

Early Detection Research Network



EDRN: Accomplishments and Future Outlook

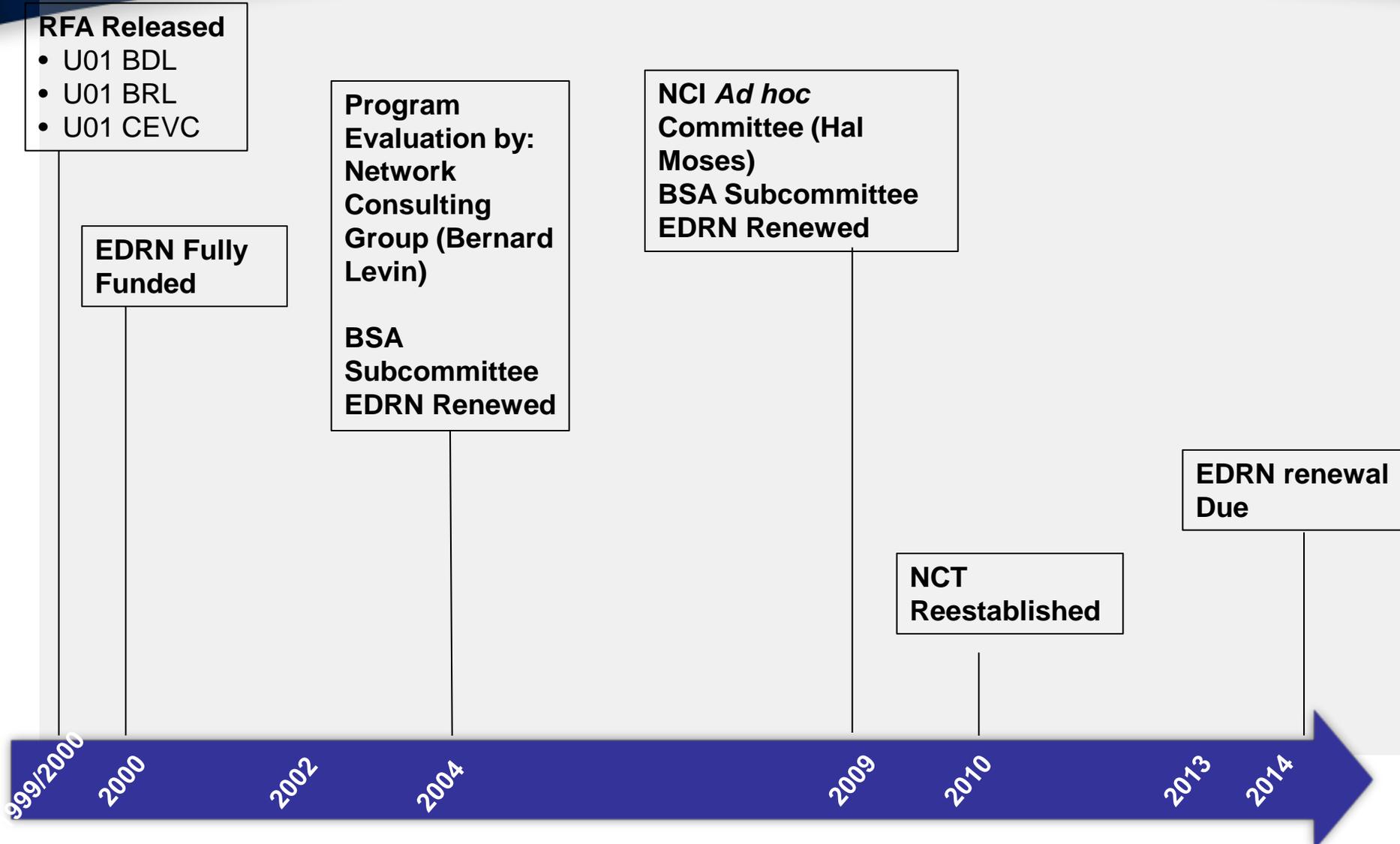
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About *my*EDRN

