate in more than one type of component. Each awardee will conduct independent and/or collaborative research using their U01 or U24 funds and will conduct collaborative research using either Core Funds from the Headquarters (see definition of a Headquarters below) and/or the set-aside funds in their U01 award. The use of Core Funds and individual set-aside funds must be approved by the Steering Committee and released by the NCI.

Each laboratory/center will be managed by a Principal Investigator 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 investigators (academic or community-based) who are able to validate the results of laboratory studies through patient accrual.

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 informatic needs of the Network are provided by a Data Management and Coordinating Center and the JPL.

Steering Committee: The Steering Committee (SC) has responsibility for scientific management and oversight, including monitoring the activities of the DMCC. For administrative structure, and responsibilities of the Steering Committee, 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 Data Management and Coordinating Center 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 EDNRN 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 Steering Committee serves as the Headquarters of the Network. The Chair of the Steering Committee can be any Principal Investigator involved in the Network. The Chair serves as the Principal Investigator 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 Principal Investigators with U01 awards will have funds available to support the development of their scientific programs and clinical protocols. The Principal Investigators with U24 awards will have funds available to cover applicable administrative costs and travel to EDNRN steering committee meetings and workshops. All investigators will be encouraged to seek supplemental funding through the Small Business Innovation Award (SBIR, R43, and/or R44), Small Business Technology Transfer (STTR, R41, and/or R42), Exploratory/Developmental grants (R21/R33), and other research support mechanisms.

Core Funds for the Headquarters: Core funds will be available to the Chair of the Steering Committee. Applicants under this RFA should not apply for the Core

Funds in their U01 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 Steering Committee.

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 Steering Committee 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 subject accrual at Clinical Epidemiology and Validation Centers. 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 Steering Committee for additional evaluation of the marker and possible support for further testing. The Steering Committee then has the responsibility to review the data on the potential marker using its standing formal criteria as a guide. The Steering Committee can consult the Advisory Committee to obtain information on the requirements and need for additional research on the marker. It also can consult the Biomarker Validation Laboratories and the Clinical Centers regarding requirements for laboratory tests, needs for quality assurance, and the availability of patient groups for clinical validation. If necessary, scientific resources from other Centers can be pooled to conduct studies. Concurrently, the informatics team in the Data Management and Coordinating Center 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 Steering Committee (e.g., Letter of Intent). To support such efforts, the Steering Committee 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 subjected to the resource sharing and intellectual property requirements set forth in Section 3 of the Supplementary Instructions of this RFA. Awardees must advise core funds recipients and outside investigators of these requirements.

C. Objectives (applicable to Network as a whole)

As described in the original RFA (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-007.html>), the goals of the Network are to discover, develop, and evaluate 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.

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 EDNRN 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.

D: Scope (applies to this RFA)

The scope of this RFA is to establish and enhance the Clinical Epidemiology and Validation Centers (CEC), which form one of the four scientific components within the Early Detection Research Network. The responsibilities of a CEC are either: 1) to serve as a Resource Center for specimens for use in collaborative research within the Network and participate in collaborative biomarker validation studies under the coordination of the Steering Committee (these centers will be supported using the U24 cooperative agreement mechanism); or 2) to both serve as a Resource Center and develop a specific scientific agenda to conduct clinical research on the validation of biomarkers in early cancer detection and risk assessment (i.e., Phase II/Phase III studies as described in J. Natl. Cancer Inst., 2001; 93:1054-1061) and limited short-term (less than 5-year duration) prospective, comparative biomarker screening studies using an established medical procedures as "gold standards" (these centers will be supported using the U01 cooperative agreement mechanism). The scientific agenda applies to research carried out within the individual Centers and to the Network, as appropriate. It is anticipated that biomarkers or tools validated through Phase III will later be validated for population use through long-duration randomized screening trials, supported through other NCI-supported programs, including cooperative groups. Applicants interested in proposing a Phase IV randomized prospective cancer biomarker screening trial should contact NCI program officials prior to submitting their application for referral to the appropriate program.

All funded Clinical Epidemiology and Validation Centers will be encouraged to

develop epidemiologic and validation studies with other EDRN investigators and seek funding from the Core Fund.

