National Cancer Institute

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

NCI Board of Scientific Advisors
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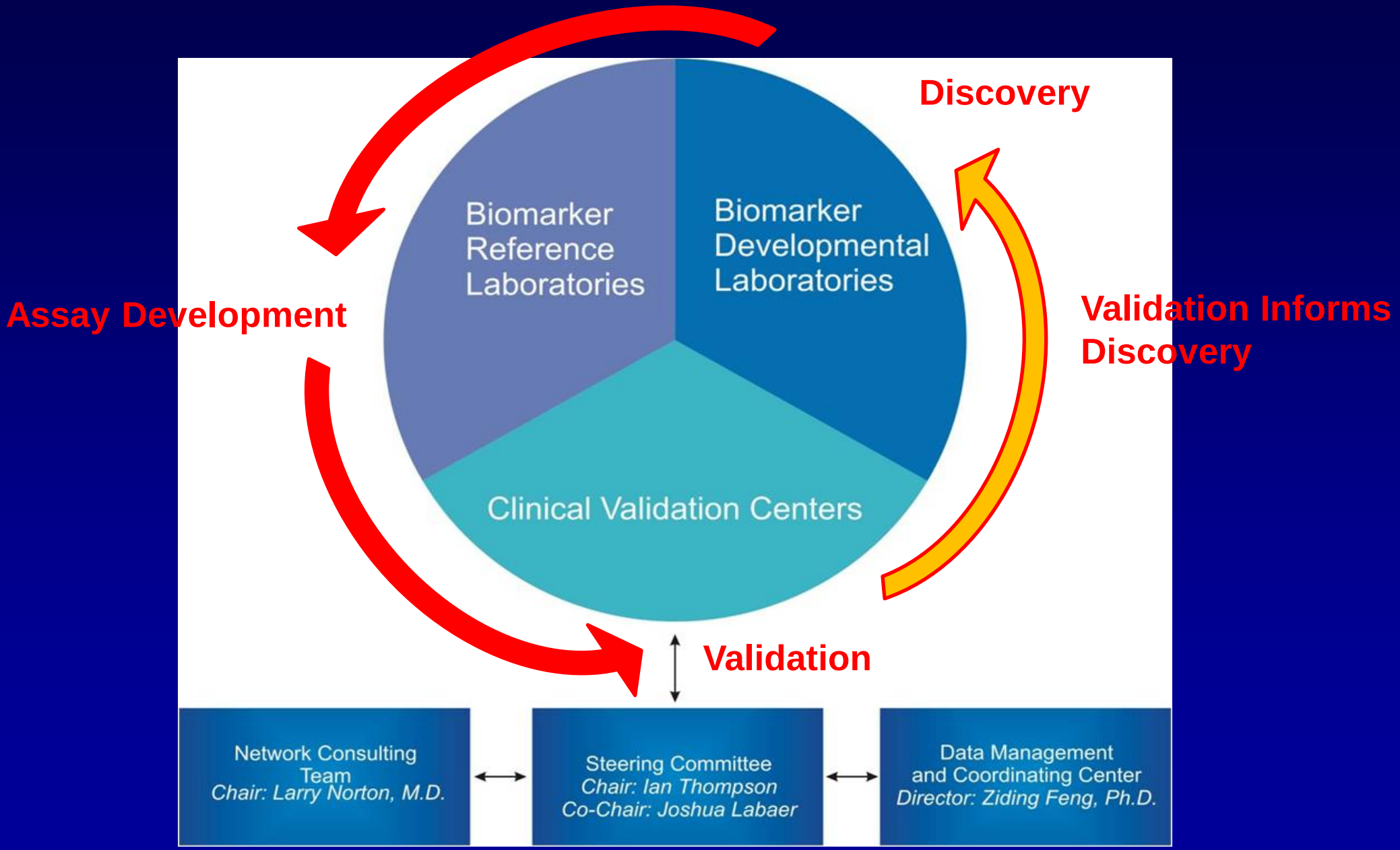
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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



