Early
Detection
Research
Network

EDRN Patient Advocacy Webinar

Early Detection Biomarkers for Lung Cancer

April 26, 2012 1pm EASTERN

NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

Agenda

Early Detection Research Network

Early Detection Research Network (EDRN) Presents
Patient Advocacy Webinar

1. **Welcome and Overview of the EDRN**
   Sudhir Srivastava, Ph.D., M.P.H.
   Chief, Cancer Biomarkers Research Group, NCI

2. **Early Detection Biomarkers for Lung Cancer**
   Pierre Massion, M.D.
   Chair, EDRN Lung Collaborative Group, Vanderbilt University

3. **Q & A**

<u>EDRN Patient Advocates</u>

Carole Siegel (GI)

Merel Grey Nissenberg (Lung, Prostate)

Elda Railey (Breast, GYN)

Welcome

Early Detection Research Network

Sudhir Srivastava, PhD, MPH
National Cancer Institute
Chief, Cancer Biomarkers Research Group

How can we save more lives?

Early Detection Research Network

- Most cancers are diagnosed when they are 1 - 4 cm in size
- By this time many have already metastasized
- To save more lives we need effective methods for:
  - Risk assessment
  - Early detection
  - Therapy

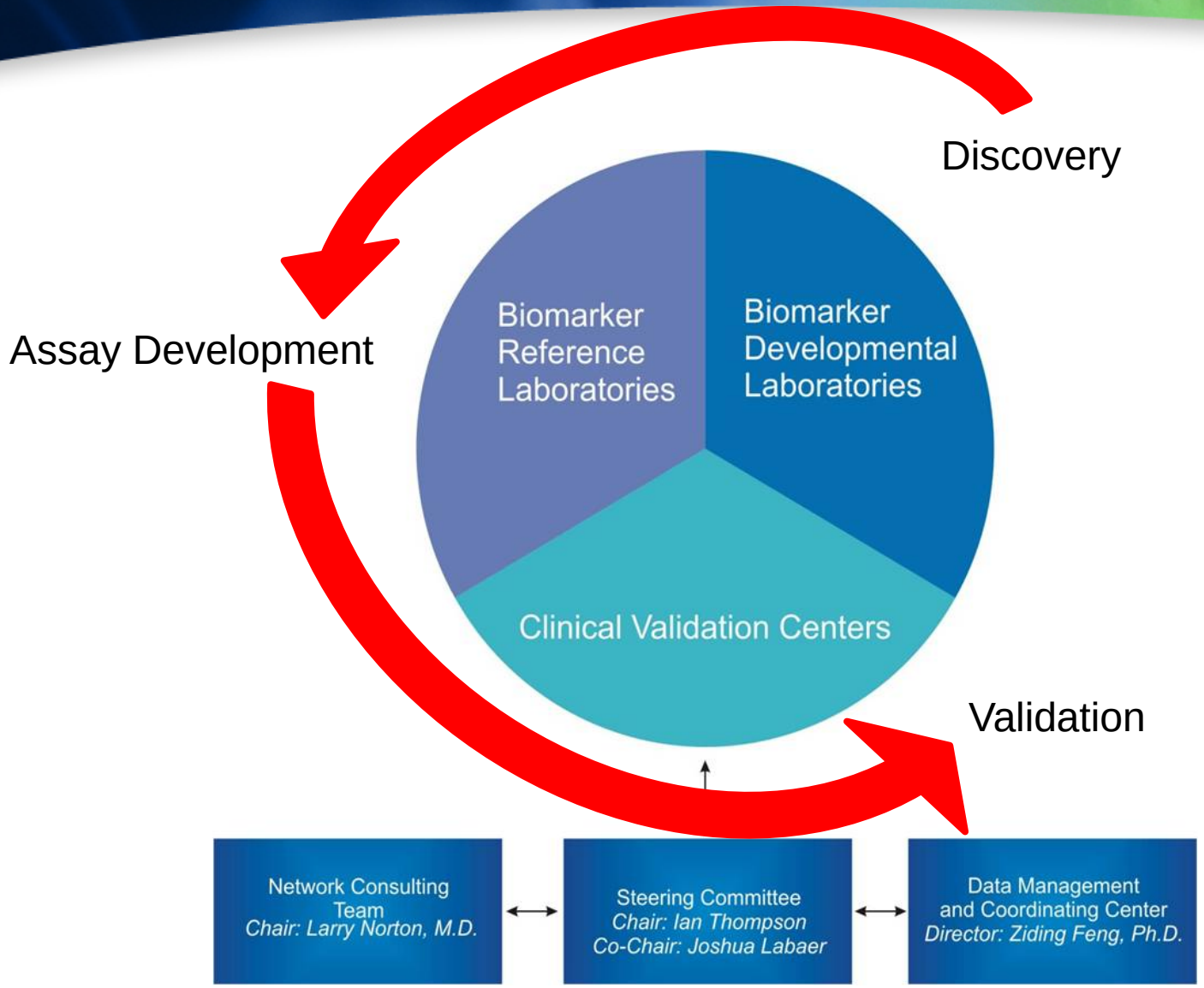
Mission

Early Detection Research Network

The National Cancer Institute's Early Detection Research Network's mission is to implement biomarker research through strategic and systematic, evidence-based discovery, development and validation of biomarkers for cancer risk assessment, early detection, diagnosis and prognosis of cancer.

Investigator-Driven Consortium

Early Detection Research Network



Objectives

Early Detection Research Network

- Provides a national infrastructure to support a “vertical” collaborative approach to move promising biomarker/technology to clinical validation
- Established guidelines and criteria for the validation
- Developing and instituting quality assurance regimens, Standard Operating Procedures, etc.
- Conduct early clinical and epidemiological studies to evaluate predictive value of biomarkers
- Foster Public- Private Partnership

Immediate Goals of the EDRN

Early Detection Research Network

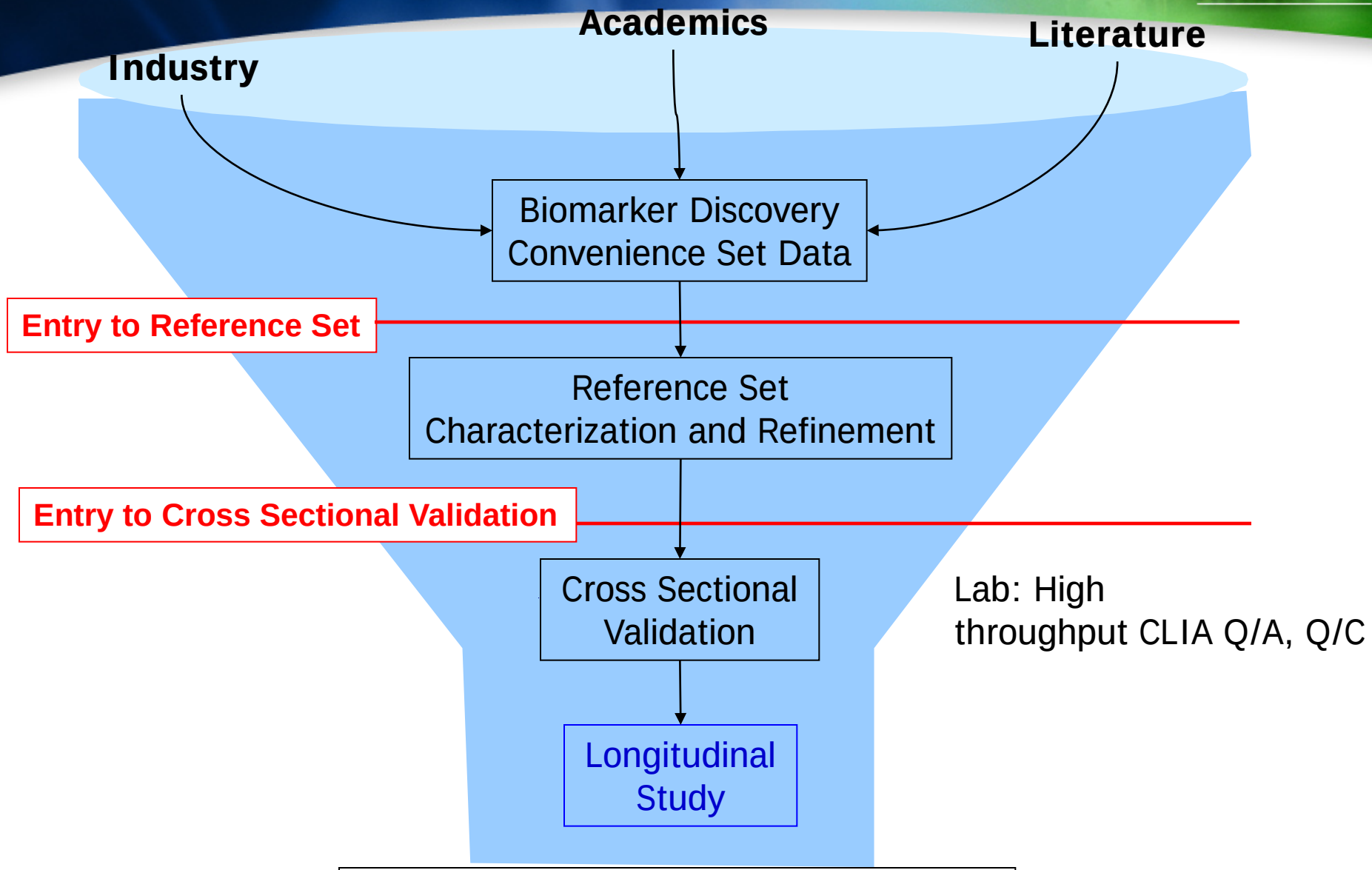
- **Develop biomarkers for:**
  - **Early Detection of Significant Cancers**
  - **Diagnosis**
  - **Risk assessment**

- **Verify and validate promising biomarkers**

- **Promote promising biomarkers to clinical application by collaboration with public-private partnership with the ultimate goal of FDA approval. (Note: EDRN's mission does not include submission to FDA).**