1) Resource for Network Clinical Collaborative Research (both U01 and U24 applicants):

As a collaborative resource for the Network, the Centers will facilitate the clinical validation and application of biomarkers through participation in multi-institutional studies. These Centers will provide clinical expertise on population studies, protocol development, and pathological assessment. It is expected that the Centers will provide specimens for validation studies or active patient recruitment, depending on sample availability to insure the success of the collaborative Network research projects. The Centers will also participate in data quality control, analysis, and interpretation of validation studies. Reimbursement for subject accrual will be on a per case basis (see "Special Instructions for Preparation of the Application"). For collaborative Network research, guidelines for the collection and distribution of specimens will be developed by the Steering Committee. Validation assays will be performed at the EDRN Biomarker Reference Laboratories or other facilities as determined by the EDRN Steering Committee.

2) Investigator-Initiated Biomarker Validation Studies (this section is applicable to those institutions that are proposing to both serve as a Resource Center for collaborative research and develop a specific scientific agenda to conduct clinical research on the validation of biomarkers in early cancer detection and risk assessment; U01 applicants):

A number of putative biomarkers exist that could be tested in clinical settings. These include, for example, loss of heterozygosity, microsatellite alterations, cancer-specific methylation abnormalities, mutated genes, gene expression analysis and protein profiling (proteomics) for classification of early disease, and products of the mutated genes. Studies conforming to the Phase II and/or Phase III of the EDRN-developed Five-Phase Guidelines will be considered. In addition, analytical studies to establish and compare the sensitivity, specificity, and predictive accuracy of biomarkers in a clinical context, including inter- and intra-laboratory reproducibility in collaboration with an EDRN Biomarker Reference Laboratory or the EDRN-designated Reference Laboratories will be entertained.

Applicants should propose a scientific agenda that includes a mix of short- and long-term clinical studies. Applicants may propose studies that can be conducted within the individual Centers or through inter-institutional collaboration with other investigators. It is essential, however, that the Centers identify and concentrate their resources on the most promising scientific opportunities, that studies be completed as planned, and that the methodologies employed are sound and, where appropriate, innovative. These studies could include, but are not limited to:

- o Relating biomarker expression to clinical outcome. Sequential molecular genetic changes are known to occur in many types of cancer. Correlating these sequences with the natural history and clinical outcome may prove valuable for therapeutic and follow-up strategies.
- o Evaluating the accuracy of biomarkers in predicting extent or severity of disease.
- o Evaluating computational methods for combining multiple biomarkers for earlier detection and risk assessment in clinical settings.
- o Identifying high-risk populations and performing comprehensive studies in targeted high-risk populations for validation and potential integration of novel detection strategies.
- o Evaluating gene-environmental interactions for understanding risk and

variations (polymorphisms) in susceptibility in high-risk cohorts.

Investigators are encouraged to develop collaboration with several high-risk tumor registries and networks that are available to investigators, such as the Cooperative Family Registries for Breast Cancer Studies, Cooperative Familial Registries for Colorectal Cancer Studies, Cancer Genetics Network, and screening trials that are supported by the NCI.

This initiative encourages the submission of applications for clinical, epidemiological, and translational research in earlier cancer detection and risk assessment. Translational research in this context is defined as the movement of discoveries from the laboratories into patient or population research settings or the movement of observations from patient settings back to the laboratory. A major component of this process is to standardize assays and develop methods of analytic quality control. The NCI has identified several high priority research opportunities in early detection and risk assessment (for details see section ADVANCING DISCOVERY AND ITS APPLICATION in the Plans and Priorities for Cancer Research (<http://plan.cancer.gov/>). While the major thrust of the Network is on cancers of the prostate, breast, colon, lung, ovary, upper-respiratory tract, pancreas, and bladder, which are the major causes of cancer-related mortality, applications on other organ sites will also be accepted for review. The applicants should develop, articulate, and follow a research plan that conforms with the individual Center's and with the Network's overall objectives (see above). Before submission, it is recommended that applicants consult the companion RFAs, CA-04-006 (The Early Detection Research Network: Biomarker Developmental Laboratories, NIH Guide, September 26, 2003) and The Early Detection Research Network: Biomarker Reference Laboratories (CA-05-009 to be published in the near future.)

Organization of the Center:

Each Center will be assembled by a Principal Investigator (PI) who will form a multidisciplinary and, if appropriate, inter-institutional arrangement for both the individual Center's research and for Network collaborative research projects. The Center should be constructed in a flexible manner to permit the ad hoc affiliation with qualified groups to participate in high-priority research across the entire range of clinical studies relevant to earlier cancer detection and risk assessment.

Study Sites:

Investigators participating in a Center may come from academic, community, and industrial settings. For participation in a particular study, the Center leadership can solicit any site that has the necessary technical qualifications and accrual potential to contribute meaningfully to the study's timely completion and to the Center's accrual responsibility.

