Early Detection Research Network

Translating Biomarker Discovery to Clinical Application

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Cancer Biomarkers Research Group

National Institutes of Health

National Cancer Institute

Goal: Establish a Comprehensive Approach to Biomarker Development

Early Detection Research Network

- Discover, develop and validate biomarkers for cancer detection, diagnosis and risk assessment
- Conduct correlative studies/trials to validate biomarkers as indicators of early cancer, pre-invasive cancer, risk, or as surrogate endpoints
- Develop quality assurance programs for biomarker testing and evaluation
- Forge public-private partnerships

ACCOMPLISHMENTS (2000-2006)

Early Detection Research Network

- SUCCESSFUL INFRASTRUCTURE
- BIOMARKER DISCOVERY
- BIOMARKER VALIDATION
- COLLABORATIONS AND PARTNERSHIPS
- BIOMARKERS AND BIOINFORMATICS

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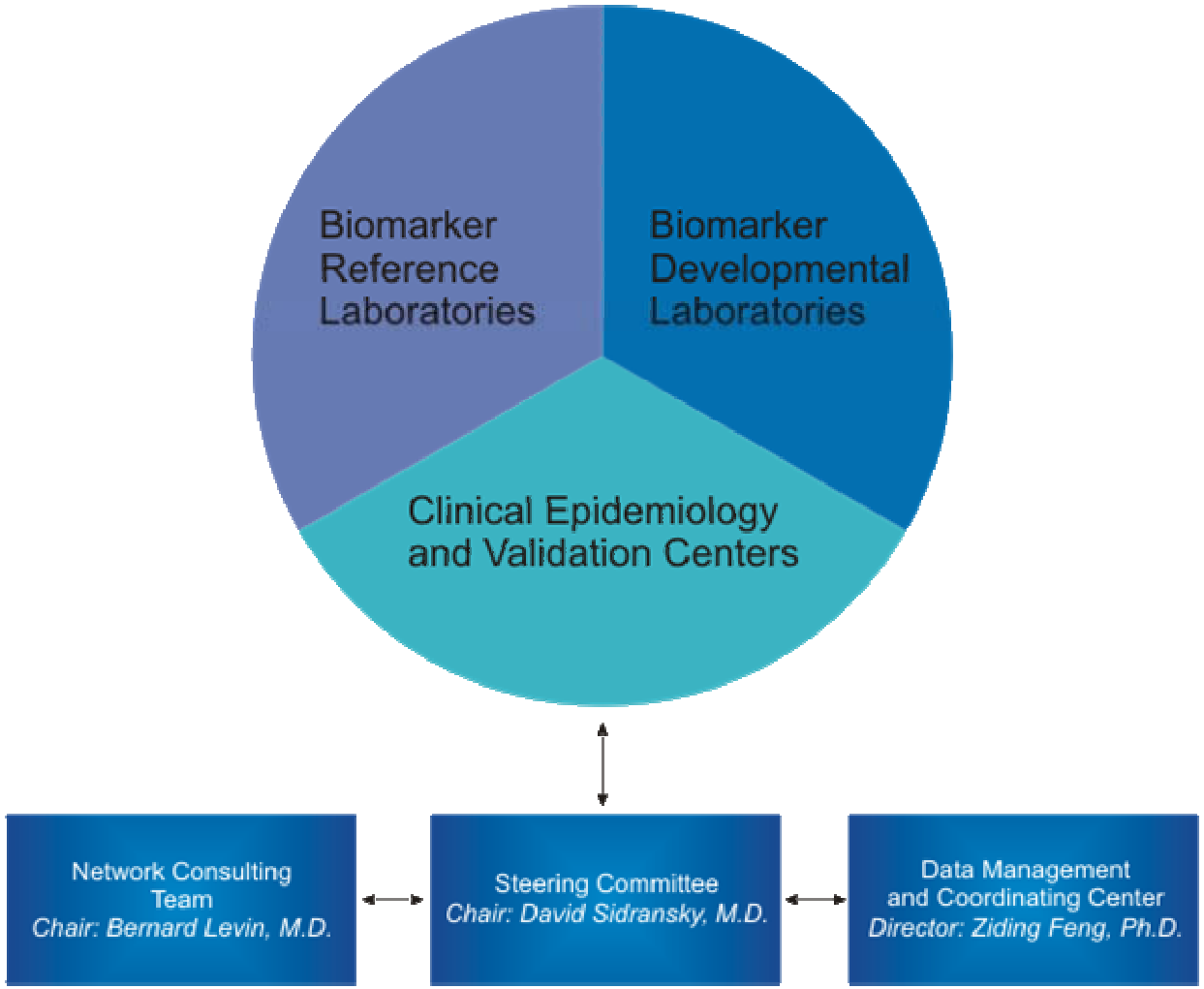
INVESTIGATOR-DRIVEN CONSORTIUM