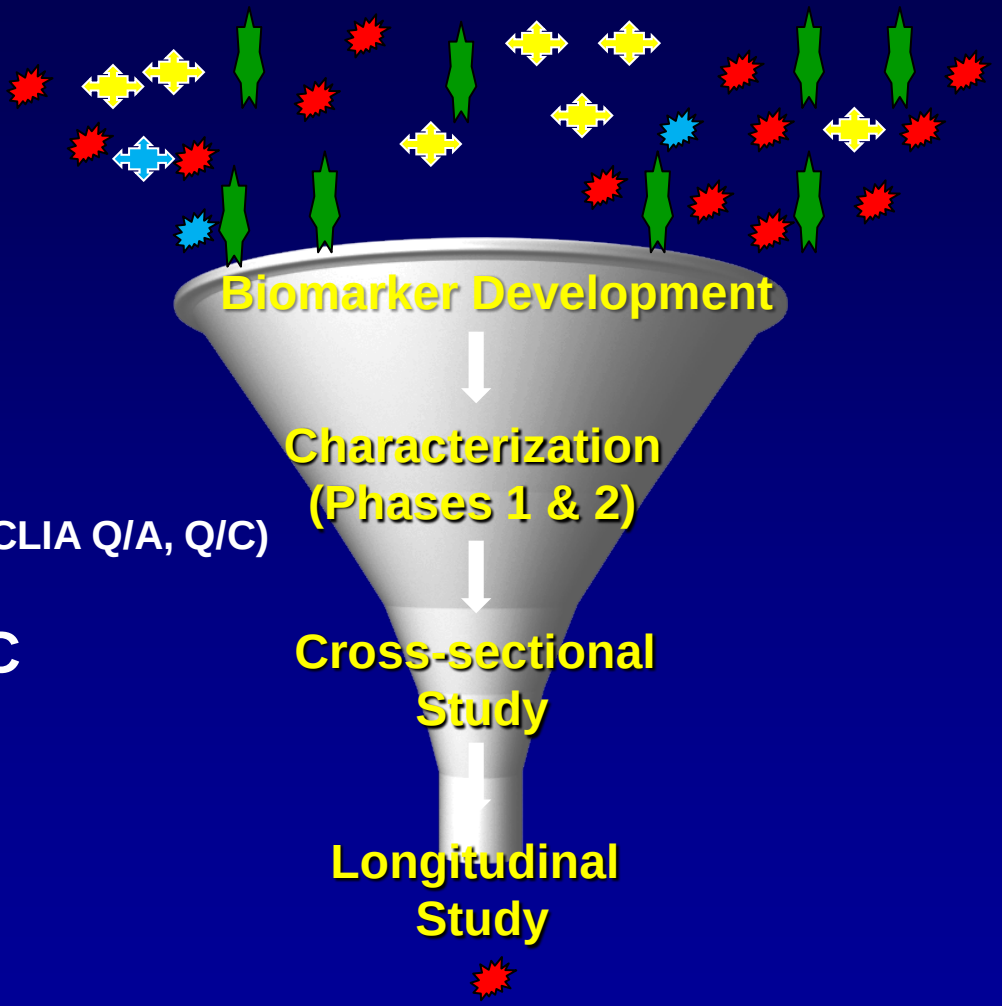
Biomarker Triage System in EDRN

BDL

Lab: BRL
(High throughput CLIA Q/A, Q/C)

Clinical: CVC

DMCC



Discovery

Markers from
both EDRN and
other researchers

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

PRoBE Study Design:
Prospective-Specimen-Collection, **R**etro**s**pective-**B**linded-**E**valuation

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*

Phases of Biomarker Development for Early Detection of Cancer
Margaret Sullivan Pepe et al.
J Natl Cancer Inst, Vol. 93, No. 14, July 18, 2001

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
  - Canary, Inc. uses EDRN Data management system for lung and prostate markers
  - Lustgarten Inc. funded 20-hybridoma cell lines for pancreatic candidate markers
- International Partnerships
  - Turkey, Chile (mesothelioma)
  - China (HCC, lung)
  - Cancer Research UK (pancreatic, lung)
  - 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

