EARLY DETECTION RESEARCH NETWORK

APPLICATION GUIDELINES

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GLOSSARY OF TERMS

Definition of Translation Research: The Translational Research Working Group (TRWG) defines Translational Research in the following way: "Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality."

Chair of the Steering Committee (SC): The Chair of the SC is a Principal Investigator (PI) of one of the EDRN Cooperative Agreement Awards and is elected by members of the SC for a five year term. The Chair provides scientific leadership, presides at SC meetings, and appoints members of Subcommittees, Review Groups, and Collaborative Groups.

Cooperative Agreement Award Mechanism: U01 or U24 award mechanisms provided by NIH where the PI has the primary responsibility and dominant role for planning, directing, and executing the proposed research project. The NIH Program Director's role in this award mechanism is one of partnership with the PI. The U01 and U24 are usually awarded for a period of five years.

Data Management and Coordinating Center (DMCC): The Data Management and Coordinating Center provides logistic support for the conduct of the Steering Committee and Network Consulting Committee meetings, provides statistical and data management support for protocol development, conducts analyses of clinical data, and develops informatics (i.e. information technologies). The DMCC also studies applied and theoretical approaches to the simultaneous analysis of multiple biomarkers.

NCI Program Coordinator: A health scientist administrator from the NCI extramural staff, who is substantially involved in the scientific coordination and collaboration within the Network, is responsible for broad scientific and programmatic issues, and serves as a voting member of the SC, as defined under the "Cooperative Agreement Terms and Conditions of Award."

NCI Program Director: A health scientist administrator from the NCI extramural staff, who provides constant stewardship for the U01/U24 grant awards.

Network Consulting Team (NCT): A separate advisory committee that ensures 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 of conflicts of interest.

Principal Investigator (PI): The investigator who is designated by the applicant organization to direct the project to be supported by the grant or NIH intramural project in response to the RFA. The PI has 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 appropriate funding mechanism or the NIH intramural project in accordance with the terms and conditions that are stated in the RFA. The PI will be a voting member of the Steering Committee (SC).

Request for Application (RFA): identifies a narrowly defined area of research for which one or more NIH institutes have set aside funds for awarding grants.

Steering Committee (SC): The SC has major scientific management oversight and responsibility for developing and implementing a collaborative Network research program including protocols, publications, and design. The Committee consists of a Chair, Co-Chair, the EDRN Principal Investigators or a designee, and the NCI Program Coordinator or a designee.

SECTION I. OVERVIEW OF EARLY DETECTION RESEARCH NETWORK (EDRN)

I.A. Introduction

In 2000, the National Cancer Institute (NCI), through the Division of Cancer Prevention (DCP), established the Early Detection Research Network (EDRN) (http://edrn.nci.gov/), a program for the development of biomarkers for early cancer detection and risk assessment using translational methods of research. ***Biomarkers*** are defined as cellular, biochemical, and molecular (genetic and epigenetic) alterations by which a normal, abnormal or biologic process can be recognized or monitored. These markers can be measured in cells, tissues or body fluids. The NCI defines **translational research** as that area which "***uses knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in humans and/or determines the biological basis for observations made in individuals with cancer or in populations at risk for cancer.***"

The Early Detection Research Network (EDRN) has a straightforward mission: translational research by implementation of cancer biomarker investigation through strategic and systematic evidence-based discovery, development and validation of biomarkers to identify cancer risk, early detection, early diagnosis and prognosis of cancer and to coordinate biomarker research and therapeutic strategies in order to reduce cancer morbidity and mortality (see Appendix 1 for EDRN's Strategic Goals).

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 first identify, and then validate, crucial molecular markers to detect cancer and to assess cancer risk. EDRN is an investigator-initiated Network for collaborative research to link the discovery of biologic markers directly to the next steps in the process of developing early detection tests. The power of bioinformatics and computer-assisted programs are being put to full use to analyze Network-generated 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 application 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 2009 Bypass Budget (http://plan.cancer.gov/).

The EDRN 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 our 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 for clinical application is now greater than ever. Early detection technologies are also rapidly evolving while existing technologies are undergoing progressive refinement in their sensitivity, specificity, and high-throughput. Improved analytic tools have allowed a more detailed

examination of the molecular basis of carcinogenesis and provided the ability to identify the molecular and cellular signatures of cancer and to explore the gene-environment interaction 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 the modulation of 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.

I.B. EDRN Objectives

The collaborative nature of EDRN continues to play an important role in the pursuit of the following goals:

- Improve the screening processes for major epithelial cancers with national recommendations for screening, such as colon, breast, cervical, and prostate. Also, facilitate the co-development of diagnostics with prevention or therapeutic interventions (theranostics).

- Develop new serum- and tissue-based methods for early detection and diagnosis. Identify clinically significant disease and predictions of clinical outcome, with or without conventional tissue examination, and identify currently available biomarker tests.

- Validation of biomarkers by conducting EDRN-defined Phase 2 and Phase 3 (as described in Section ID below) multi-center trials to evaluate the predictive value of biomarkers.

- Development of high-throughput, sensitive assay methods for the identification and development of biomarkers by encouraging collaborative interaction between academic institutions and diagnostic/biotechnology companies.

- Avoid duplication or fragmentation of investigator efforts in the discovery and development of candidate biomarkers by encouraging an open exchange of information among individuals working in this area.

- Integrate the genetic, cell signaling and biochemical pathways with biomarker discovery efforts to have a broader applicability across different tumor types. Determine the potential of novel, network- and pathway-based markers to detect and diagnose cancer. Pathway biomarkers would allow a Systems Biology approach to diagnosis, prevention and therapeutic strategies.

- Expand collaborative efforts and shared resources to improve the capacity to conduct biomarker development and validation trials.

- Leverage knowledge on genome wide chromosomal instability and genome-wide association study (GWAS) to predict progression from benign to malignant cancers. Develop biomarker tests based on already characterized regions of the genome that can potentially identify genes associated with cancer prevention, early detection, and risk assessment.

- Collaborate with Cooperative Groups, The Tumor Genome Atlas (TCGA), Mouse Models for Human Cancer Consortium (MMHCC) and other NCI Supported programs that are engaged in mechanistic studies with potential to identify biomarkers.

- Establish a biomarker database to capture and share methods and pre-competitive data on the validation and qualification of biomarkers.

- Employ cost-effectiveness measuring tools to evaluate biomarker discovery, development and validation, and to collaborate with the NCI's CISNET (Cancer Intervention and Surveillance Modeling Network) on integrating cost-benefit effect models in the discovery and development processes.

- Create well-defined standards and guidelines for biomarker development, validation and qualification using the Translational Research Working Group (TRWG)-developed Device Pathway to reduce uncertainty in discovery and development of biomarkers.

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 (e.g., Specialized Programs of Research Excellence [SPOREs](http://spores.nci.nih.gov/), Cancer Genetics Network [CGN] (http://epi.grants.cancer.gov/CGN/), Breast and Colon Cancer Family Registries (http://epi.grants.cancer.gov/CCFR/index.html; http://epi.grants.cancer.gov/BCFR/index.html), Cooperative Human Tissue Network (http://www-chtn.ims.nci.nih.gov/), Cancer Genome Anatomy Project (http://cgap.nci.nih.gov/), with ongoing NCI clinical research programs/trials (e.g., Clinical Community Oncology Program [CCOP] (http://www3.cancer.gov/prevention/ccop/) Prostate, Lung, Colon, and Ovarian Screening 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 NCI anticipates that augmenting the EDRN expertise with a broad base of

clinical and public health perspectives will enable the Network to apply existing methods and newly discovered technologies toward clinical application.

I.C. EDRN Administrative Structures

The primary scientific components of EDRN are the following:

- Biomarker Developmental Laboratories (BDL)
- Biomarker Reference Laboratories (BRL)
- Clinical Epidemiology and Validation Centers (CEVC)
- Data Management and Coordinating Center (DMCC)

The Biomarker Developmental Laboratories (BDLs) develop and characterize new biomarkers or refine existing biomarkers and assays through translational research in the etiology of cancer formation. It is anticipated that discoveries made in BDLs will move from the laboratory to the clinical and population research setting and that observations from these areas would move back to the laboratory as needed for further refinement.

The Biomarker Reference Laboratories (BRLs) serve as a Network resource for clinical and laboratory validation of biomarkers in the areas of technological development, standardized assays and high-throughput methods. The quality control of reagents and various technologies is also an important area of BRL oversight. Generally, these laboratories have a CLIA certification.

The Clinical Validation Centers (CVCs) [replacing the Clinical Epidemiology and Validation Centers (CEVCs); see previous RFA CEVC at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-005.html], are formed to collaboratively conduct early phase (Phase 2 and Phase 3) Network-wide clinical validation studies on the application of biomarkers. The scope of the CVC projects includes, but is not limited to:

- Clinical evaluation of biomarkers of risk and disease;
- Evaluation of resources and methods available for the discovery and development of biomarkers;
- Identification of molecular signatures that can predict the neoplastic progression of pre-cancerous lesions;
- The utility of specific cancer biomarkers in the clinical setting;
- Establishing and maintaining patient registries of individuals with germline mutations for hereditary forms of cancer;
- Identification of pre-malignant lesions and early stage cancer in subjects at risk due to genetic/familial predisposition or due to certain environmental and occupational exposures.

Most of these studies are conducted in collaboration with EDRN BDLs or with other external developmental laboratories approved by the NCI in consultation with the Steering Committee.

The Data Management and Coordinating Center (DMCC) provides statistical support, computational analysis and informatics infrastructure, and coordinates network-wide meetings

and conferences. The DMCC also develops theoretical statistical approaches for pattern analysis of biomarker panels and serves as the coordinating center for clinical validation studies.

Further details on the scientific components of EDRN can be found at: http://edrn.nci.nih.gov/about-edrn/scicomponents/.

Four Federal agencies participate in EDRN through interagency agreements: the National Institute of Standards and Technology (NIST), which functions as a BRL; the Centers for Disease Control and Prevention (CDCP), which functions as a CVC; the Pacific Northwest National Laboratory (PNNL) of the Department of Energy, which is developing antibody microarrays for the EDRN; and the National Aeronautics and Space Administration (NASA) Jet Propulsion Laboratory (JPL), which serves as an Informatics Center to support EDRN's efforts on the development of software systems for information management.
In addition, the Food and Drug Administration (FDA) participates on the Network Consulting Team.

All EDRN investigators are members of one or more **Collaborative Groups**. Collaborative Groups are organ-specific research groups created to support the exchange of information on organ-related biomarkers and identify various research opportunities within the Network. A major role of the Collaborative Groups is to serve as advisors or liaisons with Associate Members (see relevant information in this section below).

In addition, two oversight components exist: a **Steering Committee** (SC) and a **Network Consulting Team** (NCT). The SC is composed of all EDRN Principal Investigators and the NCI Program Coordinator. It coordinates consortium activities and provides scientific and management input into the development of study protocol design and general network operations. The Network Consulting Team is composed of a Chair and non-EDRN members appointed by NCI. The NCT reviews the progress of the EDRN, recommends new research initiatives, and ensures that the Network is responsive to promising opportunities in early detection research and risk assessment. The NCT can recommend new research projects to the SC or to NCI. Members of the NCT can serve on ad-hoc Committees of the EDRN, Review Groups, and as consultants to Subcommittees.