Early Detection Research Network



An "infrastructure" for supporting collaborative research on molecular, genetic and other biomarkers in human cancer detection and risk assessment.

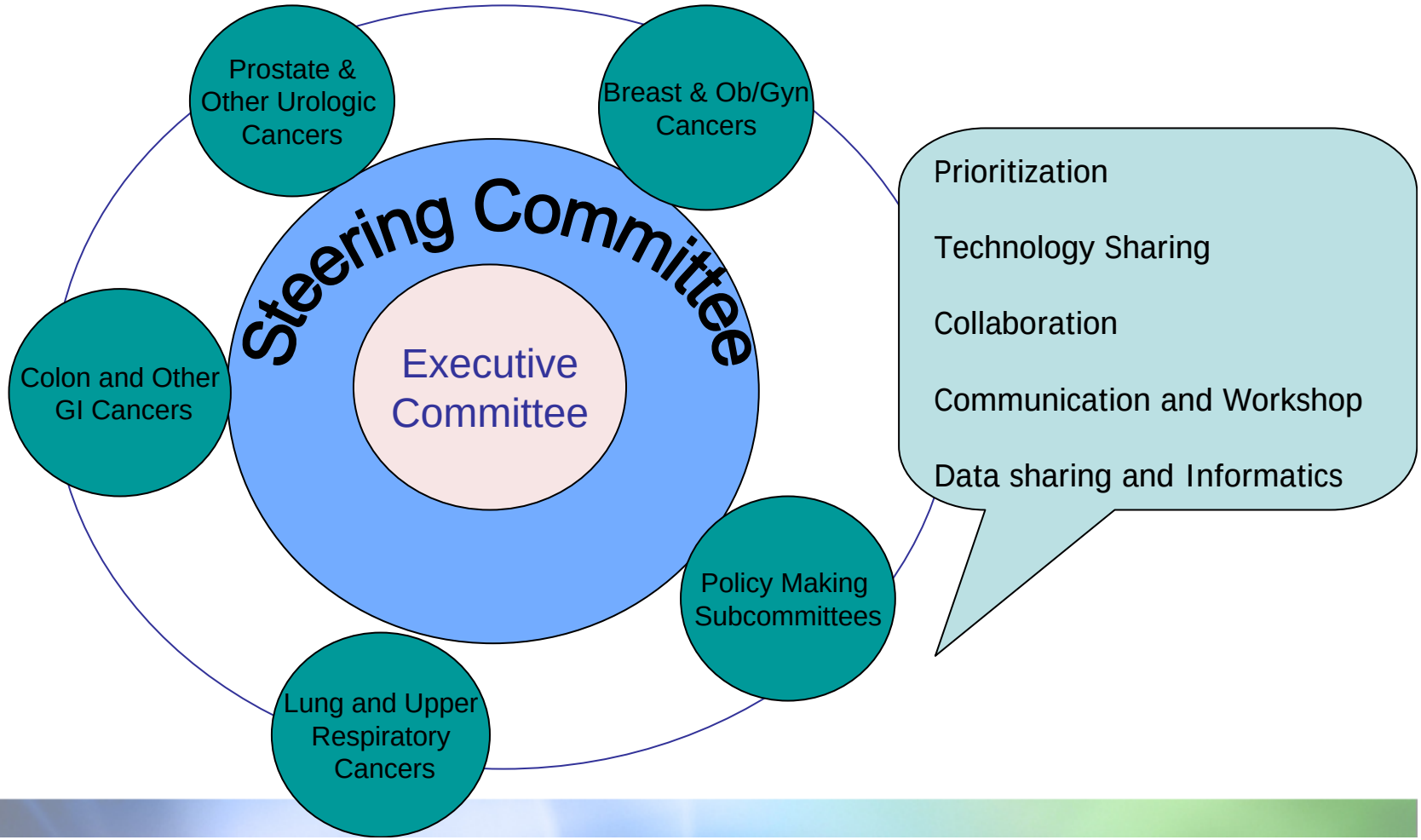
PARTNERING WITH FEDERAL AGENCIES

Early Detection Research Network

- National Institute of Standards and Technology as a Reference Laboratory
- NASA's Jet Propulsion Laboratory (JPL) as an Informatics Center
- Centers for Disease Control and Prevention as a Clinical Epidemiology and Validation Center
- DOE's Pacific Northwest National Laboratory as a Reference Laboratory for Antibody and MS
- NIEHS Genes-Environment Initiative

MANAGEMENT STRUCTURE

Early Detection Research Network



MANAGEMENT OVERSIGHT

Early Detection Research Network

NCI Staff: The Partner