Institutions proposing to serve as Resource Center are encouraged to form a formal collaboration with existing Networks, Cooperative Groups, or Community-based organizations to broaden the coverage of different organ sites and accrual. Because early detection and treatment issues are often related, the Centers may need meaningful participation from various medical organizations. 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-chn.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.

MECHANISM OF SUPPORT

This RFA will use the NIH Cooperative Agreement (U01 and U24) award mechanisms. As an applicant, you will be primarily responsible for planning, directing, and executing the proposed project and/or conducting EDRN-initiated collaborative studies. The anticipated award date is March 1, 2005.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting formats. 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 U01 and U24 are cooperative agreement award mechanisms. In the cooperative agreement mechanism, the Principal Investigator 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 Principal Investigator, 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 \$7 million in FY 2005 to fund 8-15 new and/or competitive continuation grants in response to this RFA. An applicant may request a project period of up to 5 years. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Applicants requesting more than \$800,000 in direct costs for any year are encouraged to contact program staff prior to submitting the application. 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, but Domestic institutions may propose collaborations/consortia with foreign institutions
- 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 (U01 or U24) is awarded.

Principal Investigator (PI): The investigator who is designated by the applicant organization to direct the project to be supported by the U01 or U24 grant. 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 U01 or U24 mechanism in accordance with the terms and conditions that are stated in the RFA. The PI will be a voting member of the Steering Committee and will attend two Steering Committee meetings in the first year and two Steering Committee meetings and a workshop a year in subsequent years. Attendance at these meetings are required as part of this cooperative agreement.

NCI Program Director: A scientific administrator from the NCI extramural staff will provide normal stewardship for the U01 and U24 grants awardees.

NCI Program Coordinator: A scientific 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 Steering Committee, as defined under the "Cooperative Agreement Terms and Conditions of Award."

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.

A. Rights and Responsibilities of Clinical Epidemiology and Validation Center Awardees

Network Collaborative Studies:

The Centers will collaborate with other EDRN components to push promising biomarkers towards EDRN validation studies and provide EDRN investigators appropriate specimens for quick evaluation.

The PI of a Center will be responsible for accepting and implementing the goals, priorities, common protocols, procedures, and policies agreed upon by the Steering Committee for the individual and Network collaborative studies.

The PI of a Center will ensure Network and NCI review and approval of protocols, concepts, final protocol documents, informed consents, and study amendments, and advise NCI of changes in protocol status.

The PI of a Center will be responsible for collaborating on common research designs or protocols, including methods and requirements for joint participation and collaboration as recommended by the Steering Committee, and handling of data, including appropriate sharing of methods and data among collaborating organizations.

The PI of a Center will be responsible for accruing subjects on collaborative studies approved by the Steering Committee.

Individual Center Studies:

The PI of a Clinical Epidemiology and Validation Center will have the primary authority and responsibility to define the scientific objectives and approaches for the individual Center, including research design and protocol development, if applicable, participant recruitment and follow-up, data collection, quality control, and interim data and safety monitoring, and to plan, conduct, analyze, and publish results. The cohort or specimen repositories the Center establishes will provide specimens to address the scientific hypotheses of these studies, but the main portion of these specimens should be reserved for EDRN validation studies. The PI will submit data on these resources to the EDRN-developed biorepository database on a monthly basis.

The PI of a Center will develop procedures for study monitoring to assure compliance with protocol designs and protection of patients from research risk. The PI of a Center will provide guidance to the investigators regarding clinical studies, including ethical issues involved in clinical research and conflict-of-interest considerations.

The PI of a Center will assume responsibility for managing individual protocols/research and collaborative projects approved by the Steering Committee. The PI of a Center will verify that participating sites have all relevant human risk assurance documents, as required, on file with the Office for Human Research Protections (OHRP), DHHS.

The PI of a Center will submit the final protocol to the NCI for approval before the commencement of the study. Protocol must conform to the EDRN-developed Common Data Elements (CDEs) for data collection. In case the CDEs are not available, the PI will work with the EDRN DMCC and NCI Program Coordinator to develop the CDEs.

The PI of a Center will monitor and maintain appropriate records for protocols, informed consents, assurances, and annual certifications of Institutional Review Board (IRB) review and approval (OMB No. 0990-0263, "Protection of Human Subjects, Assurance Identification/IRB Certification/Declaration of Exemption, (Common Rule) "<http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf>") for all participating sites.

The PI of a Center 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 U01 or U24 in accordance with the terms and conditions of the award.