The **DMCC** provides logistic support for the conduct of the SC and NCT meetings.

Headquarters: The institution of the Chair of the SC serves as the Headquarters of EDRN. The Chair of the SC is a Principal Investigator iof an EDRN cooperative agreement award and is elected by the SC. The Chair serves as the Principal Investigator of the Headquarters and implements the scientific, operational and organizational policies of the Network. The SC Chair provides executive leadership, scientific direction, and management for the Network. The Headquarters serves as a center for dissemination of information to investigators and institutions in EDRN, as well as to others outside the Network.

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

The Principal Investigators will have funds available through the individual U01/U24 awards to support the development of the scientific program and clinical protocols. 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 institution of the Chair of the SC. 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 support EDRN multisite biomarker validation trials.

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

3. Core Funds are used to provide support for the development of new biomarker tests to the point at which they can be validated at multiple centers and in larger populations. If test reagents are required to scale-up at this point, the SC may provide funding to contract commercial laboratories or companies that can scale up production and maintain the quality of the reagents (e.g., monoclonal antibodies, labels, etc.), and to CVCs for subject accrual.

4. Core Funds will also be required for data management, travel, meetings, and other EDRN collaborative activities.

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

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

There is also flexibility so that investigators outside the Network could form collaboration(s) with one of the existing centers, or directly bring their discoveries to the SC (e.g., By Letter of Intent). To support such efforts, the SC is able to use Core Funds to supplement the

investigator's ongoing research. The investigator, in turn, must agree to share his/her research findings and become part of the Network as an associate member.

Associate Members are not funded by an EDRN Cooperative Agreement Award. They become part of the Network by virtue of their collaborative interactions within the Consortium. There are three categories of Associate Membership (http://edrn.nci.nih.gov/colops/assoc) [1]:

Category A: domestic or foreign investigators who are supported to conduct basic or translational research consistent with the scope and priorities of EDRN;

Category B: domestic or foreign members who contribute to the Network by sharing available technologies and supplying specimens, or by making available high-risk registries and cohorts and other complementary resources;

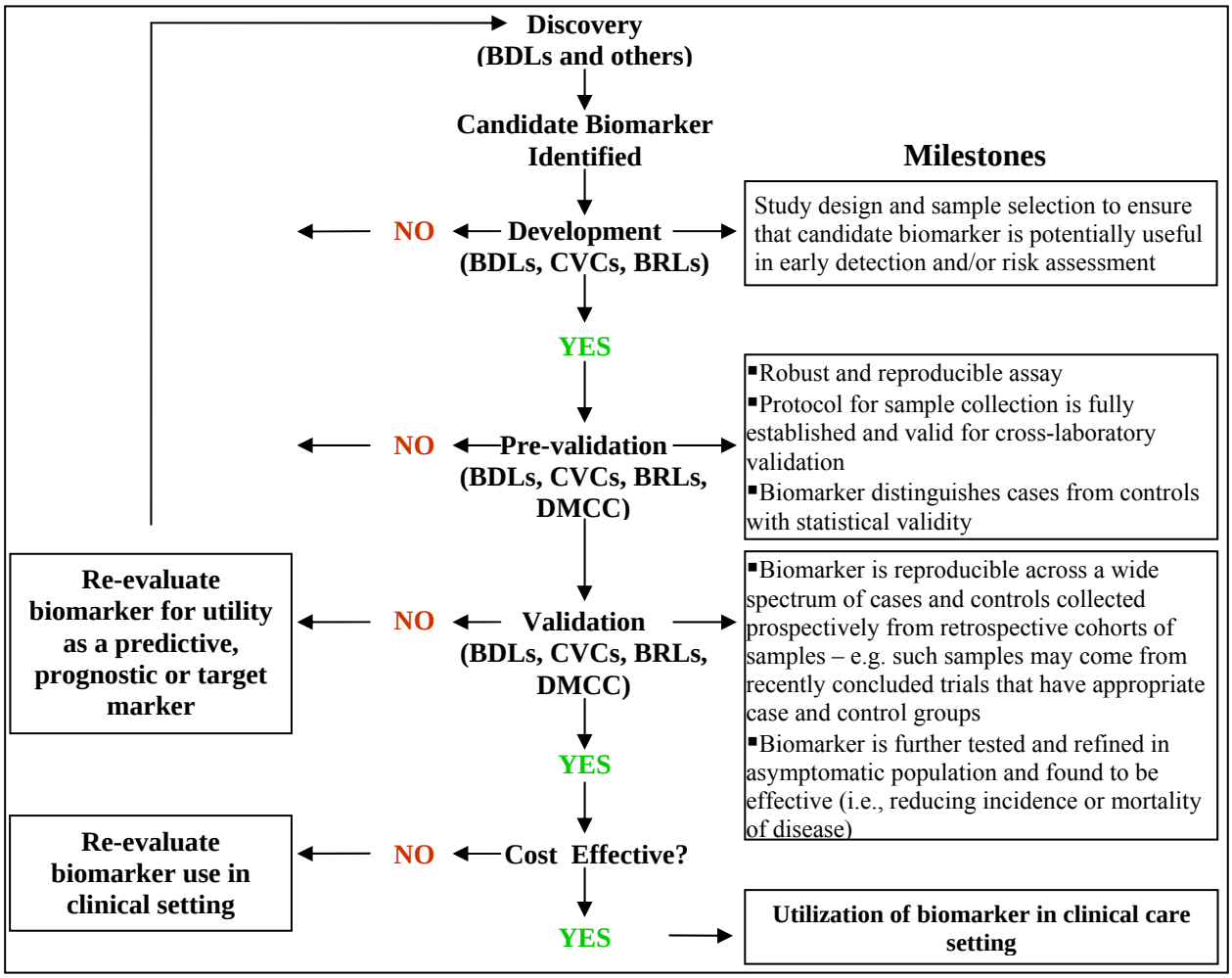
Category C: domestic or foreign corresponding members who are scientists, organizations, clinicians, patient advocates, or ethicists interested in participating in Collaborative Group meetings, workshops and conferences, without EDRN funding

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 Supplemental Instructions of the corresponding EDRN RFA. Awardees must advise core funds recipients and outside investigators of these requirements.

I.D. General Description of the EDRN Biomarker Development Plan

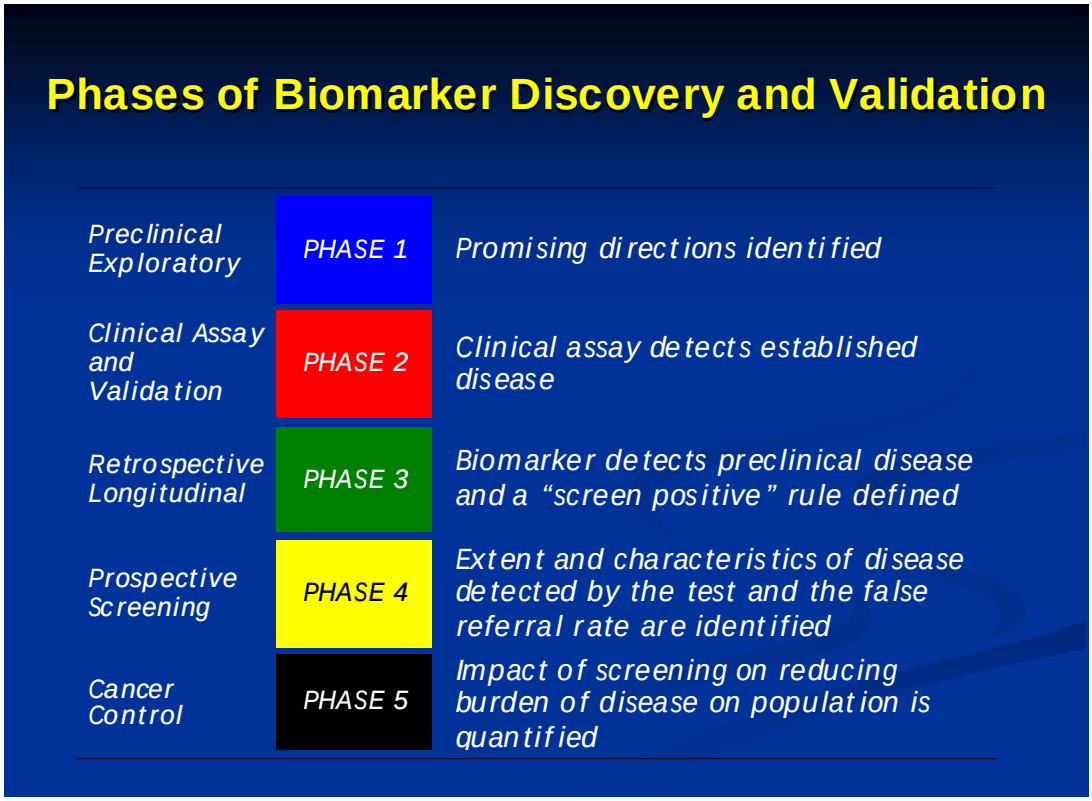
Historically, biomarker development has lacked a well defined development sequence to bring a marker from the discovery phase to the clinical application phase. Since its inception in 1999, EDRN has followed a "vertical" approach to biomarker research - that is, an established, integrated, multidisciplinary environment that would facilitate collaboration among technology developers, basic scientists, clinicians, epidemiologists, biostatisticians, and other health professionals, and therefore would expedite efficacious clinical applications of the molecular knowledge that has burgeoned in recent years [2]. Each step along the vertically integrated process of biomarker discovery, development and validation requires specific considerations, as outlined in Figure 1 below.

Figure 1. Vertical Integration of Biomarker Discovery, Development and Validation



EDRN 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). EDRN provides a consortium of investigators and laboratories with the express goal of coordinating research between biomarker developmental labs, biomarker reference labs, clinical repositories and population screening programs. A five-phase approach has been established as a standard and a road map for successfully translating research on biomarker applications from the laboratory bench to the bedside[3]. Although the EDRN's main focus is on Phases 1-3, researchers have welcomed the five-phase structure because it provides for an orderly succession of studies that build upon one another to yield an efficient and thorough approach in the development, evaluation and validation of biomarkers from the discovery laboratory (Phase 1) to use as a population screening tool in the clinical setting (Phase 5). See **Figure 2** below.

Figure 2. Five Phase Approach to Biomarker Translational Research



The key aspects of study designs for each of the five phases of biomarker development has been discussed and published. The specific steps for validating each biomarker or for a panel of biomarkers vary depending on the clinical questions and intended clinical endpoints:

Phase 1, the *pre-clinical exploratory phase,* where studies are done to identify potentially useful biomarkers, is the area of focus for most research on cancer biomarkers. Unfortunately, most studies do not advance beyond this phase for a variety of reasons, most notably, the large variability in biomarker level or the presence of only modest differences between tumor and normal tissue.

