Developing an Airway mRNA biomarker for lung cancer detection

“the road less traveled”

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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

The beginning of the journey: Addressing key unmet needs for early lung cancer detection in CT screening era:

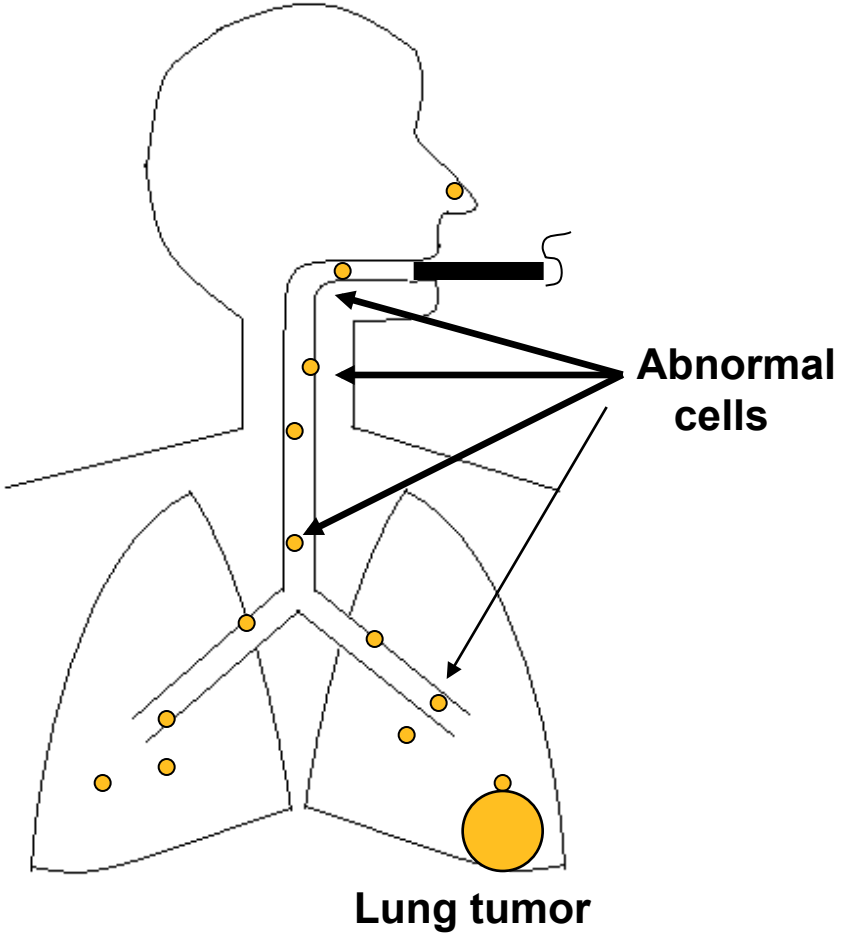
1. Distinguish benign vs. malignant lesions found on CT chest (i.e. **diagnostic** biomarker)

2. Identify highest-risk smokers who are most likely to benefit from more intense screening and/or chemoprevention (i.e. **screening** biomarker)

3. Distinguish indolent vs. aggressive screen detected tumors (i.e. prognostic biomarker)

Moving an old paradigm to a new unmet need: The airway 'field of injury'

- 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

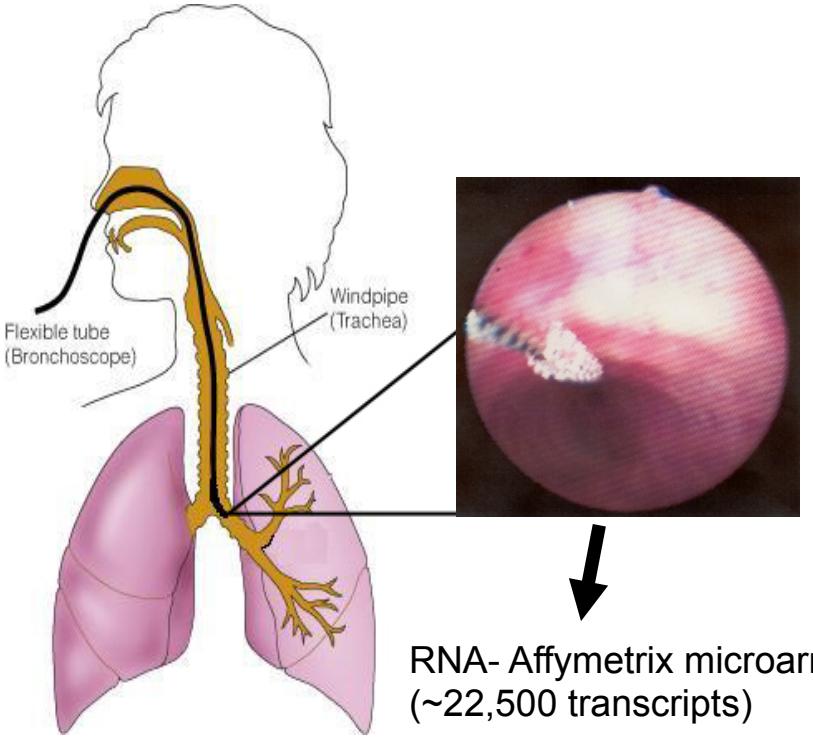


Bronchial airway gene expression as a biomarker of smoking and lung cancer

Smoking impacts airway and microRNA gene expression[1-3]

