

Airway Genomics for Lung Cancer Detection and Interception



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MEDICAL
CENTER

Disclosures

Founder of Allegro Diagnostics Inc. (acquired by Veracyte Inc. Sept, 2014)

Consultant to Veracyte Inc.

Founder of Metera Pharmaceuticals Inc.

Sponsored Research Agreements with Janssen Pharmaceuticals

How airway gene-expression can personalize early detection and prevention of lung cancer

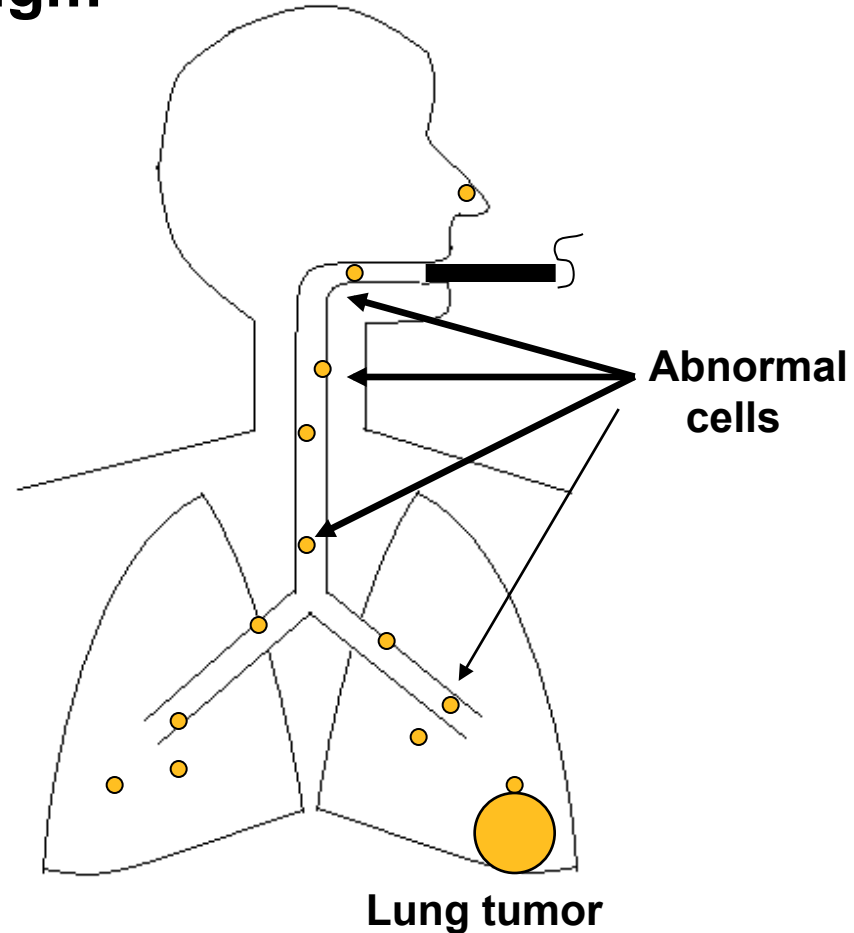
1. Airway gene expression in the “field of injury” as a diagnostic biomarker

2. Extending the “field of injury” into pre malignancy to accelerate precision prevention

3. Identifying the molecular determinants of premalignancy via the Pre-Cancer Genome Atlas

The airway 'field of injury' paradigm

- Smoking (and other inhaled toxins) alters epithelial cell gene expression throughout the respiratory tract
- Variability in epithelial cell genomic response to and damage from smoking linked to tobacco-associated lung cancer

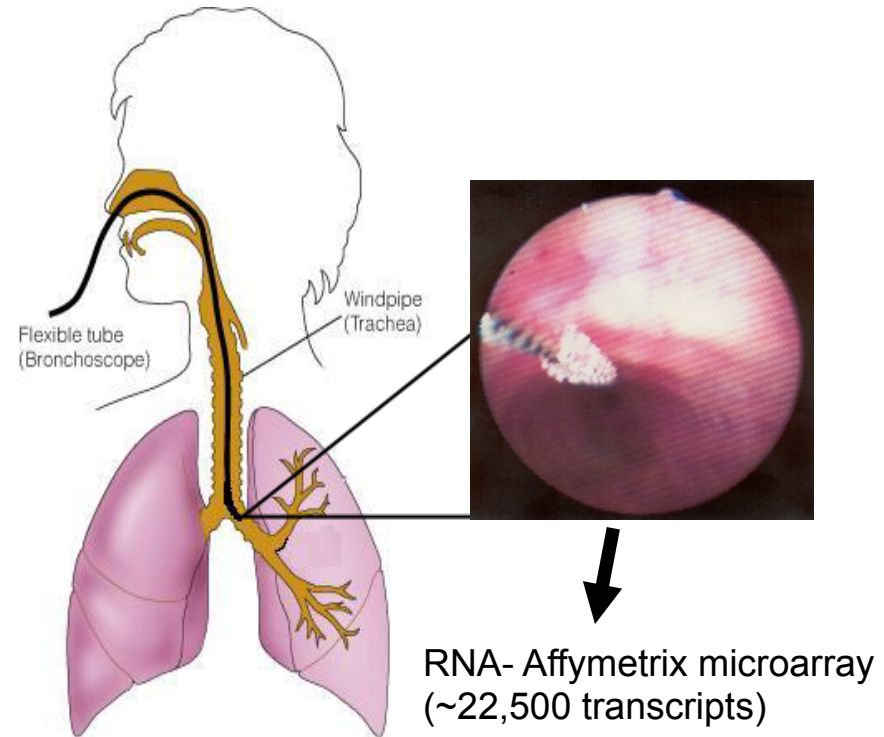


Bronchial airway gene expression as a biomarker of smoking and lung cancer

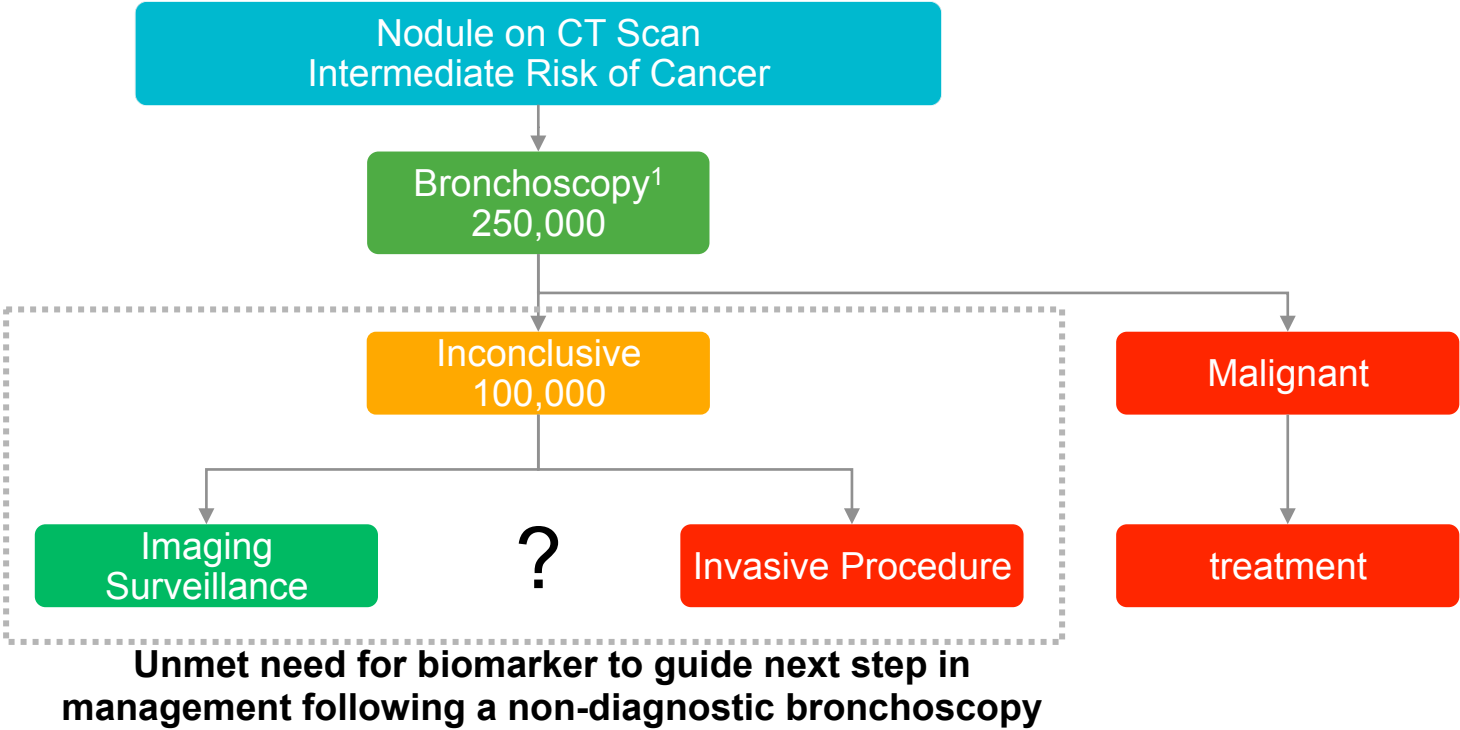
Smoking impacts airway and microRNA gene expression¹⁻³

Subset of changes are irreversible upon cessation⁴

Airway gene expression can serve as an early diagnostic biomarker for lung cancer^{5,6}