Phase 2, the *validation phase*, is where clinical assays are developed and validated in order to measure biomarkers in non-invasively obtained specimens. The objective here is to determine biomarker capacity for distinguishing between individuals with and without cancer. All too often, biomarkers do not develop beyond this phase because they lack reliable and accurate assay methods or the validation studies do not confirm that the markers have sufficiently high sensitivity and/or specificity to continue with their development.

Phase 3, the *retrospective longitudinal phase*, where studies are done to assess the capacity of a biomarker to detect pre-clinical disease involves measuring a biomarker in specimens collected from asymptomatic individuals prior to cancer diagnosis and from matched controls.

Phase 4, the *prospective screening study phase,* determines whether a biomarker can detect a cancer at an early stage of development. Asymptomatic individuals are screened, and those who test positive are followed up to determine whether they have or develop cancer.

Phase 5, the *cancer control phase,* is where definitive large scale population studies are done to determine the impact of population screening and evaluate whether screening results in a reduction of cancer morbidity and mortality.

The important considerations for each phase of biomarker development are summarized in **Table 1** below.

Table 1. Phases of Biomarker Development

Parameter	Phase 1 Preclinical exploratory	Phase 2 Clinical Assay & Validation	Phase 3 Retrospective Longitudinal	Phase 4 Prospective Screening	Phase 5 Cancer Control
	Studies conducted on case control and prediagnostic specimens			**Studies screen people & lead to diagnosis & treatment**	
Primary Aim	Find potentially useful biomarkers.	Develop & validate clinical assays to measure biomarkers & assess their ability to distinguish between cancer and non-cancer.	Determine if biomarker can detect pre-clinical disease. Define criteria for (+) screening test in preparation for Ph 4	Determine usefulness of biomarker in early cancer detection. Asymptomatic subjects with (+) screen followed to determine cancer development.	Determine impact of population screening. Determine if screening reduces cancer morbidity & mortality.
Specimen or Subject Selection	**Specimen Selection** Pre-treatment tumor tissue or body fluids from case subjects & matched control subjects	**Specimen Selection** Case & control subjects that represent the target screening population.	**Specimen Selection** Repositories of patient specimens collected prior to cancer diagnosis & in matched controls	**Subject Selection** Cohort selected from the population to be screened. Consider having unscreened control arm to provide preliminary data for Ph.5 randomized trial	**Subject Selection** Randomly selected from populations in which screening program to be used
Sample Sizes	Specimen number depends on study objective & biomarker variability	Determined by precision of TPR & FPR or ROC measurement	3 sample sizes needed: # of case subjects, # of control subjects, # of clinical specimens per subject.	Large sample sizes based on estimated detection rate and false referral rate	Large sample sizes based on computer models that consider natural cancer & biomarker hx; treatment effects on tumor & survival; cost information; & population behavior data from Ph. 2-4.

TPR= true-positive rate (i.e. proportion of case subjects that are biomarker positive)
FPR= false-positive rate (i.e. proportion of control subjects that are biomarker positive)
ROC= receiver operating characteristic

In addition to the establishment of the five-phase approach for biomarker development, a coherent and comprehensive set of guidelines for study design for the discovery and evaluation of biomarkers for use in screening and early cancer detection, diagnosis, or prognosis has been

delineated in the recent commentary by Pepe et al[4]. A prospective-specimen collection, retrospective-blinded-evaluation (PRoBE) design for biomarker development is proposed in this commentary. A set of rigorous study design standards and guidelines are described, which further address issues regarding the rate of false discovery due to the use of samples of convenience and introduction of bias and data over-fitting[5]. The PRoBE study design includes four key components. These relate to: 1) the clinical context and outcomes; 2) criteria for measuring biomarker performance; 3) the biomarker itself; and 4) the sample size included in the study.

To avoid chance and bias, and make best use of resources, discovery studies, similar to biomarker validation, should use key elements of the PRoBE design, including randomized selection of case patients and control subjects from a well-defined prospective cohort that is relevant to the intended clinical application, rigorous protocols that precisely define data items and procedures to measure them, and mechanisms to ensure that biomarker and outcome assessments cannot influence each other. Nested case–control studies, as described in the same commentary, would improve the quality of discovery research and increase the chances that truly valuable biomarkers will undergo definitive evaluation through rigorous clinical validation. One should ideally perform the pivotal PRoBE evaluation study for biomarkers that show promise in discovery studies that use the same clinical context and population. Simultaneous discovery and evaluation of the performance of a marker or marker combination can be undertaken by using a PRoBE design and randomly splitting the dataset into a training set for discovery and a test set for evaluation[6].

The importance of defining the intended clinical context in which a biomarker will be used during the initial phases of its development also entails the modeling and analysis of the cost-benefit effect of its implementation in the clinic. Such modeling and analysis is intended to aid the optimized combination of the developed biomarker with other existing modalities to increase their combined impact on the targeted population. EDRN is developing active collaborations with NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) investigators, which will facilitate the efficient incorporation of cost-benefit effect modeling and analysis in the study design and development of biomarkers.

I.D.1 Process of Biomarker Validation

An investigator within or outside EDRN 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 EDRN for additional evaluation of the marker and possible support for further testing using the Network's resources. EDRN has the responsibility to review the data on the potential marker using its established formal criteria. EDRN consults the relevant EDRN Collaborative Group and up to two external reviewers (non-EDRN). It can also consult EDRN BRLs and/or CVCs 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 at the DMCC can develop tools for the analysis of results.

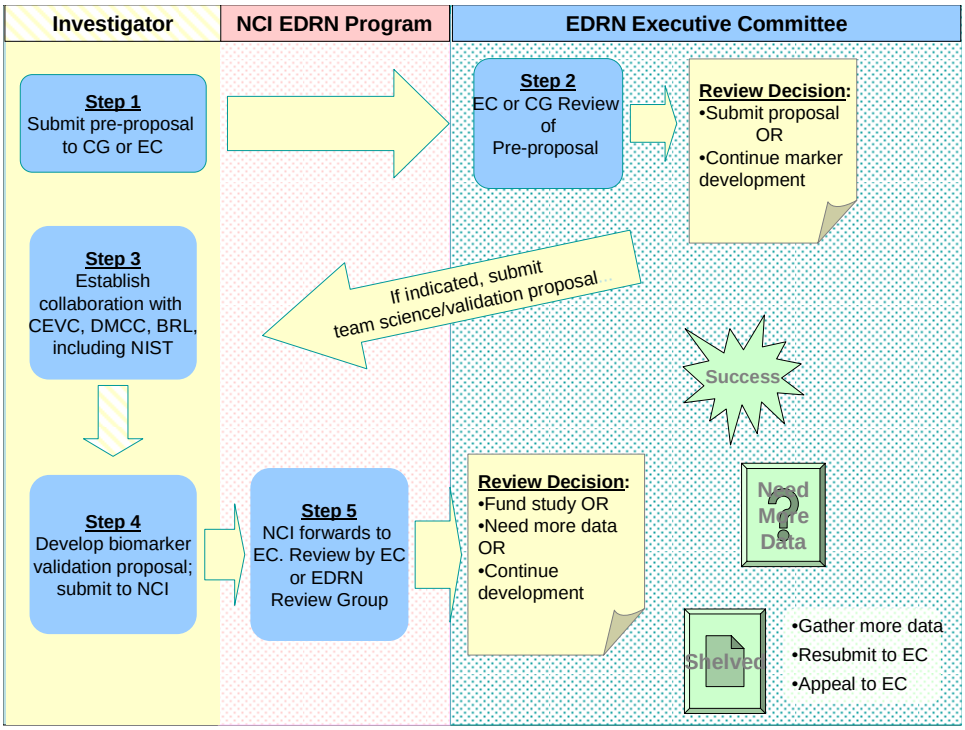
There is also flexibility such that investigators outside the Network could form collaboration(s) with one of the existing Centers, or directly bring their discoveries to the EDRN Steering Committee (e.g., By a Letter of Intent). To support such efforts, EDRN is able to use the Core Funds to supplement the investigator's ongoing research. The investigator, in turn, must agree to share his/her research findings and become part of the Network as an EDRN Associate Member.

Recipients of EDRN funds, such as institutions of outside investigators and commercial laboratories or manufacturing companies participating in validation studies will be subject to the plans that the applicant submits and EDRN accepts and which address the sharing of research resources and intellectual property, as noted in Section III below and in the Supplementary Instructions of the relevant RFAs. Awardees must advise recipients and outside investigators of these terms and conditions of the award.

I.D.1.a. Review of Application for a Validation Study

The review of applications for validation studies is the first major decision point as to whether to continue the development of a biomarker or panel of biomarkers. The process used is as follows: The investigator submits a short preliminary proposal describing the data on the performance of the marker and assay reproducibility, the design of the validation trial and an estimate of costs. The application is reviewed by the EDRN PIs in the appropriate Collaborative Group (CG). The criteria used to evaluate the preliminary proposal are:

(1) Biological Rationale/Strength of Hypothesis;
(2) Strength of Study Design;
(3) Technical Parameters;
(4) Clinical and Scientific Impact;
(5) Portfolio Balance;
(6) Practicality; and
(7) Collaborative Strength.



The CG can recommend that the applicant submits a full validation proposal or revise and resubmit the preliminary proposal; it can also recommend that EDRN does not support the proposed study. The results of the CG review along with the application are sent to the EDRN Executive Committee (EC) for discussion and recommendation to NCI. If the EC recommends that the preliminary proposal goes forward, the initiating investigator is asked to submit a full proposal and, where appropriate, to establish collaborations with EDRN CVCs and BRLs. The EDRN DMCC must be involved in the study design, monitoring of the trial, and collecting and analyzing the data. Instructions for submitting a full proposal can be found on the EDRN website http://edrn.nci.nih.gov/colops/vsp. The full proposal is then reviewed by the appropriate CG and two external reviewers identified by NCI, who are not members of the EDRN. These reviews are evaluated by the EDRN EC, which makes a recommendation to NCI. If the proposal is approved for funding, the initiating investigator is the PI of the trial, but he/she must agree that the EDRN DMCC coordinates and monitors the trial and that NCI has administrative oversight. The success of a multi-center validation trial depends on the leadership of the PI and collaboration with the DMCC and NCI.

I.E. EDRN Promotes a Hand-off Mechanism

EDRN promotes a vertical approach for conducting biomarker research, whereby biomarkers are developed in Biomarker Developmental Laboratories, refined and cross-validated by Biomarker Reference Laboratories and validated in collaboration with Clinical Validation Centers, all within one organization (see Figure 1). Its focus is in coordinating multiple resources with a goal of minimizing the barriers to the rapid and efficient "hand-off" between entities. One method used for achieving this is a structured set of criteria for assessing the roles and clinical significance of each newly discovered biomarker, along with criteria and strategies for evaluating biomarkers in relationship to one another. Such an approach was recently endorsed by the NCI's Translational Research Working Group TRWG), which developed a number of pathways that outline the processes through which fundamental scientific discoveries are transformed into clinical modalities. The diagrams specify key activities and decision points along the development pathway, clarify dependencies among different steps as well as key events that occur in parallel, and show important feedback loops and iterative processes that are embedded within the development process. For details, see www.cancer.gov/trwg.