The PI of a Center will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

B. NCI Extramural Staff Responsibilities

There will be only one NCI Program Coordinator for the Network. However, the Program Coordinator may be assisted by other NCI Program Directors and Staff on

specific scientific issues as needed.

The NCI Program Coordinator will have substantial scientific programmatic involvement during conduct of this activity, through technical assistance, initiation of Network collaborative projects, data sharing and analysis, composition of reports, advice and coordination above and beyond normal program stewardship for grants as described below.

Because of the Network's diverse research 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. A member from the Chemoprevention Branch, NCI, will be available to assist the Network on intermediate endpoints and on any ongoing chemoprevention trials relevant to the Network studies. A member from the Biometry Branch, Division of Cancer Prevention, NCI will be available to assist the Network on the issues of study design, sample size, and other statistical computations. The other NCI staff may assist and advise the Network on relevant programmatic and scientific issues through the NCI Program Coordinator.

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

Although the PI will have lead responsibilities in all collaborative tasks and activities, it is anticipated that the NCI Program Coordinator will have lead responsibilities in managing and sharing the 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, substantial shortfall in participant recruitment, follow-up, data reporting, quality control, or other major breach of the protocol, or human subject ethical issues, whenever applicable.

C. Collaborative Responsibilities

1. Steering Committee:

The Steering Committee 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 Steering Committee will be composed of the Principal Investigators from each member of the Network, the Principal Investigator 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 Steering Committee. The institution of the Chair of the Steering Committee will serve as the Headquarters (for definition see Network Organization). Subcommittees, including the existing ones, will be established/maintained by the Steering Committee, as it deems appropriate; the NCI Program Coordinator will serve on subcommittees as he/she deems appropriate.

1. After all the Network components have been funded, the Steering Committee will convene. Responsibilities of the Steering Committee include but are not limited to (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 Steering Committee will establish Data and Safety Monitoring Committee (DSMC) for clinical trials as appropriate to ensure protection of human subjects.
 3. The Steering Committee 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 Steering Committee 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 Steering Committee may ask Biomarker Developmental Laboratories, or Clinical Epidemiology and Validation Centers to serve as a Biomarker Reference Laboratory on an as needed basis. The Steering Committee 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 Steering Committee will discuss collaborative projects to be pursued jointly with the funds set aside from the Headquarters and from individual U01 awardees, or NIH intramural project budgets.
7. Collaborative studies/protocols will be approved by the Steering Committee. Data will be submitted centrally to the Data Management and Coordinating Center. The Steering Committee will define the rules regarding access to data and publications consistent with NCI policies.
8. The Steering Committee 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 Network Advisory Committee, and other NCI staff will provide the Steering Committee with advice on participants for the workshops and symposia. The Data Management and Coordinating Center will manage the logistics for these meetings.
9. The Steering Committee or its Executive Committee in consultation with the NCI will determine the PI of the Network-wide validation study.

2. Network Consulting Committee:

1. A Network Consulting Committee (NCC) was established by the NCI. The NCC advises the Steering Committee 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 Steering Committee. 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 Steering Committee 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 Steering Committee.

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

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

3. Data Safety and Monitoring Committee:

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

D. Arbitration

A panel will be formed to review any scientific or programmatic disagreement (within the scope of the U01 or U24 award) between the award recipients and the NCI. The panel will be composed of three members: one selected by the Steering Committee (with the NCI Program Coordinator not voting), or by an individual 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 appealable 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, peer review, and financial or grants management issues:

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

Sudhir Srivastava, Ph.D., MPH
Program Coordinator
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3142
Bethesda, MD 20892
Telephone: (301) 435-1594
FAX: (301)402-8990
Email: svrivasts@mail.nih.gov

Paul Wagner, Ph.D.
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3140
Bethesda, MD 20892
Telephone: (301) 496-9424
FAX: (301)402-8990
Email: wagnerp@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
Telephone: (301) 435-3110
FAX: (301) 402-2117
Email: 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
Email: chuangk@mail.nih.gov

PRE-SUBMISSION MEETING

It is the intent of the program to hold a pre-submission meeting on about March 15, 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>.

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions
- 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
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, EPN Room 3142
Bethesda, MD 20892
Telephone: (301) 435-1594
FAX: (301) 402-8990
Email: srivasts@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). 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, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS:

Special Instructions for Preparation of the Application

For to this RFA, the format for the "Research Plan" of the PHS 398 grant application is changed. Sections A. to D. of the Research Plan should be replaced with the following three sections; 1) Collaborative Clinical Validation Studies, 2) Research Plan for Clinical Biomarkers Validations Studies (Section 2 is only applicable to those applications proposing a specific scientific agenda to conduct clinical research on biomarker validation.), and 3) Compliance with terms of EDRN Cooperative Agreement. The remainder of the Research Plan, sections E. to I., remains the same.