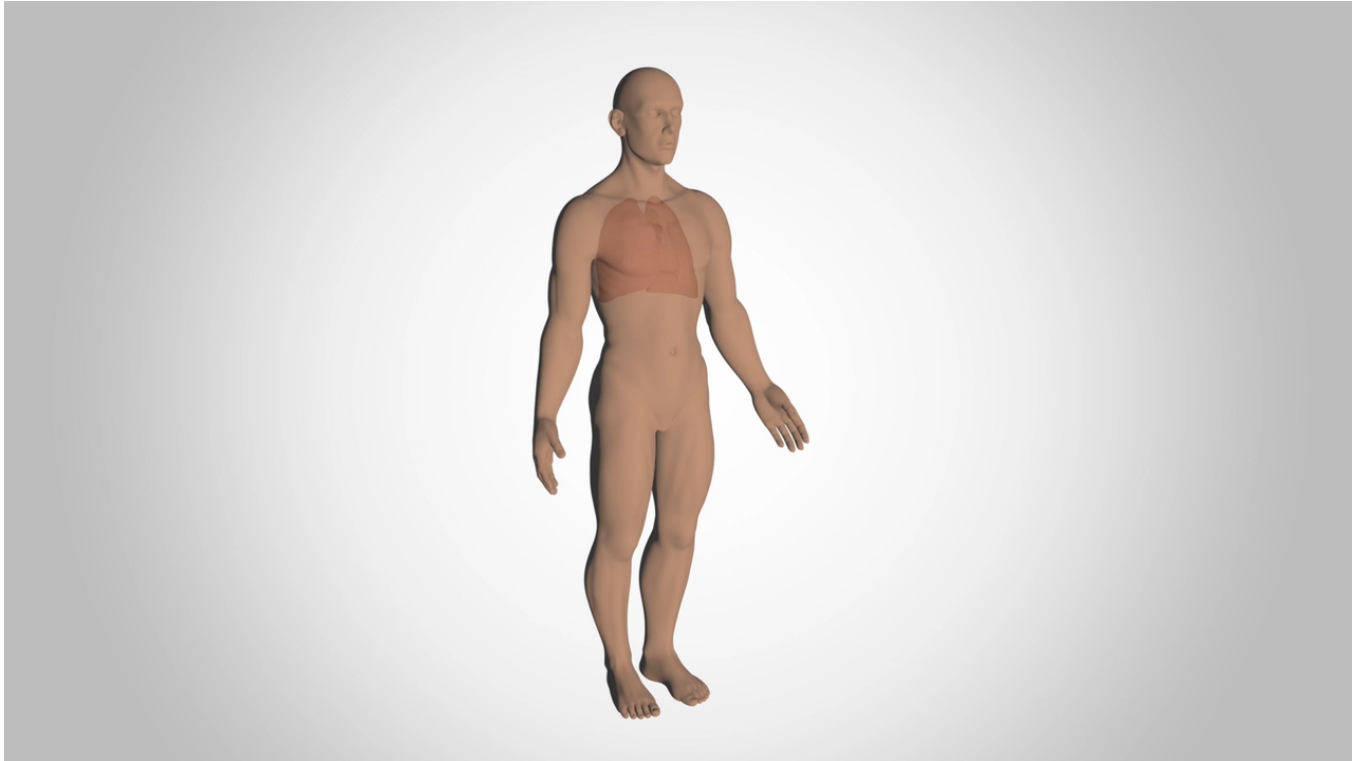


Bronchial Airway Genomic Biomarker was developed to address specific clinical unmet need

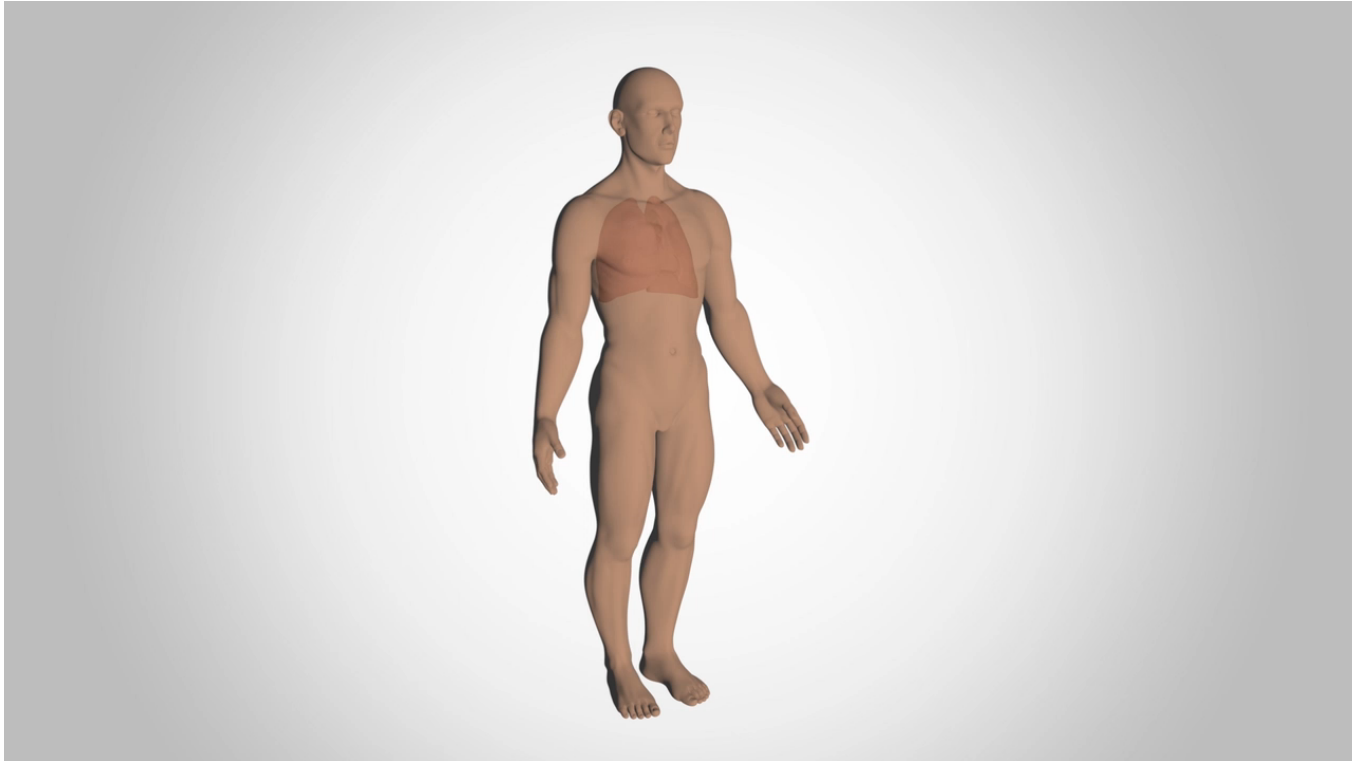


1. Centers for Medicare and Medicaid Services, Hospital Outpatient Standard Analytical Files

The elevator pitch!



The elevator pitch!



Prospective Validation of Bronchial Genomic Classifier (23 genes) in the Airway Epithelium Gene Expression In the Diagnosis of Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE

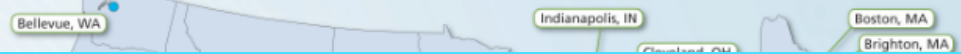
ORIGINAL ARTICLE

A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer

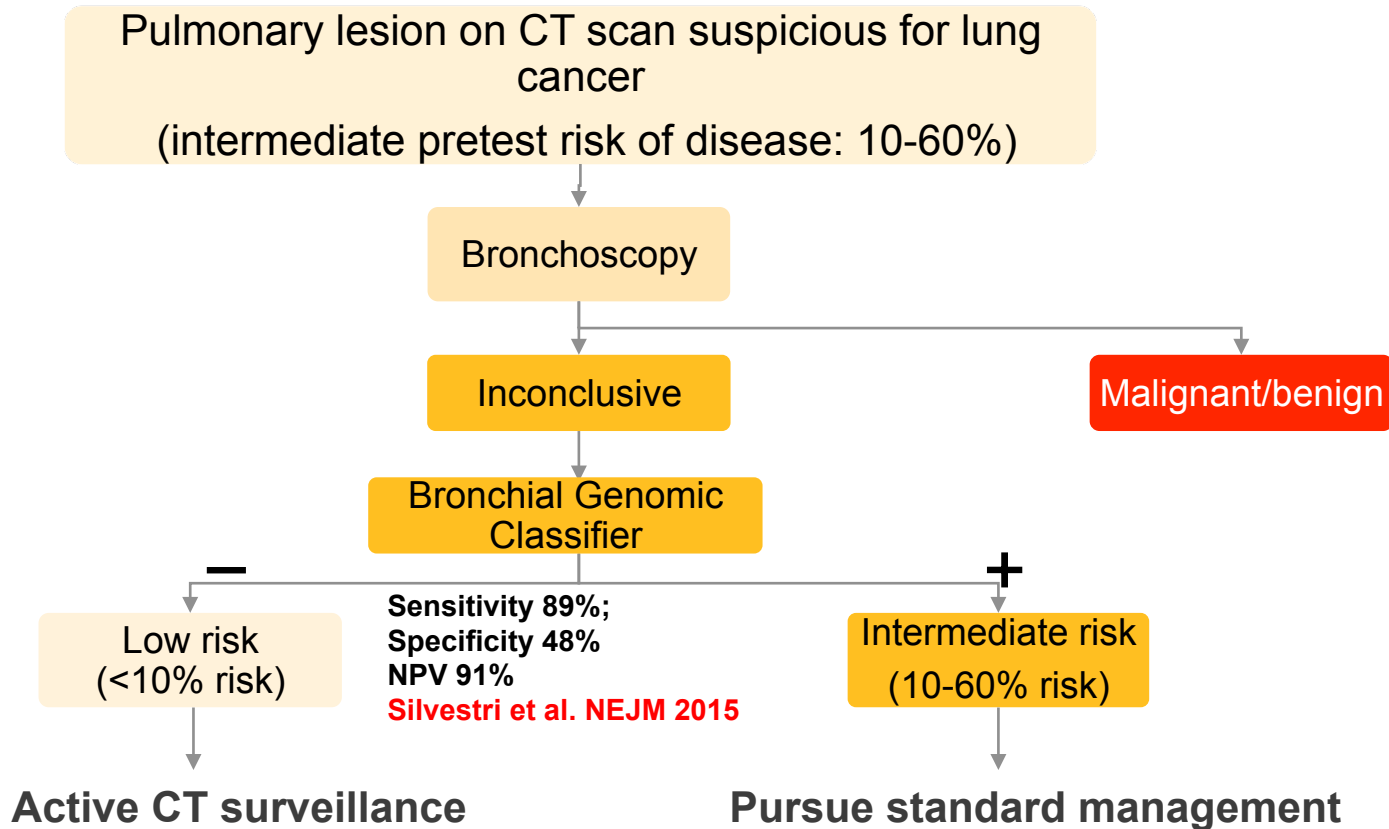
Gerard A. Silvestri, M.D., Anil Vachani, M.D., Duncan Whitney, Ph.D., Michael Elashoff, Ph.D., Kate Porta Smith, M.P.H., J. Scott Ferguson, M.D., Ed Parsons, Ph.D., Nandita Mitra, Ph.D., Jerome Brody, M.D., Marc E. Lenburg, Ph.D., and Avrum Spira, M.D., for the AEGIS Study Team*

Percepta™ launched Apr 2015 by Veracyte as CLIA test: 50+ med centers in registry trial; Recent Medicare Coverage Decision