SECTION II. CONSIDERATIONS FOR RESPONDING TO AN EDRN REQUEST FOR APPLICATION (RFA)

II.A. Planning for Application Preparation and Submission

Applicant institutions must be able to support high quality translational research on the discovery, development and/or validation of cancer biomarkers. Applications will be judged on their current and potential ability to fulfill the research objectives in order to move basic research findings into a clinical or population setting. A grantee must be willing to develop and maintain extended collaborations with laboratory and clinical scientists within the institution, in addition to sharing positive and negative research findings, assessing scientific progress in the field, identifying new research opportunities, and promoting inter-EDRN collaborations.

II.A.1 Research Objectives

The EDRN's mission is to plan, direct, and implement biomarker research (Phase 1-3) through systematic, evidence-based discovery, development and validation of biomarkers for cancer risk, detection, diagnosis and prognosis. Early detection is crucial in improving the success rate of cancer treatments; likewise, successful cancer prevention depends on being able to accurately define an individual's risk for malignancy. The EDRN seeks to improve cancer treatment and prevention. EDRN fulfills this mission by being a leading program of molecular diagnostics focusing on discovery, integration, dissemination, and clinical application of biomarker research.

EDRN provides an environment that fosters collaboration and integration of biomarker knowledge into evidence-based diagnostics and personalized treatment. Therefore, the EDRN grantees should develop research projects, which will contribute to the improved discovery, development and validation of cancer biomarkers. In addition, PIs are expected to contribute to

the development of specialized research resources, improved research model systems, and collaborative research projects with other institutions.

Emerging technologies such as genomics, epigenomics, proteomics and metabolomics, which can identify genetic, biochemical and antigenic changes in the early stages of cancer, offer the promise of developing biomarkers for detection of pre-neoplastic development or of early malignant transformation. Therefore, 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 cancer mortality.

The research supported through EDRN must be translational in nature. In this context, translational research is defined as the movement of discoveries from laboratories into patient or population research settings, or the movement of observations from patient settings back to the laboratory. The intent is to continue to foster research investigations, technological innovation, and collaboration in order to accelerate the development of biomarkers and tools that have the potential of rapidly moving to Phase 2 and Phase 3. Specifically, the objectives of the Network include:

- the development and testing of promising biomarkers or technologies at institutions with the necessary scientific and clinical expertise, to obtain preliminary information to guide further testing;
- the timely and early phase evaluation of promising, analytically validated biomarkers or technologies. These evaluations would include measures of diagnostic or 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;
- the timely development of biomarker expression patterns, sometimes of multiple markers simultaneously, which will serve as background information for subsequent large definitive validation studies in the field of cancer detection and screening;
- collaboration among academic and industrial leaders in molecular biology, molecular genetics, 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;
- conducting early phases of clinical/epidemiological studies (e.g. cross-sectional, retrospective; Phase 1-3, as described above), to evaluate the predictive value of biomarkers; and
- 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 (e.g., Specialized Programs of Research Excellence [SPOREs] (http://spores.nci.nih.gov/), Cancer Genetics Network [CGN] (http://epi.grants.cancer.gov/CGN/), Breast and Colon Cancer Family Registries

(http://epi.grants.cancer.gov/CCFR/index.html; http://epi.grants.cancer.gov/BCFR/index.html), Cooperative Human Tissue Network (http://www-chtn.ims.nci.nih.gov/), Cancer Genome Anatomy Project (http://cgap.nci.nih.gov/), with ongoing NCI clinical research programs/trials (e.g., Clinical Community Oncology Program [CCOP] (http://www3.cancer.gov/prevention/ccop/), Prostate, Lung, Colorectal, and Ovarian Cancer Screening 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 NCI anticipates that augmenting the EDRN expertise with a broad base of clinical and public health perspectives will enable the Network to apply existing methods and newly discovered technologies toward clinical application.

II.A.2. Specific Research Objectives of EDRN Scientific Components

Each EDRN scientific component is funded through a separate RFA. Hence, the specific research objectives for each of these components are separately discussed in brief below and in further detail in the corresponding RFAs.

II.A.2.a Biomarker Developmental Laboratories (BDLs): characterize new or refine existing biomarkers and assays. BDLs are responsible for Phase 1 and Phase 2 biomarker development within EDRN by conducting laboratory and clinical validation of biomarkers, in addition to providing technological development and assay refinement in this area. The purpose of the RFA is to solicit new and competing renewal applications for Biomarker Developmental Laboratories and to ensure the support of biomarker development studies on most common cancers (e.g., cancers of the breast, colon, lung, and prostate), as well as on those of lower prevalence (e.g., ovary, pancreas, renal, bladder and head and neck cancers, melanomas, lymphomas, sarcomas, etc).

The further development and validation of biomarkers, initially identified by applicants themselves or by other investigators, in accordance with EDRN-defined Phases 1 and 2, discussed earlier in this document (J. Natl. Cancer Inst., 2001; 93:1054-1061), is a primary responsibility of BDLs. Major components of this objective also include the standardization of assays and the development of analytic quality control methods. Other research objectives of the BDLs are:

- To develop molecular signatures of proteins, genes, metabolites and other relevant biochemical analytes that correlate with the presence of a pre-cancerous or cancerous lesion or a preclinical condition. Assays are to be developed that are suited for body fluids and/or for tissue specimens acquired through minimally invasive technologies.

- To develop highly specific and sensitive assays to detect tumor cells in body fluids for early detection, diagnosis or prognosis.

- To develop highly specific and sensitive assays to identify molecular risk factors, in specimens (tissue or body fluids) acquired through minimally invasive technologies or obtained from accessible surrogate anatomic sites for the less accessible cancer sites.

Prioritization of Biomarker Discovery:

EDRN has developed a robust schema to prioritize biomarker discovery and validation. The markers are ranked based on scientific and analytical data, supporting literature, independent verifications of assays and their portability. In addition, when the PIs submit their competitive renewal or new application, the Study Section will review the scientific rationale and criteria of their prioritization.

EDRN is accelerating a "go" or a 'no go" decision in biomarker development and validation efforts by establishing a number of criteria: Metrics for a biomarker development and validation study include:

- Was the biomarker assay reproduced in an independent laboratory? If not, then "no go".

- Was the biomarker's performance reproduced when evaluated using an independent set of samples? If not, then "no go".

- Does the biomarker outperform currently used marker(s), or add significant value to it? If not, then it is a "no go."

- Does the biomarker have a clear potential clinical use? If not, then it is a "no go."

More details regarding the specific objectives of BDLs can be found in the BDL-RFA at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-XX-XXX.html (incorporate link to RFA).

II.A.2.b Biomarker Reference Laboratories (BRLs): 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.

- The primary responsibility of a BRL is to participate in and perform Network collaborative studies approved by the EDRN SC.

- The secondary responsibility of a BRL is to develop an individual developmental study that is directly relevant to the goals of EDRN.

- The funded BRLs will work in collaboration with EDRN investigators under the direction of the EDRN SC.

More details regarding the specific objectives of BRLs can be found in the BRL-RFA at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-XX-XXX.html (incorporate link to RFA).

II.A.2.c Clinical Validation Centers (CVCs): [replacing the Clinical Epidemiology and Validation Centers (CEVCs); see previous RFA CEVC at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-005.html], conduct or participate in early phase (Phase 2 and 3) clinical epidemiology and validation studies for the application of biomarkers. The primary responsibilities of a CVC are:

- to develop a specific scientific agenda to conduct clinical research on the validation of biomarkers in early cancer detection, risk assessment, diagnosis and prognosis (i.e., Phase 2/Phase 3 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 procedure as a "gold standard";

- to partner with EDRN BDLs and BRLs in biomarker discovery and pre-validation by providing high quality specimens. Partnership to be set up after the U01 are awarded between the individual CVCs, BDLs and/or BRLs, and NCI, as well as to be agreed upon the types and quantities of specimens to be provided;

- to serve as a Resource Center for specimens for use in collaborative biomarker validation research within or outside the Network, by participating in collaborative biomarker validation studies under the coordination of the SC, and by providing high quality specimens for EDRN standard reference sets.

More details regarding the specific objectives of CVCs can be found in the CVC-RFA at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-XX-XXX.html (incorporate link to RFA).

II.A.2.d Data Management and Coordinating Center (DMCC): provides overall statistical, logistic and informatics support and develops the theoretical and statistical approaches for pattern analysis of multiple markers. Through its collaboration with the NCI, the Jet Propulsion Laboratory (JPL), and EDRN investigators, the DMCC will continue the development of common informatics and analytical tools for the interpretation of data, in addition to instruments for assessing uniformity, consistency, accuracy, reproducibility and privacy of the data. Further, the DMCC coordinates the activities of the Network and the Steering Committee meetings.

The DMCC is responsible for the following five major Network activities:

- Network Coordination
- Data Management and Protocol Development
- Statistical Services
- Theoretical and Applied Research
- Informatics Infrastructure and Services

More details regarding the specific objectives and responsibilities of the DMCC can be found in the DMCC-RFA at: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-XX-XXX.html (incorporate link to RFA).

II.A.2.e Other Resources

- Development of standard reference specimens and reagents, primarily plasma, serum, and urine, for the detection and evaluation of various organ-specific cancers: A common problem encountered in assessing biomarkers worthy of clinical validation is that biomarker developmental work typically has been performed on samples from cases and controls collected in a variety of ways. This makes comparisons of biomarkers from different laboratories difficult and subject to significant bias. With the creation of shared reference sets of specimens from well-characterized cancer cases and matched controls, EDRN will overcome many of the logistic and design issues in preliminary and advanced biomarker validation. Already these reference sets enable direct performance comparisons of biomarker panels from different laboratories. This resource is accessible to any investigator within or outside of EDRN based on a common and transparent set of criteria used to evaluate applications. Interested scientists can obtain further details on existing reference sets and request information on how to apply for specimens at the EDRN web site (http://edrn.nci.nih.gov/resources/sample-reference-sets).

- EDRN-supported statistical tools and informatics infrastructure are making the sharing of samples, developing collaborations, and exchanging information on biomarkers with the extramural community at large, feasible and productive. The EDRN Informatics efforts were sited as a model in a recent report by the Institute of Medicine entitled, Developing Biomarker-based Tools for Cancer Screening, Diagnosis, and Therapy: The State of the Science, Evaluation, Implementation, and Economics. One of the signature accomplishments of the informatics team is the development of common data elements (CDEs) for use among the EDRN CVCs. CDEs capture and share data among centers. State-of-the-art methods that previously did not exist have been established for data elements, e.g., acquisition and storage of biologicals, study design, outcome assessment, and biomarker validation.

- The CVC specimens are invaluable resources for biomarker validation studies. More than 100,000 specimens of good quality, clinically annotated sera, plasma, and urine have been collected as part of the validation studies. These samples are being made available to extramural scientists upon request. The request for the samples can be made through the EDRN established application process (Associate Membership: http://edrn.nci.nih.gov/colops/assoc; PRIDE program: http://grants.nih.gov/grants/guide/notice-files/NOT-CA-07-003.html; or Request for Reference Sets: http://edrn.nci.nih.gov/resources/sample-reference-sets). More than 140 investigators, mostly non-EDRN, have benefited from these resources. Availability of these samples was made through announcements in the NIH Guide, Cancer Epidemiology, Biomarkers and Prevention, and the Journal of the National Cancer Institute.