Research Plan

Section 1 - Collaborative Clinical Validation Studies (maximum 10 pages)
a) Applicant: Applicants should concisely describe what expertise the group encompasses, specialized or unique facilities, core resources, and services that are available to support their participation in EDRN collaborative validation studies. In this section, applicants should describe any ongoing grant-supported, institutional, or private sector resources that augment or complement resources for which funding from this RFA is sought. The roles of all key personnel, collaborators, and consultants who are associated with the application may be briefly described. This section should also clearly describe the formal organizational structure of the Center, including lines of authority and responsibility, with particular attention to the relationship of

the organizational structure to the Center's major objectives.

b) Patient accrual: All applicants must document their ability to recruit patients, procure specimens prospectively, collect epidemiological and clinical data using EDRN-developed Common Data Elements (<http://www3.cancer.gov/prevention/cbrg/edrn/press.html>) and process, track, and store specimens. The distribution of specimens collected through EDRN will be governed through the EDRN-established procedures, and the EDRN Executive Committee will be the final decision body. If the applicants already have specimen repositories which they are willing to make available to EDRN-collaborative studies, they should describe the purpose of the study(s) from which samples are being made available and the extent of the clinical information collected. Applicants must also describe and submit the distribution policy and procedures for their existing resources. The applicants must describe their plan to work with the EDRN Steering Committee and how their specimen distribution will be coordinated through their committee. The applicants should answer questions concerning which committee will have the veto power in case of a disagreement.

Applicants should describe the experience of their group in collaborative programs and activities with academic and industry partners. Some examples of collaborations that may be provided in support of the application are listed below:

- o demonstrated evidence of specimens collection and patient accrual history
- o demonstrated evidence of collaborative projects and publications
- o demonstrated evidence of collaborative funding
- o sharing of data and resources, e.g., specimens, technology, research protocols
- o past participation in multi-center trials

For competing renewal applications, applicants should describe their participation in the EDRN activities, and the contributions in terms of 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).

c) Quality Assurance: Applicants should describe procedures for quality assurance and laboratory quality control. This includes confirmation of pathology and radiology reports and inter-laboratory comparisons of test results and procedures. The need for formal mechanisms of medical review, audits, and quality control is clear. The applicants must discuss their experience with quality control issues and other considerations that may arise in multi-institutional studies.

Section 2 - Research Plan for Clinical Biomarkers Validations Studies (maximum 25 pages): This section is only applicable to those applications proposing to develop a scientific agenda to develop EDRN-defined Phase II and Phase III studies.

Applicants should concisely describe the Center's proposed research objectives. Depending on the composition and structure of the group, this section may be organized as distinct projects or as one integrated plan; in either case, the page limitation is the same.

Applicants must describe the significance, background, rationale, and approaches for the proposed studies. For competing renewal applicants, this section should have a description of the goals of the previous grant and include the scientific progress from the previous project period. Indicate the status of developed markers according to the biomarker developmental phases (Pepe et. al., 2001). Applicants should highlight their progress using the EDRN-developed Evaluation Metrics

(http://www3.cancer.gov/prevention/cbrg/edrn/edrn_report2002.pdf).

Applicants should define the major research questions and opportunities related to objectives of EDRN that their group effort proposes to undertake. Applicants should describe the approaches to be taken by the group in the aggregate or as inter-dependent projects, and should describe the rationale for approaches to be used. Applicants are encouraged to use this section of the application to highlight how the diverse expertise of the group members contributes to the innovation of which the group is capable, the flexibility they possess to redirect research when scientific progress warrants it, and their ability to anticipate new directions, based on their individual experience and ability to contribute to a collective effort. The roles and expertise of all key personnel, collaborators, and consultants who are associated with the application should be documented; letters from collaborators and consultants should be included in Section I of the research plan as specified in the instructions for the Form PHS398 application.

Applicants should list and summarize each of the agreements with industry collaborators, including a description of the materials, technologies and/or expertise to be provided by such collaborators. Detailed documentation of license agreement(s), intellectual property arrangements, and data sharing concerning the proposed or existing collaboration with industrial partner(s) will be requested as appropriate if an applicant is selected for consideration for funding. These documents must be submitted by the Institutional Technology Transfer Office.

Awardees under the auspices of this RFA should obtain appropriate licenses for technologies that are necessary for the conduct of the proposed research so that the goals that are proposed can be accomplished. A statement from the applicant institution to that effect is required in the letter to be appended to Section 3.