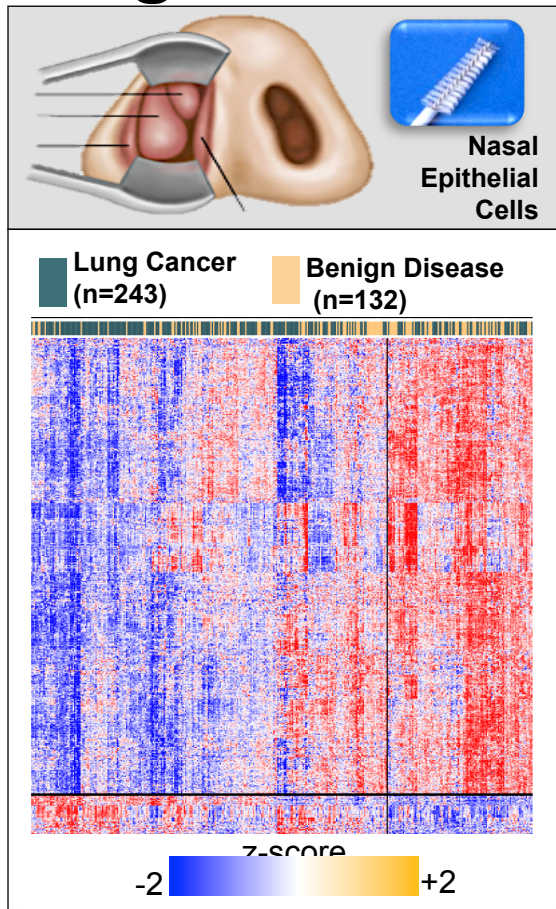
~650 current/former smokers undergoing bronchoscopy for suspect lung cancer
-followed for up to 1 year until final diagnosis made



How the bronchial genomic classifier can impact the diagnostic workup

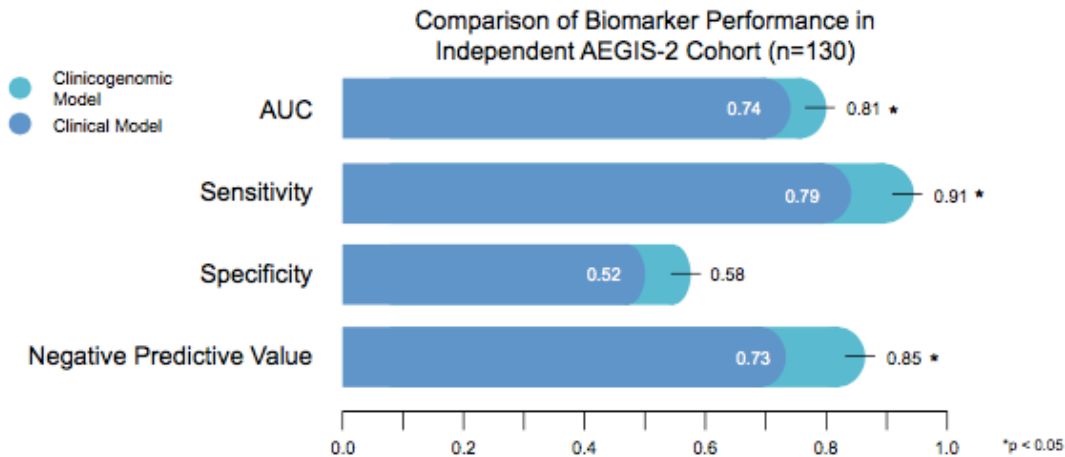


Extending the “field” to the nasal epithelium (NCI/EDRN)

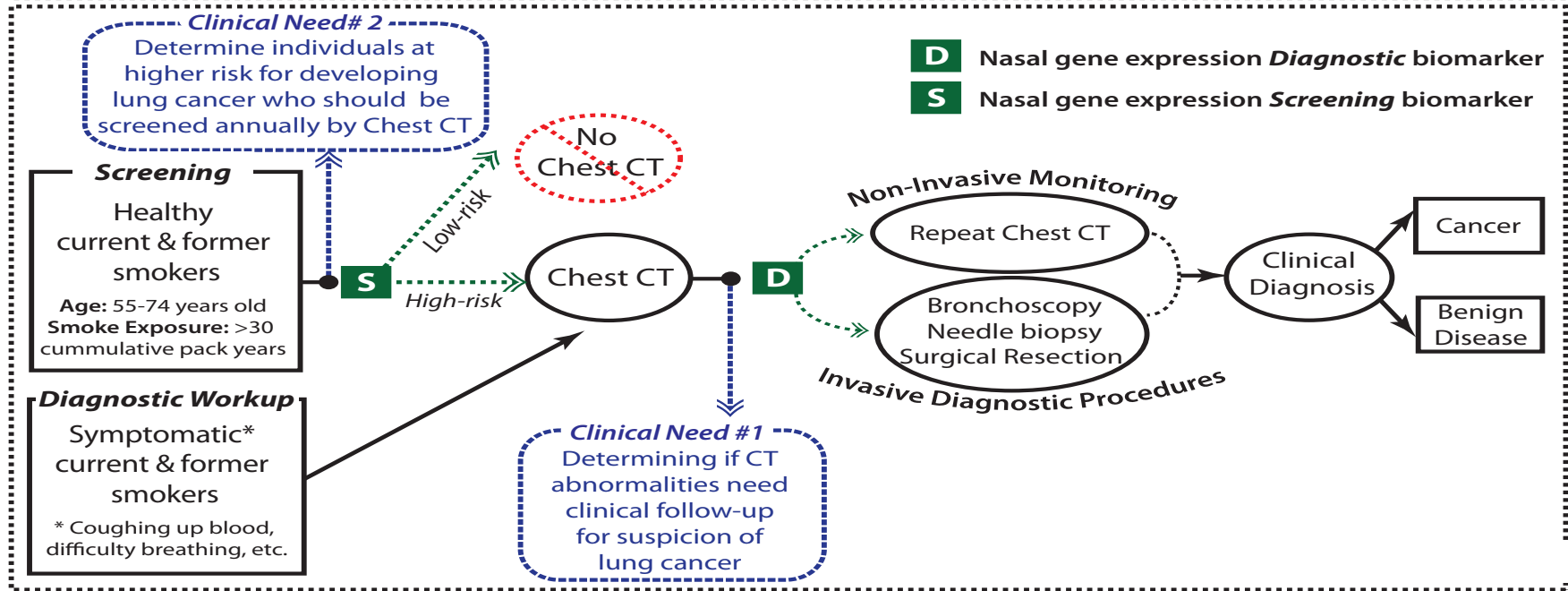


Concordance of bronch and nose

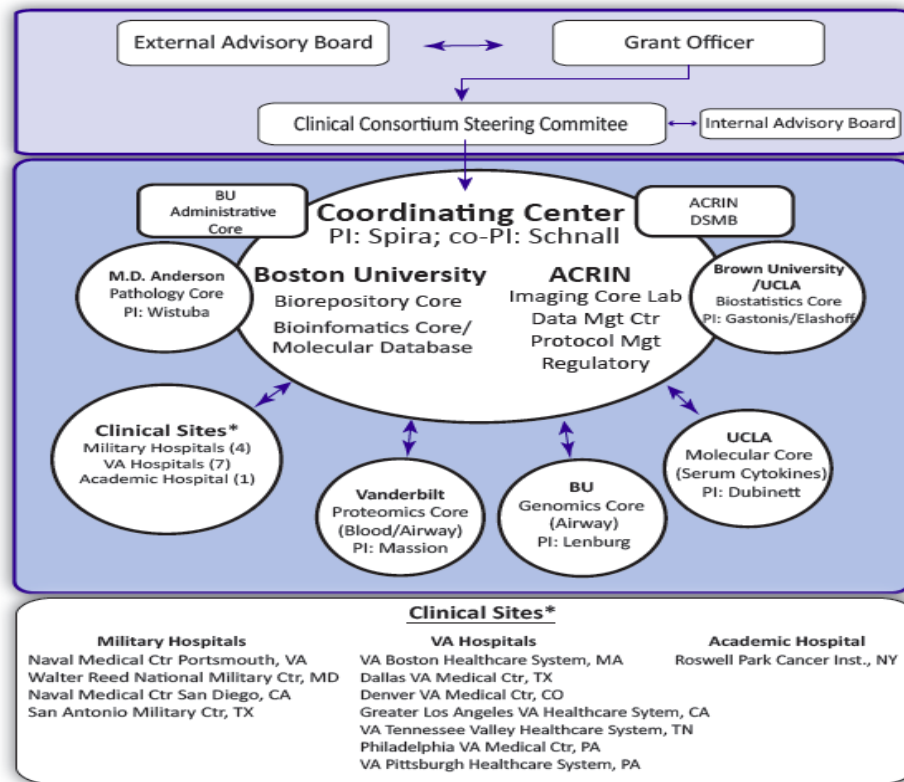
Validation of a clinical model vs. clinical model + 30 gene nasal marker (n=130)



Potential clinical applications for a nasal biomarker



The Detection of Early Lung Cancer Among Military Personnel (DECAMP) Consortium



Funded by
DOD, NCI
and Janssen

Military Hospitals
 Naval Medical Ctr Portsmouth, VA
 Walter Reed National Military Ctr, MD
 Naval Medical Ctr San Diego, CA
 San Antonio Military Ctr, TX

VA Hospitals
 VA Boston Healthcare System, MA
 Dallas VA Medical Ctr, TX
 Denver VA Medical Ctr, CO
 Greater Los Angeles VA Healthcare System, CA
 VA Tennessee Valley Healthcare System, TN
 Philadelphia VA Medical Ctr, PA
 VA Pittsburgh Healthcare System, PA

Academic Hospital
 Roswell Park Cancer Inst., NY

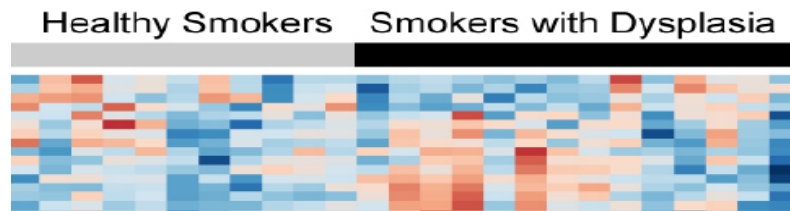
How airway gene-expression can personalize early detection and prevention of lung cancer

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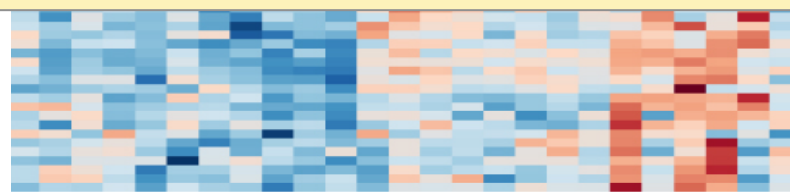
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The airway “field of injury” as a potential companion diagnostic and intermediate marker for therapeutic efficacy in chemoprevention setting



**Validation in Phase-2b clinical trial:
~75 subjects with dysplasia randomized to placebo vs. myoinositol
(*Lam et. al CaPR 2016*)**