- ❑ A Network of its kind - Investigator-initiated infrastructure modeled after Cooperative Groups and established in 2000
- ❑ Collaborative and team science driven biomarker discovery, development and validation
- ❑ Built-in reward mechanisms for collaboration and team science
- ❑ Milestones-driven projects with incremental peer-review evaluation
- ❑ Inclusive infrastructure that solicits extramural investigators' participation through a unique Associate Membership Program throughout the funding period
- ❑ Follows industrial/biotechnology standard practice for biomarker pipeline development

EDRN Program History



Extensive Coverage Of EDRN in Peer-Reviewed Journals

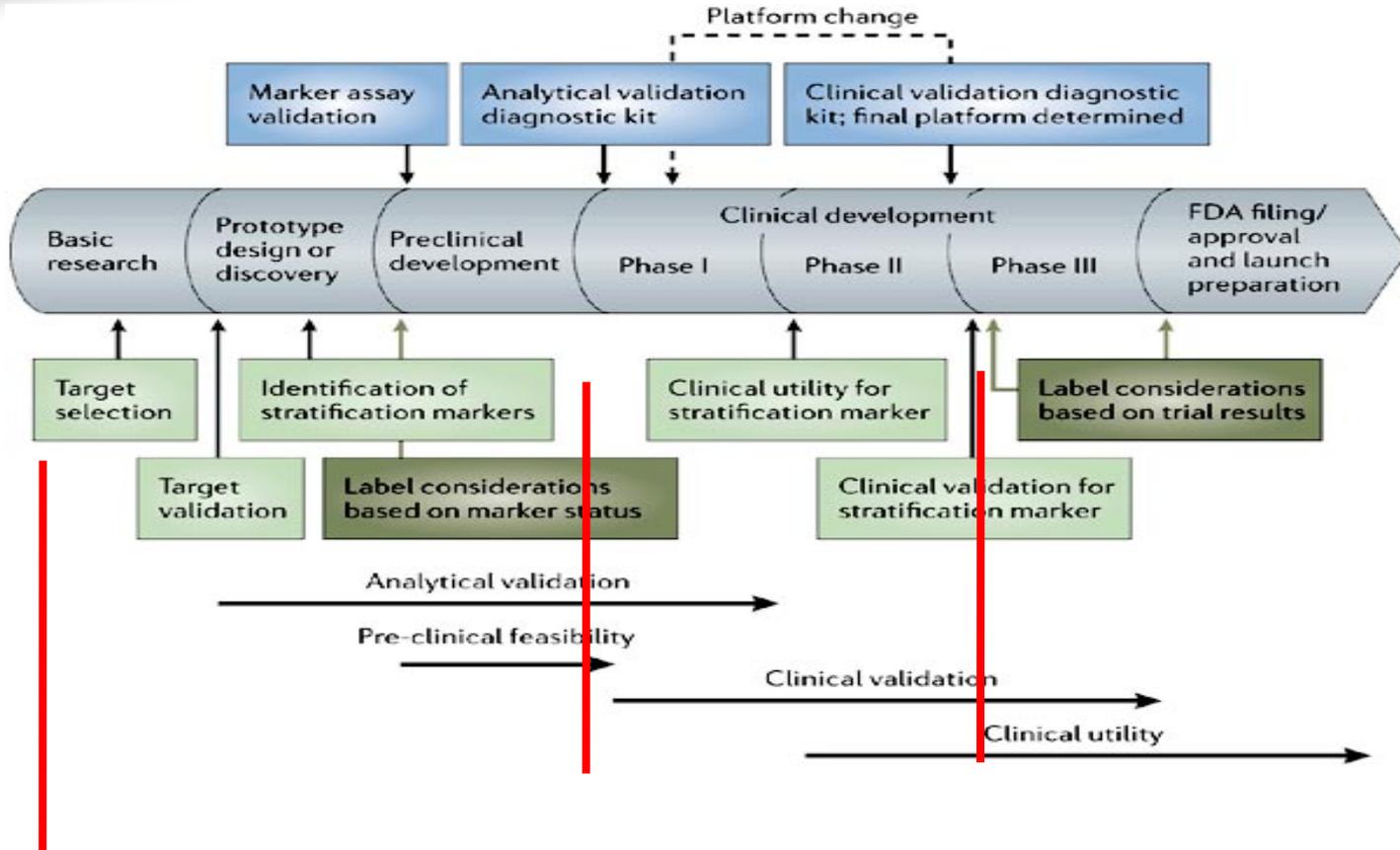
□ EDRN Business Model and Project Management Reviewed and Cited by Many Scientific Journals and Working Groups for Best Practices:

- Informatics to manage and support biomarker research (NCI-FDA-AACR Biomarker Collaborative Working Group Reports, Institute of Medicine on Biomarker)
- Discovery and validation research (JNCI, J. Proteome Research, Nature)
- Collaborative model for biomarker research (Nature)
- Milestones-driven project management that ensure timely completion
- NCI Translational Research Working Group

The EDRN structure has been cited by the National Academy of Sciences Institute of Medicine as an effective team-based organization (*Large Scale Biomedical Science*, Institute of Medicine 2001); and for following best practices in *Biospecimen Resources for the Genomic and Proteomic Era* (Rand Science and Technology Publication, 2003), and *Cancer Informatics* (Eds. Silva, Ball, Chute, et. al., 2002).

Continues...

EDRN Structure is Based on Biomarkers Development Pipeline



EDRN Biomarker Pipeline

- Hundreds of biomarkers reviewed and evaluated
- More than 500 failed in rigorous testing
- More than 800 prioritized (EDRN Data Base)
- Many of them are in Phase II

<https://edrn.nci.nih.gov/biomarkers>

Organized into Collaborative Groups



<https://edrn.nci.nih.gov/collaborative-groups>

Collaborative Activities

- ❑ Extensive interactions; Monthly phone calls including scientific presentations, biomarker prioritization, guest speakers
- ❑ Two Steering Committee meetings each year combined with scientific workshop every 18 months; attended by non-EDRN members
- ❑ Dedicated Webpages for Each Collaborative Group
- ❑ More than 60 network-wide collaborative projects
- ❑ Partnerships with other NCI Programs, e.g. CPTAC, SPORES

- ❑ **Conducting multi-center, multidiscipline trials for biomarker validation**
- ❑ **CLIA-Approved laboratories to develop and test assays using GLP and GMP**
- ❑ **Informatics and bioinformatic support for data collection, curation, storage and queries (through JPL)**
- ❑ **Centralized Statistical Center for data analysis and statistical support;**
- ❑ **Fail-safe mechanism for efficient biomarker triaging for large, expensive validation studies (use of reference sets)**
- ❑ **Availability of large number of biospecimens (more than 100,000) using a uniform protocol, CDEs, multi-center collections**
- ❑ **Shared technologies on genomics, proteomics, and other 'omics' for collaborative studies**

Collaborative Opportunity for Community and Public

- More than 200 Associate members, many of which are collaborating with EDRN members;
- Active partnership with Canary Foundation of America on prostate cancer; prostate active surveillance study (PASS) and lung cancer in nonsmokers;
- Partnership with Lustgarten Foundation N.Y. on production of hybridoma cell lines for 20 pancreatic antigens;
- Collaboration with China (C-EDRN) and Cancer Research UK;
- EDRN Advocacy Forum through quarterly Webinar.