Section 3 - 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 Steering Committee and be bound by its decisions, and to share data and research resources with each other and the NCI. Successful applicants will be expected to submit (via the internet) information on specimen collections per the Network's Common Data Elements and register their protocols with the Network's Data Management and Coordinating Center. Applicants should state their willingness to adapt their data management system so that it is compatible with EDRN data infrastructures.

At the end of this section, applicants must append a letter from the applicant institution describing how that institution intends to meet 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. The new policy becomes effective with the October 1, 2003 receipt date for applications or proposals to NIH.

Applicants to this RFA must also include a research tools and resources sharing plan in the letter to be appended to this section. 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. NIH recognizes that certain research

activities may result in inventions and that grantees are entitled to protect such inventions through patenting and licensing activities in accordance with the Bayh-Dole Act, 35 USC SS 200 et seq. and the implementing regulations, 37 CFR Part 401 ("Bayh-Dole Act"). However, the EDRN's core mission of collaboration both between Network members and between Network members and third party industry partners necessarily anticipates the sharing of intellectual property arising out of research resources developed in Network-related activities. To address the interest in assuring that research resources are accessible, NIH 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 (described below), should any be generated through this grant, while making such research resources available to the broader scientific community.

The sharing of research resources and intellectual property plans 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 Guidelines"). These documents define terms, parties, and responsibilities. The documents also 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 research tools sharing plan must explain how such collaborations will not restrict their ability to share research materials produced with NIH funding. NCI believes that applicants can satisfy the requirement to submit the research resources plan and intellectual property plan in a number of ways.

GUIDANCE FOR PREPARATION OF RESEARCH RESOURCES PLAN AND INTELLECTUAL PROPERTY PLAN

The EDRN is premised on the belief that an established integrated, multi-disciplinary environment will expedite clinical applications of biomarker research. Comprised of thirty-one principal members, the EDRN is organized in four components: eighteen Biomarker Developmental Laboratories, three Biomarker Validation Laboratories, nine Clinical and Epidemiology Centers, and one Data Management and Coordination Center. 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/company collaborations have been harder to implement.

The NCI recognizes the rights of applicants under the Bayh-Dole Act to elect title to inventions made with federal funds by their investigators, which rights must be exercised in accordance with the NIH grants policy, including the NIH Research Tools Guidelines. These guidelines in turn require investigators to make unique research resources readily available for research purposes to qualified individuals within the scientific community. NIH encourages the filing of patent applications on unique research resources if doing so will aid in the prompt commercialization of diagnostic, prognostic or

therapeutic products. Institutional ownership of such inventions may be of concern to collaborators, especially those who are the source of proprietary biomarkers, reagents, and/or technologies. Since active involvement by the industrial laboratories is critical to the EDRN's objective of basic research and development of new biomarkers/reagents, it is essential that applicants provide plans to assure both adequate patent coverage and opportunities to license such patent rights, as appropriate, 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. The following guidance is intended to assist applicants in their preparation of the required intellectual property plan.

Each applicant, therefore, must provide a description of the approach to be used for licensing patented inventions developed through EDRN activities. This requirement may be easily satisfied when the applicant's plans involve collaboration with a single industry partner. Attention is drawn to the approach utilized by the NCI's Cancer Therapy Evaluation Program (CTEP), which obtains the voluntary agreement of participating extramural grantees to grant exclusive options to negotiate exclusive, world-wide, royalty-bearing licenses for all commercial purposes, including the right to grant sub-licenses, to all inventions resulting from the use of compounds supplied by collaborators. For more information, including the specific terms of the intellectual property option ("IP Option") granted voluntarily by NCI CTEP grantees, please see the CTEP website (<http://ctep.cancer.gov/industry/ipo.html>). However, since multiple institutions and industry collaborators may be involved in a plan to develop diagnostic assays based on novel biomarkers, developed in part with proprietary biomarkers/reagents/technologies supplied by their collaborators, the situation can become quite complex. Under these circumstances, applicant's institution might want to use the IP Option to license inventions within narrow fields of use so as not to preclude additional individual collaborations with other companies to develop these inventions. Alternatively, applicant's institution could enter into a multi-party agreement that appropriately incentivizes the companies for moving the products forward. Possible approaches include: (i) granting an IP Option to each individual company for an exclusive commercialization license relating solely to such company's product; or (ii) an IP Option for a co-exclusive license of intellectual property relating to a combination of products. In situations where multiple patents are involved but exclusive (or co-exclusive) access is not required, applicants and their collaborators may wish to explore the creation of patent pools, which would enable all necessary patents relating to a technology to be licensed nonexclusively at reasonable royalty rates. For more information on the use of patent pools for biotechnology patents, see (<http://www.uspto.gov/web/offices/pac/dapp/opla/patpoolcover.html>; <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>); see also, "Antitrust Guidelines for the Licensing of Intellectual Property", issued by the US Department of Justice and the Federal Trade Commission (April, 1995) (<http://www.usdoj.gov/atr/public/guidelines/ipguide.pdf>); "Antitrust Guidelines for Collaborations Among Competitors", issued by the Federal Trade Commission and the U.S. Department of Justice (April, 2000) (<http://www.ftc.gov/os/2000/04/ftcdojguidelines.pdf>). 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>).

