Early Detection Research Network (EDRN)
A National Infrastructure for Biomarker Development

NCI Board of Scientific Advisors
June 2014

Barry Kramer, M.D., M.P.H.
Director, Division of Cancer Prevention
EDRN Program Objectives

- Establish an investigator-initiated infrastructure to support development and validation of early detection biomarkers and markers of progression
- Foster interaction between academic, clinical and industrial leaders
- Standardize biomarker validation criteria
- Develop a quality assurance program
- Bring biomarkers to clinical use
Organization of EDRN

Biomarker Reference Laboratories

Biomarker Developmental Laboratories

Clinical Validation Centers

Network Consulting Team
Chair: Larry Norton, M.D.

Steering Committee
Chair: Ian Thompson
Co-Chair: Joshua Labaer

Data Management and Coordinating Center
Director: Ziding Feng, Ph.D.

Discovery
Assay Development
Validation Informs Discovery
Validation
Biomarker Triage System in EDRN

BDLs = Biomarker Development Labs; BRLs = Biomarker Reference Labs; CVCs = Clinical Validation Centers; DMCC = Data Management and Coordinating Center.
Scientific Accomplishments
Study Designs for Biomarker Development

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

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**Phases of Biomarker Development for Early Detection of Cancer**
Margaret Sullivan Pepe et al.

**Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design**
Margaret Sullivan Pepe et al.
*J Natl Cancer Inst* 2008; 100:1432-1438
Partnering Organizations

- National Institute of Standards and Technology
- Center for Prostate Disease Research, DOD
- Pacific Northwest National Laboratory, DOE
- Jet Propulsion Laboratory, NASA
- Canary Foundation of America
- Lustgarten Foundation N.Y.
- International collaborations:
  - China (C-EDRN), Cancer Research-UK, Turkey, Japan, Chile, Israel
- Industry (15 active)
- Associate Members (more than 200)
Strategic Partnerships

• Precompetitive data sharing (e.g., proPSA with Beckman Coulter, PCA3 with GenProbe)

• Leveraging Resources
  o **Canary, Inc.** uses EDRN Data management system for lung and prostate markers
  o **Lustgarten Inc.** funded 20-hybridoma cell lines for pancreatic candidate markers

• International Partnerships
  o **Turkey, Chile** (mesothelioma)
  o **China** (HCC, lung)
  o **Cancer Research UK** (pancreatic, lung)
  o **EU European Advanced Translational Research Infrastructure** (www.eatris.eu)
Meeting the Goals

- Provide Integrated Infrastructure
- Build Resources for Biomarker Research
- Establish Standardized Criteria for Biomarker Discovery and Validation
- Quality Assurance Programs
- Ensure Research Reproducibility
- Improve Screening and Diagnostic Tests for Common Clinical Dilemmas
# EDRN Milestones: From Structure to Process to Outcomes

