

# Request for Biomarkers

## Background

Biomarkers are defined as “a characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions”. A major priority of the Early Detection Research Network (EDRN) is the selection and rapid validation of biomarkers for early detection of cancer. To address this priority, organ-focused groups have been organized with the goal of reviewing the status of potential biomarkers, either individually or included in panels of biomarkers.

## Opportunities for Support of Translational Validation of Biomarkers

EDRN solicits potential biomarkers for the early detection of neoplasia from the research community. A product may be proposed by any individual investigator, group or corporate entity. The EDRN offers a high quality human biosample resource consisting of samples collected from a wide spectrum of cancer stages. The current sample bank consists of aliquots of human serum and plasma (200 microliters), urine (5 ml aliquots), DNA from white blood cells, and matched paraffin tissue sections for a variety of cancers. The samples are collected using standard operating procedures that include bar coded tracking, a web-front ended relational database, and data elements that have been piloted and validated for EDRN use. The samples are managed in a professional biosample repository at -80°C in freezers that are sensor controlled, backed up with diesel generators, and equipped with an automated call in system.

The EDRN Collaborative Groups provide multidisciplinary expertise to investigators or research groups with novel products with high potential from any source that may enhance early diagnosis or risk prediction. The Collaborative Groups will provide high quality epidemiology and biostatistics expertise for the design, implementation and analysis of prevalidation and validation studies aimed at demonstrating diagnostic efficacy of such novel products. The EDRN will provide experienced analytical support including scale up methodologies using state of the art technology. The analytical support is performed using CLIA quality control standards, thus ensuring future regulatory approval should a product prove effective.

The EDRN offers financial support for translational validation with the aim of demonstrating efficacy for early diagnosis or risk assessment for a variety of neoplasia selected by the respective Collaborative Group. Assigned review groups within each Collaborative Group will consider biomarker tests that are highly innovative and provide potentially effective diagnostics for neoplasia.

## Process

1. Complete the attached submittal form that consists of the following elements:

- a. Investigator/Research Group name and contact information
- b. Biomarker metrics
- c. Two-to-Three page proposal that briefly and succinctly adheres to the following organizational structure:

i. Background: Describe the theoretical and then practical basis of the proposed biomarker target. Provide preclinical support for the proposed target or rationale for a profile that does not have a direct mechanistic rationale. There is no need to justify research into the early detection of neoplasia.

ii. Technological Approach: Describe the technology as it is applied to the biomarker proposed for development. Provide preliminary evidence of reproducibility and potential scale-up of an assay.

iii. Preliminary Data: Describe preliminary studies in rodent models or with human biosamples. These data need not be extensive or conclusive but must provide evidence of innovation and potential usefulness in humans.

iv. Research Proposed: Briefly describe the research strategy you propose to move your biomarker to a formal, cross sectional or longitudinal validation project using human samples. Describe the type (serum, urine, tissue) of biosample necessary for a translational clinical study and the absolute minimum quantity needed to assay each sample. If a reagent is needed to move a biomarker forward, describe the strategy to obtain this reagent and the necessary support or expertise that the EDRN might provide. While EDRN will provide translational clinical research design and biostatistical support for those biomarkers selected, estimate the numbers of subjects you believe will be necessary to generate sufficient data to support a large validation project.

2. Submit the proposal to

For Colon and Other GI Cancers: [wagnerp@mail.nih.gov](mailto:wagnerp@mail.nih.gov).

For Lung and Upper-Aerodigestive Cancers: [kruegerk@mail.nih.gov](mailto:kruegerk@mail.nih.gov)

For Breast, Ovarian and Other Ob/Gyn Cancers: [maruvadp@mail.nih.gov](mailto:maruvadp@mail.nih.gov)

For Prostate and other Urologic Cancers: [kaganj@mail.nih.gov](mailto:kaganj@mail.nih.gov)

ELECTRONIC SUBMISSIONS ONLY.