Biomarker Discovery, Development and Validation

Early Detection Research Network



Statistically Derived Panels of Biomarkers

SOP and Standards

Early Detection Research Network

Assays	Application
Validation of bleomycin-induced chromosomal breakage in lymphocytes	Biomarker of Lung Cancer susceptibility
Validation of 3.4KB mitochondrial DNA deletion	Biomarker for Prostate Cancer Risk
Development of high-density breast and prostate tissue microarrays	Testing of ISH and other molecular probes
Validation of SOPs for Microsatellite Instability (MSA) and DNA methylation assays	Biomarkers for Bladder Cancer
Validation of saliva-based mRNA assay	Biomarkers of Oral Cancer
Validation of proteomic prostate-specific biomarkers, including percent proPSA and other PSA Isoforms	Biomarkers for Improving PSA Screening of Prostate Cancer
Urine PCA3 Assay	Detection of Prostate Cancer
Urine/TMA Assay for T2S:ERG Fusion	Detection of Prostate Cancer
FISH assay for T2S:ERG Fusion	Detection of Prostate Cancer
Aptamer-Based Assay	Detection of Lung Cancer
Proteomic panel for Lung Cancer	Detection of Lung Cancer
OVA1 test for Ovarian Cancer	Differential Diagnosis of Benign Pelvic Mass from Ovarian Cancer
ROMA algorithm for Ovarian Cancer	Differential Diagnosis of Benign Pelvic Mass from Ovarian Cancer
Vimentin methylation in stool	Detection of Colon Cancer
SOPs for Blood, Sera, Plasma, Urine, stool	Standard Reference sample sets
8-oxyguanine DNA glycosylase (8OGG); Alkyl-adenine DNA Gycosylase; APE1 Endonuclease	Measuring DNA repair capacity for Lung Cancer risk

Adoption of Clinical Assays

Early Detection Research Network

Detection/ Biomarker Assay	Discovery	Refine/ Adapt for Clin Use	Clinical Validation	Clinical Translation
Blood proPSA		√	√	FDA IVD pending review
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

EDRN Accomplishments

Early Detection Research Network

Lung and Upper Aerodigestive Cancers

- Autoantibody panel of markers (c-Myc, Cyclin A, Cyclin B1, Cyclin D1, CDK2 and Suvivin) for early detection of lung cancer.
- miRNA profile in sputum for early detection.
- TCF21 and Ras-related GTPase gene methylation as diagnostic markers.
- Development of 8-oxyguanine DNA glycosylase (8OGG), alkyl-adenine DNA gycosylase and APE1 endonuclease DNA repair capacity-based assays as risk measures of lung cancer.
- Identification of mass spectrometry 9-panel for lung cancer detection.
- validated SMRP (Mesothelin) as a diagnostic marker of mesothelioma.
- mir29c miRNA as a prognostic marker for mesothelioma.

Early Detection Research Network

Early Detection Biomarkers for Lung Cancer

Pierre P. Massion, MD

Chair, EDRN Lung Collaborative Group

Vanderbilt University
Nashville, TN

Vanderbilt-Ingram Cancer Center

Lung Collaborative Group

Early Detection Research Network

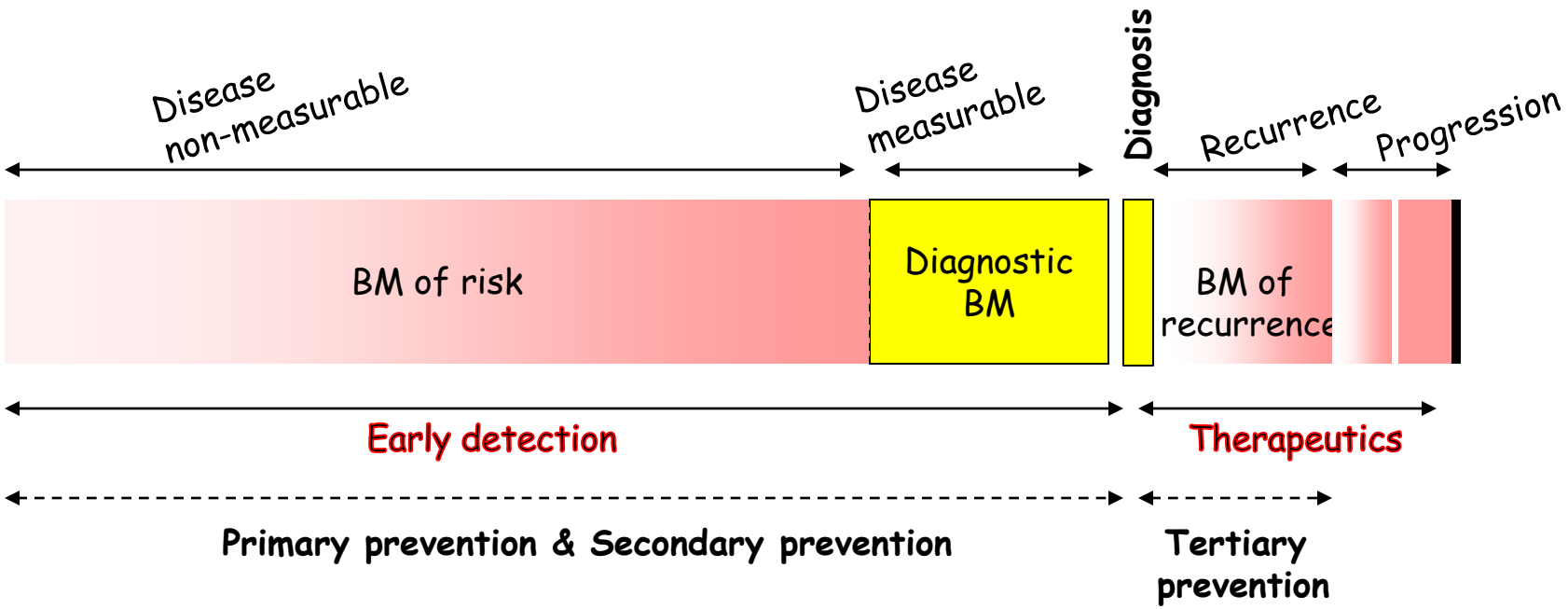
Principal Investigator BDLs	Institutions
Carlo Croce	Ohio State University
Steven Dubinett David Elashoff	University of California, Los Angeles
Avrum Spira Marc Lenburg	Boston University School of Medicine
Daniel Liebler David Tabb	Vanderbilt Medical Center
Harvey Pass Margaret Huflejt	New York University
David Sidransky	Johns Hopkins University School of Medicine

Principal Investigator CVCs	Institutions
Pierre Massion	Vanderbilt Ingram Cancer Center
William Rom	New York University School of Medicine

Principal Investigator BRLs	Institutions
Laurie Locascio	National Institute of Standards and Technology
Sanford Stass	University of Maryland, School of Medicine

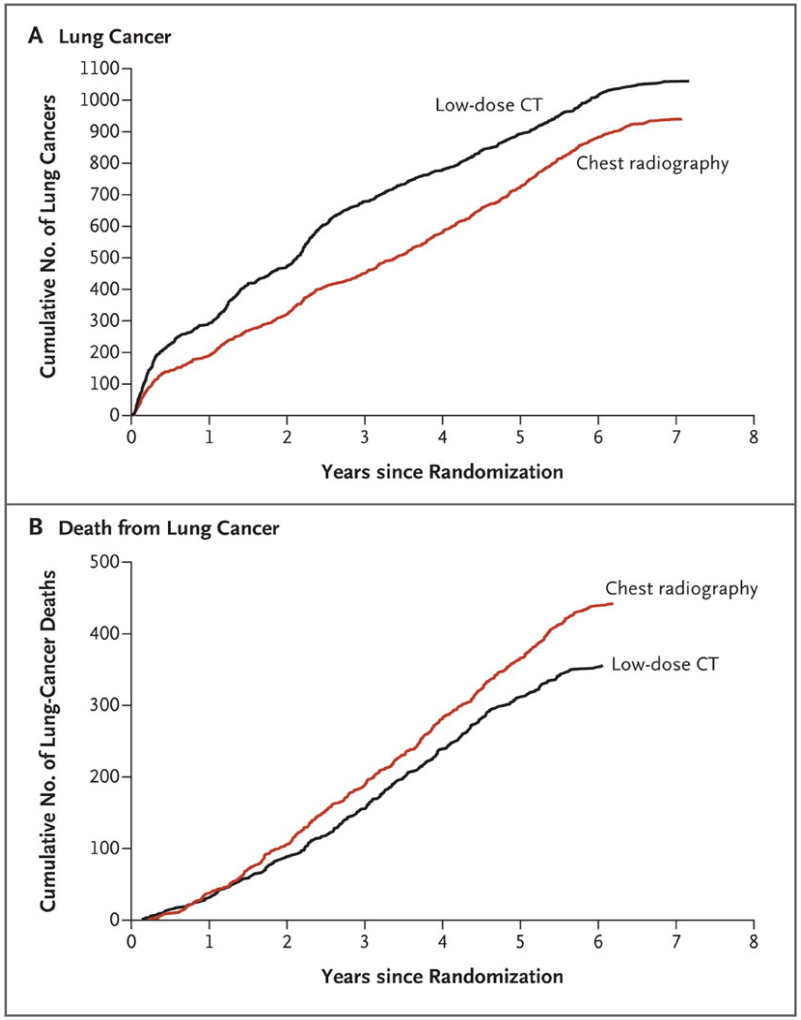
Natural History of Lung Cancer and Biomarkers