2000-2005 Coordinate, Communicate and Collaborate	2005-2010 Learn, Improve and Deliver	2010-Present Productivity, Outcome and Dissemination
✓ 33 Principal Investigators ✓ Steering Committee Attendance: 85; Workshop 300 ✓ Associate Membership Program Initiated; 32 Associate Members ✓ EDRN-Gordon Research Tie-up (2002, 2003) ✓ Initiated EDRN-Human Proteome Organization Plasma Proteome Project ✓ Guidelines for Biomarker Discovery and Validation ✓ Project Management Tools Created ✓ Multi-center Trial Informatics Infrastructure created, verified ✓ Virtual Specimen Bank Established ✓ IRB Approvals Monitored: 38 sites	✓ 45 Principal Investigators ✓ Steering Committee Attendance: 120; Workshop 300 ✓ 123 Associate Members ✓ 2 EDRN-Gordon Research Workshops (2005, 2007) ✓ MOUs signed With Canary Foundation, Lustgarten Foundations, Turkey ✓ OVA1 FDA Approved ✓ EDRN-FDA Educational Biennial Workshop ✓ EDRN-NIST Workshop on Standards ✓ IRB approvals monitored: About 80 sites	✓ 57 Principal Investigators ✓ Steering Committee Attendance: 150; Workshop: 350 ✓ 231 Associate Members ✓ DCP and AFP-L3 FDA Approved for Liver Cancer and ROMA for Ovarian Cancer ✓ proPSA and PCA-3 FDA Approved for Prostate Cancer ✓ 11 CLIA-approved Diagnostic Tests ✓ 10 Clinical Reference Sets completed and stored at Frederick, MD ✓ IRB Approvals Monitored: 216; 200 Protocols;100 MTAs

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

EDRN cited as a model organization (best practices for project management driven by milestones and operational guidelines, manual of operations, and team approach) by AACR, NCI Translational Research Working Group, IOM, Nature, Science, J. Proteome Research.

“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

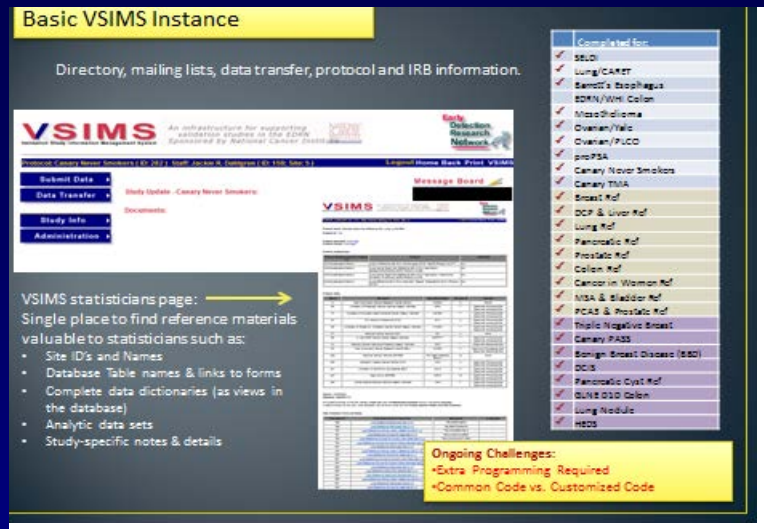
Housed at Frederick National Laboratory

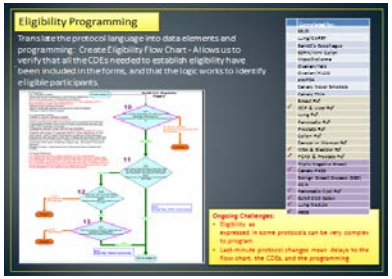
- **Bladder**
- **Breast**
- **Colon**
- **Lung**
- **Liver**
- **Pancreas**
- **Prostate**
- **Ovary**

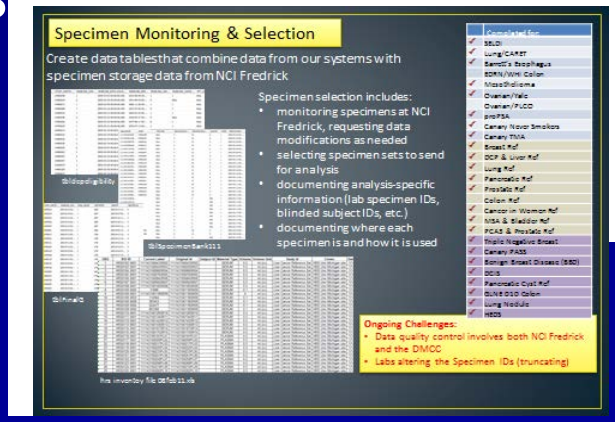
http://edrn.nci.nih.gov/resources/sample-reference-sets