Subset of changes are irreversible upon cessation[4]

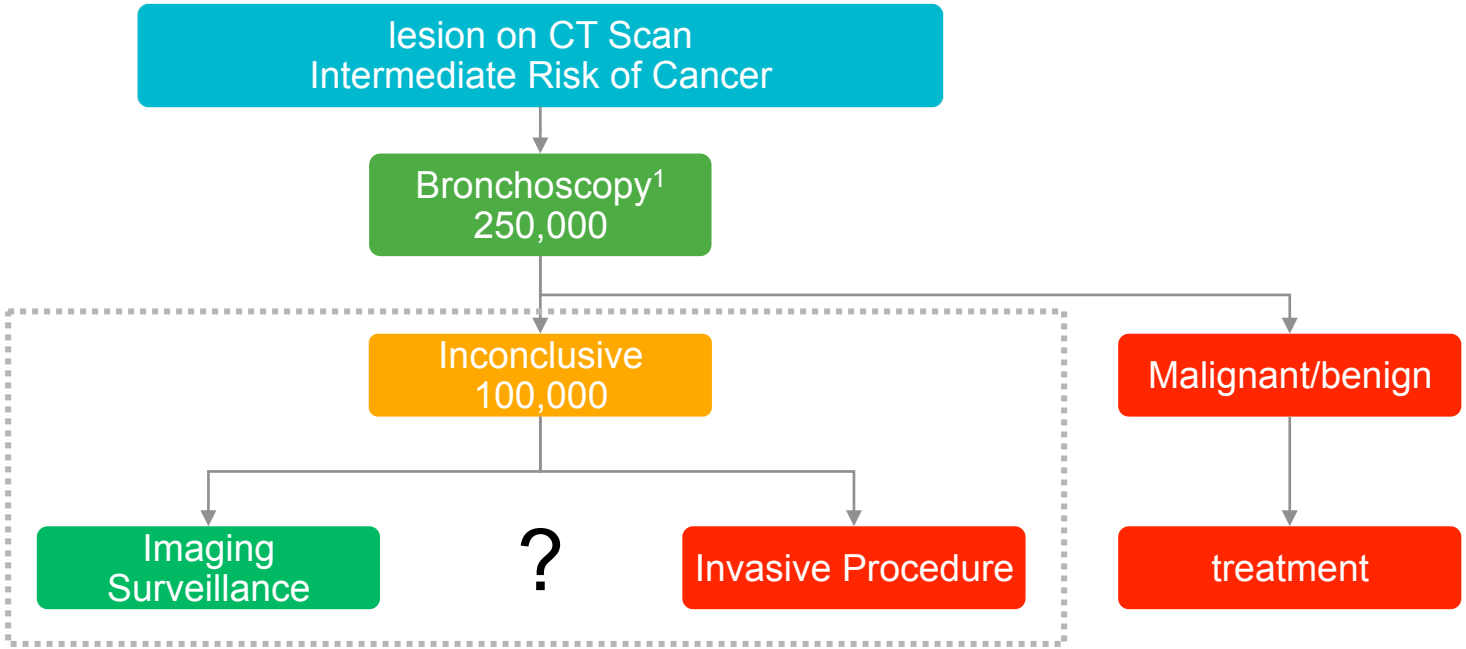
Airway gene expression can serve as an early diagnostic biomarker for lung cancer[5]



RNA- Affymetrix microarray
(~22,500 transcripts)

1. Spira et al. PNAS 2004;101:10143-48; 2. Shah et al. NAR 2005;33:D573-79; 3. Schembri et al. PNAS 2009:106:2319-24;
4. Beane et al. Genome Biology 2007;8:R201; 5. Spira et al. Nature Medicine 2007;13:361-366; 6

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



Unmet need for biomarker to guide next step in management following a non-diagnostic bronchoscopy