Regardless of the structure of the arrangement, the scope of the

commercialization license should be commensurate with the research plan and relate to the proprietary product (drug, test, device, etc.) of the collaborator(s). In addition, institutions should reserve a research use license for any resulting inventions in the final negotiated commercialization license, which ideally should include the right to share such inventions with others for noncommercial purposes. In the event that institutions desire to use intellectual property resulting from such collaborations for the benefit of third parties for commercial purposes, they will want to obtain the consent of the relevant industry collaborators before doing so.

The foregoing guidance is provided by way of example to assist applicants in preparing the required research resources sharing and intellectual property management plans in a manner that encourages partnerships with industry. While these approaches will likely suit most situations, these approaches are not exclusive and applicants should feel free to submit alternative versions for consideration.

Budget:

Those applications that propose to function solely as a Resource Center and do not propose a specific scientific research agenda in biomarker validation should budget only for applicable administrative costs and travel expenses. When they join an EDRN collaborative study, funds will be allocated from EDRN core funds to cover costs of specimen collection, clinical testing, data management, etc.

1. Applicants must budget for travel and per diem expenses for Steering Committee meetings. In the first year, applicants should plan for two investigators, the Principal Investigator and an additional senior investigator, to attend a Planning Meeting and two Steering Committee meetings. In the second and subsequent years, applicants should plan for the PI and another investigator to attend two Steering Committee meetings per year.

2. Applicants must budget for travel and per diem expenses for participation in Network workshops and symposia. Applicants should plan that at least two investigators will attend a workshop or symposium every year.

3. Applicants (except those resource centers requesting only administrative costs and travel expenses) must set aside funds for Network Collaborative studies as follows:

o Competing renewal applicants, who are participating in ongoing validation or collaborative studies, should set aside funds that were approved by the NCI program staff for the years of these ongoing studies, otherwise they should set aside 20% of their annual budgets for Network collaborative studies.

o New applicants should set aside 20% of their annual budgets from the second year onward for Network collaborative studies.

The use of these set aside funds will be restricted and must be reviewed and approved by the Steering Committee and then recommended to, and approved by the NCI for release from the individual U01 awards. Indicate this amount in the Other Expenses category under the heading 'Network Collaborative Funds.'

4. Applicants must budget for data collection on relevant common data elements (CDEs) for specimens during the course of study. For CDEs, please visit the EDRN web site (<http://www.cancer.gov/edrn>).

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-05-005 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: CLINICAL EPIDEMIOLOGY AND VALIDATION

CENTERS, and number, RFA CA-05-005, 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
Rockville, MD 20852 (express courier)
Bethesda MD 20892-8329

Appendix materials should be 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 <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 14, 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, applications will be reviewed for completeness by the CSR and for responsiveness by NCI program staff. Incomplete or unresponsive applications will not be reviewed.

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; and
- o Receive a second level review by the National Cancer Advisory Board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application.

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

All applications will be evaluated on issues related to patient accrual, collection of clinical data using EDRN-developed Common Data Elements (<http://www.cancer.gov/edrn>) and collaboration within the network. Applications proposing to develop a specific scientific agenda to conduct clinical research on biomarker validation, EDRN-defined Phase II and/or Phase III studies, will also be evaluated on the proposed research.

Although the applications will be peer-reviewed, all validation protocols, patient accruals, and data collection will also be reviewed by the EDRN Steering Committee, the DMCC, and NCI Staff in order to meet the Network-established guidelines prior to initiation of the study.

1. Significance:

All applications: Are the types and numbers of patients or longitudinal samples to which the applicants have access relevant to EDRN validation studies? Are they unique or difficult to obtain?