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





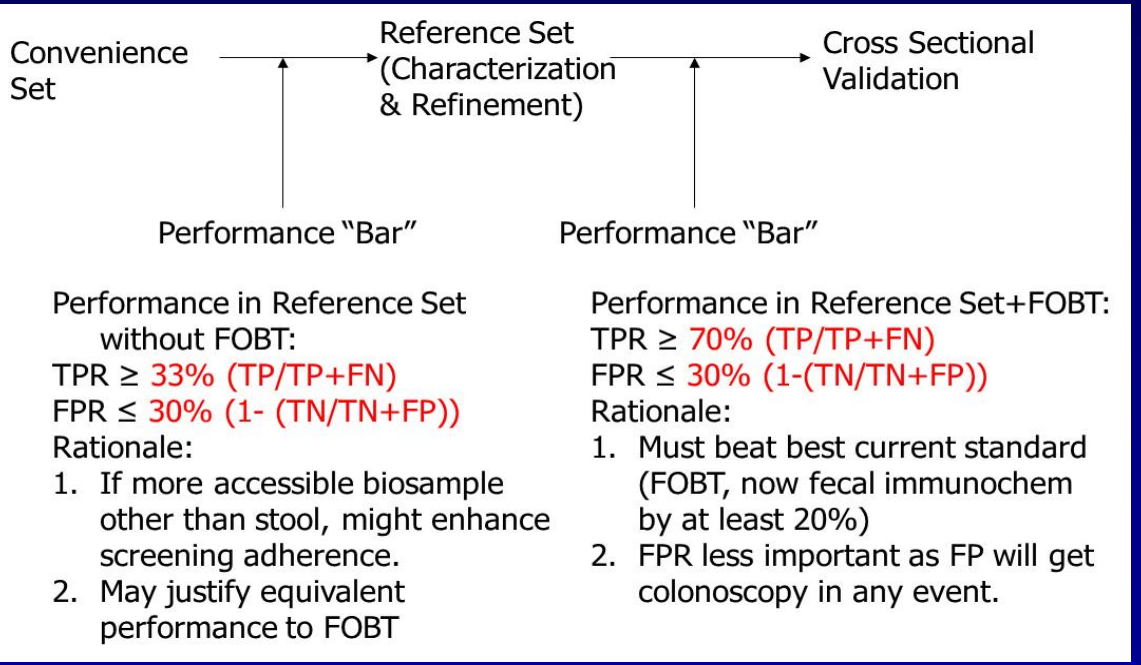


http://edrn.nci.nih.gov/informatics/informatics

Scientific Accomplishments

Decision Criteria for Biomarker Triaging

Example: Colon Cancer



Decision Rules

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

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

Biomarker	Clinical Utility	Year of Approval	EDRN PI/ Industrial Partner
%[-2]proPSA	Reduce the number of unnecessary initial biopsies. Also, appears to be highly associated with increased risk of aggressive disease.	2012	Dan Chan/ Beckman Coulter
PCA3 (in urine)	Repeat biopsy decisions in patients at risk for prostate cancer.	2012	John Wei/ Gen-Probe
OVA1™ (5 analytes: CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin)	Prediction of ovarian cancer risk in women with adnexal mass.	2010	Dan Chan/ Vermillion
Risk of Ovarian Malignancy (ROMA) algorithm with CA125 and HE4 blood tests for pelvic mass malignancies	Prediction of ovarian cancer risk in women with pelvic mass.	2011	Steve Skates/ Fujirebio Diagnostics
DCP and AFP-L3 combined panel of markers	Risk assessment for development of hepatocellular carcinoma.	2011	Jorge Marrero/ Wako Diagnostics (> 1 million sold)

Eleven CLIA (Clinical Lab Improvements Amendments) Certified Diagnostic Tests

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

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

- Two independent working groups: chaired by Drs. Bernard Levin (2004) and Harold Moses (2008)
- 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

Scientific Priority Areas

NCT Recommended New Directions

- 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 indentified 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