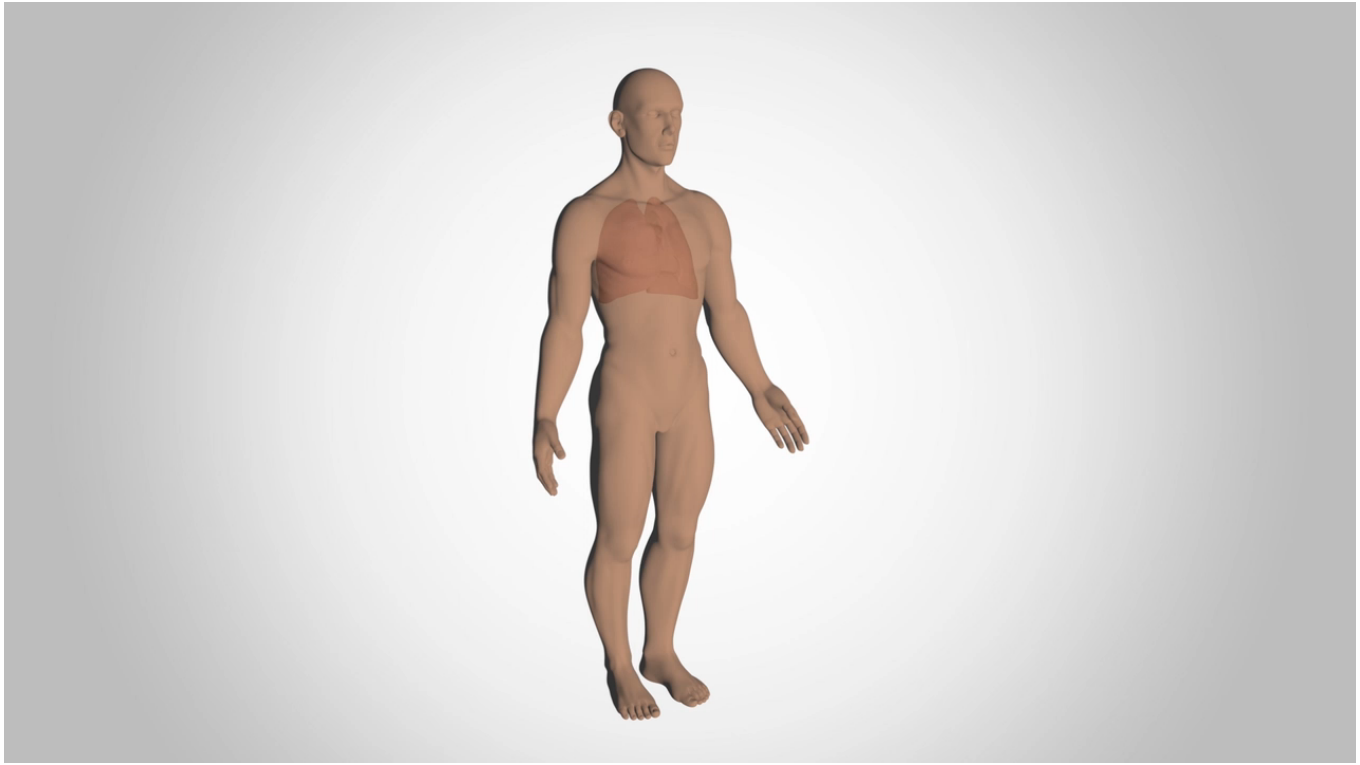
1. Centers for Medicare and Medicaid Services, Hospital Outpatient Standard Analytical Files

The Next Step on the journey: Avoiding “the valley of death”

Our options in 2007 for conducting a phase-4 prospective validation study in the intended use population to move this biomarker into the clinic where it can benefit patients:

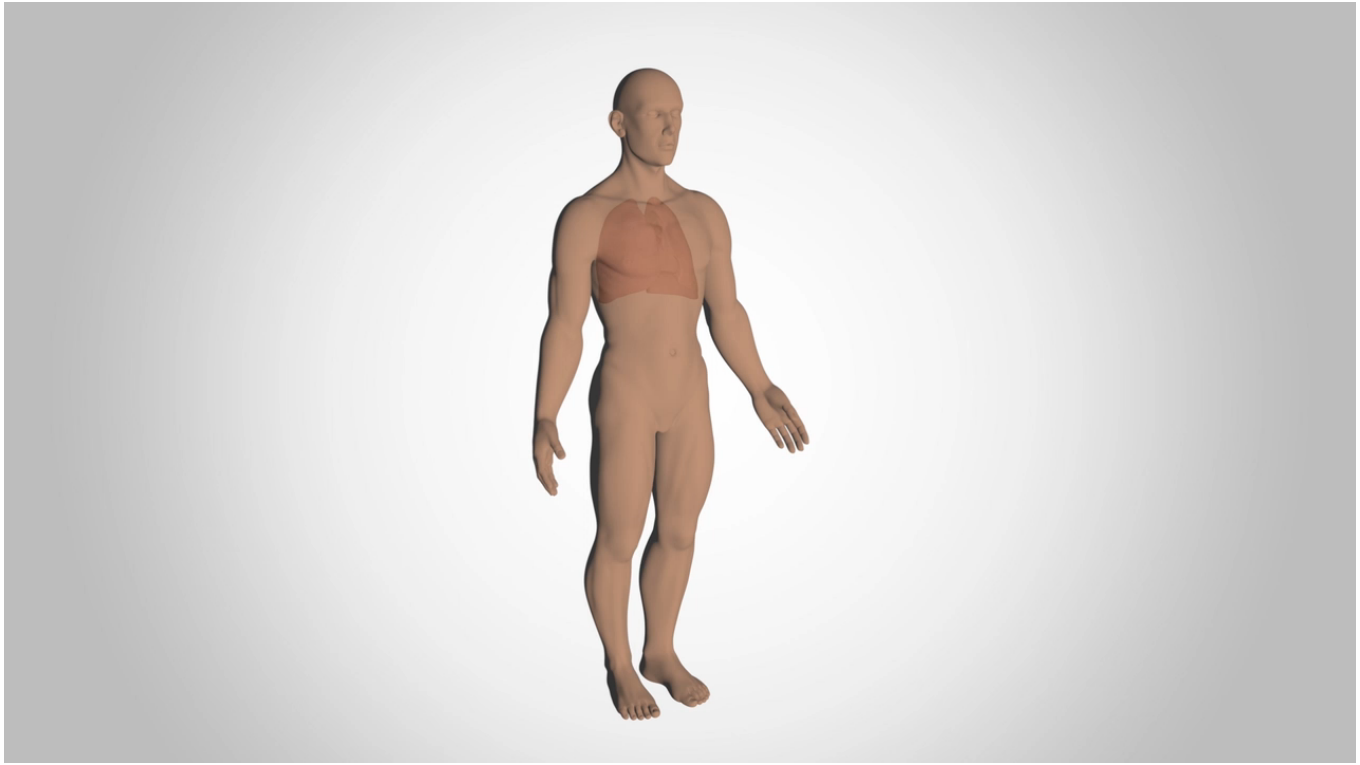
1. ***NIH/foundation support****
2. ***License to existing molecular diagnostics company***
3. *Startup company and raise venture capital (VC) financing*