- Innovative Technologies, Study Designs and Approaches**
- Biomarker Discovery**
- Preamalytical Validation**
- Analytical Validation**

<https://edrn.nci.nih.gov/network-consulting-team>

Foundational Studies on Phases and Study Design for Biomarker Development

COMMENTARY

Phases of Biomarker Development for Early Detection of Cancer

Margaret Sullivan Pepe, Ruth Etzioni, Ziding Feng, John D. Potter, Mary Lou Thompson, Mark Thornquist, Marcy Winget, Yutaka Yasui

Journal of the National Cancer Institute, Vol. 93, No. 14, July 18, 2001

Phases of Biomarker Discovery and Validation

Preclinical Exploratory	PHASE 1	Promising directions identified
Clinical Assay and Validation	PHASE 2	Clinical assay detects established disease
Retrospective Longitudinal	PHASE 3	Biomarker detects preclinical disease and a "screen positive" rule defined
Prospective Screening	PHASE 4	Extent and characteristics of disease detected by the test and the false referral rate are identified
Cancer Control	PHASE 5	Impact of screening on reducing burden of disease on population is quantified

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design

Margaret S. Pepe, Ziding Feng, Holly Janes, Patrick M. Bossuyt, John D. Potter

Research methods for biomarker evaluation lag behind those for evaluating therapeutic treatments. Although a phased approach to development of biomarkers exists and guidelines are available for reporting study results, a coherent and comprehensive set of guidelines for study design has not been delineated. We describe a nested case-control study design that involves prospective collection of specimens before outcome ascertainment from a study cohort that is relevant to the clinical application. The biomarker is assayed in a blinded fashion on specimens from randomly selected case patients and control subjects in the study cohort. We separately describe aspects of the design that relate to the clinical context, biomarker performance criteria, the biomarker test, and study size. The design can be applied to studies of biomarkers intended for use in disease diagnosis, screening, or prognosis. Common biases that pervade the biomarker research literature would be eliminated if these rigorous standards were followed.

J Natl Cancer Inst 2008;100:1432-1438

PRoBE Study Design:
Prospective-specimen collection,
Retrospective Blinded Evaluation

Robust Biomarker Development

- Robust discovery and development of biomarkers for prostate, lung, colon, breast and pancreas
- Rich array of discovery platforms, e.g., genomics, proteomics, epigenomics, metabolomics, etc.
- Verifiable development using quality specimens provided by EDRN Clinical Validation Center and verified by Biomarker Reference Laboratory
- A rich pipeline of more than 800 biomarkers (listed in EDRN Biomarker Database) being readied for verification and validation
- Quality of biomarkers and reproducibility of data are rapidly evaluated and test through the EDRN Reference Samples and BRL

Biomarker Discover by EDRN BDL: Highlights

- ❑ Vimentin methylation as a biomarker of advance adenoma (Sandy Markowitz) undergoing validation
- ❑ TMPRSS2-ERG Fusion (Arul Chinnaiyan) undergoing Phase III validation
- ❑ MicroRNA panel in serum and sputum for lung (Carlo Croce, Avi Spira, Harvey Pass) for early stage lung cancer undergoing Phase II validation
- ❑ DNA Repair enzyme (8-oxyguanine DNA Glcosylase, Alkyl-adenine DNA Glycosylase and APE1 Endonuclease) developed by Zvi Livenh (Weissman) undergone Phase II validation and work in progress for Phase III validation
- ❑ 80-gene panel for lung cancer detection (Avi Spira); verifying its application for nasal epithelium

Active and Ongoing Clinical and Validation Studies

- ❑ More than 200 active protocols
- ❑ More than 12 clinical validation studies
- ❑ More than 10,000 subjects enrolled
- ❑ Completed 7 validation studies - five leading to FDA approval and two with negative results (SELDI and MSA); and many validation studies/developmental projects in the pipeline
- ❑ 10 clinical reference sets, more than 100 MTAs and IRBs, facilitates validation studies.