3. Deadline for Submission:: Refer to a specific announcement

## **Review Process**

All submissions will be reviewed by the relevant EDRN Collaborative Groups *in confidence*. Submissions will be reviewed by at least two members of the group and assigned a NIH-type merit rating. Each submission will then be discussed by the reviewers and a NIH review score will be assigned to each proposal. All reviews are confidential and follow NIH guidelines for confidentiality and privacy.

## **Outcome of Review Process**

Investigators submitting successful applications will be invited to a meeting sponsored by the EDRN to review their biomarkers in more detail. At that meeting, biomarkers will be reviewed by members, Associate Members, and invited investigators as a panel to select biomarkers for EDRN Support for prevalidation and validation projects.

Attachment 1

**EARLY DETECTION RESEARCH NETWORK  
BIOMARKER SUBMITTAL FORM**

IDENTIFICATION

Name of Biomarker

Investigator:

Organization:

Address:

Telephone Number:

Email Address:

BIOMARKER METRICS

Instructions: Please provide brief summary data regarding the current status of your biomarker(s).

1. Analytical Method Used to Detect Biomarker:

2. Preliminary Data with Animal Models:

a. Animal Model Used:

b. Carcinogen or implanted tumor used:

c. Biomarker in Controls (mean $\pm$ variation):

d. Biomarker in Tumor/Carcinogen (mean $\pm$ variation):

3. Preliminary Data in Humans

a. Type of Biosamples:

b. Tumor/Precancer:

c. Number of Controls:

d. Number of Cancer/Precancers:

e. Biomarker in Controls (mean $\pm$ variation, or specificity):

f. Biomarker in Cancer/Precancer (mean $\pm$ variation, or sensitivity):

g. Comments regarding performance of biomarker, potential use:

## Attachment 2

# Concepts and Approach to Clinical Validation of Biomarkers: A Brief Guide

### Rationale

#### Concepts of Biomarker Validation

There are 3 fundamental concerns related to clinical biomarker validation (1, 2):

(1) Overfitting. Are results (discrimination) due to chance (e.g., overfitting of a multivariable model, without checking for reproducibility)? This refers to the tendency of models trained on large numbers of variables measured on small numbers of observations to produce extraordinarily high sensitivity and specificity, and then fail on independent validation sets (2-5).

(2) Bias. Are results due to differences between cancer and control samples that do not exist in the cancer and control populations? This refers to misidentification of the cause of differences between samples, for instance, if a sample of patients is much older than a sample of controls, then differences due to age may be misattributed to disease (6, 7).

(3) Generalizability. Are results generalizable to appropriate clinical populations? This refers to the similarity of the distribution of markers or sets of markers between the samples studied, and samples derived from a larger clinical or screening population.

### Current Barriers in the EDRN Towards Addressing these Concepts

The EDRN has formalized biomarker validation procedures using a phased approach (8). Nevertheless, despite the discovery of a large number of biomarkers for the detection and risk assessment of common epithelial cancers, few have progressed to large cross-sectional or longitudinal validation trials in humans. Moving a biomarker beyond the first, discovery, phase to validation phases remains difficult because moving to Phase II or III depends upon statistical evidence of predictive power and robustness in a sample set that is representative of the clinical population.

### **Reference Sets to Overcome the Barriers**

Various Collaborative Groups are establishing reference sample sets for prevalidation and validation to speed validation of promising biomarkers for cancer early diagnosis and risk assessment.

### Definition

A reference set comprises biosamples collected under good clinical practice (GCP) conditions that are sufficient to permit decision analysis with statistical precision.

### Good Clinical Practice Conditions

Good Clinical Practice is defined as collection of human biosamples and accompanying data elements using Standard Operating Procedures. Such procedures are defined in advance in a written protocol document and enforced through internal and external auditing mechanisms.

### Management of Reference Sets

Preliminary data, defined in advance, are required to trigger use of a reference set. The quantity and quality of the preliminary data vary with the proposed biomarker indication and estimate of clinical impact. Agreements regarding publications, data management, sample release, and analytical quality control are made in advance. Samples are assayed based upon scientifically rigorous design. Data from both open and closed labeled assays are analyzed by biostatisticians who have no vested interest in success or failure of a given product.