SECTION III: ELIGIBILITY AND ADMINISTRATIVE RESPONSIBILITIES, REQUIREMENTS AND IP GUIDELINES

III.A. Eligible Institutions

Any investigators may submit an application(s) if their institution has any of the following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic or, where applicable, foreign institutions/organizations
- Faith-based or community-based organizations

Eligible institutions may include foreign components as full research projects, or shared resources, or as part of a research project. Consortia agreements with foreign institutions must include provisions that ensure adequate representation of women, minorities, and children in all research components that involve clinical trials or any other type of human intervention and must be in compliance with NIH policies.

III.B. Intellectual Property (IP) Rights

III.B.1. General Overview

The EDRN is premised on the belief that an established integrated, multi-disciplinary environment will expedite clinical applications of biomarker research. NCI anticipates that EDRN members will 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 EDRN investigators have had active collaborations with industry. Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. The NIH is interested in ensuring that the research resources developed through its grants also become readily available to the broader research community in a timely manner for further research, development, and application, with the expectation that this will lead to products and knowledge of benefit to the public health.

Since it is the policy of the NIH to make available to the public the results and accomplishments of the activities which it funds, applicants who respond to an EDRN RFA are required to submit an intellectual property management plan (IPMP), which addresses the strategy to be followed

for both solely or jointly owned inventions (including patents and licensing issues) and as to how these resources will be made available to the broader scientific community, consistent with the EDRN initiative. This plan should be included in the program description of the RFA. Reviewers will comment, as appropriate, on the adequacy and feasibility of the sharing of research resources plan and the IPMP. Comments on the plans and any concerns will be presented in an administrative note in the Summary Statement. These comments will not affect the priority score of the proposal. NCI program staff will consider the adequacy of the plans in determining whether to recommend an application for award. The approved plans will become a condition of the grant award and Progress Reports must contain information on activities for the sharing of research resources and intellectual property.

The EDRN grantee shall provide written assurance that neither he/she, nor his/her home institution will compromise the intellectual property rights resulting from inventions of EDRN investigators and their collaborators by entering into agreements with pharmaceutical or biotechnology companies that would hinder the ability of EDRN investigators to have unrestricted access to institutional resources that have been developed through EDRN supported research or to participate fully in collaborations with other researchers. The grantee shall also include a written statement that any interactions with commercial entities during sponsored research agreements will be compliant with requirements of the *Bayh-Dole Act* (37 CFR 401; https://sedison.info.nih.gov/iEdison/37CFR401.jsp), 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://www.ott.nih.gov/policy/rt_guide_final.html) and the *NIH Tools Research Policy* (http://ott.od.nih.gov?NewPages/64FR72090.pdf). These documents define terms, parties, and responsibilities, prescribe the order of disposition of rights and provide 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 at http://www.iedison.gov. Applicants should also see 35 USC § 210 (c); Executive Order 12591, 52 FR 13414 (April 10, 1987) and Memorandum on Government Patent Policy (February 18, 1983).

If 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 approval 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.

If applicants plan to collaborate with third parties, the sharing plan must address how such collaborations will not restrict their ability to share biomedical research materials produced with NIH funding, to the scientific research community. Therefore, any relevant third parties (including external co-investigators, collaborators or consultants) should also provide written assurance that they are willing to follow these policies and detail the agreement between them and the grantee or his institution. An EDRN grantee (or the grantee's institution) should be familiar with the following document prior to entering into sponsored research agreements with

commercial entities: "*Developing Sponsored Research Agreements: Consideration for Recipients of NIH Research Grants and Contracts*" (Federal Register, Vol. 59, No. 215; Tuesday, November 8, 1994; pp 5564-5567).

An applicant should become familiar with his institution's policies regarding technology transfer-related matters and or sponsored research in order to develop and submit a reasonable IPMP to the RFA. NCI provides resources (http://ttb.nci.nih.gov/ipplans.html) that give examples of approaches considered by other institutions in the development of IPMPs. In addition, NCI Program Directors are available to answer questions of the grantees regarding development of IPMPs.

III.B.2. IP Issues Related to Biomarker Discovery and Validation

During the biomarker discovery and validation phases of collaborative research, Intellectual Property (IP) issues can become complex given that diagnostic assay development on the basis of novel biomarkers can involve multiple institutions and industry collaborators. Further complicating matters, is the situation where these diagnostic assays are developed, to some extent, with proprietary biomarkers, reagents, and/or technologies supplied by collaborators.

For the situation where EDRN evaluates an individual biomarker from an individual source, then IP is maintained by the source as EDRN will not claim IP. If a pre-existing single individual biomarker with IP rights established for one use is later used for a different indication, for example the prostate specific antigen (PSA) used to screen for breast cancer, then IP rights could be sought for this marker on its completely new application.

A more complicated situation arises when various investigators contribute multiple biomarkers to a panel for EDRN evaluation. In this case, EDRN has stated that "*No one partner or contributor will claim IP on the panel of markers they are contributing to. Each partner may claim and keep IP on their individual biomarker but the panel remains IP-free*". In order to achieve this result and ensure fair and equitable outcomes for all parties involved, EDRN would publish positive or negative results on the biomarker panel as quickly as possible through press releases and scientific publications. EDRN has considered the idea of "shared IP" with respect to biomarker panels where each party contributing a biomarker(s) to a panel would each share in the IP of the combined panel. This arrangement could be more problematic from the legal perspective given that each individual, company or institute would need to agree to the shared IP.

III.B.3. IP Options and Licensing

Given these circumstances, a grantee and his institution may want to use the IP option to license inventions within narrow fields of use in order to allow additional individual collaborations with other companies to develop these inventions. Alternatively, a grantee's institution could enter into a multi-party agreement that incentivizes the companies for moving the products forward. Possible approaches include:

- Granting an IP Option to each individual company for an exclusive commercialization license relating solely to such company's products, or
- An IP Option of a co-exclusive license of intellectual property relating to a combination of products. If 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 non-exclusively at reasonable royalty rates. Further information on the use of patent pools for biotechnology patents can be found at the following websites:
  http://www.uspto.gov/web/offices/pac/dapp/opla/patpoolcover.html
  http://www.uspto.gov/web/offices/pac/dapp/opla/patpool.pdf

The Cancer Therapy Evaluation Program's website (http://ctep.cancer.gov/industry/ipo.html) provides a model of an intellectual property option ("IP Option") given voluntarily by grantees of this NCI program. In this model, extramural grantees agree to give 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. Cost related to the patenting and/or licensing of intellectual property may be allowable as F&A costs (see http://grants.nih.gov/grants/guide/notice-files/NOT_OD_04-045.html).

The US Department of Justice and Federal Trade Commission (April, 1995) has published anti-trust guidelines for the licensing of Intellectual Property and can be found at the following website: http://www.usdoj.gov/atr/public/guidelines/ipguide.pdf. The Federal Trade Commission and the U.S. Department of Justice (April, 2000) has published anti-trust guidelines for collaborations among competitors and can be found at:
http://www.ftc.gov/os/2000/04/ftcdojguidelines.pdf .

If an investigator decides to license methods or biomarker assays supported fully or in part by the NCI EDRN, a prior consultation with the NCI is required. NCI wants to ensure that the commercialization license should be broad enough to cover the research plan and relate to the proprietary product (device, drug, test, etc) of the collaborator. A research use license for resulting inventions in the final negotiated commercialization license should include the right to share such inventions with others for non-commercial 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.

III.B.4. Protection of Confidentiality

The EDRN SC recognizes the necessity of protecting certain proprietary information relating to inventions and potential and/or present patent rights, research, development, business plans and other technology or confidential information. Therefore, the Committee has agreed that all discussions concerning unpublished data, research results, theories, drawings, figures or visual

depictions of research data or results regardless of format that occur in the closed Committee sessions will be treated as proprietary and confidential.

The EDRN maintains the confidentiality of proprietary information by asking each individual to sign a two year Confidentiality and Non-Disclosure Agreement (CDA), which legally binds him or her from discussing such information with non-EDRN associated individuals, unless the consent of the owning party has been secured. This enables investigators to share the results of their undisclosed or unpublished work in an atmosphere of openness and collegiality, which is essential in fostering the collaborative effort among investigators that the EDRN seeks to maintain. Grantees may view the EDRN CDA in Appendix 2 of this guidelines document.

III.C. Partnership with Public-Private Companies

Creating public-private partnerships is at the core of EDRN's achievements. Four federal agencies─The National Institute of Standards and Technology (NIST) (BDL), the Centers for Disease Control and Prevention (CDC) (CVC), the Pacific Northwest National Laboratory (PNNL) (BDL), and JPL (informatics support) ─ participate with EDRN through interagency agreements. Other intergovernmental collaborative partnerships are those between EDRN and FDA, and those among EDRN and NIH Institutes, including the National Heart, Lung, and Blood Institute (NHLBI) on the Women's Health Initiative for discovery and validation of biomarkers on sera/plasma from this 15-year clinical trial; the Collaboration of Consortium of Functional Glycomics (funded by NIH's National Institute of General Medical Sciences [NIGMS]); and four carbohydrate research centers (funded by NIH's National Center for Research Resources [NCRR]). Two non-profit foundations, Canary Foundation, CA and Lustgarten Foundation, NY, are supporting discovery and validation studies on prostate and lung (canary) and pancreatic cancers (Lustgarten) in collaboration with EDRN.

EDRN has fostered collaborations with industry as the needs of the Network have evolved. During its inception, EDRN worked with NCI's Technology Transfer Unit to develop innovative methods for sharing confidential information with industry, and EDRN's Technology Resources Sharing Committee developed guidelines for working with industry. EDRN has also conducted a workshop on Public-Private Partnerships. Several collaborations with industrial partners and foundations have been established and are yielding benefits (see the EDRN 4th Report http://edrn.nci.nih.gov/docs).

III.C.1. Roles and Responsibilities of the EDRN

The EDRN recognizes that it can play a major role in advancing the collaboration and partnering of industry with academia and perhaps even industry with industry. EDRN has considerable experience in facilitating and forming collaborative efforts. Its infrastructure is set up and designed to encourage and reward its own members for their collaborative work through their cooperative agreement funding policies. However, EDRN may be able to further collaborative research by: 1) allowing companies to realize the full value of their new products or platforms and their research investments (i.e. by validating their products in large scale assays with "gold

standard" specimens); 2) connecting the research community to new products, reagents, technologies and services that industry can provide; and 3) most importantly, EDRN can act as an honest broker. The role of the honest broker is important in keeping with the idea of encouraging all parties to set appropriate terms and conditions at the very outset of any partnering agreement. Being the conduit of transparency and ensuring that all parties understand their role and responsibilities as well as their rights may be one of the most important contributions that EDRN can make in advancing and streamlining collaborative efforts. Since cooperative agreements and contracts are the mainstay of its funding opportunities, EDRN has the experience necessary to outline, streamline and clarify the documentation required to undertake collaborative efforts.