EDRN Executive Committee: Subgroup of the Steering Committee that meets monthly to consider routine EDRN issues.

Steering Committee: The "Housekeeper" Main governing body of the Network that meets three times annually. Subcommittees develop EDRN management policies.

Network Consulting Team: The "Spell Checker" provides independent scientific oversight team.

ORGANIZATIONAL SUCCESS

Early Detection Research Network

- **Instilled a sense of urgency among investigators for collaborative needs on biomarker research**
- **Rewards collaboration**
- **EDRN-like structures have been emulated NIH-wide and internationally**

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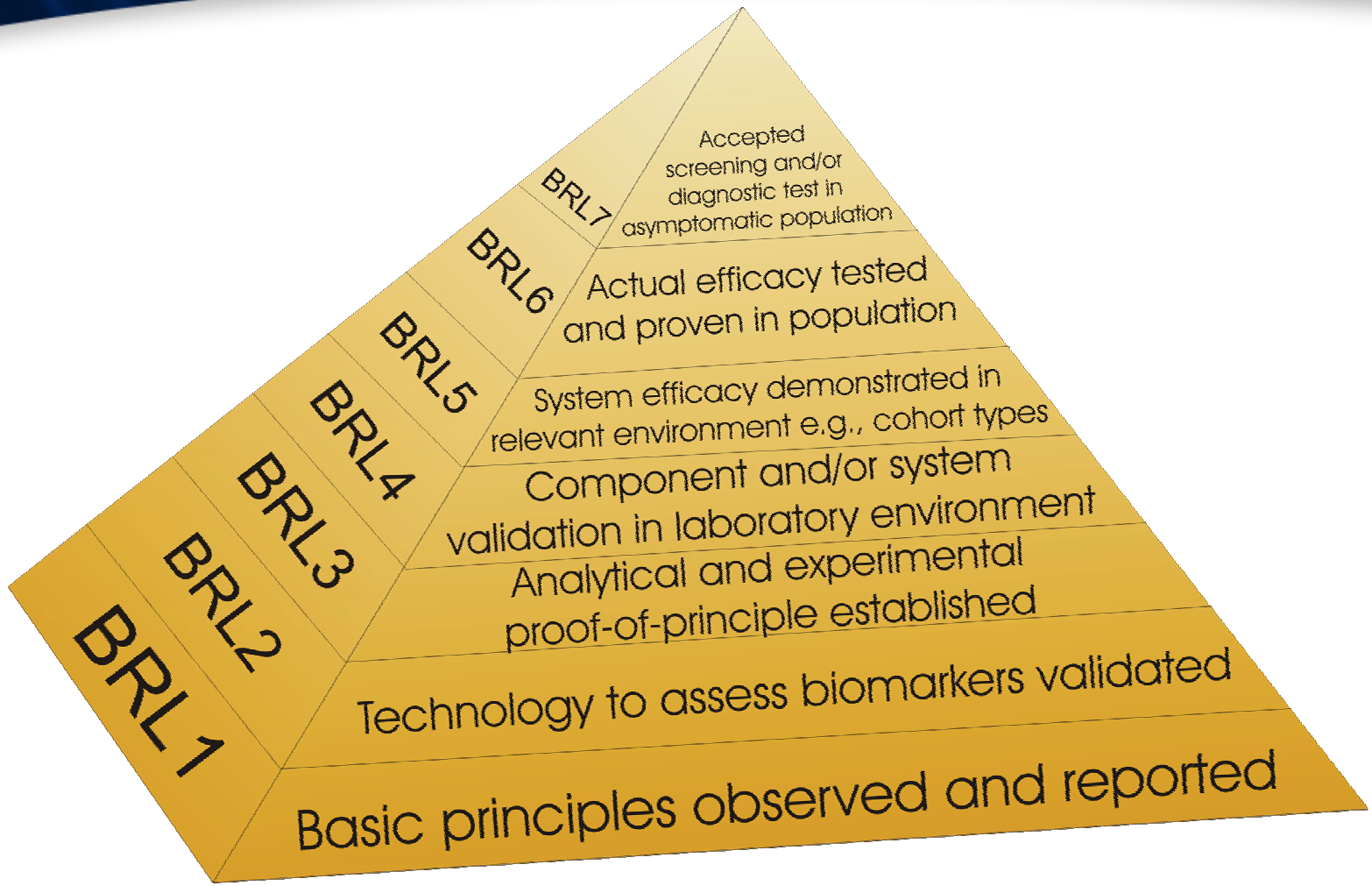
Systematic Approach To Biomarker Discovery: An Engineering Approach