All these activities are tracked through the electronic Study Information System (eSIS)

Completed and Ongoing Major Clinical Validation Trials by EDRN

- Chan – prostate ([-2]proPSA, FDA approved)
- Wei – prostate (PCA3, FDA approved)
- Skates – HE4 and CA125 and ROMA for ovarian
- Chan - %-protein marker panel for ovarian cancer (FDA approved)
- Waco and Marrero – DCP for HCC (FDA approved)
- Shoenberg – Bladder cancer (MSA) – negative findings
- Semmes - SELDI for prostate cancer (negative results)
- Brenner – DNA methylation and protein markers for Colon cancer
- Harvey Pass - SMRP Validation in Mesothelioma

Resources for Community Clinical Sample Reference Sets

- ❑ Clinical validation studies are expensive and require multi-center, multi-disciplinary teamwork to succeed.
- ❑ Only few biomarkers may succeed.
- ❑ There is a need for triage system that allows a “Go or No-Go” decision.
- ❑ EDRN has developed a mechanism through which biomarkers are first tested in Standard Reference Samples for the intended use.
- ❑ If successful, then a large validation study is planned.

Reference Sets are samples of cases and controls statistically powered to allow rapid, cross-sectional assessment of technologies and biomarkers discovered through a wide variety of technology platforms.

First-ever concept originated and implemented within EDRN for rapid evaluation of technologies and biomarkers - <https://edrn.nci.nih.gov/resources/sample-reference-sets>

Available EDRN Standard Reference Sets

Liver

Rapid Liver Reference Set (serum)

Full Reference Set (serum/plasma/DNA)

Lung (EDRN/SPORE Collaboration)

Set A Retrospective and Set C Prospective (serum/plasma)

Set B Retrospective CT Screening Trial (plasma)

Cancers in Women (Breast and Ovarian)

Retrospective (serum, pooled)

Pancreas

Case-control (serum/plasma/cystic fluid/DNA)

Prostate

Case-control (serum/plasma/DNA)

Bladder

Case-control (serum/plasma/DNA)

Breast

ADH, DCIS, IBD

Colon

Obtain application form from EDRN public portal

(<http://edrn.nci.nih.gov/resources/sample-reference-sets>) .

Example: Use of Reference Set in Triaging Biomarkers

Biomarker	Sensitivity	Specificity
Galectin-3 ligand	68%	95%
Company A Marker1	10%	96%
Company A Marker 2	12%	92%
Company A Marker 3	27%	94%
Company A Markers 1+2+3	29%	60%
Company A Markers+FOBT	42%	97%
Proteomics-Agilent	78%	88%
Proteomics-PBSIIc	70%	76%
Proteomics-SELDI-TOF	19%	98%
Proteomics-MALDI-TOF	63%	48%
Company B Stool Marker	77%	49%
Company B Marker +FOBT	27%	97%

Infrastructure Resource for Biomarker Research

- **CLIA-certified Laboratories for Biomarker Analytical Validation and Assay Development (EDRN BRL)**
- **Biomarker Database**
- **Data Archival and Mainlining Ability (EDRN eCAS)**
- **Training on Biomarkers Statistics Each Year by EDRN DMCC**
- **Biospecimen Locator and Sharing (EDRN Exchange Network)**
- **Bioinformatics Tools for Multi-Center Validation Trials (eQuestionnaire, on-line accrual ability, auditing, etc)**
- **Protocols for Specimen Collections, Processing and Analyte Measurements**
- **Standards for Molecular Assays, e.g., T2-ERG, DNA repair Enzymes, etc.**