The elevator pitch!



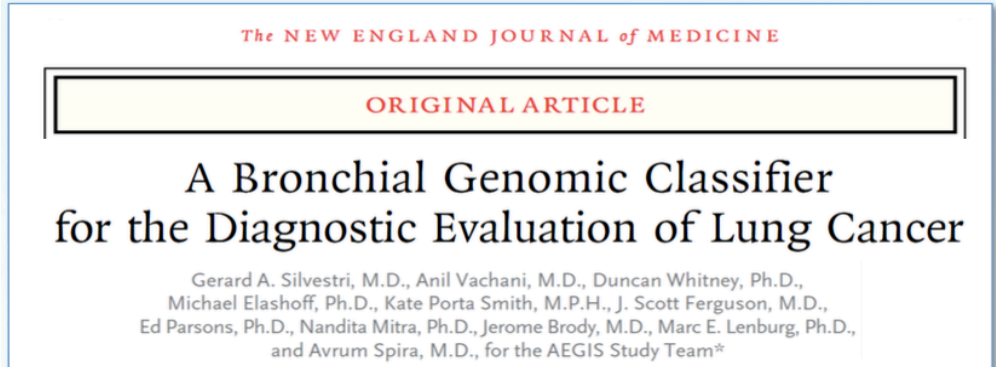
Silvestri et al. NEJM 2015;373:243-251

The elevator pitch!



Silvestri et al. NEJM 2015;373:243-251

Prospective Validation of Bronchial Genomic Classifier (23 genes) in the Airway Epithelium Gene Expression In the DiagnosiS of Lung Cancer (AEGIS I and AEGIS II) clinical trials

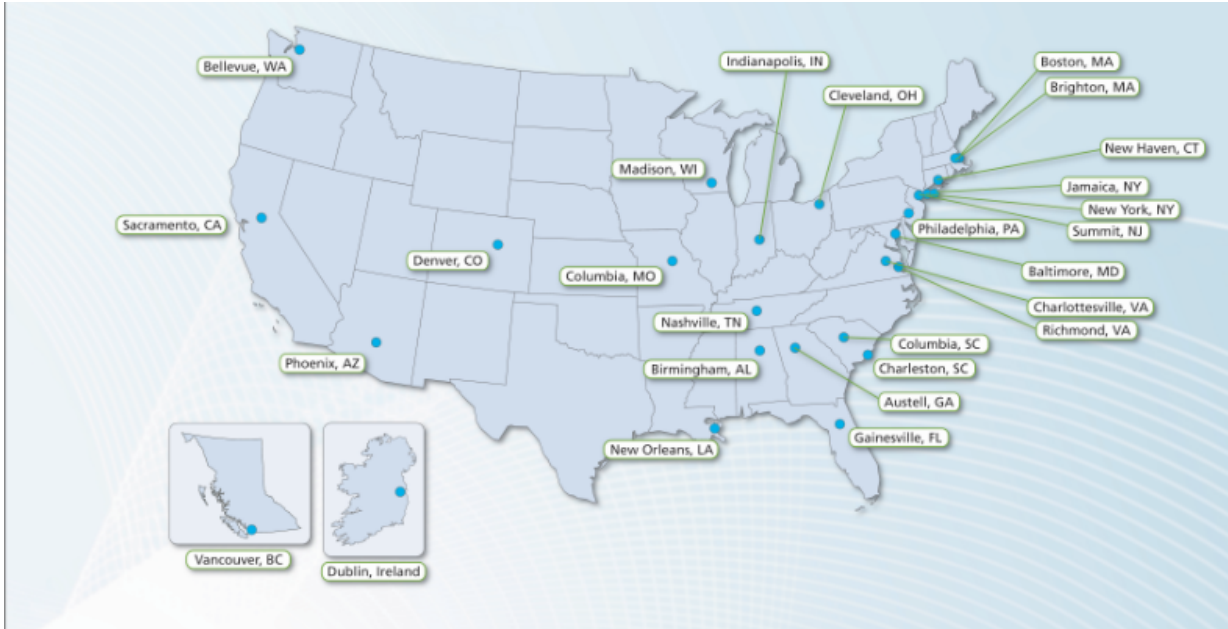


The NEW ENGLAND JOURNAL of MEDICINE

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*



AEGIS Study Summary

Prospective multicenter study of ~1000 current and former smokers undergoing bronchoscopy for suspect lung cancer.

- AEGIS 1 (n=597): Feb 27, 2008 to Sept 9, 2011
- AEGIS 2 (n=341): October 25, 2010 to July 10, 2012

23 gene biomarker refined on AEGIS-1 training set (n=299)

Whitney et al. BMC Medical Genomics, 2015

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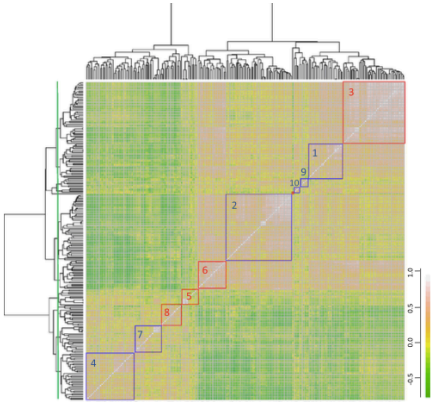
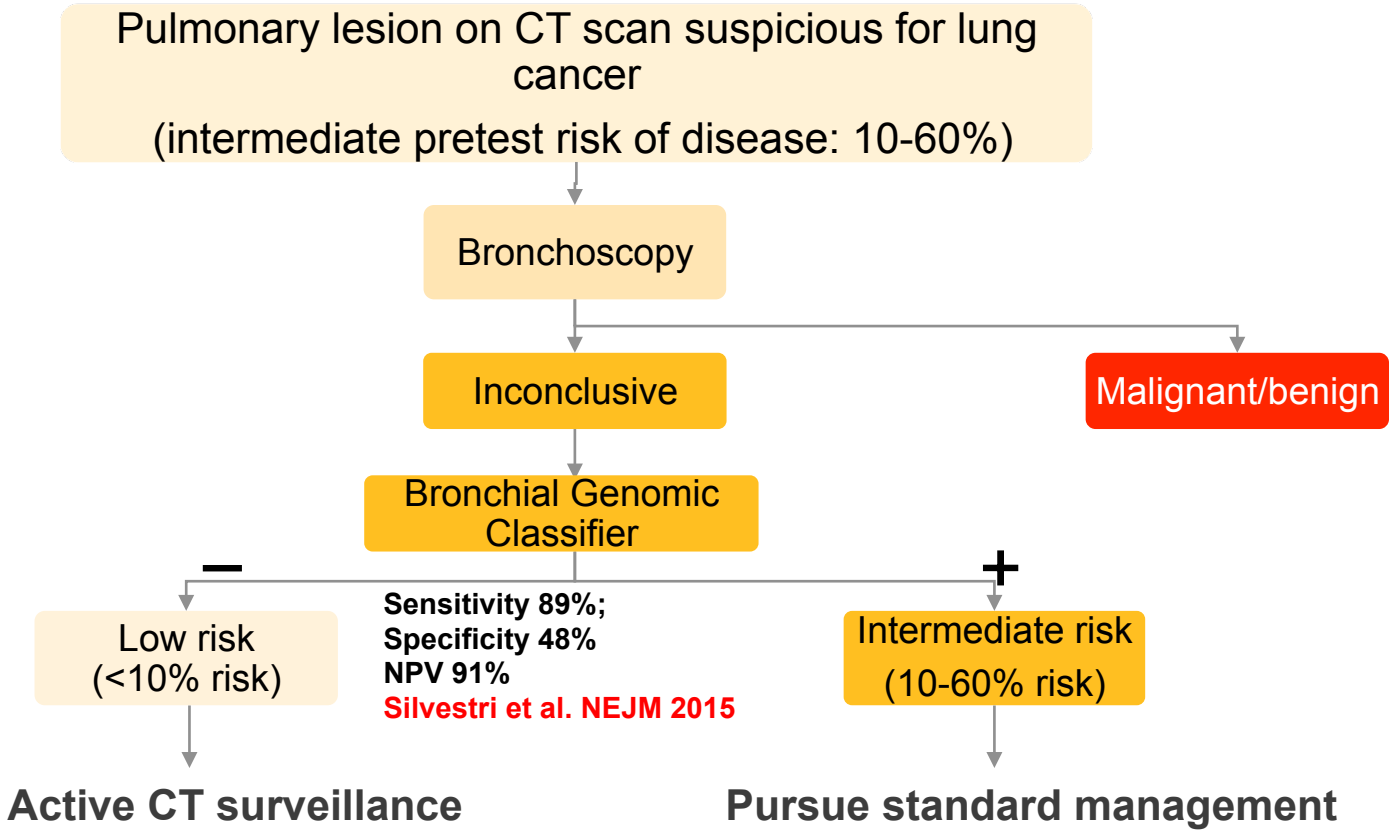
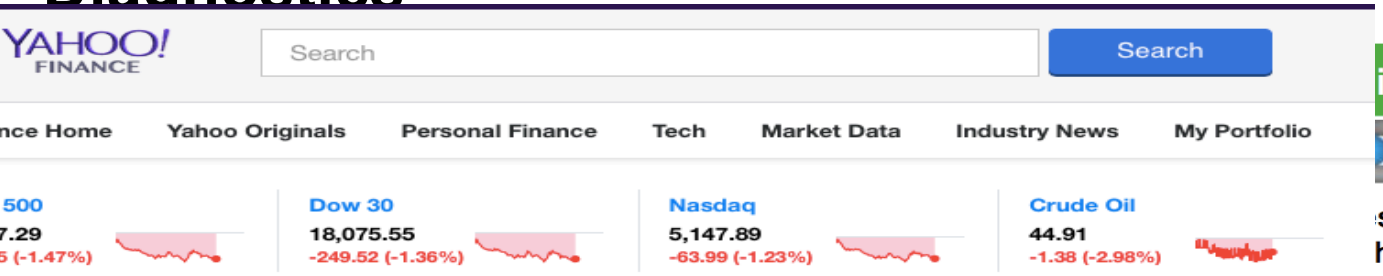