<table>
<thead>
<tr>
<th>2000-2005</th>
<th>2005-2010</th>
<th>2010-Present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coordinate, Communicate and Collaborate</strong></td>
<td><strong>Learn, Improve and Deliver</strong></td>
<td><strong>Productivity, Outcome and Dissemination</strong></td>
</tr>
<tr>
<td>✓ 33 Principal Investigators</td>
<td>✓ 45 Principal Investigators</td>
<td>✓ 57 Principal Investigators</td>
</tr>
<tr>
<td>✓ Steering Committee Attendance: 85; Workshop 300</td>
<td>✓ Steering Committee Attendance: 120; Workshop 300</td>
<td>✓ Steering Committee Attendance: 150; Workshop: 350</td>
</tr>
<tr>
<td>✓ Associate Membership Program Initiated; 32 Associate Members</td>
<td>✓ 123 Associate Members</td>
<td>✓ 231 Associate Members</td>
</tr>
<tr>
<td>✓ Initiated EDRN-Human Proteome Organization Plasma Proteome Project</td>
<td>✓ MOUs signed With Canary Foundation, Lustgarten Foundations, Turkey</td>
<td>✓ proPSA and PCA-3 FDA Approved for Prostate Cancer</td>
</tr>
<tr>
<td>✓ Guidelines for Biomarker Discovery and Validation</td>
<td>✓ OVA1 FDA Approved</td>
<td>✓ 11 CLIA-approved Diagnostic Tests</td>
</tr>
<tr>
<td>✓ Project Management Tools Created</td>
<td>✓ EDRN-FDA Educational Biennial Workshop</td>
<td>✓ 10 Clinical Reference Sets completed and stored at Frederick, MD</td>
</tr>
<tr>
<td>✓ Multi-center Trial Informatics Infrastructure created, verified</td>
<td>✓ EDRN-NIST Workshop on Standards</td>
<td>✓ IRB Approvals Monitored: 216; 200 Protocols;100 MTAs</td>
</tr>
<tr>
<td>✓ Virtual Specimen Bank Established</td>
<td>✓ IRB approvals monitored: About 80 sites</td>
<td>✓ IRB Approvals Monitored: 216; 200 Protocols;100 MTAs</td>
</tr>
<tr>
<td>✓ IRB Approvals Monitored: 38 sites</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Integrated Infrastructure
(BDLs, BRLs, CVCs, DMCC)

- Vertically integrated infrastructure for discovery, development and validation of biomarkers:
  - >200 active protocols; >100 MTAs and IRBs
  - >800 candidate biomarkers prioritized for evaluation;
  - ~300 moved forward to Phase II and Phase III validation
  - >10,000 subjects enrolled
  - >12 clinical validation studies

- Policy and Procedures in place for transparency and effective management

- Effective hand-off mechanism from BDL to BRL to CVC

“The EDRN [process]…helps the field to avoid numerous competing claims of being ‘the biomarker of choice,’ the notion of which arises simply from marketplace competition or differences between laboratories.

The EDRN approach facilitates well-designed clinical studies that have an increasing hierarchy of complexity.”

AACR-NCI Think Tank: Charting the Future of Cancer Prevention, 2008
Building Resources for Clinical Studies

- Platform for multi-center biomarker validation studies
- CLIA-approved laboratories to develop and test assays using GLP and GMP
- Centralized statistical center for data analysis and informatics infrastructure to share data
- Mechanism for biomarker triaging prior to large, expensive validation studies (use of Reference Sets)
- > 100,000 clinically-annotated biospecimens using common data elements (CDEs)
Building Resources for Clinical Studies
Standard Biospecimen Reference Sets

Housed at Frederick National Laboratory

- Bladder
- Breast
- Colon
- Lung
- Liver
- Pancreas
- Prostate
- Ovary

http://edrn.nci.nih.gov/resources/sample-reference-sets
Building Resources for Clinical Studies
Informatics and Bioinformatics (Jet Propulsion Lab)

- VSIMS for multicenter validation studies
- eSIS for study management
- ERNIE for Virtual Specimen Banks established (tracks >100,000 biospecimens)
- Prioritized Biomarker Database
- >2600 Common Data Elements
- Validation data collected through LabCAS (proteomic and genomic data) and eCAS
- Crowd-sourcing being considered on stored data

http://edrn.nci.nih.gov/informatics/informatics
Scientific Accomplishments
Decision Criteria for Biomarker Triaging