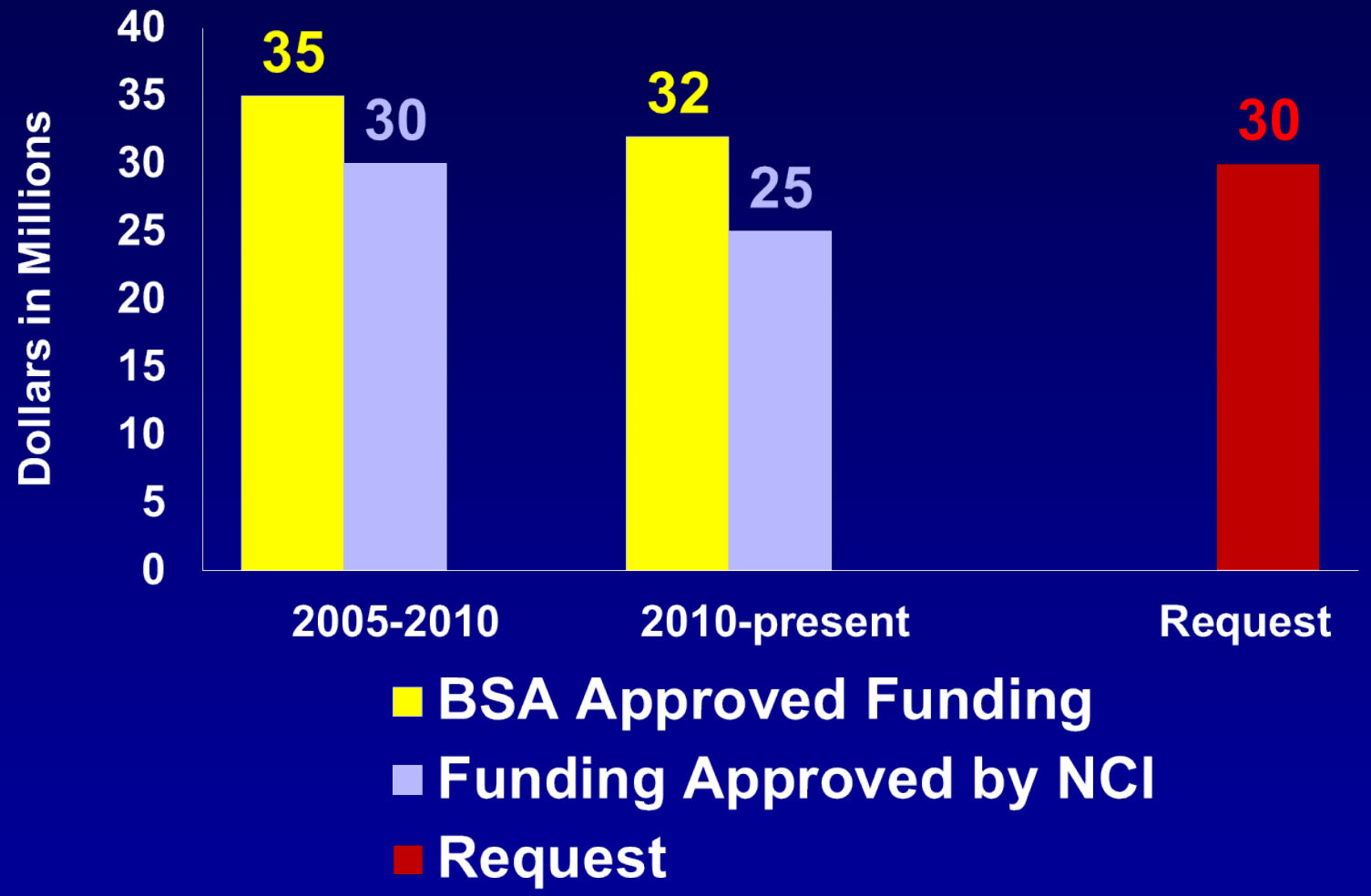
Justification for Reissuance Request

- 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
  - Checks and balances for unsubstantiated claims and data reproducibility
  - 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



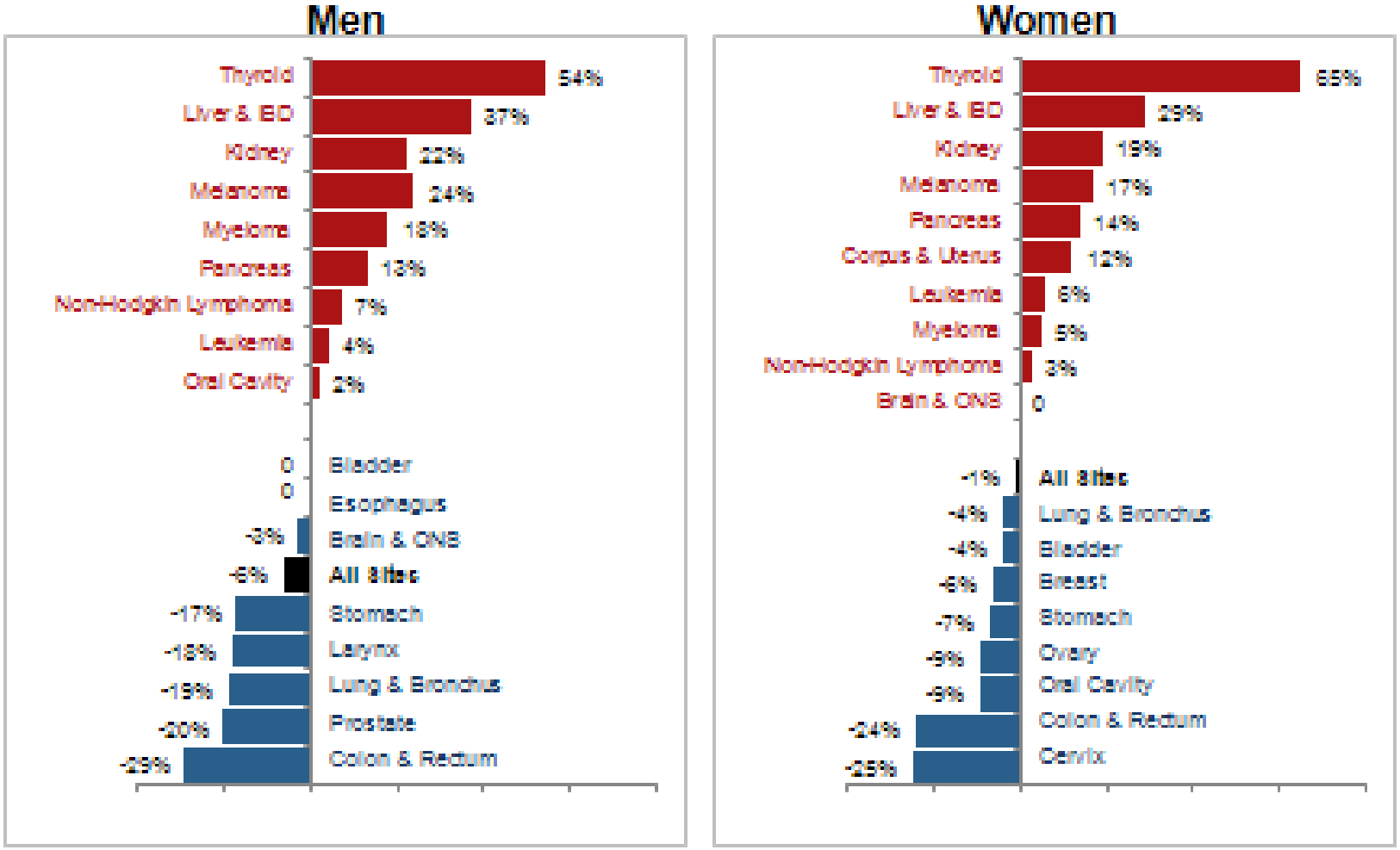
Justification for Budget Request

$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**
  - Many meritorious validation projects on hold
- **EDRN requests a budget of $30 M/year for 5 years (2015–2020)**
  - Biomarker Developmental Laboratories (BDL) – $9 M
  - Biomarker Reference Laboratories (BRL) – $2 M
  - Clinical Validation Centers (CVC) – $10 M
  - Data Management and Coordinating Center (DMCC) – $3 M
  - 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
  - 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).
  - Only one-third were cancer and two-thirds were benign
  - The costs of CT Scan, bronchoscopes or FNAs, PET scans, and VATS were about $9 billion
  - One-third of these costs ($3 billion) could be saved by a blood test. (Courtesy: Integrated Diagnostics.)