III.C.2. Responsibilities of Collaborating Parties

When setting up collaborations (one-to-one, one-to-many, many-to-many) specific documentation is to be outlined and agreed upon by all parties that will include the areas described below. Clarity and understanding of these issues will lead to greater supportive trust among the stakeholders. A template agreement could be formulated by EDRN in conjunction with industry to streamline these arrangements.

(1) ***Resources and contributions to the project***: Clear documentation describing the contribution of specimens, reagents, labor, supplies, and resources to be outlined and agreed upon at the outset of the partnership. These can be set up similarly to the Statement of Work (SOW) of a contract. In turn, the recipients (investigators, companies, etc.) of the resources who are utilizing the "gold standard" repository specimens will be obligated to share the resulting data with EDRN.
(2) ***Success/non-success of the project*:** clear definitions, milestones, goals and metrics of the project's successes are to be outlined and made available for all parties. These are to be negotiated and agreed upon by all partners prior to any collaborative research or transfer of materials. Clear definitions of action(s) to be taken when the goals and milestones are not met in a timely fashion are to be written and agreed upon at the outset of the collaborative project.
(3) ***Data sharing and statistical support***: There must be agreement and written documentation on how the data will be shared among the collaborators; on the "language of the data" and the analysis of combined datasets; which partners will be responsible for the statistical support; which partners will have access to the data and when and how the data will be used for regulatory filings or further development.

SECTION IV: SPECIAL REQUIREMENTS

Prospective applicants should be aware of the following EDRN special requirements that must be fulfilled by grantees:

IV.A. EDRN WORKSHOP AND MEETINGS

According to the requirements of the Cooperative Agreement, there are two Steering Committee business meetings and one scientific workshop each year that EDRN members should attend; additional meetings may be called as needed. The time and site for these meetings are determined by Steering Committee members. The Principal Investigator from each Cooperative Agreement is required to attend at least one Steering Committee meeting each year. There must be at least one representative from each Cooperative Agreement at every Steering Committee meeting. NCI reserves the right to terminate a grant for failure to attend or have representation at Steering Committee meetings.

The PI will serve as a voting member of the Steering Committee and will attend the Planning meeting and two Steering Committee meetings and an EDRN-Sponsored workshop. The attendance of the PI at this meeting is considered an essential part of the grant. 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 and one workshop per year.

SECTION V: COLLABORATIVE RESPONSIBILITIES

V.A. Steering Committee (SC): will have major scientific management, oversight, and responsibility for developing collaborative research designs, protocols and manuals, for facilitating the conduct and monitoring of studies, and for reporting study results. The SC will be composed of the PIs from each U01/U24-funded BDL/BRL and CVC in the Network, the PI of the Data Management and Coordinating Center, and the NCI Program Coordinator. Each member will have one vote. The Chair (non-NIH person) will be selected by the SC. The institution of the Chair of the SC will serve as the Headquarters. Subcommittees, including the existing ones, will be established and maintained by the SC as it sees appropriate. The NCI Program Coordinator will serve on subcommittees as he or she determines appropriate. After all the Network components have been funded, the SC will convene. Responsibilities of the SC include, but are not limited to, the following activities:

- Updating and refining established Network policies and procedures
- Updating and refining established policies and procedures for collaborative projects, protocols, and Network-defined projects
- 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 is not permitted)

- Updating and refining established standards or "decision criteria" for validating biomarkers/reagents for further clinical studies, such as testing strategies for early detection or for risk assessment
- Updating and refining established policies and procedures for accepting, reviewing and recommending proposals from investigators outside of the Network for supplemental funding and for expanding the Network participation
- The SC will establish a Data and Safety Monitoring Committee (DSMC) for clinical trials as appropriate to ensure protection of human subjects
- The SC will review patient accrual, follow-up, protocol compliance, results of audits and regulatory requirements at the participating Centers and formally report the results of its reviews to the NCI
- The SC will promote and foster the inclusion of women and ethnic minorities in clinical studies and assure the completeness of informed consent
- The SC will track the Network research progress and assure that the results of laboratory research and clinical studies are published in peer-reviewed journals in a timely manner and in accordance with the publication policies of the Network. At any time during a Network project, the SC may ask a BDL or CVC to serve as a Biomarker Reference Laboratory on an as needed basis. The SC may also examine the validation data for biomarkers/reagents developed by the Network, and decide when a biomarker is sufficiently validated or recommend when to stop non-productive experiments relating to biomarker validation
- The SC will discuss collaborative projects to be pursued jointly with the funds set aside from the Headquarters and from individual U01 or U24 awardees
- Collaborative studies and protocols will be approved by the SC. Data will be submitted centrally to the DMCC. The SC will define the rules regarding access to data and publications consistent with NCI policies
- The SC will plan one of several workshops during the network project period to inform the scientific community and relevant advocacy groups of the progress made toward development and clinical application of biomarkers developed through the Network. The NCI Program Coordinator, the NCT, and other NCI staff will provide the SC with advice on participants for the workshops and symposia. The DMCC will manage the logistics for these meetings
- The SC or its Executive Committee (EC) in consultation with the NCI will determine the PI of the Network-wide validation study

V.B. Network Consulting Team (NCT): was established by the NCI. The NCT advises the SC through the NCI on relevant scientific issues, including study design, prioritization of biomarker development, development of collaborative study protocols, including decision criteria for clinical applications, e.g. early detection, risk assessment, prognosis, etc. Membership on the Committee and duration of service is decided by the NCI in consultation with the SC. The membership includes members or institutions not participating in the Network. The NCT includes basic scientists, clinicians, prevention scientists, epidemiologists, ethicists, statisticians, and members from relevant advocacy groups. Scientific experts are drawn from

various disciplines relevant to multi-center detection research and experts in data management, biostatistics, and clinical study design. The Chair of the NCT is elected by its members and also serves as a member of the SC. The NCI is represented by relevant program staff. The NCT evaluates the progress and success of the Network against the criteria developed by the SC. The NCT assists the NCI on site visits to the participating institutions, as needed. The NCT collaborates with the SC to suggest participants for and to assist in the implementation of workshops and symposia and to provide liaison between the cancer research community and the Network.

V.C. Data Safety and Monitoring Committee (DSMC): will be appointed by and report to the SC in consultation with the NCI Program Coordinator who will also be a member of this committee. The DSMC will be composed of external, non-participating scientists appointed by the SC to monitor patient safety, conduct data audits, and document progress to the NCI Program Coordinator and the NCT.

V.D. Arbitration: A panel will be formed to review any scientific or programmatic disagreement (within the scope of the U01/U24 award) between awardees and the NCI. The panel will be composed of three members: one selected by the SC (with the NCI Program Coordinator not voting), or by an individual U01 or U24 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.

SECTION VI: INQUIRIES

We encourage inquiries concerning the Guidelines 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.

Scientific/programmatic questions for an RFA should be sent to:

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

Questions about intellectual property, technology licensing, data sharing and research tool issues for an RFA should be sent 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

REFERENCES

1. The Early Detection Research Network: Investing in Translational Research on Biomarkers of Early Cancer and Cancer Risk; NCI Publication No. 07-6135, January 2008.
2. Srivastava, S.. Early Detection Research Network. Disease Markers 1999; 15(4): 213-219
3. Pepe, M.S., Etzioni, R., Feng, Z., Potter, J., Thompson, M.L., Thornquist, M., Yasui, Y.. Phases of Biomarker Development for Early Detection of Cancer. J Natl Can Inst 2001; 93: 1054-1061.
4. Pepe MS, Feng, Z., Janes, H., et al.. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. J Natl Can Inst 2008; 100: 1432-1438.
5. Ransohoff DF.. How to improve reliability and efficiency of research about molecular markers: roles of phases, guidelines, and study design. J Clin Epidemiol 2007; 60: 1205–1219.
6. Pepe MS. The Statistical Evaluation of Medical Tests for Classification and Prediction. Oxford: Oxford University Press, 2003.
7. Draft of EDRN Public Private Partnership Guidelines provided by Dr. Lynn Sorbara.

APPENDIX 1

ORGAN SPECIFIC CANCERS

Breast Cancer

Strategic Goals

The ultimate goal of detection, diagnosis and prognosis research is to develop non-invasive methods for confidently detecting and characterizing pre-cancerous and cancerous breast lesions when the lesions are small and/or more easily treatable. Mammography remains the mainstay of screening. However, the technology is beset by low sensitivity and specificity, thereby yielding a high number of false-positive cases. There is critical need to develop biomarkers that can either augment mammography in the short-term or replace mammography in the long-term. Strategic goals are to:

- Improve the interpretation of conventional mammography or other computer-aided technologies.
- Detect characteristics of specific types of benign and malignant breast lesions and stratify benign disease into high- and low-risk for progression.
- Identify tumor-specific biomarkers and use as contrast agents to improve the performance of any imaging modality.

The Plan

- Assess epigenomic changes (i.e., DNA methylation) in benign breast lesions as potential predictive markers. Substantiate a general hypothesis that a panel(s) of these markers could be configured that would accurately predict the risk of future breast cancers. Accrue a sufficient number of tissue specimens to address this question, which will involve a multi-institutional effort.
- Develop Breast Cancer reference sets. Currently, reference sets are being developed that include serum from pre- and post-menopausal healthy women and women with breast cancer. Additional reference sets will contain serum, plasma, DNA, RNA, and buffy coat (the fraction of an anti-coagulated blood sample that contains most of the white blood cells and platelets) from normal healthy women, women with benign disease, DCIS (ductal carcinoma *in situ*), and invasive breast cancer.

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Ovarian Cancer

Strategic Goals

The absence of accurate screening biomarkers coupled with the typical late-stage diagnosis of ovarian cancer contributes to the significant lethality of the disease. Thus, early detection is important as there are no reliable biomarkers available for screening of ovarian cancer. Transvaginal Sonography (TVS) and the serum tumor marker CA-125 have been explored as a strategy for the early detection of ovarian cancer, but the sensitivity, specificity, and lead time (earliness of detection) are not optimal. For example, increased CA-125 levels are found in about three percent of post-menopausal women, resulting in false positives for this biomarker. Additional biomarkers need to be developed for ovarian cancer that are cost-effective, accurate, and which identify women at increased risk. The development of multiplexed assays of CA-125 coupled with other serum biomarkers as a first-tier screening modality for the general or high-risk population is a strategic goal that would not only improve the early detection of ovarian cancer but also help recognize women with a pelvic mass, who may need more specialized primary surgery. Strategic goals are to:

- Use biomarkers to identify and stratify ovarian masses as either benign or high risk for progression to ovarian cancer.
- Improve the interpretation of conventional TVS or other computer-aided technologies.
- Develop a strategy involving the use of risk stratification, accurate biomarkers, and secondary diagnostic imaging tests as a cost-effective model for ovarian cancer screening in a high risk or even general population.

The Plan

- Establish an ovarian cancer reference set that contains serum from pre- and post-menopausal healthy women and women with ovarian cancer.
- Test serum samples using a panel of biomarkers against currently used biomarkers, such as CA-125. Identify and compare the ability of the biomarker panel(s) to detect ovarian cancer.
- Develop a rapid ovarian cancer screening test to measure circulating proteins using an ELISA (Enzyme-Linked ImmunoSorbent Assay), or variation thereof, and test these in pre-diagnostic specimens obtained months prior to the clinical diagnosis of ovarian cancer.