Example: Colon Cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>TPR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galectin-3 ligand</td>
<td>72%</td>
<td>20%</td>
</tr>
<tr>
<td>Vimentin Methylation</td>
<td>83%</td>
<td>15%</td>
</tr>
<tr>
<td>K-ras in Urine</td>
<td>77%</td>
<td>35%</td>
</tr>
<tr>
<td>K-ras FOBT card</td>
<td>14%</td>
<td>35%</td>
</tr>
<tr>
<td>GOS</td>
<td>77%</td>
<td>51%</td>
</tr>
<tr>
<td>GOS +FOBT</td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td>Proteomics-Agilent</td>
<td>78%</td>
<td>12%</td>
</tr>
<tr>
<td>Proteomics-PBSIIc</td>
<td>70%</td>
<td>24%</td>
</tr>
<tr>
<td>Proteomics-SELDI-TOF</td>
<td>19%</td>
<td>2%</td>
</tr>
<tr>
<td>Proteomics-MALDI-TOF</td>
<td>63%</td>
<td>52%</td>
</tr>
<tr>
<td>p53</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>CEA</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Topoisomerase II</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Cathepsin D</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Cyclin B</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>IGF Binding Protein 2</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>TRAILR2 (diaDexus)</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>CIN248 (diaDexus)</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>P108 (diaDexus)</td>
<td>27%</td>
<td>6%</td>
</tr>
<tr>
<td>Three diaDexus Alone</td>
<td>29%</td>
<td>40%</td>
</tr>
<tr>
<td>Three diaDexus+FOBT</td>
<td>42%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Decision Rules

Rapid Biomarker Screening in Reference Sets
Scientific Accomplishments

> 800 Verified Biomarkers in the Pipeline

- Vimentin methylation in stool as a biomarker of advanced adenoma (Sandy Markowitz)
- TMPRSS2-ERG (T2-ERG) fusion for detection of aggressive prostate cancer (Arul Chinnaiyan)
- 80-gene panel for lung cancer detection now being verified for application in nasal epithelium (Avrum Spira)
- Circulating DNA for colon, ovary and endometrial cancer (Ken Kinzler/Bert Vogelstein)

>1900 publications; ~22% in journals with impact factor ≥7

Source: EDRN Strategic Plan and EDRN: A Quantitative Analysis of Productivity
## Completed Validation Studies

Five FDA Approved Diagnostic Tests

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Clinical Utility</th>
<th>Year of Approval</th>
<th>EDRN PI/Industrial Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>%[-2]proPSA</td>
<td>Reduce the number of unnecessary initial biopsies. Also, appears to be highly associated with increased risk of aggressive disease.</td>
<td>2012</td>
<td>Dan Chan/Beckman Coulter</td>
</tr>
<tr>
<td>PCA3 (in urine)</td>
<td>Repeat biopsy decisions in patients at risk for prostate cancer.</td>
<td>2012</td>
<td>John Wei/Gen-Probe</td>
</tr>
<tr>
<td>OVA1™ (5 analytes: CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin)</td>
<td>Prediction of ovarian cancer risk in women with adnexal mass.</td>
<td>2010</td>
<td>Dan Chan/Vermillion</td>
</tr>
<tr>
<td>Risk of Ovarian Malignancy (ROMA)</td>
<td>Prediction of ovarian cancer risk in women with pelvic mass.</td>
<td>2011</td>
<td>Steve Skates/Fujirebio Diagnostics</td>
</tr>
<tr>
<td>DCP and AFP-L3 combined panel of markers</td>
<td>Risk assessment for development of hepatocellular carcinoma.</td>
<td>2011</td>
<td>Jorge Marrero/Wako Diagnostics (&gt; 1 million sold)</td>
</tr>
</tbody>
</table>
Eleven CLIA (Clinical Lab Improvements Amendments) Certified Diagnostic Tests