Cataloging Mutations, Proteomics, Genomics, Metabolomics

Some companies are already doing this

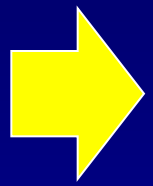
Sage Bionetworks / Steven Friend, M.D.

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

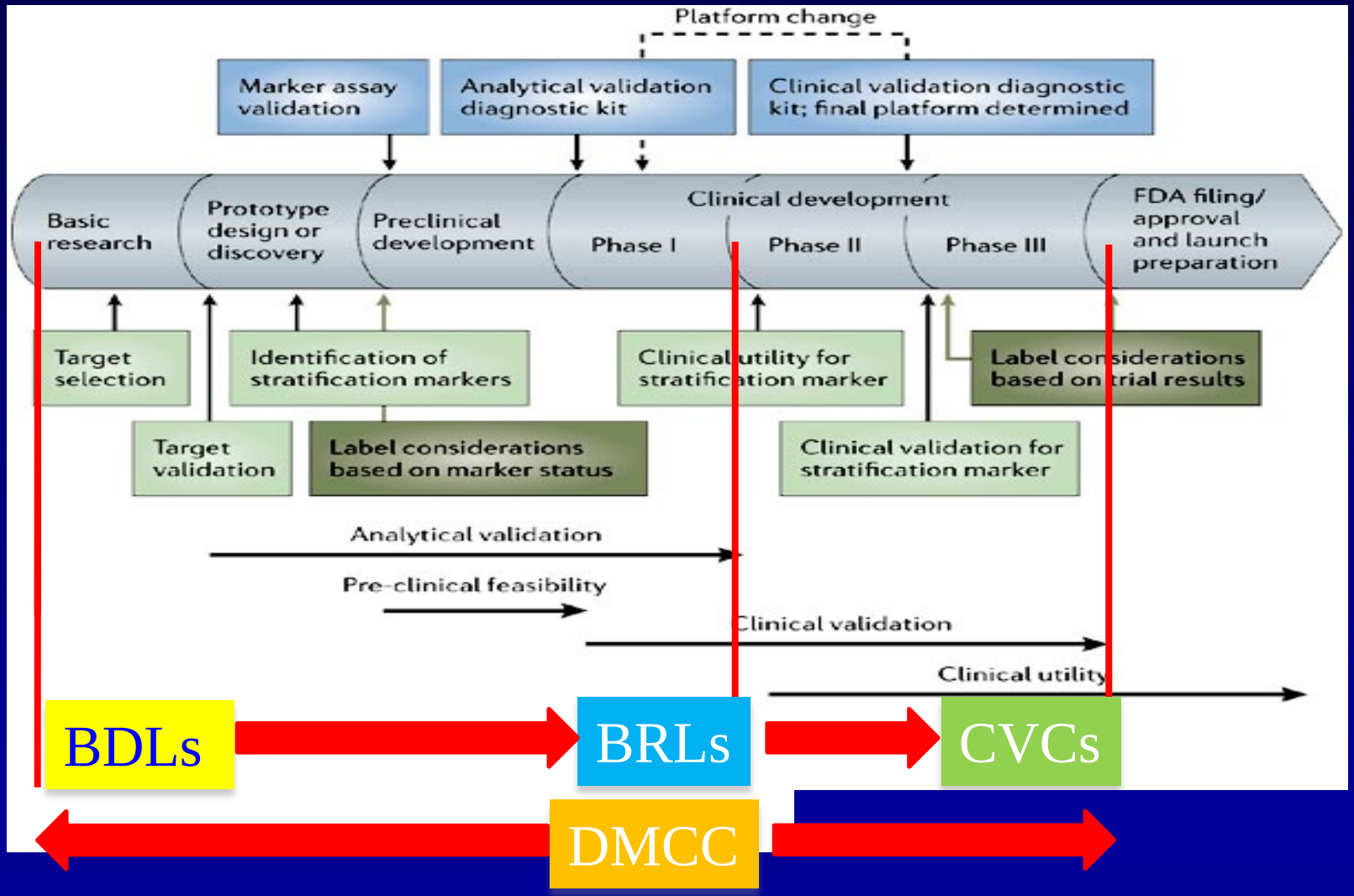


NOW

- 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



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