Early Detection Research Network



NLST- Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer

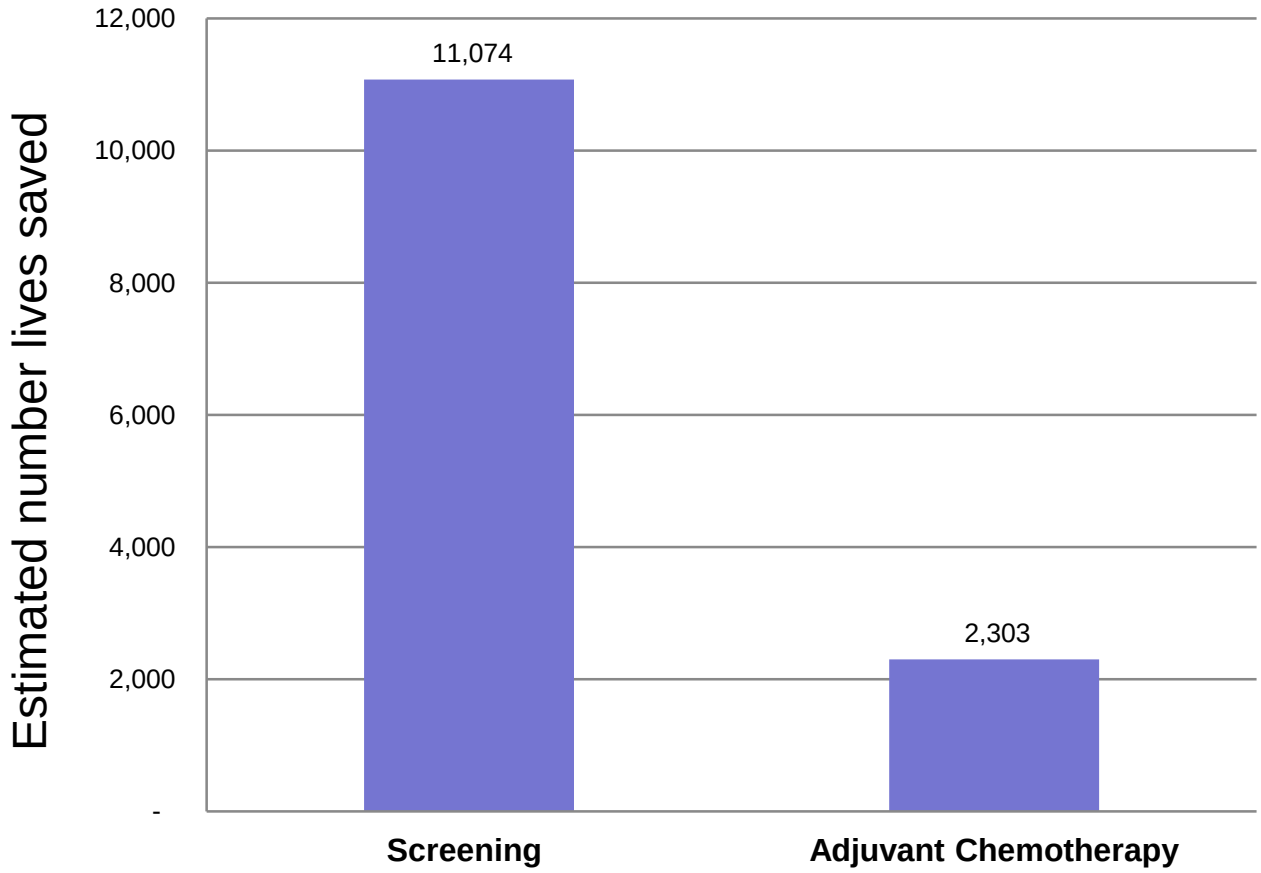
Early Detection Research Network



Berg et al. NEJM 2011

Projected Number of Lung Cancer-Related Lives Saved by CT Screening /Year

Early Detection Research Network



Massion, Unpublished data

Challenges

Early Detection Research Network

- Who to screen? Risk group?
- How often should chest CT be offered?
- How to handle the high false positive rate (benign lung nodules) ?
- How to streamline the Follow-up?
- Is it Cost effectiveness | implications
- How to implement for public policy
- What is the Impact on surgical | treatment approaches?
- Role(s) of molecular biomarkers?

Lung Cancer Diagnostic Biomarkers

Early Detection Research Network

Candidates	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Discovery, Prediction	Assay validation	Retro-longitudinal	Prospective screening	Cancer Control
SERUM/PLASMA					
MALDI TOF MS profiling	x	x	x		
autoantibodies	x	x	x		
Specific antigens	x	x			
miRNA	x	x	x		
DNA methylation Blood	x	x			
Circulating Tumor cells	x				
TUMOR/airway epith					
Preinvasive histo/cytology	x	x	x		
DNA methylation	x	x	x		
RNA tumor profiling	x	x			
MALDI MS profiling	x	x			
Chromosome aberrations	x	x			
SPUTUM/EBC					
DNA Methylation Sputum	x	x	x		
DNA CN -FISH	x	x			
VOC	x	x			

How Good Should the Biomarker Be?

Early Detection Research Network

Risk assessment/screening: focus on low FPR (1-spec).

- In discriminating high risk from low risk individual
- In identifying candidates for screening, and chemoprevention
- Better than what the inexpensive clinical history will give you.

Diagnostics: focus on high TPR (sens)

- In discriminating early cancers from relevant other conditions
- In identifying disease with poor outcome
- Better than a history and another test will give you. (Hx-LDCT)

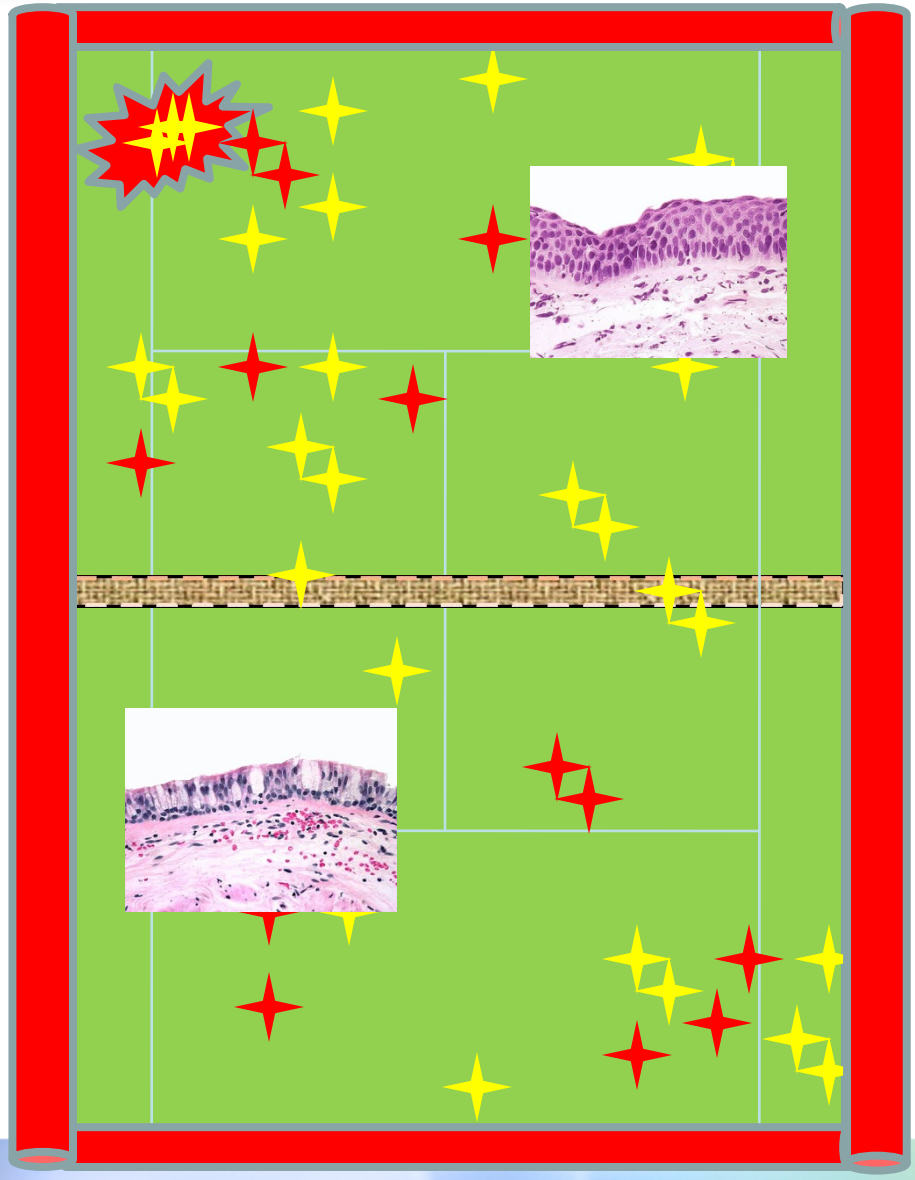
What are the metrics?

- Performance of the test: PPV/NPV
- ROC curves (TPR vs FPR). C index comparison
- Net reclassification Improvement (NRI) index

and Integration Discrimination Improvement (IDI) for continuous variables.