<table>
<thead>
<tr>
<th>Biomarker Assay</th>
<th>Purpose</th>
<th>PI/CLIA Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiPS (Mi Prostate Score Urine test), Multiplex analysis</td>
<td>Detection of prostate cancer</td>
<td>A. Chinnaiyan/Gen-Probe</td>
</tr>
<tr>
<td>of T2-ERG gene fusion, PCA3 and serum PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC and FISH for T2-ERG fusion</td>
<td>Detection of prostate cancer</td>
<td>A. Chinnaiyan/Roche</td>
</tr>
<tr>
<td>GSTP1 methylation</td>
<td>Repeat biopsies in prostate cancer</td>
<td>D. Sidransky/OncoMethylome</td>
</tr>
<tr>
<td>Mitochondrial deletion</td>
<td>Detection of prostate cancer</td>
<td>NIST/Mitomics</td>
</tr>
<tr>
<td>Proteomic panel</td>
<td>Detection of lung cancer</td>
<td>W. Rom/Celera</td>
</tr>
<tr>
<td>Aptamer-based markers</td>
<td>Detection of lung cancer</td>
<td>W. Rom/Somalogic</td>
</tr>
<tr>
<td>80-gene panel</td>
<td>Detection of lung cancer</td>
<td>A. Spira/Allegro</td>
</tr>
<tr>
<td>Vimentin methylation in stool</td>
<td>Detection of colon cancer</td>
<td>S. Markowitz/LabCorp</td>
</tr>
<tr>
<td>Galectin-3 ligand</td>
<td>Detection of advanced adenomas and colon cancer</td>
<td>R. Bresalier/BG Medicine</td>
</tr>
<tr>
<td>GP73</td>
<td>Risk of hepatocellular carcinoma</td>
<td>T. Block/Beckman Coulter</td>
</tr>
<tr>
<td>8-gene Panel for Barrett’s Esophagus</td>
<td>Progression Prediction of BE</td>
<td>Stephen Meltzer//Diagnovus</td>
</tr>
</tbody>
</table>
Scientific Accomplishments
Ongoing and Planned Studies: Examples

**Ongoing: >12 studies**

- DNA methylation and Galectin-3 ligand, and DNA markers for advanced adenoma and colon cancer detection (D. Brenner; Exact Sciences)
- SMRP and Fibulin-3 in mesothelioma (H. Pass; Chile)
- T2-ERG fusion and PCA3 score combined for detection of aggressive prostate cancer (Martin Sanda)
- Molecular biomarkers in airway and blood for detection of early stage lung cancer in indeterminate nodules (in collaboration with DOD)
- Hepatocellular Carcinoma Early Detection Strategy: biomarkers in detecting preclinical HCC

**Planned: >15 studies**

- PHI (pro-PSA) and PCA3 for improved prostate cancer detection
- SCHLAP1 (non-coding RNA) and SPOP in urine to complement PCA3/T2-ERG
- Biomarkers for prostate cancer progression among patients on Active Surveillance
- Partial wave spectroscopic [PWS] microscopy for screening for colorectal cancer and advanced adenoma
- Circulating ovarian cancer biomarkers in PLCO and UKCTOCS prediagnostic biospecimens
Program Evaluation

- BSA Review every 5 years
- EDRN Network Consulting Team (Chair: Dr. Larry Norton)
- Two site visits of each funded grant during the 5-year funding period, conducted with external consultants

Source: NCT Report 2014 and EDRN: A Quantitative Analysis of Productivity
Collaborate with Cooperative Groups and other NCI programs, e.g., NCORP, BeTRNet, PLCO and other NCI Consortia and Cohorts

Build on current EDRN/FDA interactions

Comparative Effectiveness Research, with attention to cost-effectiveness of biomarker-based diagnostics

Integrate quantitative imaging analysis of precancerous lesions with biomarker validation

Reduce screening-associated overdiagnosis and overtreatment of indolent cancers

Integrate genetic, cell signaling and biochemical pathways with biomarker discovery
Adapting to Changing Landscape of Biomarker Science

- Focus on indeterminate nodules identified by screening lung CT (25% of subjects in National Lung Screening Trial)
- Changing regulatory requirements for biomarker qualifications (FDA)
- Responding to regulatory needs, e.g., a laboratory selected for e-cigarette evaluation
- Response to congressional directives on ‘recalcitrant cancers’, e.g. pancreas, liver and lung
- Focus on developing biomarkers for overdiagnosed cancers such as breast, prostate
Justification for Reissuance Request

• Maintain collaborative, comprehensive infrastructure and resources critical for biomarker discovery and validation; does not exist without EDRN

• Accelerate the development of biomarkers that will change practice – an important mission of the NCI

• Ensure data reproducibility and integrity; negative findings are as important as positive ones
  o Checks and balances for unsubstantiated claims and data reproducibility
  o Economy of scale compared to individual efforts
Justifying the Request for RFA Mechanism

- Required to maintain EDRN infrastructure (akin to NCTN, NCORP), resources and integrated systems for new biomarker development and validation trials.

- Program oversight and coordination is required to maintain a network of multidisciplinary groups and institutions.

- Set-aside funding is required to ensure adequate funding for conducting large scale, multi-institutional biomarker validation studies and maintain biorepositories as a national resource.
EDRN Funding History

- 2005-2010: BSA Approved Funding = 35 Million
- 2010-present: Funding Approved by NCI = 32 Million
- Request = 30 Million

Legend:
- BSA Approved Funding
- Funding Approved by NCI
- Request
Justification for Budget Request

$5 million/year increase will:

• Cover increased complexity and cost of mid/late phase marker validation (relative to early phase costs)

• Permit addition of laboratories and centers focused on recalcitrant cancers (e.g., pancreas, lung, liver)

• Allow expansion of research to additional high-priority tumors
Recent Delay-adjusted SEER Incidence Trends with Approximate Percent Change, 2001-2010
By Cancer Site

Approximate Percent Change from 2001 to 2010
Based on jointpoint models fit to SEER 13 delay adjusted rates from 1992-2010
Budget

• Substantial reductions in prior years (2010–2015) from $32 M to $25 M per year
  o Many meritorious validation projects on hold

• EDRN requests a budget of $30 M/year for 5 years (2015–2020)
  o Biomarker Developmental Laboratories (BDL) – $9 M
  o Biomarker Reference Laboratories (BRL) – $2 M
  o Clinical Validation Centers (CVC) – $10 M
  o Data Management and Coordinating Center (DMCC) – $3 M
  o Core Fund, which supports large multi-center biomarker validation studies involving patient accrual and biospecimen collection – $6 M
Thank you
Health Economics
Use of Biomarkers Can Reduce Healthcare Costs

• 7.5 million screening colonoscopies at an average cost of $1,600 each year
  o Just a 10% reduction in screening colonoscopies using could save $1.2 billion.

• 600,000 indeterminate lung nodules 8-30 mm undergo diagnostic work-up each year (calculated by a random sample of private and academic pulmonologist practices).
  o Only one-third were cancer and two-thirds were benign
  o The costs of CT Scan, bronchoscopes or FNAs, PET scans, and VATS were about $9 billion
  o One-third of these costs ($3 billion) could be saved by a blood test. (Courtesy: Integrated Diagnostics.)
Some companies are already doing this
Sage Bionetworks / Steven Friend, M.D.
Canary Foundation collaborated with Sage Bionetworks to integrate proteomic, genomic, epigenomic data on lung cancer signatures in nonsmokers; bioinformatic analysis continues...
Does the Total Exceed Sum of Its Parts?

THEN (Prior to 2000)
- No SOPs for biosamples, reagents, methodologies, etc.
- No common data elements (data dictionary) to enable the development of common databases for biosample annotation
- Fragmented studies with convenience samples, not generalizable

NOW
- Network of integrated resources for supporting validation
- Checks and balances ensure good biomarkers are promoted without regard to pecuniary interests
- Provides infrastructure for promising markers to become medical tools
- Standard operating procedures for biosample collection and management.
- Developed roadmap for study designs for clinical verification and validation
- EDRN activities are not replicated within industry or academia
EDRN Biomarker Pipeline: Modeled After Drug Discovery Pipeline

BDLs = Biomarker Developmental Labs; BRLs = Biomarker Reference Labs; CVCs = Clinical Validation Centers; DMCC = Data Management and Coordinating Center.