Applications proposing a scientific agenda in biomarker validation: Does the proposed clinical epidemiologic research address an important need for earlier cancer detection and risk assessment? What is the immediacy of the research opportunity in light of the EDRN-established phases of biomarker development for early detection of cancer? Over the project period, is there potential for the applicant to develop biomarkers/reagents other than those specified in the application?

2. Approach:

All applications: Are issues related to specimen collection, clinical testing, and data management adequately addressed? Are the plans for recruitment of special populations including both genders and minorities and relevant subgroups adequate and appropriate for the scientific goals of the research? Do the applicants present a sound plan for patient recruitment, retention, and follow up, for high quality specimen collection, processing, and storage, and for obtaining high quality clinical and epidemiological information linked to specimens? Do appropriate quality assurance and quality control programs exist, including on-site audits that assure high-quality research and patient safety? Are institutional data management and statistical analyses, procedures, and

policies adequate, appropriate, and consistent with accepted standards? Will the Network collaboration be utilized when necessary to satisfy the requirements for timely completion of proposed studies? Has the applicant adequately addressed his/her institutional patent policy?

Are the plans for administering and organizing the Center adequate and appropriate? Will these plans allow it to meet the Network's major objectives? Are the Center's organizational and administrative plans likely to lead to a well functioning, cohesive research group?

Are there adequate plans for effective interaction and coordination with the Network components, the Steering Committee, the Data Management and Coordinating Center and the NCI? Do the investigators state their willingness to collaborate and share information? Do the investigators state their willingness to share specimens and data in collaborative EDRN-validation studies? Do the investigators state their willingness to abide by the priorities and policies agreed upon by the Steering Committee for collaborative studies? Have the applicants proposed sound strategies for communication among themselves, with the other Network components, and with the NCI? Have they agreed to adapt their data management system to be compatible with EDRN data infrastructure?

Applications proposing a scientific agenda in biomarker validation: Are the conceptual framework, design, methods, and analyses adequately developed and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Are the criteria chosen to characterize the biomarker(s)/reagent(s) sufficient and appropriate? Can the proposed method(s) be used to measure the biomarker(s) in a clinical setting? Do the biomarker(s)/reagent(s) have the potential to detect incipient neoplastic lesions or to be useful for cancer risk assessment? Will the Center be able to carry out its planned studies in a reasonable period of time?

3. Innovation:

All applications: Do the applicants propose innovative or novel approaches to patient accrual and/or specimen collection?

Applications proposing a scientific agenda in biomarker validation: Does the project employ novel concepts, approaches or methods? Is the project original and innovative? Does the project challenge existing paradigms or develop new clinical parameters? Will the approaches advance the field of biomarkers in the context of early cancer detection and risk assessment?

4. Investigators:

All applications: Are the principal investigator and collaborators appropriately trained and well suited to carry out this work? Have collaborations been established or consultants identified who will provide the appropriate depth and breadth of scientific expertise required for the project? Will these investigators contribute unique skills to the overall Center and to the Network? Will they provide guidance to other collaborators regarding clinical studies, including ethical issues involved in clinical research and conflicts of interest?

Applications proposing a scientific agenda in biomarker validation: Are the numbers and roles of staff for each study defined and justified? Do their research experience and qualifications demonstrate understanding of biomarkers research, of the design, administration, and analysis of multi-institutional clinical research, and of laboratory studies?

5. Environment:

All applications: Are the facilities appropriate to support the endeavor? Does the scientific environment in which the research will be done contribute to the likelihood of success? Do the principal investigator and collaborators have access to the appropriate patient populations? Does the applicant have access to pathology review and documentation of the pathology report? Does the

applicant have access to treatment information and other necessary patient data, such as medical history? Do they have a good biorepository, in particular, of preclinical samples?

Do the proposed experiments take advantage of unique features of the scientific environment and incorporate the appropriate collaborative arrangements? Is there evidence of institutional support? Is there institutional support for computer services including Internet access? Are the PI and collaborators willing to use common (paper or electronic) forms required for the collection of collaborative Network study data?

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

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

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 Federal Citations, below.)

Budget. Does the apportionment of the budget for clinical epidemiologic and validation research indicate that the applicants understand the requirements of managing the Centers within the Network enterprise? Is the commitment of effort appropriate to the scope of the project?

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: May 14, 2004
Application Receipt Date: June 14, 2004
Peer Review Date: October/November 2004
Council Review: February 16, 2005
Earliest Anticipated Start Date: March 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; and
- 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); 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 principal investigator/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:

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.

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

Srivastava, S. 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.

The Early Detection Research Network: Translational Research to Identify Early Cancer Risk; NCI Publication No. 01-4852, August 2001.