<https://edrn.nci.nih.gov/resources>

Key Accomplishments - Biomarker Science Before and After EDRN

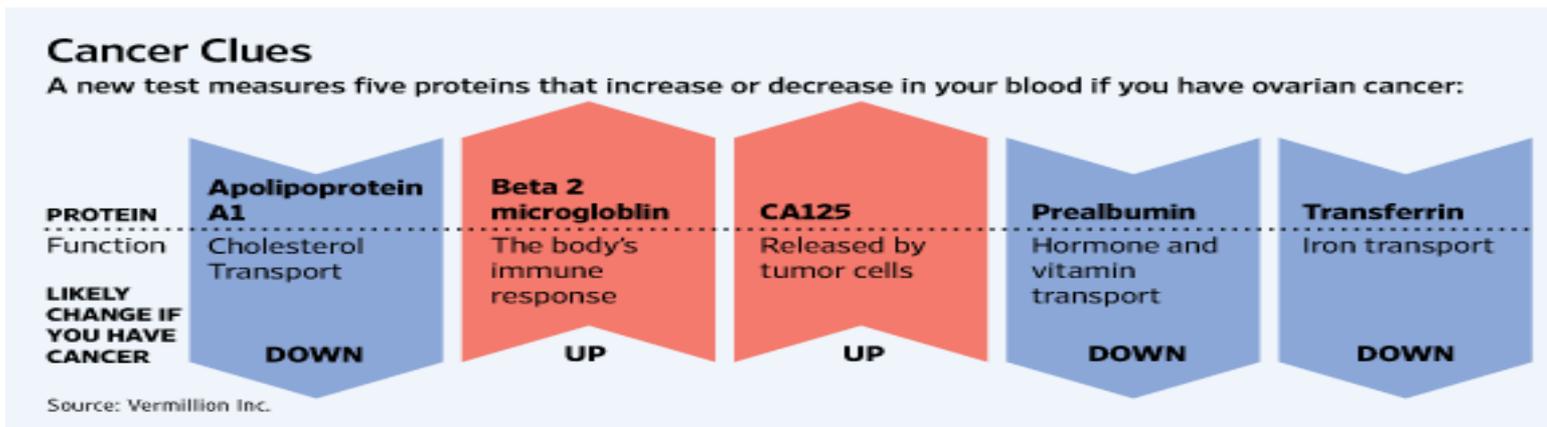
Problems:

- SOPs for biosample collection non-existent. Cannot reproducibly manage biosamples across the collaborative
- No common data elements (data dictionary) to enable the development of common databases for biosample annotation
- Fragmented studies with convenience samples, not generalizable

Solutions:

- Partnered statisticians and epidemiologists. Created, validated data elements for all EDRN biosample annotation.
- Created standard operating procedures for biosample collection and management.
- Disseminated these procedures outside EDRN.
- Developed roadmap for study designs for clinical verification and validation
 - ✓ Published 2 manuscripts, both top citation papers.

The 1st proteomics IVDMIA (In vitro diagnostic multivariate index assays) cleared by the US FDA. 3-9-2010



Proteomic Approaches to Tumor Marker Discovery: Identification of Biomarkers for Ovarian Cancer. Alex J. RaiDaniel W. Chan. *Archives of Pathology and Laboratory Medicine*. 126:1518–1526, 2002.

Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. Z ZhangDW Chan. *Cancer Research* 64, 5882-5890, 2004.

EDRN Public-Private Partnership

Prostate Health Index –

$$phi = ([-2]proPSA/free PSA) \times \sqrt{PSA}$$

Multi-Center study showed 31% reduction in unnecessary biopsies.

Approved by FDA on June 25, 2012

Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi A, Broyles D, Partin AW, Srivastava S, Thompson IM, Wei JT, Zhang Z and Chan DW. Cancer Epidemiology, biomarkers & prevention 19:1193-1200 (2010)

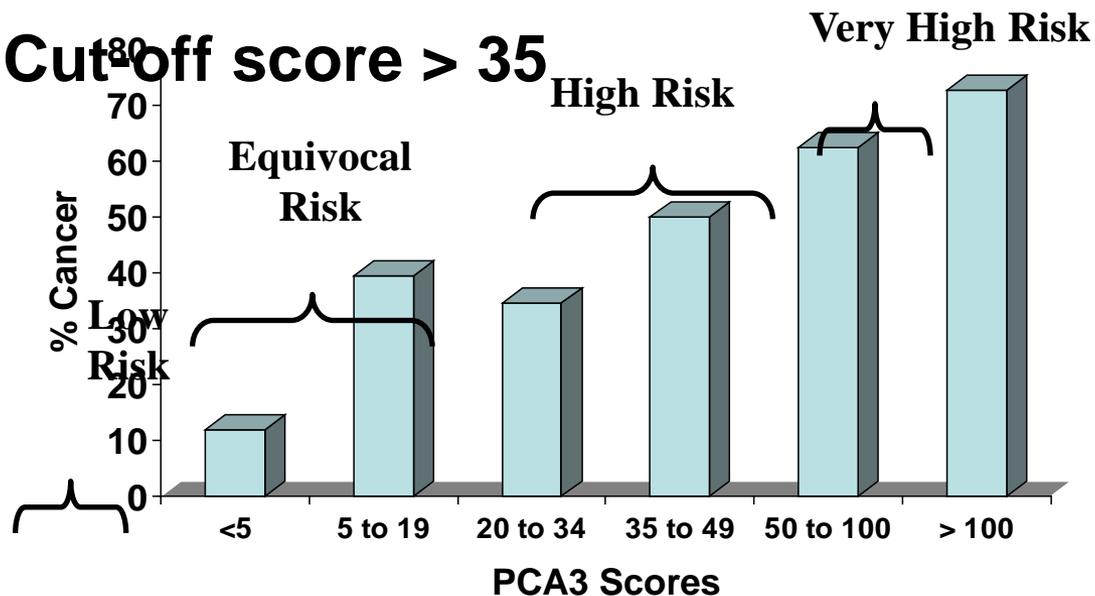


PCA3 Molecular Urine Test - Non-coding mRNA (PROGENSA)

To determine the need for repeat prostate biopsies in men who have had a previous negative biopsy: Gen-Probe, Inc.

FDA approved 2/15/2012.

High risk Cut-off score > 35



Clinical Assays in Use

<u>Detection/ Biomarker Assay</u>	<u>Discovery</u>	<u>Refine/ Adapt for Clin Use</u>	<u>Clinical Validation</u>	<u>Clinical Translation</u>
Blood proPSA		√	√	FDA approved
Urine PCA3		√	√	FDA approved
Urine/TMA assay for T2S:Erg fusion for Prostate Cancer	√	√	√	CLIA in process
FISH to detect T2S:Erg fusion for Prostate Cancer	√	√	√	In CLIA Lab
Aptamer-based markers for Lung Cancer		√	√	In CLIA Lab
Proteomic Panel for Lung Cancer		√	√	In CLIA Lab
OVA1™ for Ovarian Cancer		√	√	FDA Approved
SOPs for Blood (Serum, Plasma), Urine, Stool,		√		Frequently used by biomarker research community
Vimentin Methylation Marker for Colon Cancer		√	√	In CLIA Lab
ROMA Algorithm for CA125 and HE4 Tests for Pelvic Mass Malignancies		√	√	FDA Approved
Blood/DCP and AFP-L3 for Hepatocellular Carcinoma		√	√	FDA Approved
Blood GP73	√	√	√	Together with AFP-L3 used in China for monitoring/risk assessment of cirrhotic patients for HCC
Bronchogen		√	√	In CLIA Lab

Leveraging Resources

- ❑ Leveraging federal agencies' technology and resources at no developmental cost and EDRN in return provides the test beds for verification and validation of these technologies;
- ❑ Challenging clinical questions within EDRN drive technology innovation and development, e.g., Nanobubble (Stanford); PRISM SRM (PNNL); IgY14 (NIST)
- ❑ Leveraging EDRN funding to seek funding from other mechanisms: 2 SPORES, 2 DOD Lung Program, 4 CPTAC, one FDA, more than 30 R01s and R21

EDRN Scientific Highlights

EDRN research activities as listed in EDRN Scientific Research Highlights, www.cancer.gov/edrn/network-consulting-team include:

- a focused, integrated technology development
- ‘Omic’ discovery driven by clinical needs
- preclinical verification and prevalidation of biomarkers and associated data to ensure reproducibility
- validation studies meeting FDA standards and criteria
- informatics and statistical tools and databases

□ EDRN Program Analysis Posted on

www.cancer.gov/edrn which summarizes:

- EDRN is unique resource
- EDRN activities are not replicated within industry or academia (traditional funding mechanisms)
- Number of patents and licenses far exceeds its peers
- EDRN results enhance efficiency and cost effectiveness of biomarker research as evident by cost per grant and productivity (# FDA approved biomarkers, patents, licenses, publications, collaborations, citations of EDRN work)

Health Economics and Economy of Scale in Biomarker Research

- **Organized efforts reduce redundancy, improve efficiency, results in economy of scale and ensure reproducibility of the results.**
 - a large number of grants with the lowest per grant cost as compared to it peers among the NCI-supported programs.
 - Five biomarkers to date approved by FDA; considering the cost of discovery to development to validation to FDA approval about \$80 to \$120 M each, funding of EDRN is well worth it.
- **In light of health economics, biomarker-diagnostics is also considered successful in reducing the cost of unnecessary diagnostic workups.**

- ❑ **Screening modality for cirrhotic patients:**
 - AFP at conventional threshold (20 ng/mL) has specificity~90% but misses about 50% HCC. Ultra-Sound is operator dependent.
 - Annual CT/MRI increase sensitivity (DCP validation study data: sensitivity = 95%) but costs ~\$2,100 per test and the concern of the repeated radiation for ~95% of cirrhotic patients who do not have HCC.

- ❑ **A biomarker test (combination of AFP and DCP) has approximate 35% specificity at 95% sensitivity. DCP increased this specificity from 24% by AFP test alone.**

- ❑ **Estimated 1.2 million cirrhotic patients in US alone. If CT/MRI is only referred for whom with positive biomarker tests:**
 - 35% of cirrhotic patients would be spared from annual CT/MRI.
 - Save ~\$900 millions annually in CT/MRI cost.

- ❑ Pooling data from multiple CT trials, the rate of lung cancer detection is ~1.3% with ~12% false positive benign tumors that require subsequent follow-up.
- ❑ Annexin has approximately 30% specificity at 90% sensitivity.
- ❑ Cost of a chest biopsy (assuming no complications) is ~ \$20,000. If there are complications the cost can be significantly greater.
- ❑ For every 1,000 individuals screened via CT, if annexin was then used to determine who should have a biopsy:
 - 13 individuals with lung cancer would be found via CT scan, 1 would be a false negative from annexin.
 - 120 individuals with false positive benign tumors would be found by CT screen, 36 would be indicated by annexin not to need biopsy.
 - \$720,000 saved in biopsy costs, with one lung cancer case missed.
- ❑ This does not address whether all lung cancers detected by CT screen actually need to be treated; some data suggest overdiagnosis of lung cancer by CT screen by a factor of 3. If this is the case, then use of annexin would reduce biopsy cost by \$2.2 million for every 3,000 individuals screened via CT, while missing one malignant lung cancer.

Future Directions

EDRN Strategic Plan

- ❑ EDRN Strategic Plan on www.cancer.gov/edrn available for review. The plan lists:
 - priority areas for research
 - ❑ Biomarker and Pathogens, including Viruses
 - ❑ Network and Pathways-based Biomarker panels
 - ❑ Molecularly-informed Discovery and Verification
 - ❑ Biology of Overdiagnosis
- ❑ Emphasis on Data Reproducibility and Verification
- ❑ Building Interconnected ‘omic’ approach to secreted biomarkers

Motivation for Request for Reissuance

- 1. EDRN program continues to account for the majority of NCI's support for investigator-initiated biomarkers discovery, development and validation addressing an area unmet by other FOAs**
- 2. EDRNT solicitations continue to receive a substantial number of high-scoring applications**
- 3. A significant record of success, as verified by multiple FDA biomarker approval; CLIA-approved tests, standard SOPs**
- 4. More than ever reliable and robust preclinical data are needed given the broad range of potential diagnostic and therapeutic applications**

National Cancer Institute



Thanks

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Early Detection *“the Cure for Cancer”* !!!!

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