Eva Szabo, Stephen Lam, Paul Limburg

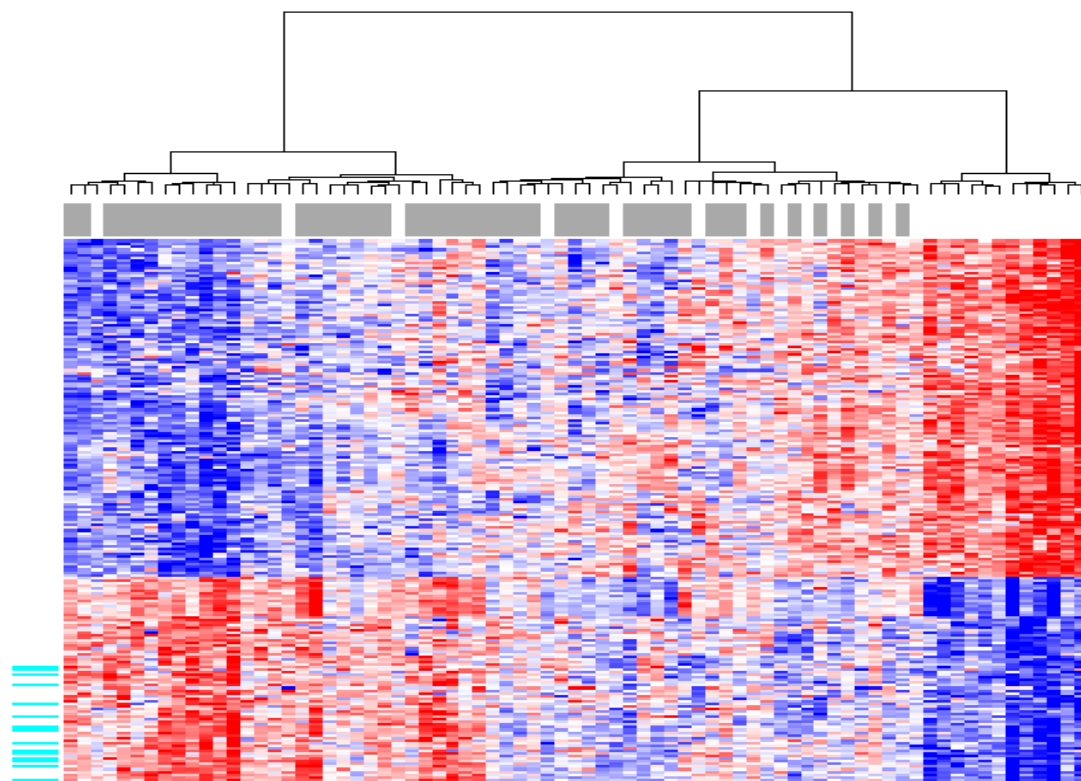


Activity of PI3K gene-expression pathway is significantly reduced post-treatment with **myo-inositol** in those smokers who had regression of their dysplastic lesions:

potential marker for selecting patients likely to respond?

Gene expression alterations in the “field” associated with presence of premalignant lesions

RNA-seq on airway epithelium from 75 smokers with dysplasia vs. 25 without dysplasia



□ Subjects without Lesions
■ Subjects with Premalignant Lesions

149 pathways enriched among up-regulated genes at FDR<0.05

- *Oxidative Phosphorylation*
- Respiratory Electron Transport
- Mitochondrial Protein Import
- Nucleotide metabolism
- DNA repair
- Cell cycle