Candidate Diagnostic Biomarker in Lung Cancer

Early Detection Research Network



1. Bronchial Bx
2. Bronchial Brush
3. Plasma miRNA
4. Serum proteomics

1. Bronchial Biopsy-Based Biomarker

Early Detection Research Network

Published OnlineFirst April 12, 2011; DOI:10.1158/0008-5472.CAN-10-2510

Cancer Research

Prevention and Epidemiology

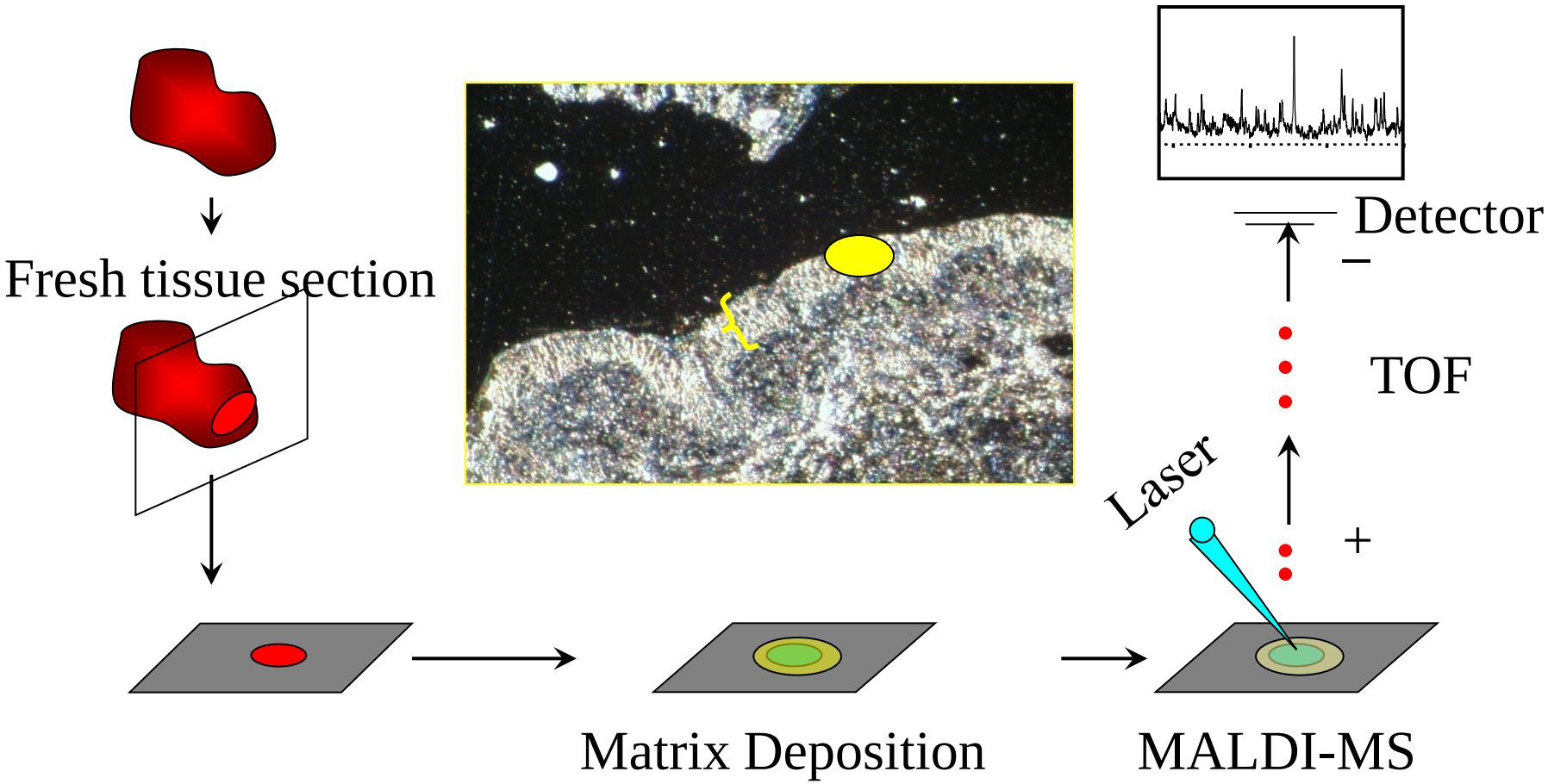
Lung Cancer Diagnosis from Proteomic Analysis of Preinvasive Lesions

S.M. Jamshedur Rahman[1], Adriana L. Gonzalez[2], Ming Li[5], Erin H. Seeley[3,4], Lisa J. Zimmerman[4], Xueqiong J. Zhang[5], M. Lisa Manier[1,3,4], Sandra J. Olson[2], Ronak N. Shah[1], Alison N. Miller[1,10], Joe B. Putnam[7], York E. Miller[11], Wilbur A. Franklin[12], William J. Blot[8], David P. Carbone[3,4,6,9], Yu Shyr[5], Richard M. Caprioli[3,4], and Pierre P. Massion[1,9,10]

MALDI-MS Tissue Based Analysis

Matrix-Assisted Laser Desorption Ionization Mass Spectrometry

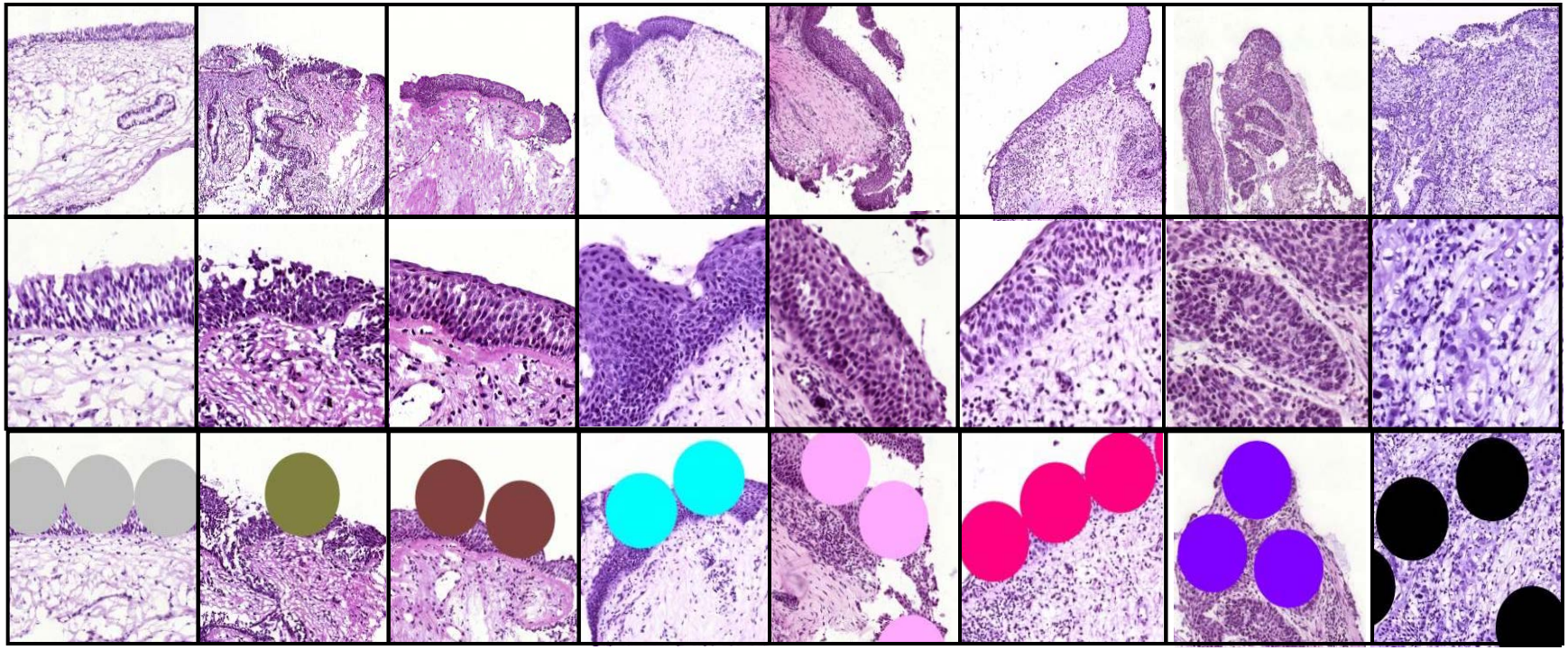
Early Detection Research Network



Signature of Risk of Having Lung Cancer

Early Detection Research Network

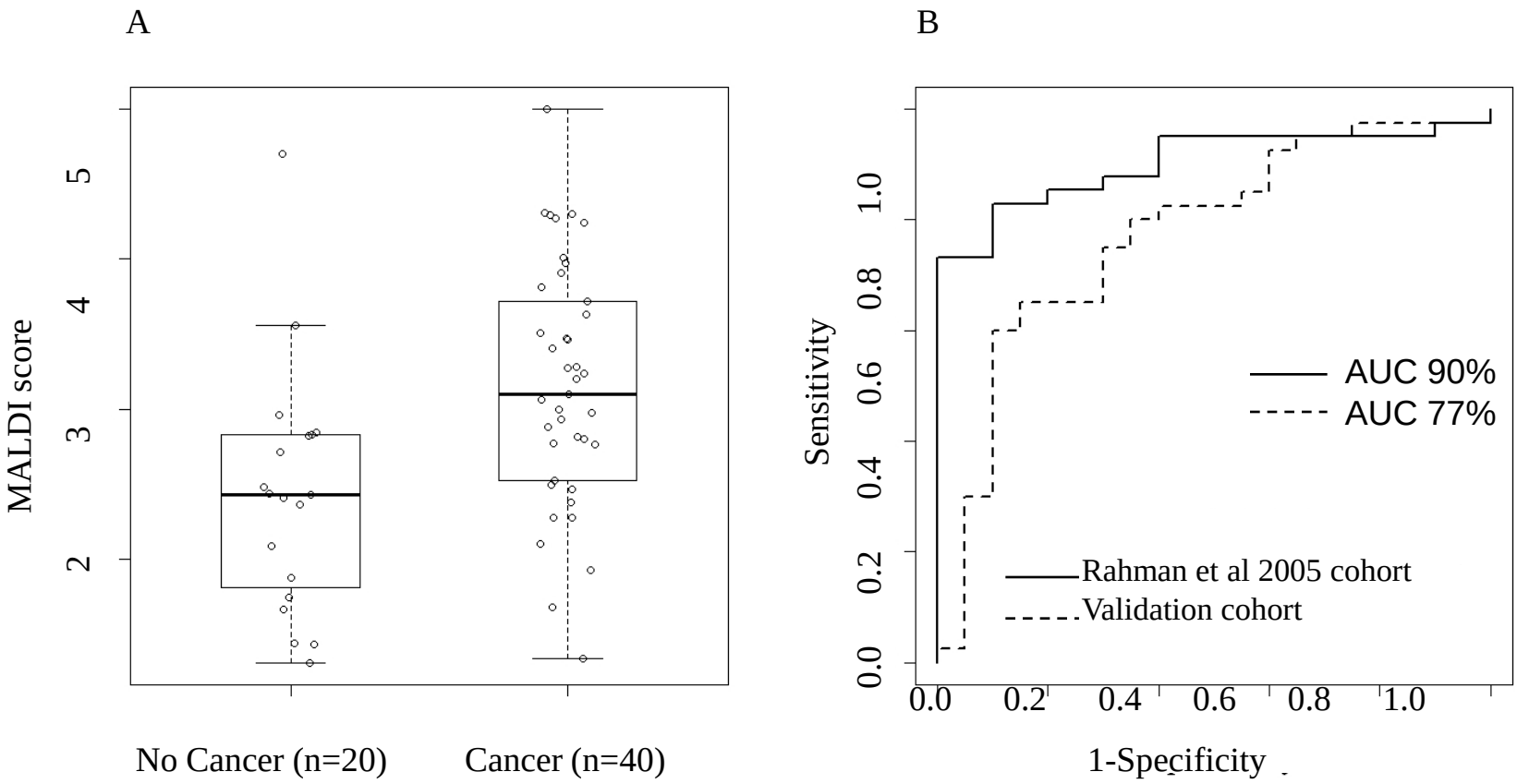
Normal bronchial	Hyper-plasia	Squamous metaplasia	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in situ	Invasive lung ca