Early Detection Research Network



BRL: Biomarkers Readiness Level

Source: JPL/NASA

BIOMARKER DISCOVERY (2000-2006)

Early Detection Research Network

- More than 400 papers published on new biomarkers
- Seminal discoveries and study foundations

BIOMARKER DISCOVERY: Seminal Discoveries

Early Detection Research Network

- **Gene Fusion in Prostate Cancer; first ever report for a major epithelial tumor (Chinnaiyan); Translocation in Bladder Cancer (Sidransky)**
- **Auto-antibodies as Biomarkers for Lung and Prostate cancers (Hanash, Chinnaiyan, Tainsky)**
- **Pioneering Work in Protein Patterns as Diagnostic Biomarkers (Semmes, Liotta)**
- **Mitochondrial Mutations as Cancer Biomarkers (Sidransky)**

DISCOVERY IN CONJUCTION WITH VALIDATION IS CRITICAL

Early Detection Research Network

EDRN-supported discoveries are:

- **Linked to clinical needs**
- **Verifiable**
- **Triaged to minimize bias, chance and confounders**

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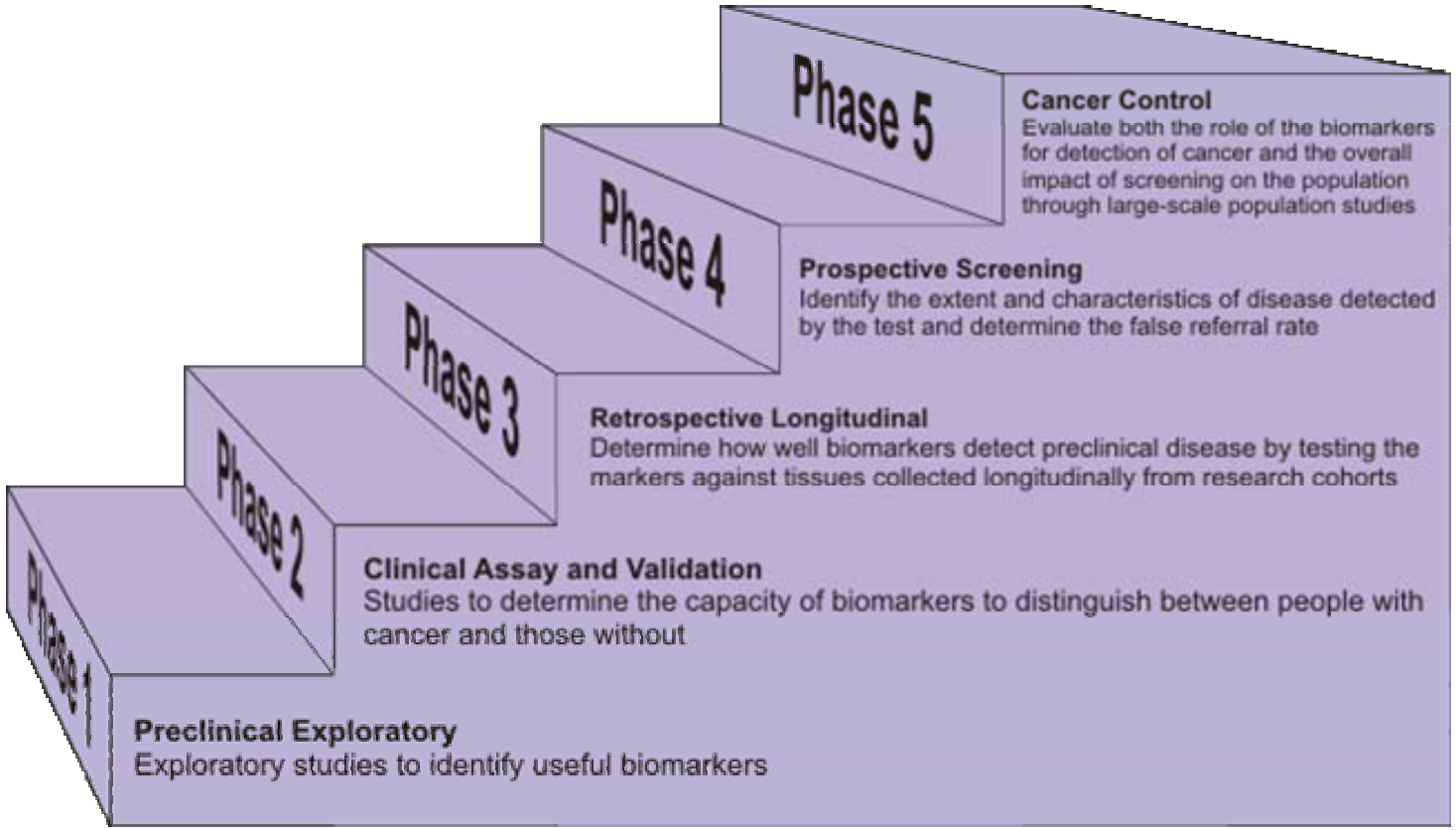
OUT OF DISCOVERY, GET INTO CLINICS… BIOMARKER VALIDATION

Early Detection Research Network

- Systematic Approach to Biomarker Validation
    - Phases of Biomarker Validation
    - Two-stage Validation Design
    - Sample Reference Libraries
- EDRN Validation Studies in Progress
- EDRN Validation Studies in the Pipeline

PHASES OF BIOMARKER VALIDATION

Early Detection Research Network



Source: J. Natl. Cancer Inst. 93, 1054-1061, 2001

Sample Reference Libraries

Early Detection Research Network