luster	Direction in Cancer	Biomarker genes	Biological themes
1	Down	BST1, CD177.1, CD177.2	Innate immune response
2	Down	ATP12A, TSPAN2	Mitotic cell cycle
4	Up	GABBR1, MCAM, NOVA1, SDC2	Response to retinoic acid, cell cycle
7	Up	CGREF1, CDR1, CLDN22, NKX3-1	Submucosal gland markers
9	Down	EPHX3, LYPD2	Xenobiotic detoxification
10	Down	MIA, RNF150	Cartilaginous markers

How the bronchial genomic classifier can impact the diagnostic workup



CDC Chain of Evidence for Evaluating Molecular Diagnostics



Veracyte Achieves Major Medicare Coverage Milestone for the Percepta® Classifier to Improve Lung Cancer Diagnosis

PRNewswire September 8, 2016

SOUTH SAN FRANCISCO, Calif., Sept. 8, 2016 /PRNewswire/ -- Veracyte, Inc. (VCYT) today announced that Noridian Healthcare Solutions, the nation's largest Medicare Administrative Contractor (MAC), has issued a draft local coverage determination (LCD) for the Percepta Bronchial Genomic Classifier. When finalized, this LCD will enable coverage for over 30 million – or more than half – of the Medicare beneficiaries in the United States. The Percepta classifier is the first genomic test for use in lung cancer diagnosis to achieve this important Medicare coverage milestone. The test is supported by multiple published studies demonstrating its ability to make lung cancer screening and diagnosis more accurate and safe by reducing unnecessary surgeries on

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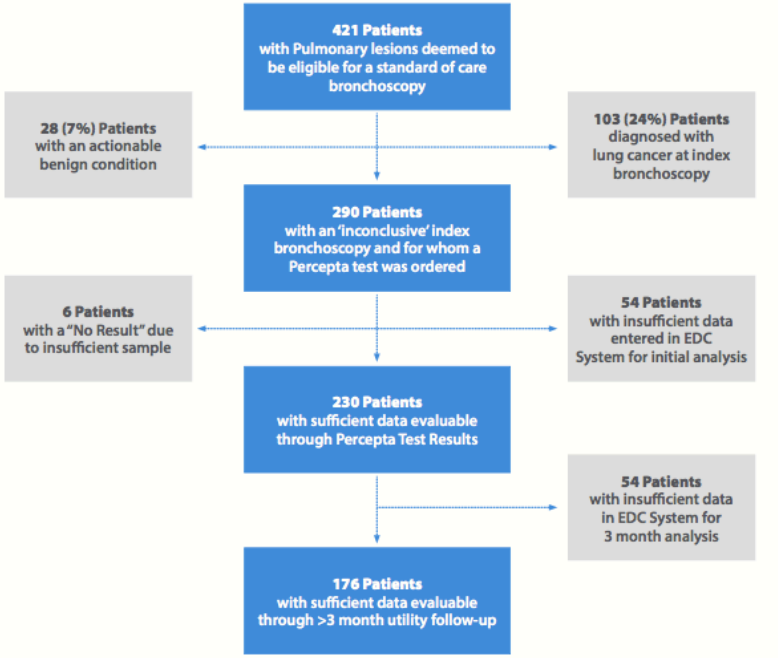
A Vachani, et al.
"Modeling the Clinical Utility of a Bronchial Genomic Classifier in Patients with Suspected Lung
Chest 2016

JS Ferguson, et al.
"Impact of a bronchial genor classifier on clinical decisior
BMC Pulmonary Medicin

ch, et al.
"Cost effectiveness of a bronchial genomic classifier
Submitted

Hogarth et al.
Measuring the impact of Percepta on patient outcomes in a real world setting
Chest/ACCP 2016

The Percepta Registry



Pre Test ROM				
Enrolled with Data	**Low N=25 (10%)**	**Intermediate N=151 (67%)**	**High N=54**	**Total N=230**
Mass size:				
≤1cm	16	38	8	62
>1 to ≤2	4	66	23	93 (87%)
>2 to ≤3	4	20	21	45
≥3	1	27	2	30
Mass location:				
Central	5	44	19	68
Peripheral	20	107	35	162 (70%)
R/L Upper Lobe	12	83	33	128 (56%)
R/L Lower lobe	9	48	20	77
R Middle Lobe	2	19	4	25
Characteristics:				
Solid	10	98	32	140 (61%)
Partial Solid	2	20	7	29
Infiltrate / GGO	5	20	5	30
Other	7	14	10	31
Navigation:				
EMN	11	51	24	86 (67%)
Radial EBUS	6	43	19	68
Fluroscopy	6	6	1	13
None / Other	2	51	10	63

Hogarth et al. Chest. 2016;150:1026A.

Next Steps

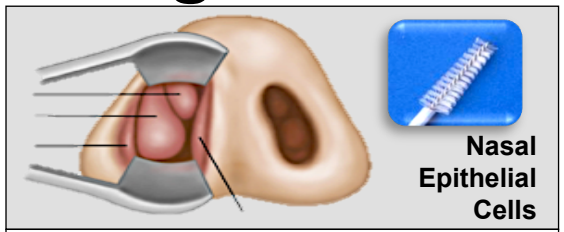
- Improving the NPV and PPV of airway gene-expression
  - Zhang et al. A Bronchial Airway Gene Expression Signature Associated with Adenocarcinoma vs. Squamous Cell Lung Cancer. ATS 2017

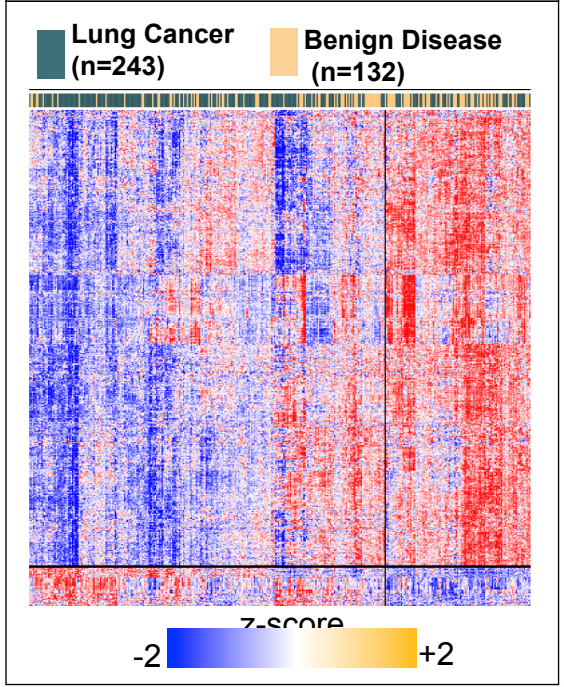
- **Single cell transcriptomic profiling to address heterogeneity in the biomarker signal**

- **Increase the clinical utility of biomarker by extending the "field" to the nose**

- Integration with imaging-based biomarkers (NCI R01) and other molecular biomarkers

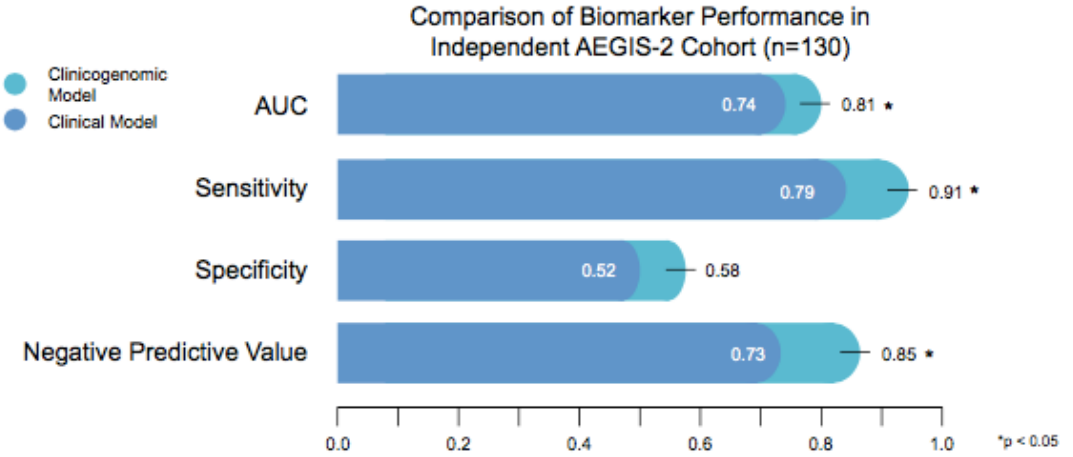
Extending the cancer “field” to the nasal epithelium





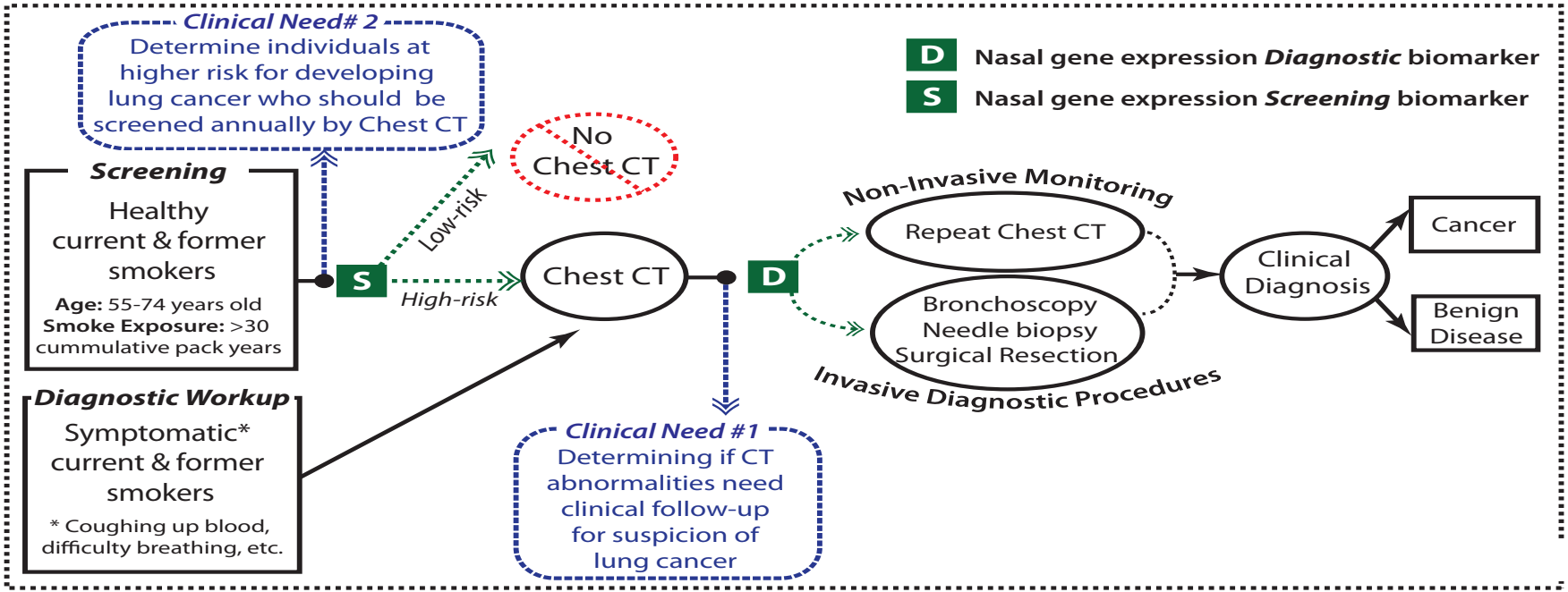
Concordance of bronch and nose

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



Perez-Rogers et al. JNCI. 2017 in press

Potential clinical applications for a nasal biomarker



Summary

Airway gene-expression can serve a biomarker of the physiological response to smoking and serve as an early detection biomarker for lung cancer

Bronchial genomic classifier (Percepta™) can improve the performance of bronchoscopy for lung cancer detection

- -High sensitivity and NPV in two prospective clinical validation studies
- -Clinical utility studies indicate the potential to avoid unnecessary invasive procedures among those who are unlikely to have lung cancer

The “field of injury” extends into the nasal epithelium which may enable lung cancer detection among those not undergoing bronchoscopy as part of their diagnostic workup

- -Potential to serve as non-invasive screening tool

New Models for Academic-Industry Partnerships are key for Translation

Acknowledgements

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