Rahman et al, Cancer Res 2011

Lung Cancer Diagnosis from Proteomic Analysis of Preinvasive Lesions

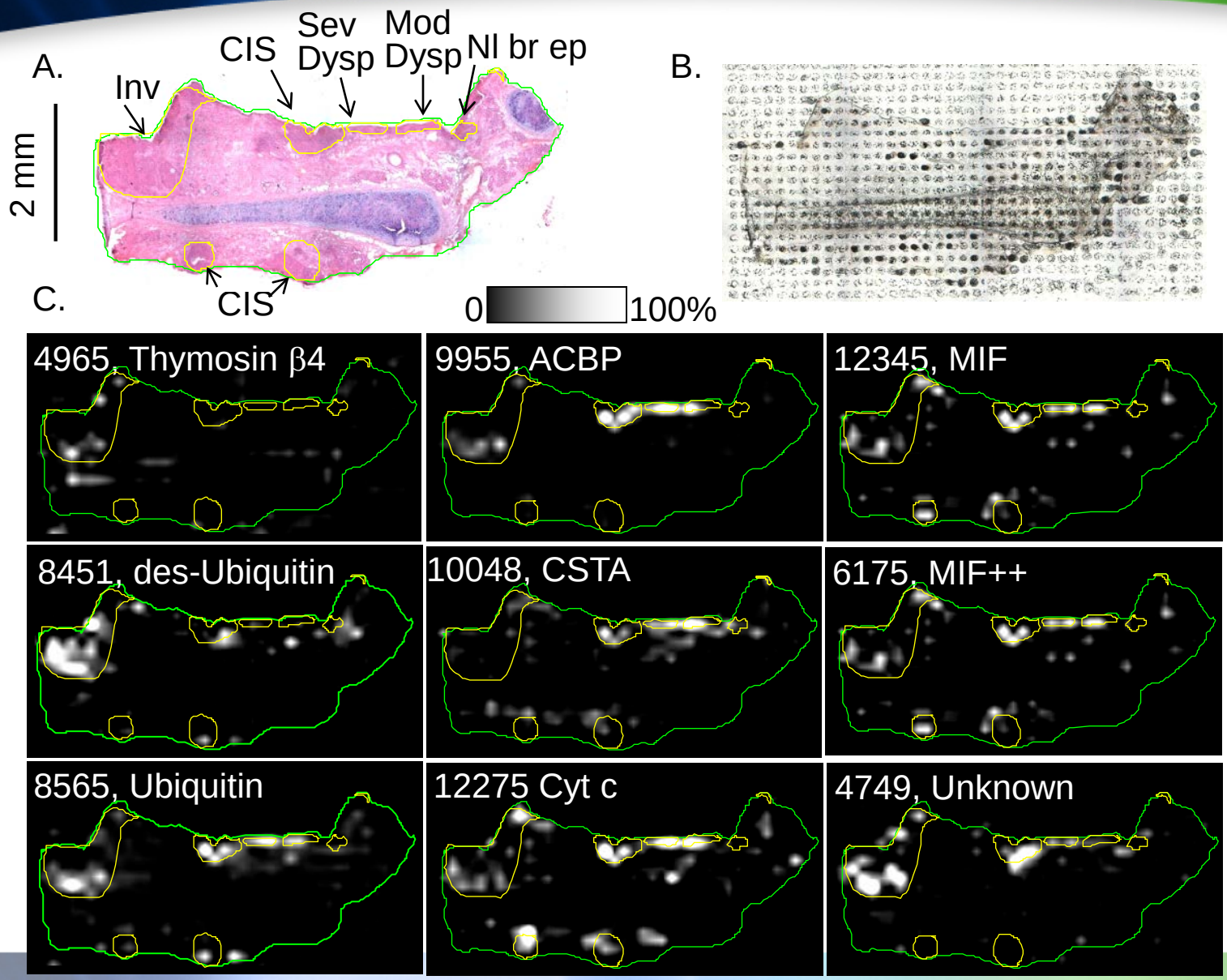
Early Detection Research Network



Rahman et al. Cancer Res 2011

Validation of Candidate BM by MALDI Imaging

Early Detection Research Network



2. Bronchial Brushing-Based Biomarker

Early Detection Research Network

Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer

Avrum Spira[1], Jennifer E Beane[2,8], Vishal Shah[2,8], Katrina Steiling[1], Gang Liu[1], Frank Schembri[1], Sean Gilman[3], Yves-Martine Dumas[1], Paul Calner[4], Paola Sebastiani[5], Sriram Sridhar[1], John Beamis[3], Carla Lamb[3], Timothy Anderson[6], Norman Gerry[7], Joseph Keane[4], Marc E Lenburg[7] & Jerome S Brody[1]

NATURE MEDICINE VOLUME 13 | NUMBER 3 | MARCH 2007

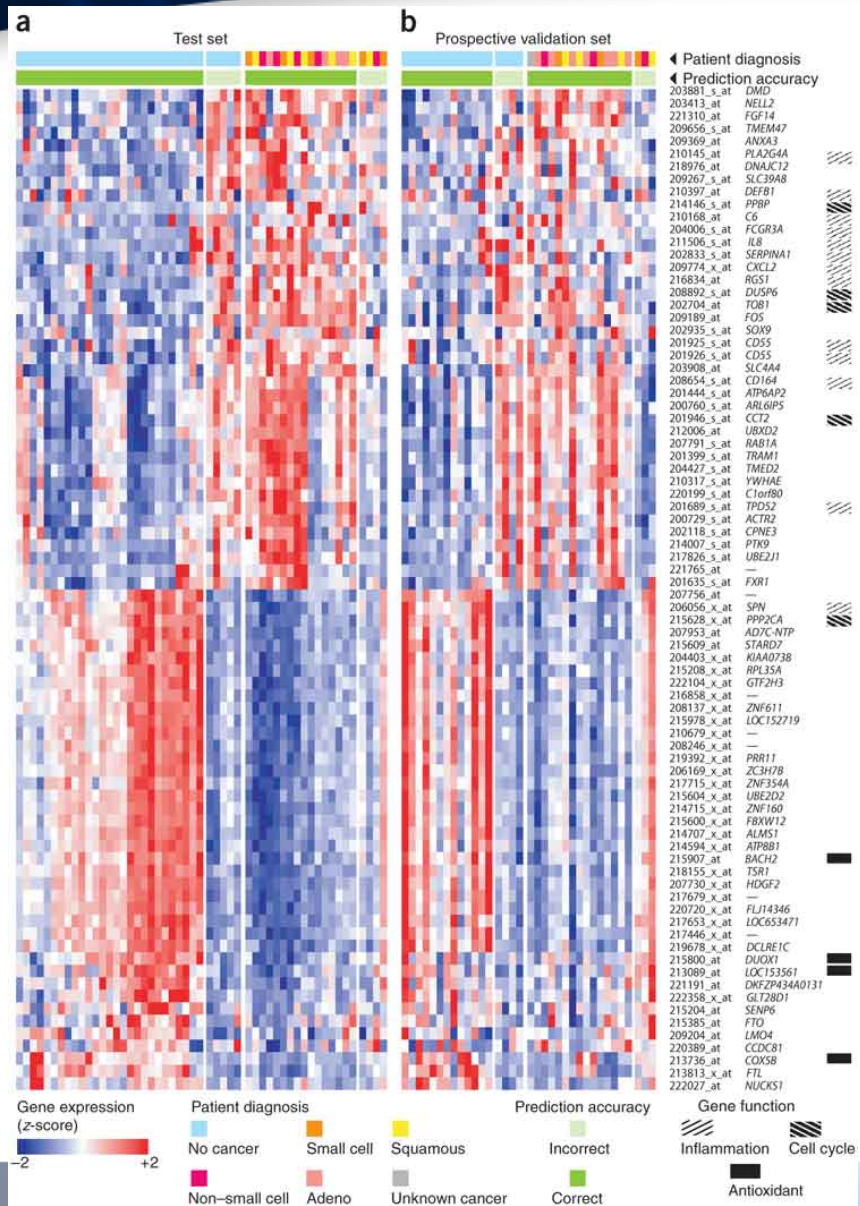
Pattern of Antioxidant and DNA Repair Gene Expression in Normal Airway Epithelium Associated with Lung Cancer Diagnosis

Thomas Blomquist, Erin L. Crawford, D'Anna Mullins, et al.

Cancer Res 2009;69:8629-8635. Published OnlineFirst November 3, 2009.

Airway Epithelial Gene Expression in the Diagnostic Evaluation of Smokers with Suspect Lung Cancer