Reference Libraries are sets of samples with cases and controls statistically powered to allow rapid 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

Example: Sample Reference Libraries

Early Detection Research Network

	Reference Set A	Reference Set B
Clinical context	**Diagnosis of lung cancer**	**Early diagnosis of lung cancer**
Study design	**Case-control study**	**Case-control study**
Study population	**All suspicious lung lesions on CXR or on CT**	**CT screening**
Cases	**Lung cancers, ≥50% Stage I**	**Detected by CT- lung cancer >0.5cm and <3cm**
Controls	**Clinically free of lung cancer at 1year after enrollment 75 patients with other cancers (25 breast, 25 colon,25 prostate)**	**Detected by CT with a lung nodule >0.5cm and <3cm Detected by CT without a lung nodule All free of disease at the 1 year F/U CT 75 patients with other cancers (25 breast, 25 colon, 25 prostate)**
Matching criteria	**Age, sex, smoking status, PKYs**	**Age, sex, smoking status, PKYs**
Sample size Rapid pre-validation (1) Combined pre-validation (2)	**(1) 50 cases 100 controls, 25 other cancer controls (2) 475 (200 cases and 200 controls, 75 other cancer controls)**	**(1) 50 cases 100 controls, 25 other cancer controls (2) 675 (200 cases, 400 controls, 75 other cancer controls)**
Pulmonary diseases	**Enriched across whole population**	**Enriched in controls with CT detected lung nodules**
Institution provider candidates	**Pittsburgh, Vanderbilt, MDACC, Moffitt, NYU, UCLA, Mayo, Lovelace**	**Pittsburgh, Moffitt, NYU, UCLA, Mayo**