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ORGAN SPECIFIC CANCERS

Cervical Cancer

Strategic Goals

Cervical cancer remains a significant public health problem. Worldwide, cervical cancer is a leading cause of cancer mortality in women. In the United States, cervical cancer screening and follow-up and treatment cost an estimated 2.3 billion dollars, annually. Newly approved HPV vaccines promise to provide primary prevention of cervical cancer, but as only ~70% of cancers are targeted, screening cannot be eliminated. In addition, the best-case scenario for the time-frame in which an impact on the incidence of cervical cancer will be seen is on the order of 20 years. If successful, vaccination will significantly reduce true disease, but have much less impact on transient abnormalities that contribute to the large number of women referred to colposcopy, who do not need treatment.

Developing countries without screening programs stand to benefit the most by the introduction of vaccination. Implementation is being delayed because of the cost of the vaccine and because vaccination without screening is unacceptable to most countries. We need to develop markers that will improve the efficiency of current screening based on high risk HPV detection and cytology so that health care costs can be shifted to other areas of need. The assays for these markers should be robust and easy to perform in low resource settings. Strategic goals are to:

- Improve the effectiveness of cervical cancer screening in the U.S.
- Improve on risk-stratification provided by HPV testing to allow screening intervals to be increased in order to reach unscreened populations by using a more culturally acceptable sampling method (self-sampling, urine, blood).

The Plan

- Use EDRN Cervical Cancer biorepository as the basis of a “screening sample” reference set (i.e., serum, plasma, PBMCs, cervical mucous, exfoliated cervical cell DNA/RNA extracts) to evaluate a panel of new markers targeting multiple sample and analyte formats (e.g., methylation in cervical cells, protein markers in cervical mucous, etc.).
- Develop biomarkers for cervical mucous using integrated approaches and multiple platforms (i.e., genomics, proteomics, etc.) using the samples assembled above.

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ORGAN SPECIFIC CANCERS

Barrett's Esophagus and Esophageal Adenocarcinoma

Strategic Goals

Barrett's esophagus is a premalignant condition associated with chronic gastroesophageal reflux disease (GERD). Patients with Barrett's esophagus are at increased risk of developing esophageal adenocarcinoma. Therefore, patients with Barrett's esophagus are subjected to endoscopic surveillance every two to three years. Although these patients undergo repeated endoscopies, most patients with Barrett's esophagus never progress to cancer. An important goal is to find biomarkers that can identify patients likely to progress to adenocarcinoma from a low-risk population. This would reduce the number of unnecessary endoscopies and improve surveillance of high-risk patients.

More than 90% of esophageal adenocarcinoma patients have never had a diagnosis of Barrett's esophagus. However, endoscopy is unsuitable for population-based screening or detection of asymptomatic Barrett's esophagus or esophageal adenocarcinoma. Therefore, a non-invasive diagnostic test for Barrett's esophagus and esophageal adenocarcinoma is an unfulfilled medical need. Strategic goals are to:

- Develop biomarkers to identify high-risk patients that will progress to esophageal cancer.
- Develop a non-invasive test to screen for Barrett's esophagus and/or esophageal adenocarcinoma.

The Plan

- Develop a panel of biomarkers to screen for Barrett's esophagus and/or esophageal adenocarcinoma in an asymptomatic population.
- Develop a panel of biomarkers for progression from Barrett's esophagus to esophageal adenocarcinoma using genomics, epigenomics, proteomics, and metabolomics. For example, identify epigenomic changes (i.e., methylation patterns, microRNA, etc.) of genes associated with Barrett's esophagus.
- Develop functional tests based on reported genome-wide chromosomal instability [i.e., chromosome copy gain or loss and LOH (Loss of Heterozygosity)] and GWAS (Genome Wide Association Studies) to predict progression from Barrett's esophagus to esophageal adenocarcinoma.

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Colon Cancer

Strategic Goals

Colon cancer is both the third most frequently diagnosed cancer and the third most common cause of cancer deaths. Successful prevention of colon cancer depends on early detection. Current screening technologies include fecal occult blood tests, sigmoidoscopy, colonoscopy, and barium enemas. Although these screening technologies have the potential to reduce cancer deaths, the technologies are invasive, expensive and cause patient discomfort. The goal is to identify less invasive means for early detection through biomarkers to identify those individuals at high risk and in need of further testing from those at low risk. Genetic, epigenetic, and proteomic methods are being used to identify potential colon cancer biomarkers. Strategic goals are to:

- Identify biomarkers to help discriminate patients at greater risk and in need of further testing (i.e., colonoscopy) from low-risk patients.
- Characterize benign and malignant lesions and stratify benign disease into high- and low-risk for progression.
- Develop biomarkers in conjunction with imaging to improve the performance of any imaging modality.

The Plan

- Develop biomarkers or panel(s) of biomarkers that can accurately detect colon cancer or polyps by using sera, stool, or urine. Conduct rigorous clinical evaluation of promising biomarkers and modalities, especially in adenoma detection before implementation at the population level.
- Develop colon cancer reference sets comprised of serum, plasma, urine, DNA from WBC (white blood cells), and paraffin embedded tissues from normal colon, adenomas, inflammatory bowel disease, and colorectal cancer.
- Discover serum proteomic markers that identify patients at high-risk for adenocarcinoma and in need of colonoscopy.

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Liver Cancer

Strategic Goals

Hepatocellular carcinoma has a high mortality rate due to late-stage diagnosis when therapy is not as successful. The 5-year survival rate for liver cancer is less than five percent. Hepatocellular carcinoma incidence is rising in the United States. Infection with HBV (Hepatitis B virus) or HCV (Hepatitis C virus) is responsible for at least 80% of all liver cancers. Although there is a vaccine for HBV, currently there is no effective preventative therapy for HCV infections. Cirrhosis of the liver (with or without HBV or HCV infection) is a risk factor for the development of hepatocellular carcinoma. Surveillance of patients with cirrhosis is an important goal for early detection of hepatocellular carcinoma. The AFP (alpha-fetoprotein) level in the blood is the current standard used to detect liver cancer. This biomarker has a high false-positive rate and can miss many early stage cancers. Better biomarkers are needed for hepatocellular carcinoma for early detection and diagnosis. Strategic goals are to:

- Develop biomarkers that identify populations at risk for the development of hepatocellular carcinoma.
- Develop biomarkers to detect cirrhotic liver and stratify patients at high risk from low risk for progression to cancer.
- Develop a diagnostic test with better sensitivity and specificity than the current standard of care (alpha-fetoprotein test).

The Plan

- Identify novel glycoproteins and glycans as biomarkers of liver cancer. Research indicates that glycosylation of proteins changes with the disease state. Changes in the glycosylation patterns of serum proteins can provide a window into cellular changes associated with progression to liver cancer.
- Mine the tumor microenvironment for biomarkers. (Note: Recent research has shown that gene expression profiling of the tumor microenvironment can determine the prognosis of hepatocellular carcinoma). The tumor microenvironment can be another potential source for biomarkers associated with progression. These can be developed for early detection.
- Develop liver cancer reference sets comprised of serum, plasma and tissue blocks from normal liver, cirrhotic liver (with or without hepatocellular carcinoma), and hepatocellular carcinoma.

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Pancreatic Cancer

Strategic Goals

Pancreatic cancer has a very high mortality rate, with the mean survival time of less than six months after diagnosis. This poor survival rate is largely due to the late stage diagnosis of this cancer. Commonly used imaging methods include endoscopic ultrasound, abdominal CT scan or MRI. These methods are increasingly detecting mucinous cystic lesions in the pancreas. The ability of these lesions to progress and whether these lesions represent a progression pathway for the vast majority of pancreatic cancers is unknown. Clinically, the study of cystic lesions that have the potential to progress to pancreatic cancer is important and has potential in early detection in identifying asymptomatic patients. The current standard for diagnosis of pancreatic cancer is the serum marker, CA 19-9. In an asymptomatic population, this biomarker has a positive predictive value below one percent. Better biomarkers need to be developed for the early detection and diagnosis of pancreatic cancer, thereby reducing its high mortality. Recent studies have also shown that Type II diabetes occurred less than four years prior to the onset of pancreatic cancer. Understanding this link between Type II diabetes and pancreatic cancer has the potential to identify individuals associated with a greater risk of pancreatic cancer development. Strategic goals are to:

- Identify populations at risk for the development of pancreatic cancer.
- Evaluate the role of Type II diabetes in the early detection of pancreatic cancer.
- Assess biomarkers in improving imaging techniques to better identify cysts with potential to progress toward pancreatic cancer.

The Plan

- Identify gene profiles associated with pancreatic cancer. These marker panels should include the current standard, CA 19-9 in combination with other markers.
- Use bioinformatics approaches to mine “omics” databases to identify potential pathways and markers for early detection and diagnosis.
- Develop pancreatic cancer reference sets that are enriched with sera and plasma from Stage 1 and 2A tumors. This would be a unique resource as most patients are diagnosed at later stages.

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Lung Cancer

Strategic Goals

Lung cancer continues to be the most lethal cancer in the United States with over 160,000 deaths per year. The incidence of lung cancer is driven predominantly by smoking, with a prevalence of lung cancer in the smoker and former-smoker population in the range of 10-15%. About 80% of patients with lung cancer have a significant history of smoking. CT imaging or chest X-rays are currently used on patients suspected of having lung cancer or, in some cases, are being used to screen high-risk cohorts. Although the sensitivity of CT imaging is very high, the false-positive rate is also high.

In the EDRN, a variety of lung cancer markers have been pursued that include panels of gene methylation markers, mitochondrial DNA mutations, mitochondrial number, and chromosomal abnormalities. Within a high-risk population of smokers, these markers were not able to distinguish nondiseased smokers from lung cancer patients, even though the markers clearly differentiate smokers from nonsmokers. These markers persist later in life as evidenced in cohorts of former smokers, who stopped smoking five years before. These findings highlight how smoking induces profound molecular alterations in the epithelial linings of the lungs, setting them on a path towards neoplasia. Strategic goals are to:

- Develop a test for early detection of lung cancer that achieves a performance above the overriding risk factor than smoking presents.
- Assess biomarkers for use in conjunction with CT imaging in order to determine which patients may need further clinical work-up for diagnosis of lung cancer.

The Plan

- Conduct a study to test an autoantibody panel in conjunction with CT imaging. A panel of autoantibodies, which has been discovered and developed, has shown considerable promise. These autoantibodies proved their utility in a blinded validation study of prediagnostic lung cancer specimens from CARET (Carotene and Retinol Efficacy Trial). Additional autoantibody panels from other investigators within and outside of the EDRN will be included in this study to maximize the potential outcome and determine whether different markers are complementary and thus improve the sensitivity/specificity of the panel. The clinical objective is to determine whether an autoantibody marker panel can be developed to augment CT diagnosis of lung cancer in asymptomatic individuals by:

- Examining prediagnostic sera taken within one year prior to the diagnosis of lung cancer. Requests for such samples are being made to the PLCO (Prostate, Lung, Colorectal, and Ovarian Screening Trial) and WHI (Women's Health Initiative studies). Appropriately matched controls will be included in this retrospective blinded study to provide a more in-depth analysis of the biomarkers' performance in prediagnostic samples at least six months before the cancer was diagnosed. The most productive biomarkers from the first segment will be used to construct a panel for use in the second part of the study.
- Testing a longitudinal collection of sera from a number of CT-detected cases from the CEVC (Clinical Epidemiology and Validation Centers) at New York University and possibly other sites in conjunction with matched controls that were also subjected to CT imaging. This validation will reveal whether the biomarker panel augments CT imaging in predicting which patients are likely to have early stage lung cancer, thus requiring further follow-up. It is anticipated that once the NLST (National Lung Screening Trial) is completed, this study will be expanded to make use of the wealth of samples collected under a CT-screening protocol from that long-term study.

➢ Examine ground-glass opacities (GGOs) in lungs of high-risk smokers. In over half of high-risk (>20 pack-years) smokers, non-calcified nodules 4-8 mm in size are found and approximately another 10% of subjects have ground-glass opacities (GGOs). These nodules and GGOs require follow-up to determine whether these are cancerous lesions. Identify biomarkers in blood or sputum that are applicable to the diagnosis of these suspicious abnormalities that also complements CT-screening.

➢ Develop biomarkers for lung cancer in nonsmokers or distant former smokers. This study may offer a window into early diagnosis in this smaller but growing subset of lung cancers.

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Prostate Cancer

Strategic Goals

Prostate-specific antigen (PSA) test remains the mainstay for the detection of prostate cancer. Although clinically localized prostate cancer has become highly curable, the overall mortality toll is still high due to recurrence and progression to hormone-refractory and metastatic disease, which remains incurable. PSA tests result in the detection of a large number of false positive cases, leading to "over-diagnosis" and repeated biopsies.

There is an urgent need for predictive markers for early detection of prostate cancer, especially the aggressive forms that could, therefore, be distinguished from the less aggressive non-lethal forms of prostate cancer. The recently discovered fusion transcripts (TMPRSS2-ETS), which are frequently expressed in prostate cancers, are promising markers that should be further tested and validated for early detection and as prognostic markers for the development of aggressive cancer. Strategic goals are to:

- Use integrated "*omics*" approaches (i.e., gen*omics*, epigen*omics*, metabol*omics*, and prote*omics*) to develop biomarkers.
- Develop fusion transcript-based biomarkers or other biomarkers that differentiate between non-aggressive and aggressive forms of prostate cancer.
- Identify biomarkers that estimate the risk of progression to aggressive forms of prostate cancer.

The Plan

- Establish collections of body fluids (plasma, serum, urine, EPS) as "reference sets" for rapid evaluation of biomarkers before entering the validation trials and for discovery purposes using well annotated and well represented collections of specimens to minimize the presence of confounders and bias. Current "reference sets" contain blood (serum and plasma) and urine from biopsy-proven cases and controls.
    - General population screening with biomarker(s) adding or replacing PSA, and all cases and controls should have a biopsy. This collection should not be triggered by elevated PSA.

- Identify and test biomarkers that will be used to assist in clinical decisions (i.e., whether a patient needs a radical prostatectomy). The current practice is based on clinical predictors (e.g., Gleason score).
- Prediction of cancer progression including the development of metastases and outcome of disease; there is a need for specimens from cohorts with many years of follow-up. For this purpose, the plan is to collaborate with the appropriate programs (i.e., Cooperative Groups, PLCO, etc).
- Expand the collection biopsy from high-risk individuals [e.g., men with elevated PSA, or abnormal DRE (Digital Rectal Exam)].
- For the biopsy negative population, there is a need to develop a tissue resource and combine tissue based markers with body fluid markers to increase negative predictive value.

➢ Develop surrogate markers (i.e., WBCs from cancer and control patients). Surrogate markers such as functional biochemical tests and polymorphisms need to correlate with risk. (Note: The capacity to repair damaged DNA by certain DNA repair enzymes such as OGG1was recently correlated with risk of developing lung cancer due to smoking. The activity of this enzyme was identical in the surrogate tissue, WBC, and in lung epithelial cells in the same individuals).

➢ Develop biomarkers based on stromal cell-associated biomarkers. Also assess the ability of prostate cancer stem cells to detect early stage prostate cancer *in vivo*. The approach will be based on a combination of imaging techniques with affinity reagents specific for the cancer stem biomarkers.

➢ Initiate validation studies based on new generation of biomarkers such as gene fusion products (TMPRSS2-ETS) and differentially expressed metabolites in body fluids (urine, EPS, and serum).

➢ Develop Circulating Tumor Cells (CTC)-based assays to assess risk of cancer progression and early recurrence. CTC could be early indicators for the development of aggressive cancers.

APPENDIX 1

ORGAN SPECIFIC CANCERS

Bladder Cancer and Other Urogenital Cancers

Strategic Goals

Bladder cancer is the fifth most common cancer in the Western world, affecting about 4% of all cancer patients and is the cause of about 3% of all cancer-related deaths. The estimated life probability of developing bladder cancer in U.S. *men* is 1 in 28 and in U.S. *women* is 1 in 87. Bladder cancer occurs in two clinically significant forms: Superficial (TNM: Ta, TIS, T1) and Invasive (TNM: >T2). Seventy-five percent of the patients are diagnosed with superficial disease, and only a minority (about 15%) is at risk for progression. Approximately 70% of these patients will experience recurrence of the disease within 10 years. The majority of recurrences occur within the first two years after diagnosis. The vast majority of invasive bladder cancers occur in patients without a prior history of papillary tumors. Although urine cytology and cystoscopy are considered standards of care, these are less than optimal in detecting all forms of bladder cancer. The sensitivity and specificity of urinary cytology are 25-50% and 90-100%, respectively. The sensitivity and specificity of cystoscopy is 90-100% and 75%, respectively. In recent years, several new biomarkers and tests for detection of bladder cancer gained acceptance and FDA approval (BTA™, BTA stat™ FDP™ NMP22™and the UroVysion). Most of these FDA-approved tests can augment, but not replace, the cystoscopy for diagnosis of bladder cancer. Consequently, there is a need to improve the current practice of bladder cancer detection and surveillance. Strategic goals are to:

- Develop non-invasive diagnostic tests for early detection of superficial bladder cancer (to minimize the number of unnecessary cystoscopies) and for early recurrence of superficial bladder cancer.

The Plan

- Develop biomarkers associated with the four major subtypes of bladder cancer: (1) transitional cell carcinoma; (2) squamous cell carcinoma; (3) adenocarcinoma; and (4) small cell carcinoma. Also, indentify biomarkers associated with bladder cancer stem cells, bladder stroma cells, and others.

- Validate (analytical and clinical validation) promising biomarkers for the various subtypes of bladder cancer [i.e., methylated DNA sequences, genetic alterations (mutations, amplifications, and deletions) in candidate oncogenes and tumor suppressor genes, and alterations in mtDNA, etc.].

- Assemble bladder cancer "reference sets" and appropriate controls for biomarker discovery and validation studies. The composition of each collection of "reference sets" should be tailored to answer specific clinical questions. For prediction of cancer progression, including the development of metastasis and mortality, there is a need for specimens from cohorts with many years of follow-up. For this purpose, EDRN will collaborate with the appropriate programs (i.e., collaborative groups). Collected specimens will include body fluids (urine, plasma, and serum), tissues, circulating tumor cells, and WBCs.

- Develop biomarkers including biomarkers derived from stromal and stem cells for molecular classification of bladder cancer subtypes.

- Use Circulating Tumor Cells (CTC) to estimate cancer progression and early recurrence. CTC could be early indicators for the development of an aggressive cancer.

Other Urogenital Cancers

At present, there is no established serum or urinary biomarker for the diagnosis or management of kidney cancer as well as a lack of specific symptoms in people with early stage disease. Furthermore, an increasingly larger subgroup of patients with small renal masses are not treated but are instead monitored for disease progression by CT or MRI.

The Plan

- Priorities for kidney cancer are the development of biomarkers for non-invasive early detection and as prognostic indicators of aggressiveness of disease.

APPENDIX 2

NON-DISCLOSURE AGREEMENT

This document is executed with the intent to maintain the confidentiality of proprietary information and the potential for patenting the products that arise from the individual efforts put into this collaborative effort while still enabling investigators to share the results from their undisclosed and unpublished work. Open discussion is fundamental to the attainment of the goals of this collaborative effort.

In order to protect certain proprietary information relating to inventions and potential and/or present patent rights, and to research, development, business plans, know-how, and/or other technology or property of a confidential nature ("Confidential Information"), participants in the 18th Steering Committee Meeting of the Early Detection Research Network (EDRN), as identified on the Meeting Roster form signed by all participants ("Participants"), agree that **all discussions and exchanges occurring in the closed Committee sessions will be considered proprietary and confidential**. Confidential Information shall include, but not be limited to, unpublished data, research results, theories, drawings and figures or visual depictions of research data or results regardless of format. The proceedings of the Meeting will be audio recorded.

Each Party receiving Confidential Information signing this document intends to be legally bound, to the extent permitted by law, from divulging such information to any person other than employees, consultants, contractors, subcontractors, designees, or assignees of Participants to whom it is necessary to further the purposes of the EDRN. Confidential Information shall not be disclosed, copied, reproduced or otherwise made available to any other person or entity without the consent of the owning Party except as required by law, regulation or court order. Any person receiving Confidential Information will have received a copy of this Non-Disclosure Agreement or similar agreement providing for exchanges of information under terms at least as restrictive as those specified herein. The Receiving Party shall protect the information by using a reasonable degree of care that is at least as restrictive as the Receiving Party uses to protect its own confidential information. The obligations of a Receiving Party shall not extend to any part of the Confidential Information which is in the public domain or publicly known or becomes so through no fault of the Receiving Party or which is already known to the Receiving Party or was independently developed by the Receiving Party as demonstrated by competent documentary evidence. Each Party further agrees not to use the Confidential Information or attempt to commercialize it, its unmodified derivatives, or products using or embodying either, unless and until a further signed agreement is first made providing the terms and conditions under which rights are to be acquired by the Participant**.**

In the event that the Receiving Party or anyone to whom the Receiving Party transmits Confidential Information pursuant to this Agreement becomes legally required to disclose any such information, the Receiving Party shall provide the Disclosing Party with prompt notice and consult with the Disclosing Party prior to any disclosure.

This Agreement constitutes the entire understanding between parties hereto with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the parties hereto. The obligations of this Agreement will continue for two years after the signing of the Agreement.

This Agreement will be re-affirmed by all Participants in the closed portions of the 18th Early Detection Research Network (EDRN) Steering Committee Meeting, March 29 – April 1, 2009, by signing a copy of the meeting roster before entering the initial closed session.

NON-DISCLOSURE AGREEMENT

18th EDRN Steering Committee Meeting, March 29 – April 1, 2009

Authorized Official's Signature	**Date**
Printed Name	**Title of Authorized Official**

FOR NATIONAL CANCER INSTITUTE:

Wendy E. Patterson, Esq. **Senior Advisor** **Technology Transfer Center** **National Cancer Institute**	**Date**