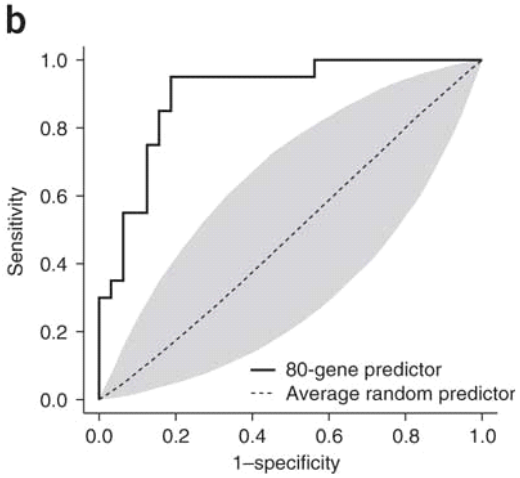
Early Detection Research Network



a. n=52
b. n=35

Affy HG-U133A

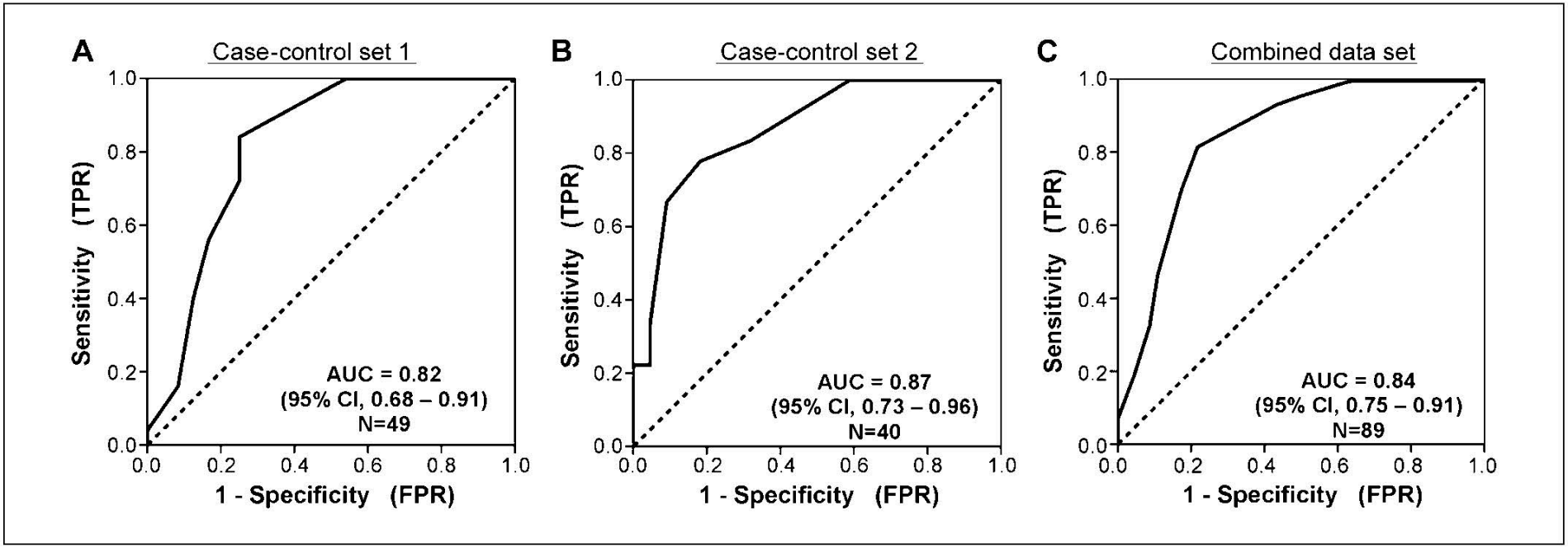
Accuracy of classification
a: 83%
b: 80%



Spira et al. Nature Medicine 2007

Airway Epithelial Gene Expression in the Diagnostic Evaluation of Smokers with Suspect Lung Cancer

Early Detection Research Network



Blomquist et al, CR 2009

3. Circulating miRNAs-based Biomarkers

Early Detection Research Network

PNAS

MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer

Mattia Boeri[a,1], Carla Verri[a,1], Davide Conte[a,1], Luca Roz[a,1], Piergiorgio Modena[b], Federica Facchinetti[a], Elisa Calabrò[c], Carlo M. Croce[d,2,3], Ugo Pastorino[c,2], and Gabriella Sozzi[a,2,3]

[a]Tumor Genomics Unit, Department of Experimental Oncology and Molecular Medicine, and [c]Unit of Thoracic Surgery, Fondazione IRCCS Istituto Nazionale Tumori, 20133 Milan, Italy; [b]Unit of Experimental Oncology 1, Centro di Riferimento Oncologico, 33081 Aviano (PN), Italy; and [d]Ohio State University Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210

Contributed by Carlo M. Croce, January 12, 2011 (sent for review December 22, 2010)

The efficacy of computed tomography (CT) screening for early lung cancer detection in heavy smokers is currently being tested by a number of randomized trials. Critical issues remain the frequency of unnecessary treatments and impact on mortality, indicating the need for biomarkers of aggressive disease. We explored microRNA (miRNA) expression profiles of lung tumors, normal lung tissues and plasma samples from cases with variable prognosis identified in a completed spiral-CT screening trial with extensive follow-up. miRNA expression patterns significantly distinguished: (*i*) tumors from normal lung tissues, (*ii*) tumor histology and growth rate, (*iii*) clinical outcome, and (*iv*) year of lung cancer CT detection. Interestingly, miRNA profiles in normal lung tissues also displayed remarkable associations with clinical features, suggesting the influence of a permissive microenvironment for tumor development.

of blood-based biomarkers useful for cancer detection and prognosis definition because, for their nature, they seem to remain rather intact and stable and are detectable with simple assays like quantitative real-time PCR (qRT-PCR). Initial studies in prostate, colon, and lung cancer patients showed that plasma levels of specific miRNAs had remarkable sensitivity and specificity to distinguish cancer patients from healthy subjects (8–11).

The intent of the present study was to perform an extensive miRNA profiling of primary lung tumors, paired normal lung tissues, and multiple plasma samples collected before and at the time of disease, from two independent spiral CT-screening trials. We aimed to identify biomarkers able to predict tumor development and prognosis, therefore improving lung cancer diagnosis and treatment options.

MEDICAL SCIENCES

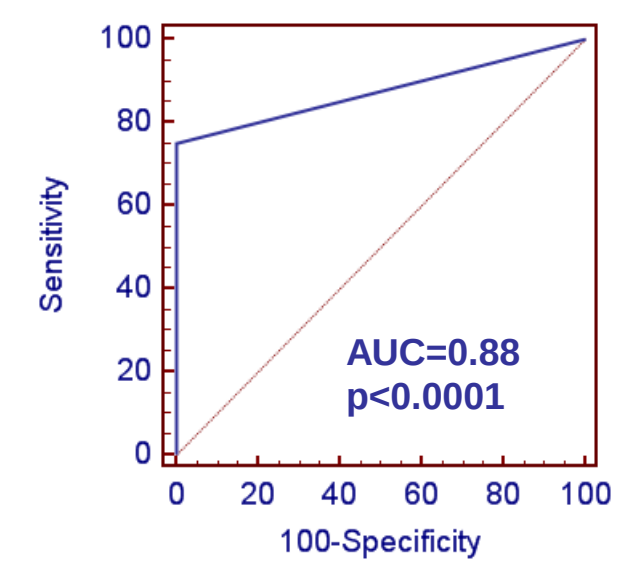
Boeri et al., PNAS 2011

Fondazione IRCCS Istituto Nazionale dei Tumori

DIAGNOSIS OF LUNG CANCER

Early Detection Research Network

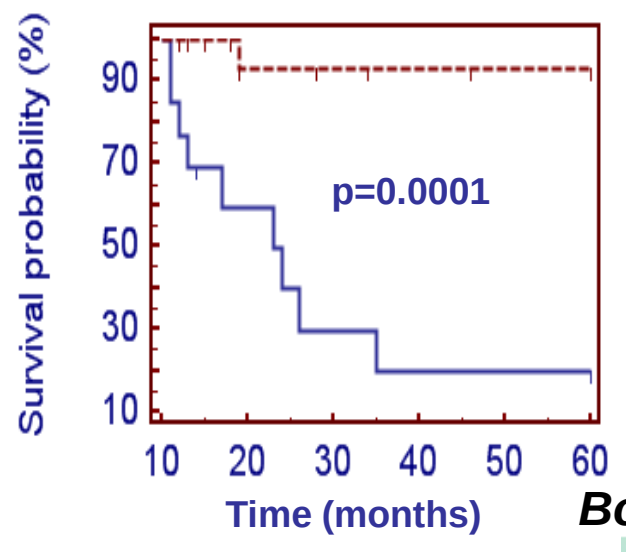
mir ratios	direction
21/92a	up
140-3p/17	down
106a/140-3p	up
140-5p/660	up
19b/660	up
19b/451	up
17/30c	up
106a/30c	up
19b/92a	up
15b/92a	up
28-3p/92a	up
28-3p/660	up
17/486-5p	up
15b/660	up
106a/486-5p	up
17/451	up



Sample size	26
Patients	16
Controls	10

DIAGNOSIS OF AGGRESSIVE LUNG CANCER (PAD)

mir ratios	direction
106a/486-5p	up
142-3p/486-5p	up
148a/486-5p	up
17/486-5p	up
221/486-5p	up
197/486-5p	up
28-3p/486-5p	up
21/486-5p	up
126/486-5p	up
15b/486-5p	up



Sample size	31
PAD+	13
PAD-	18

Boeri et al., PNAS 2011

4. Serum proteomic profiling in the evaluation of lung nodules

Early Detection Research Network

Published OnlineFirst on February 28, 2012; DOI:10.1158/1055-9965.EPI-11-0932

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Added Value of a Serum Proteomic Signature in the Diagnostic Evaluation of Lung Nodules

Chad V. Pecot[1], Ming Li[2], Xueqiong J. Zhang[2], Rama Rajanbabu[6], Ciara Calitri[6], Aaron Bungum[7], James R. Jett[7], Joe B. Putnam[3,9], Carol Callaway-Lane[9], Steve Deppen[3], Eric L. Grogan[3,9], David P. Carbone[1,6], John A. Worrell[4], Karel G.M. Moons[2,8], Yu Shyr[2], and Pierre P. Massion[1,5,6,9]

Pecot et al., CEBP 2012

Lung Nodule Cohorts Characteristics

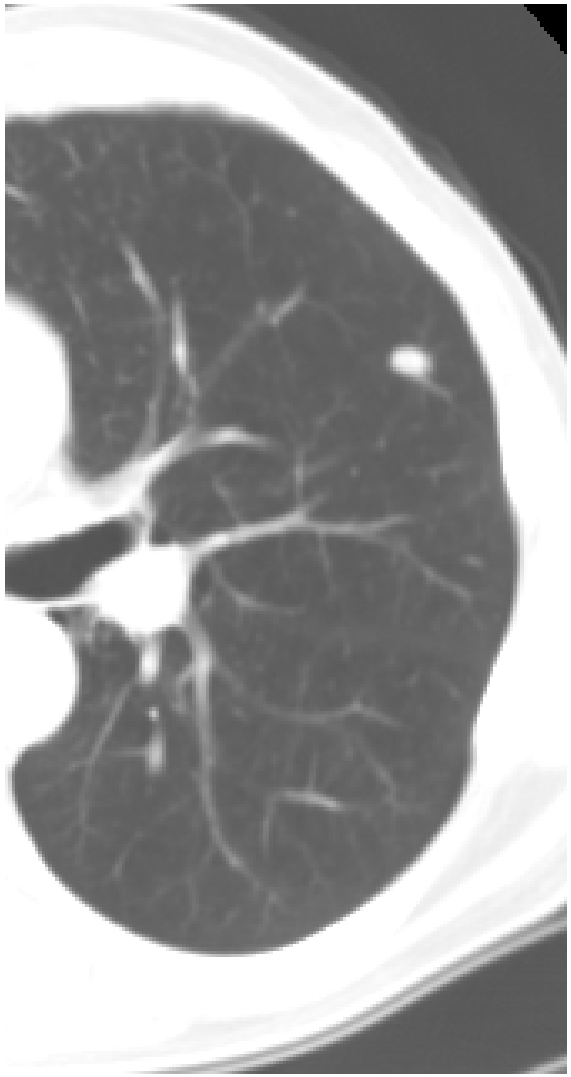
Early Detection Research Network

	Cohort A (VU/VA)	Cohort B (Mayo)
Sample size	265	114
Age, years (SD)	64 (10)	68 (10)
Gender (%)		
M	158 (60)	65 (57)
F	107 (40)	49 (43)
Race (%)		
White	247 (93)	91 (80)
Black	16 (6)	15 (13)
Other	2 (1)	8 (7)
Pack years of smoking Avg (SD)	61.2 (38)	33.5 (27)
CT Characteristics		
Mean Size (mm) (SD)	31.2 (23)	19.4 (13)
Spiculation Present (%)	146 (55)	37 (41)
Laboratory Characteristics		
C-Reactive Protein mg/dl, mean (SD)	4.9 (14)	6.1 (9)
Hemoglobin g/dl, mean (SD)	13.2 (2)	
Alkaline Phosphatase, mean (SD)	99 (47)	
Albumin g/dl, mean (SD)	3.9 (1)	