VALIDATION STUDIES IN PROGRESS: MICROSATELLITE ALTERATIONS (MSA) IN URINE SEDIMENT

Early Detection Research Network

1. **Determine the sensitivity and specificity of a panel of 15 MSA markers in urine sediment to detect bladder cancer, both for first malignancy and for recurrence.**

2. **Determine the temporal performance characteristics of MSA in urine sediment.**

3. **Determine which markers or combination of markers are most predictive of the presence of bladder cancer.**

Design: Case-control study

Status:

Cases: 200 enrolled out of 300

Control: 130 enrolled out of 200

MSA in Urine Sediment: Participants

Early Detection Research Network

Name	Institution
Joseph W. Basler, M.D., Ph.D.	University of Texas
Guido Dalbagni, M.D.	Memorial Sloan-Kettering
Colin P. Dinney, M.D.	M.D. Anderson Cancer Center
Margaret F. Fay, PhD, RN, MA, CCRC	LURN (Linked Urology Research Network)
Adam Kibel, M.D.	Washington University
Laurence Klotz, M.D., FRCSC	University of Toronto
Cheryl T. Lee, M.D.	University of Michigan
Seth P Lerner, M.D., F.A.C.S	Baylor College of Medicine
Edward Messing, M.D.,F.A.C.S.	University of Rochester Medical Center
Joseph C. Presti, Jr., M.D.	Stanford University
Mark P. Schoenberg, M.D. (PI)	Johns Hopkins University
Neal Shore, M.D.	Carolina Urologic Research Center
Gary D. Steinberg, M.D., F.A.C.S.	University of Chicago Urology Center
Donald Urban, M.D.	University of Alabama, Birmingham

VALIDATION STUDIES IN PROGRESS: AFP versus DCP for Hepatocellular Carcinoma

Early Detection Research Network

1. **Determine the sensitivity and specificity of des-gamma carboxyprothrombin (DCP) for the diagnosis of early hepatocellular carcinoma (HCC).**

2. **Compare performance characteristics of DCP and Alpha-fetoprotein (AFP) in the diagnosis of early HCC.**

3. **Determine whether demographic or etiology of underlying liver disease alter the expression of DCP or AFP.**

<u>Design:</u> Case-control study

cases: modified TNM stage I and II HCC (eligible for liver transplant), prior to any cancer therapy

controls: cirrhosis without tumor

VALIDATION STUDIES IN PROGRESS: AFP versus DCP for Hepatocellular Carcinoma

Early Detection Research Network

Name	Institution
Jorge Marrero, MD PI	University of Michigan
Myron Schwartz, MD & Josep Llovet, MD	Mount Sinai University Hospital
Rajender Reddy, MD	University of Pennsylvania
Lewis Roberts, MB, ChB, PHD	Mayo Clinic, Rochester
Alex Befeler, MD	Saint Louis University
Mindie H. Nguyen, M.D	Stanford University
David Chia, PhD	University of California Los Angles

Status:

- **Cases: 250 enrolled out of 450**
- **Controls: 200 enrolled out of 450**

VALIDATION STUDIES IN PROGRESS: EDRN-PLCO-SPORE Ovarian Markers

Early Detection Research Network

1. **Identify a consensus panel comprised of biomarkers that are most informative in detecting early ovarian cancers (CA 72-4, CA 15-3, CEA, CA 19-9, SMRP-1, OV-1.10, HE-4, Osteopontin, HK-11, HK -10, Spondin-2, Prolactin and CA-125).**