206 genes differentially expressed at FDR<0.001

Beane et al. under revision

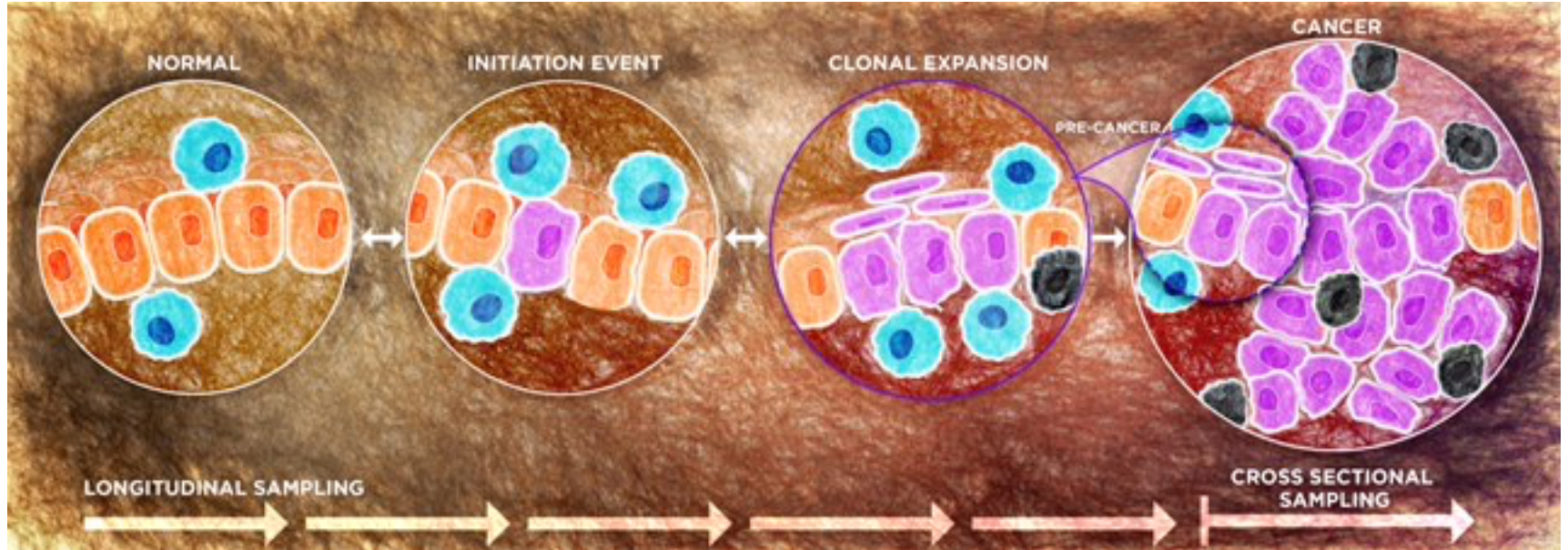
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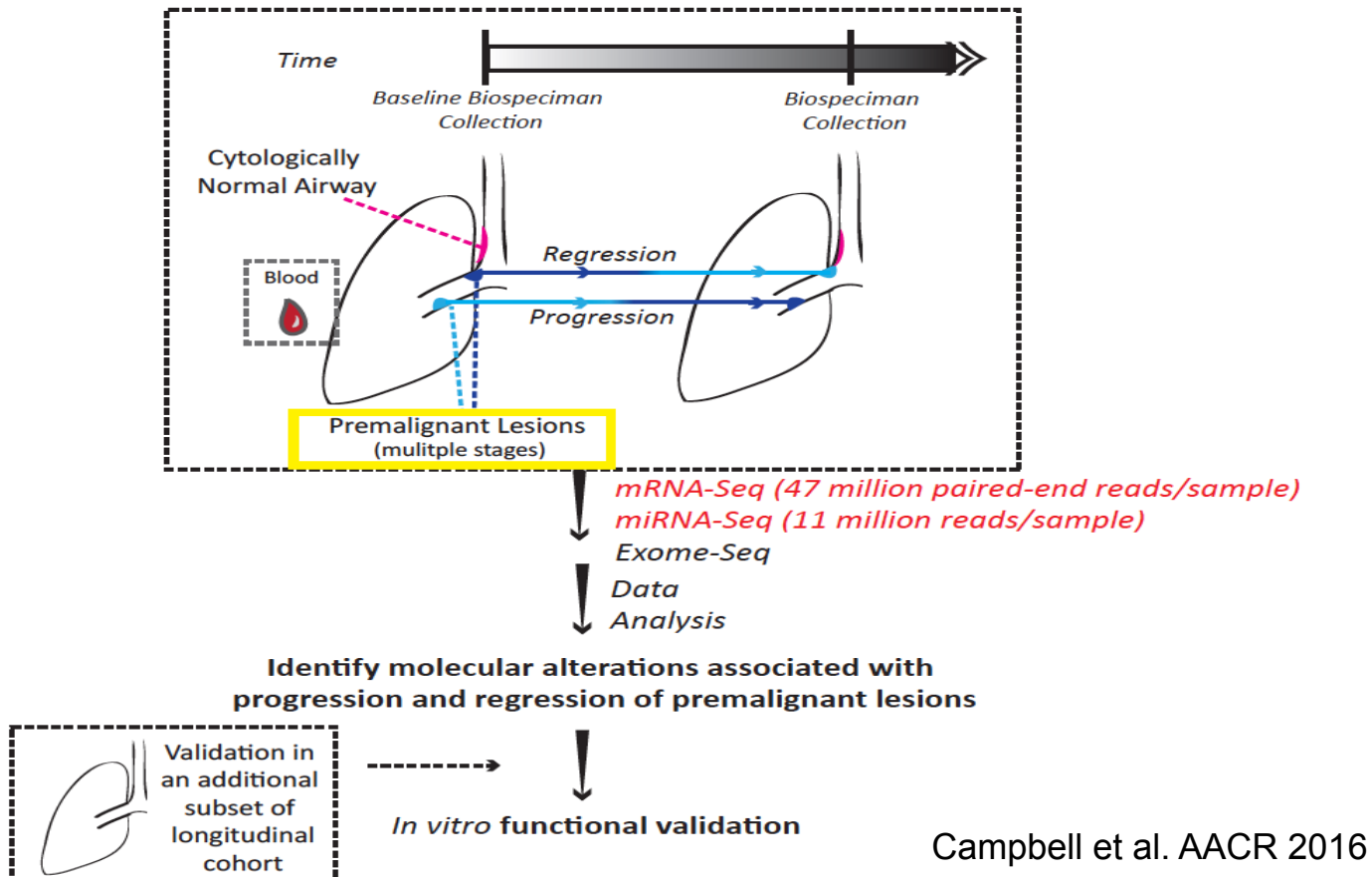
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The Case for A Pre-Cancer Genome Atlas (PCGA)



Campbell et al. CaPR 2016
Spira et al. PNAS 2016

The PCGA for Squamous cell lung carcinoma (in collaboration with Mary Reid, Roswell Park; funded by NCI/JNJ)



Summary

Airway gene expression is a biomarker of the physiological response to smoking and can serve as a diagnostic biomarker for lung cancer

- cancer “field of injury” extends into nasal epithelium

Alterations in airway gene-expression in the pre-malignant setting may serve as companion diagnostic and surrogate marker of efficacy in chemoprevention trials

PCGA needed to identify earliest molecular events associated with lung carcinogenesis: novel early detection biomarkers and targets for cancer interception

Acknowledgements



UCLA: Steve Dubinett, Denise Aberle, David Ellashoff

Vanderbilt: Pierre Massion

UPenn: Anil Vachani

DECAMP investigators

Funded by NCI/EDRN, DOD; Janssen