Pecot et al. CEBP 2012

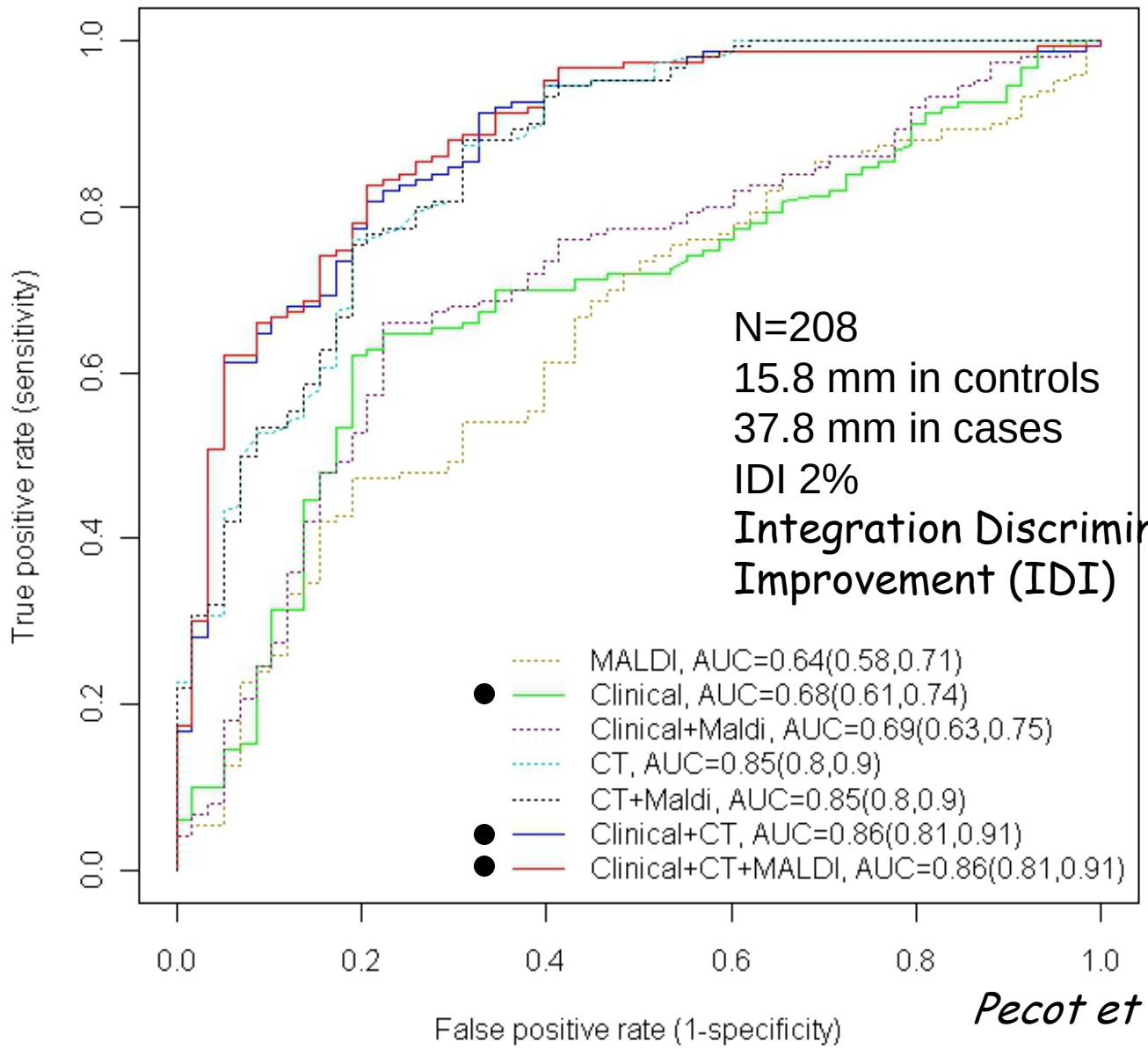
Lung Nodule, Malignant?

Early Detection Research Network



Performance of the Signature in Cohort A

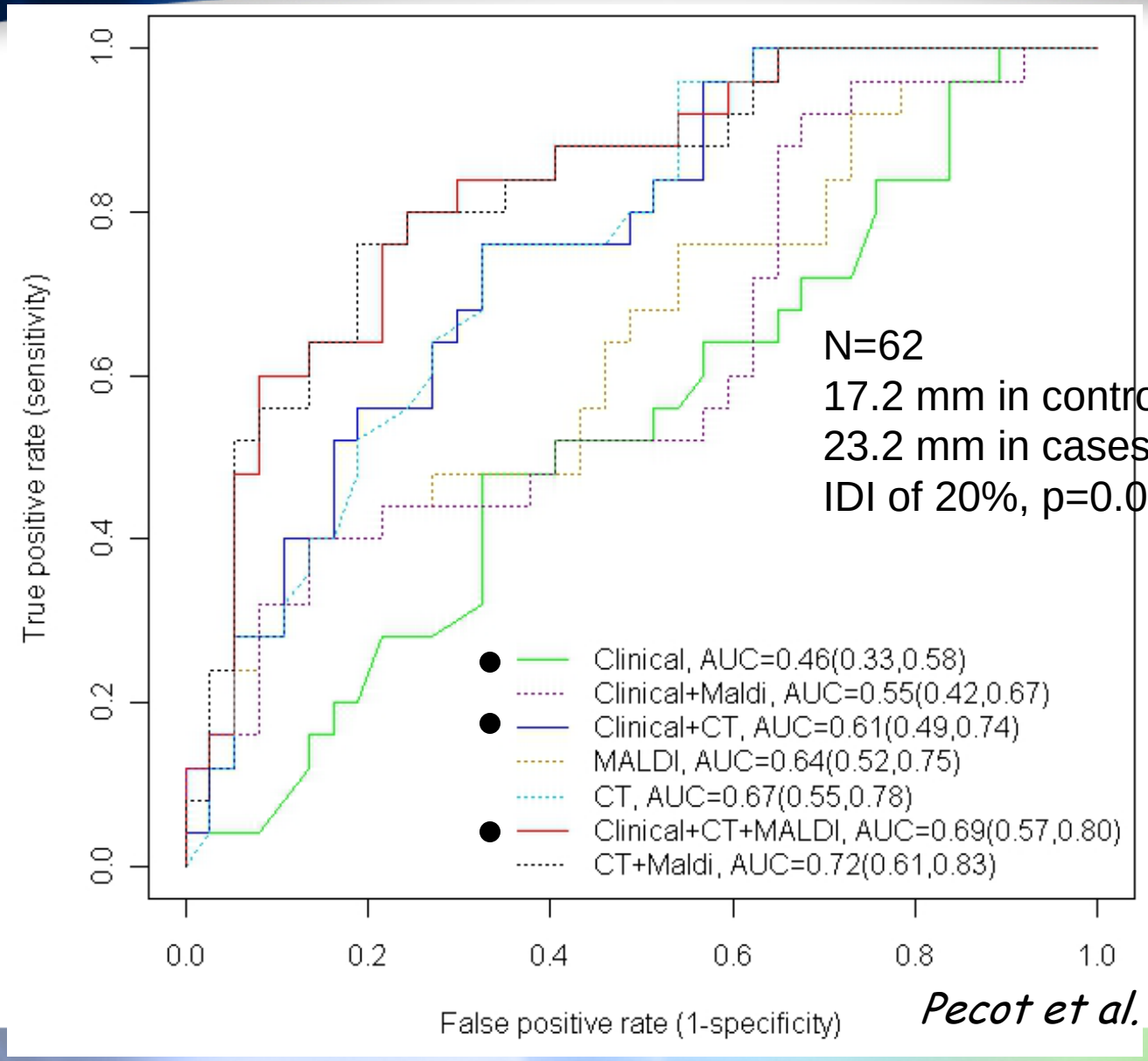
Early Detection Research Network



Pecot et al. CEBP 2012

Performance of the Signature in Cohort B

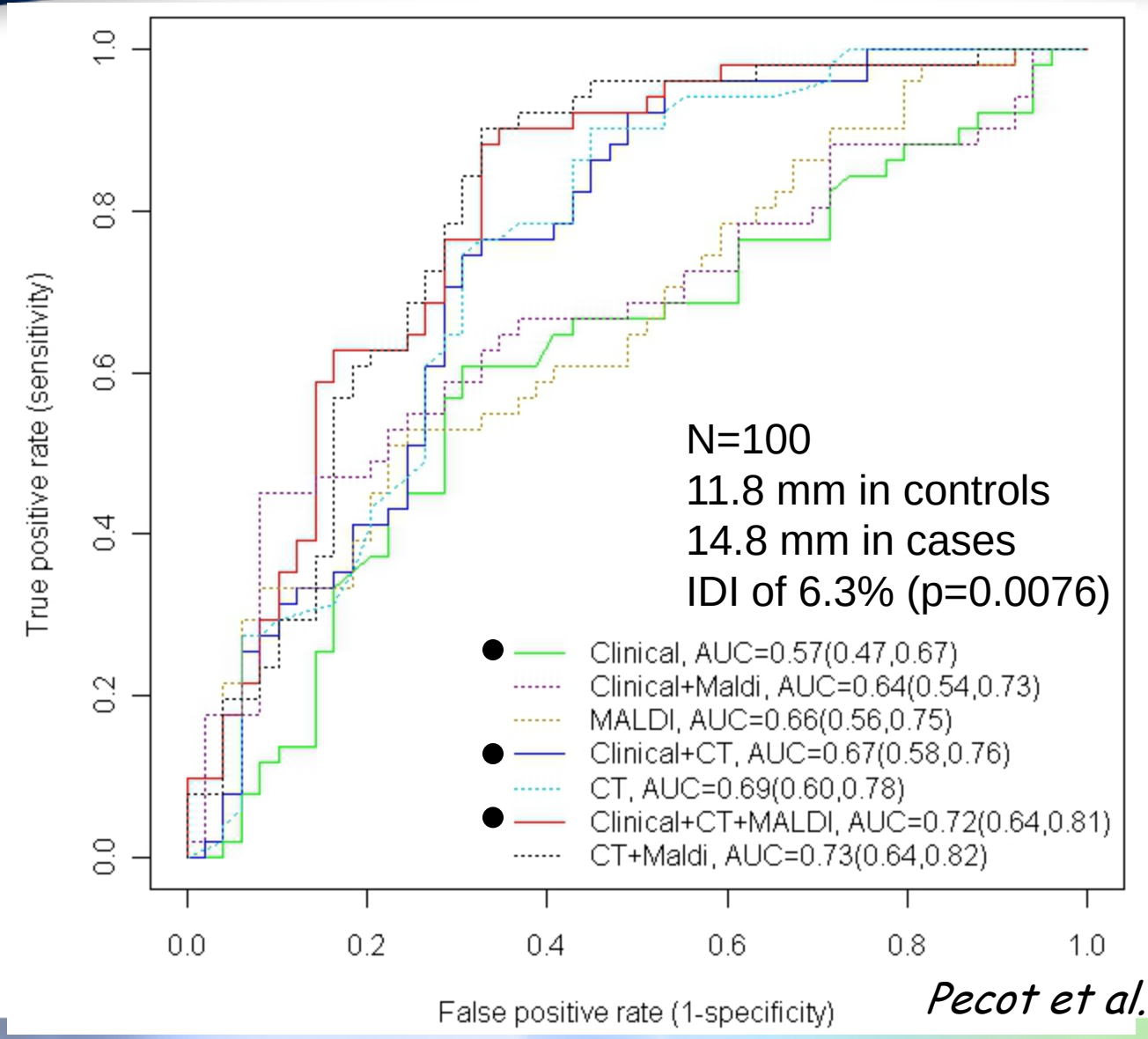
Early Detection Research Network



Pecot et al. CEBP 2012

Performance of the Signature in Nodules 5-20 mm

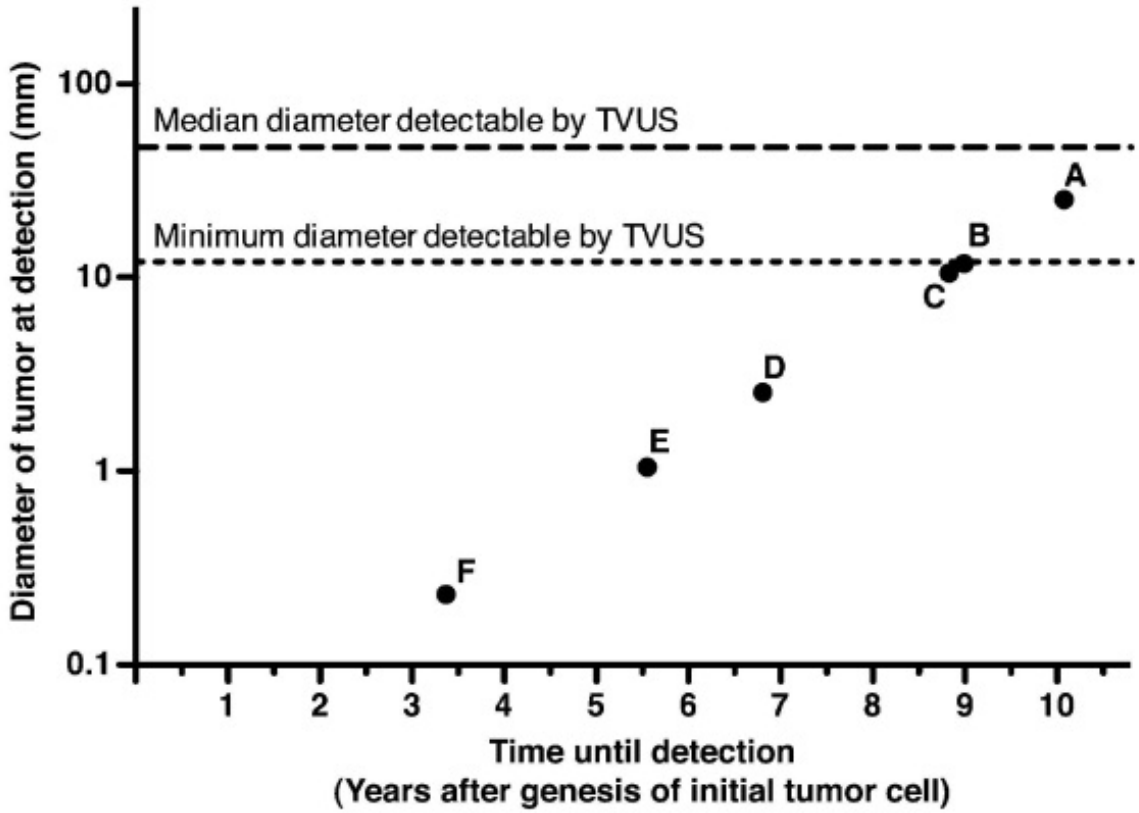
Early Detection Research Network



Pecot et al. CEBP 2012

Mathematical Model Identifies Blood Biomarker-based Detectability

Early Detection Research Network



A: ELISA

B: 100% vasc permeability

C: not shed by healthy cells

D: shedding is 1000x nl

E: not shed in nl and improved 1,000 x assay sensitivity from baseline

F: not shed in nl and improved 100,000 assay sensitivity from baseline

Specific marker, sensitive test

Hori Gambhir STM 2011

Lung Cancer Cooperative Group within EDRN

Early Detection Research Network

	Set A	Set B	Set C
Collection	Prospectively collected		Prospective collection
SOP	No or not unique SOP		Unique SOP
Date	2000-2005		2006-on
Clinical setting	Diagnosis	Screening	Diagnosis
Cases	180	170	180
Controls	180	250	180
Other ca	75		75

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

NLST Biorepository

http://www.acrin.org/ACRIN-NLSTBIOREPOSITORY.aspx

Early Detection Research Network

RESEARCHERS > POLICIES > NLST-ACRIN BIOREPOSITORY

ACRIN™ American College of Radiology Imaging Network

- ABOUT ACRIN
- CONDUCTING RESEARCH
- ACRIN MEETINGS AND AWARDS
- MAJOR SCIENTIFIC MEETINGS
- PARTICIPATING SITES
- POLICIES
  - PUBLICATIONS POLICY
  - DATA AND IMAGE SHARING POLICY
  - HIPAA POLICY
  - NLST-ACRIN BIOREPOSITORY
- PUBLICATIONS
- REGULATORY

NLST-ACRIN BIOREPOSITORY

Overview

A major objective of NLST-ACRIN is the creation of a national resource of biospecimens consisting of serial collections of blood components (plasma and buffy coat), urine, and sputum from a subset of participants at each of the three annual NLST screening exams as well as resected tissues from trial participants with lung cancer.

By coupling biospecimen collection with imaging-based screening, the NLST-ACRIN Biorepository is relatively enriched for early clinical stage lung cancers and associated biospecimens, and should provide a unique resource of extremely well characterized biospecimens with longitudinal data. The NLST-ACRIN Biorepository is available for all research platforms that will validate biomarkers of early lung cancer that are proven to have potential in preliminary testing.

NLST-ACRIN Biospecimen Research Opportunity [PDF]

ACRIN Data Sharing Policy and Biorepository Process

The NLST-ACRIN Biorepository is governed by the ACRIN Data Sharing Policy, which outlines ACRIN's data sharing process and summarizes what information ACRIN will release to requesters.

NLST-ACRIN Biorepository Application Review Process [PPT]

Data Sharing Policy [Link]

Data Sharing Policy [DOC]

Requests Forms for NLST-ACRIN Biospecimens, Images and Clinical Data

Individuals interested in obtaining ACRIN-NLST biospecimens, images and/or clinical data for projects unrelated to ACRIN-NLST study aims described in the protocol (www.acrin.org/6654_protocol.aspx) should review the Biorepository Summary and complete the following forms.

Pre-Application for NLST-ACRIN Biospecimens [DOC]

Full Application for NLST-ACRIN Biospecimens [DOC]

Current Collaborative Projects

Early Detection Research Network

1. 200 Lung nodules project to validate airway and blood based biomarkers for lung cancer diagnosis.
2. Two high-risk screening cohorts followed for prevalent and incident lung cancers (NYU and Vanderbilt)
3. Effort leveraged by the DoD sponsored DECAMP study (detection of lung cancer among military personnel). 2 cohorts: 500 Lung nodules cohort and 850 high-risk individuals screening cohort.

Conclusions

Early Detection Research Network

- Many early detection candidate biomarkers exist
- Few are validated or tested in preclinical setting. Priority to validate existing candidates.
- Difficult to bring BM to assist the non invasive dx of nodules > 20 mm. There may be room for BM in indeterminate nodules (5-20mm).
- BM may be best if derived from within a cohort of patients in whom test is intended for
- We need to de-emphasize Sensitivity and Specificity
- BM should provide knowledge about added value and therefore should be integrated to clinical, laboratory and imaging routine data.

Questions

Resources and Reading

Early Detection Research Network

- **EDRN web site** **http://edrn.nci.nih.gov/**

- **Research Advocacy Network**
  - Biomarkers in Cancer Tutorial for Advocates
    www.researchadvocacy.org

Contacts

Early Detection Research Network

EDRN Staff:

Annalisa Gnoleba **Email: gnolebaad@ mail.nih.gov**

Phone: 301-594-7635

EDRN Patient Advocates:

- Merel Grey Nissenberg, Esq. Email: mgrey@ucsd.edu
- Elda Railey Email: erailey@researchadvocacy.org
- Carole Seigel Email: caroleseigel@yahoo.com