2. **Establish and estimate the lead time of each individual marker in the panel and estimate a marker combination rule.**

3. **Evaluate the performance of final biomarker panel in PLCO preclinical samples.**

VALIDATION STUDIES IN PROGRESS: EDRN-PLCO-SPORE Ovarian Markers

Early Detection Research Network

NAME	*Institution*
Daniel Cramer, M.D.	**Brigham and Women's Hospital (BWH)**
Nicole Urban, ScD.	**Fred Hutchinson Cancer Research Center (FHCRC)**
Robert C. Bast, M.D.	**MD Anderson (MDA)**
Andrew Godwin, Ph.D	**Fox Chase Cancer Center (FCCC)**
Anna Lokshin, Ph.D	**Univ. of Pittsburgh Cancer Institute (UP)**
Martin McIntosh, Ph.D	**Fred Hutchinson Cancer Research Center (FHCRC)**
Edward Partridge, M.D.	**Univ. of Alabama at Birmingham (UAB)**
Steven Skates, Ph.D	**Mass General Hospital (MGH)**

VALIDATION STUDIES IN PIPELINE

Early Detection Research Network

Samir Hanash
Validation of Protein Markers of Lung Cancer (autoantibodies to annexins I & II and PGP9.5., includes acute phase reactants CRP and serum amyloid A)

Harvey Pass
Serum Protein Biomarkers for Early Detection of Mesothelioma (serum mesothelin related-protein and osteopontin)

David Sidransky
Circulating DNA Methylation Markers of Lung Cancer (6 gene panel)

Alan Partin
GSTP1 Methylation Markers in Screen-Detected Prostate Biopsy as reflex markers

continues…

VALIDATION STUDIES IN PIPELINE, continued…

Early Detection Research Network

Stephen Meltzer
A panel of methylation markers (p16, HPP1, RUNX3) to determine the risk of progression from Barrett's esophagus to esophageal adenocarcinoma

Robert Getzenberg and Robert Schoen
Novel serum based markers, Colon Cancer Specific Antigen-3 and -4 (CCSA-3 and CCSA-4), for detection of colorectal cancer.

Brian B. Haab
Discrimination of benign from malignant prostatic disease in men with elevated PSA using serum TSP-1.

Eleftherios Diamandis
Human Kallikreins, biomarkers for early detection and progression of prostate cancer.

Robert Getzenberg
EPCA (Early Prostate Cancer Antigen) as a markers for earlier detection of prostate cancer (sensitivity 92%, specificity is 94%).

Continues..

Have Biomarkers, Will Validate… Request for Biomarkers (RFB)

Early Detection Research Network

- R01 Investigators (David Beer, Ed Hirschowitz, Avi Spira) have joined with EDRN Investigators on Lung Cancer Biomarkers
- R01 Investigator (David Wong) Biomarkers for oral cancer in saliva are being tested in an EDRN Reference Laboratory
- NCI Intramural Investigator (Thomas Ried) has requested help from the EDRN on cervical cancer biomarkers
- SPORE Investigator (Robert Coffey in collaboration with EDRN PI Dean Brenner) Urinary PGE-M as a biomarker for the detection of large polyps or colorectal cancers
- R01 Investigators (David Ward and Gil Mor) Ovarian cancer biomarkers are being verified by EDRN

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COLLABORATIONS

Early Detection Research Network

- **More than 100 collaborative efforts within EDRN**

- **Active collaborations with major programs, such as: MMHC, SPORE, WHI, CARET, PCPT, PLCO and Consortium for Functional Glycomics (NIGMS)**

  - EDRN and PCPT Investigators have developed Prostate Cancer Risk Calculator

- **Much sought-after EDRN Associate Memberships expanding; many industrial/biotech companies joining EDRN**

- **On-going collaborations with HUPO, AACR and Gordon Conference**

Continues…

Collaborations, continued

Early Detection Research Network

Validation Studies/Trials Sponsored by Biotech/Pharmaceutical firms:

- **Cangen: MSA Study (non-exclusive license for MSA test)**
- **Eisai and Wako: DCP Study (provide free test kits)**
- **Ciphergen: Protein Profiling for Prostate Cancer**

EDRN'S RAID-Like Program For Rapid Independent Diagnostic Evaluation (PRIDE)

Early Detection Research Network

- **EDRN encourages extramural investigators to seek assistance from EDRN in cross-laboratory validation of their biomarker assays**
- **PRIDE develops and institutes quality assurance programs for biomarker testing and evaluation**
- **PRIDE announcement will be made through NIH Guide**

PARTNERSHIPS

Early Detection Research Network

- **Ontario Cancer Biomarkers Research Network (Dr. Elefitherios Diamandis)**
- **Irish Cancer Biomarkers Research Network (Dr. Mark Lawler)**
- **Canary Foundation for Early Detection Research (Donald Listwin)**
- **Human Proteome Project, HUPO**

OUTREACH ACTIVITIES

Early Detection Research Network

- **AACR-Sponsored Sunrise Program on NCI Early Detection Research Network**
- **EDRN Investigators and Program Officers Invited to "Meet-the-Expert" sessions by AACR and ASCO**
- **EDRN-Sponsored Sessions in HUPO, AACR Special Meetings, ASMP, RSNI, Am. Urol. Soc.**

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BIOMARKERS AND BIOINFROMATICS IN SUPPORT OF EDRN-SPECIFIC NEEDS

Early Detection Research Network

EDRN Informatics Infrastructure Blueprint was established in 2001 to:

- **Support multi-institutional Validation Studies**
- **Establish Virtual Specimen Bank**
- **Support secure data transfer, data analysis and communication**
- **Support EDRN-wide data storage, curation and retrieval of multidimensional, multi-format data**
- **Details on EDRN Informatics Infrastructure published in Informatics in Proteomics, ed. Srivastava 2005, Marcel Dekker)**

EDRN has Created a Biomarker Knowledge Environment

COLLABORATION WITH caBIG

Early Detection Research Network

- EDRN Common Data Elements (CDE) posted on caBIG portal
- Integration of ERNE and caTISSUE is underway
- Request for Bioinformatics Biomarkers Interest Group is pending with caBIG leadership

SUMMARY

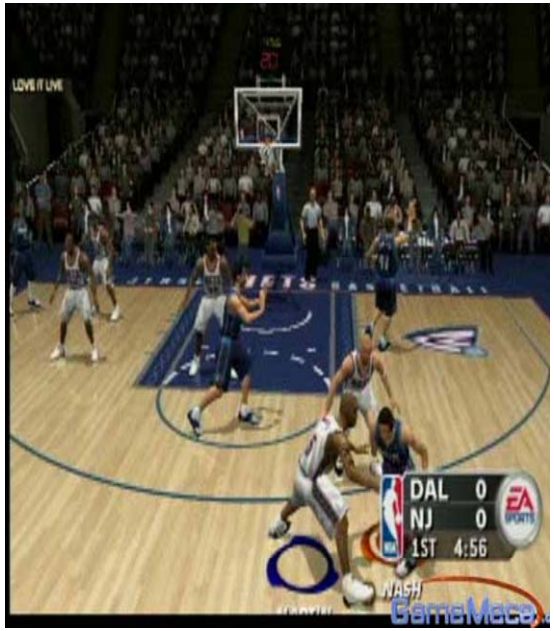
Early Detection Research Network

- **EDRN is a dynamic infrastructure meeting the challenge of rapidly evolving technologies and translational biology**
- **EDRN empowers investigators and challenges them to meet scientific expectations**
- **EDRN rewards collaborations and teamwork**

Team Science

Early Detection Research Network

“The most successful and efficient research about molecular markers will require effective interdisciplinary communication and collaboration involving fields of molecular biology, observational epidemiology and biostatistics.”



Ransohoff, Nature Rev Cancer 2004; 4:309-314

Early Detection Research Network

SUCCESSFUL INFRASTRUCTURE

BIOMARKER DISCOVERY

BIOMARKER VALIDATION

COLLABORATIONS AND PARTNERSHIPS

BIOMARKERS AND BIOINFORMATICS

NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE