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How to Complement Biomarker Testing with Diagnostic Imaging

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3. Some trade names are used in this talk

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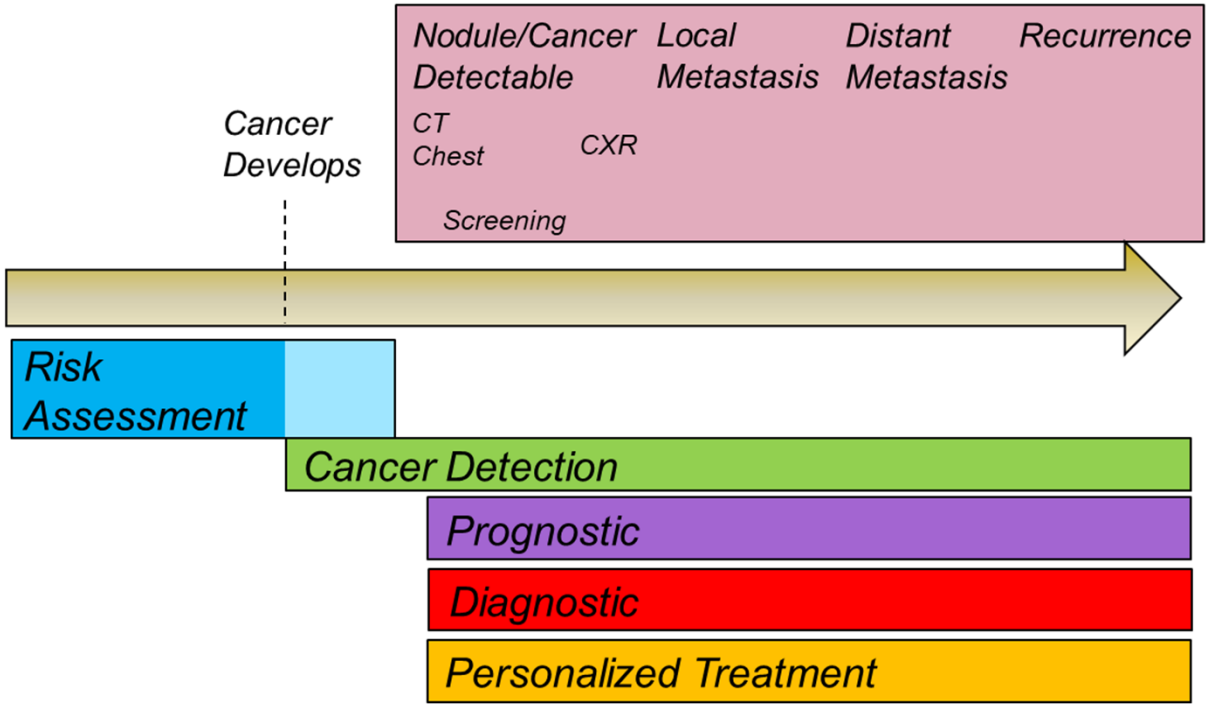
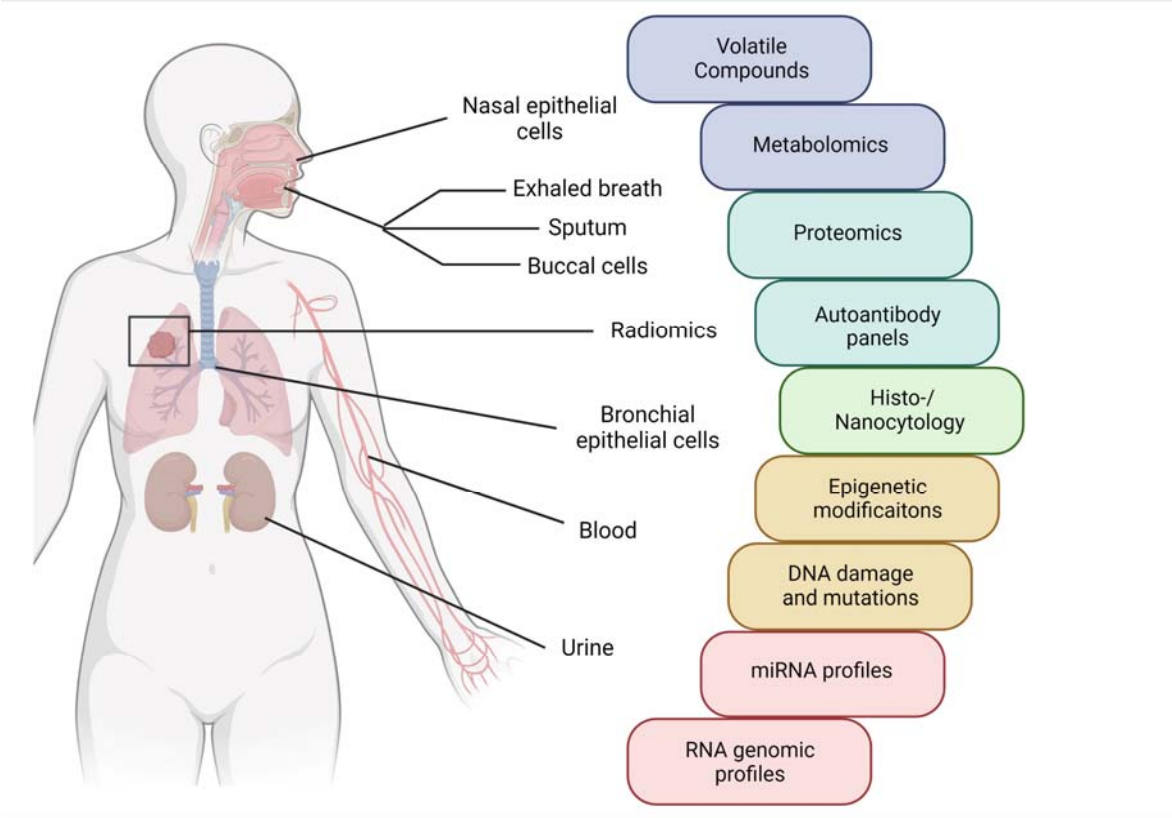
Biomarkers in lung cancer continuum



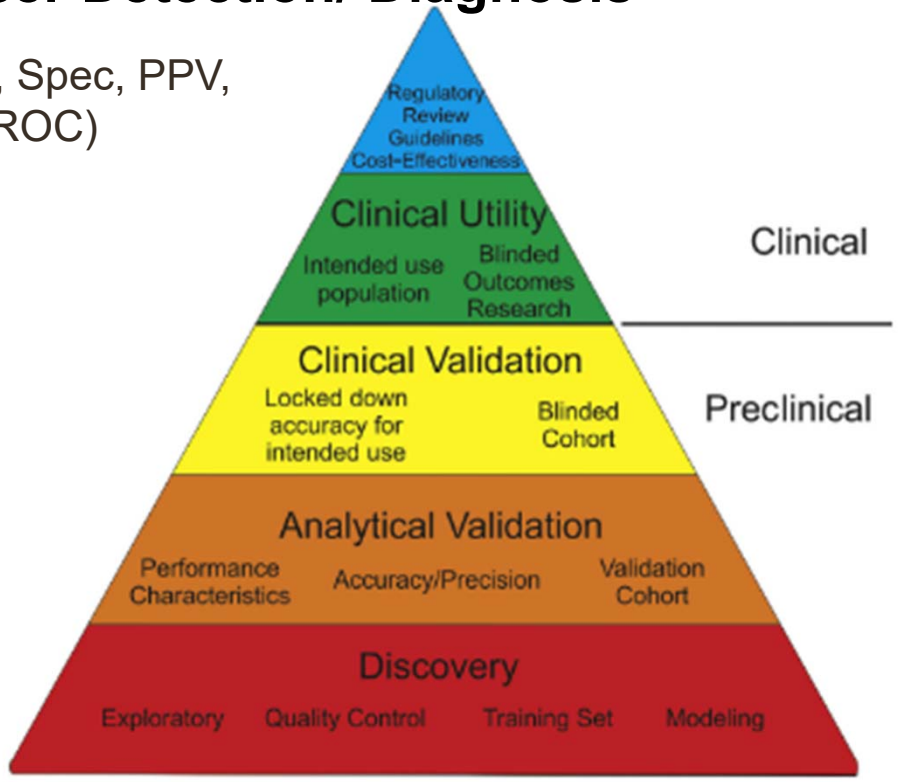
Biomarkers



Vedachalam, Tanner and Sears. Chapter 4: Approach to Lung Nodules. Respiratory Medicine (Ed. MacRosty and Rivera). *In Review.*

Ideal Biomarker for Early Lung Cancer Detection/ Diagnosis

1. Favorable Performance Metrics (Sens, Spec, PPV, NPV, ROC)
2. Easily Accessible Material
3. Small amount needed
4. Little/simple sample preparation
5. Inexpensive/Cost Effective
6. Applicable to Large Target Population
7. Clinically Useful
   - Advantage over/with standard of care
   - Easy to interpret / act on results

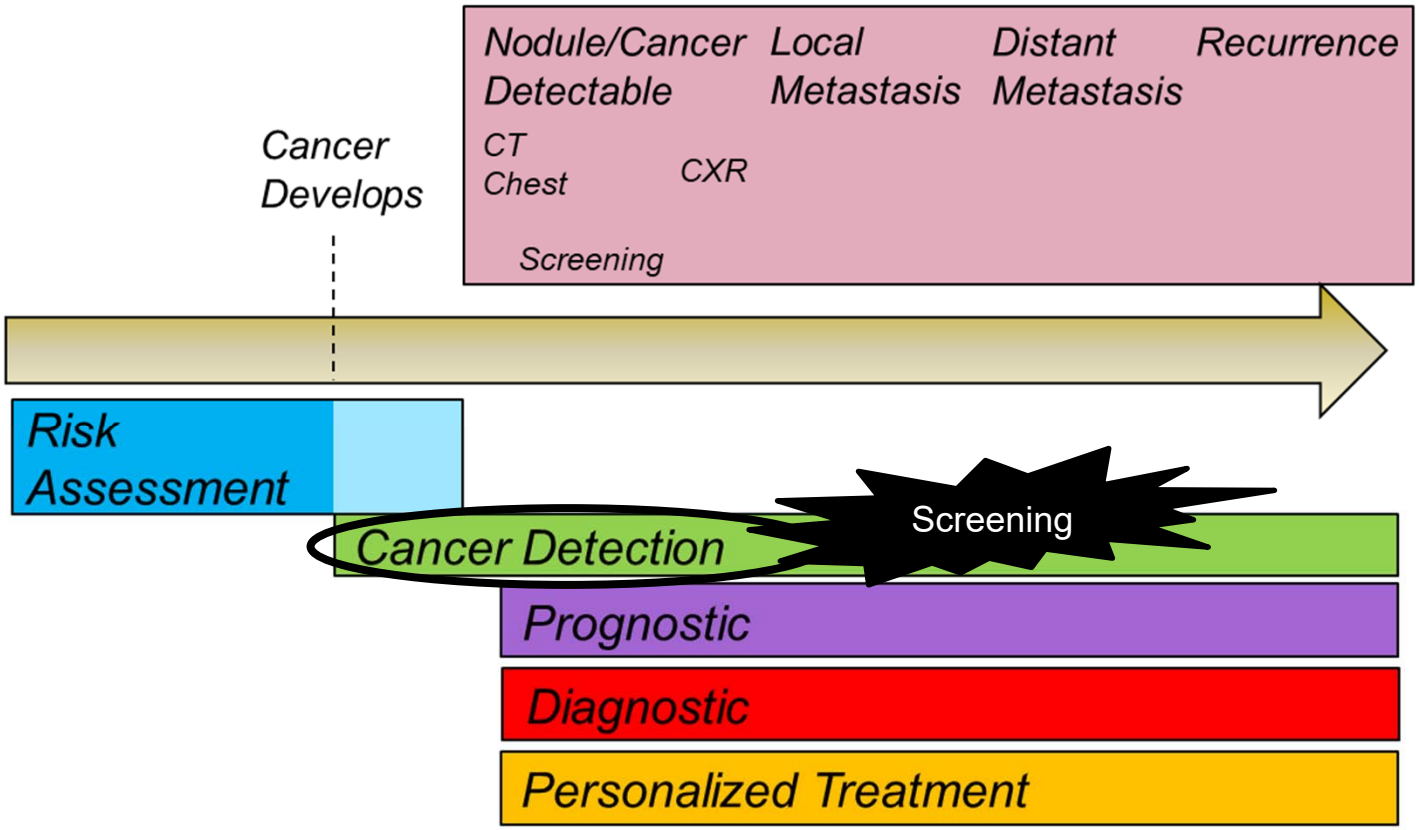


Sears and Mazzone. Clin Chest Med. 2020;41(1):115-127

Complementing Biomarker Testing
with Diagnostic Imaging

Biomarkers to Select for Lung Cancer Screening

INDIANA UNIVERSITY MELVIN AND BREN SIMON COMPREHENSIVE CANCER CENTER


Nodule/Cancer Detectable
Local Metastasis
Distant Metastasis
Recurrence
CT Chest
CXR
Screening
Cancer Develops
Risk Assessment
Cancer Detection
Screening
Prognostic
Diagnostic
Personalized Treatment

Current lung screening guidelines (2022-)

	USPSTF	CMS	NCCN
Age	50-80 yo	50-77yo	≥50*
Smoking history	≥ 20 PY	≥ 20 PY	≥ 20 PY
Smoking Status	Current or quit ≤ 15yrs	Current or quit ≤ 15yrs	Current or quit ≤ 15yrs
Secondary criteria	None	None	Additional risk factor(s) (race, exposure to radon, risk calculator, etc)

*-77 yo or older if healthy and likely to benefit

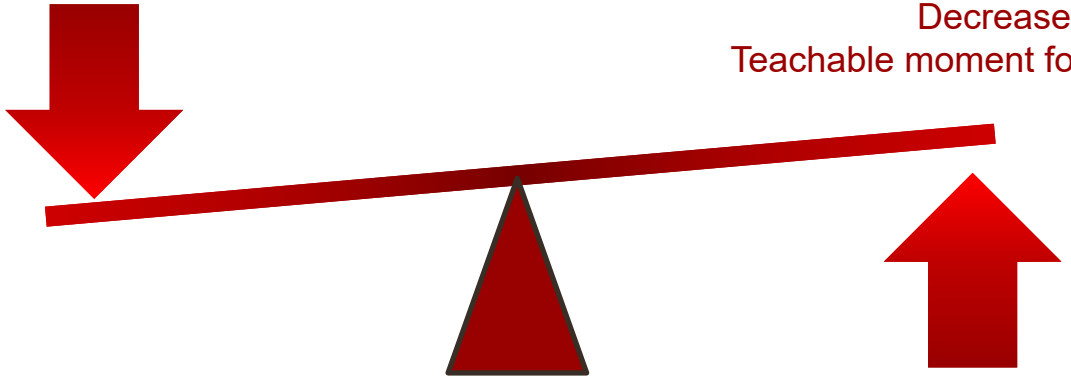
Biomarkers for LCS: Optimize Benefit to Risk Ratio

RISKS:

Nodules: False positives (high)
Overdiagnosis Psychological stress
Procedure complications
Radiation exposure
+/- Cost

BENEFITS:

Decreased lung cancer mortality
Decreased anxiety
Teachable moment for smoking cessation



Clinically Useful Biomarker for Lung Cancer Screening

Currently Screen Ineligible

Define High Risk Cohort who will Benefit from LCS

Refine/Combine with Clinical Risk Factors

- Radon Exposure
- Occupational Exposures (asbestos, chromium, coal smoke, diesel fumes, uranium, radiation, silica, soot)
- HIV+ on ART
- Lung diseases (COPD, pulmonary fibrosis)
- Family history of lung cancer (early, never-smokers)
- Prior cancer history (lymphoma, H&N cancer, smoking-related cancers)
- Heavy 2nd-hand smoke, biofuel, open stove exposure
- Populations at high risk for EGFR mutant lung cancer

Clinically Useful Biomarker for Lung Cancer Screening

Currently Screen Eligible

Increase cost-effectiveness of LCS

Patients with comorbidities: highest benefit

Appropriate duration to follow-up LDCT (negative)

Duration to LDCT f/u (positive LDCT)

Increase LDCT uptake in those not getting screened (Low Resource or Disadvantaged Groups)

- Rural/Geographic, Socioeconomically disadvantaged, *non-compliant*

Lung Cancer Biomarkers - Screening

	Measurement	Validation Cohort	Sensitivity Specificity*	Proposed Use	Availability/ Clinical Utility
Nodify CDT (Biodesix)	Blood auto-antibody panel (7): ELISA	Patients: 1613 Cancers: 61	Sens: 37% Spec: 91%	**Screening** risk assessment (outside LCS criteria, more frequent LDCT)	CLIA/ **US** (NCT01700257 – completed 2020)/ **UK** (ECLS) – Stage Shift with more frequent screening
miR-Test	Blood: miRNA	COSMOS Patients: 1115 Cancers:48	Sens: 78% Spec: 75%	Enrichment of high-risk screening cohort	No/**Clinical utility trials ongoing** (COSMOS II)
MSC signature (miRNA)	Blood: miRNA	MILD pts: 1085/939 Cancers: 85	*Sens: 95% *Spec: 78%	Enrichment of high-risk **screening** cohort	No/ **Clinical utility trial completed 3/2022** (BIOMILD) – More lung cancers diagnosed, supported longer duration btwn scans if negative
PAULA's (Protein Assay Using Lung Cancer Analytes) (Genesys)	Blood antigen / protein panel: ELISA	Patients: 150 Cancers: 75	Sens: 71% Spec: 88%	Enrichment of high-risk **screening** cohort	CLIA / **Recent new clinical validation trial using 5th biomarker**
4-MP	Blood auto-antibody panel (4): immunofluorescence bead/flow cytometry + PLCO2012	PLCO pts: Patients: 2,745 Cancers: 552	Sens: 83.5%*/88.4% Spec: 71.6%*/56.2% (*$PLCO_{2012} \geq 1.7\%$ $PLCO_{2012} \geq 1\%$)	Enrichment of high-risk **screening** cohort/ Early nodule diagnosis	No
Lung EpiCheck (Nucleix)	DNA methylation	European/Chinese Patients: 361 Cancers:209	Sens 78%-90% (Stage I-IV). Spec: matched control 64%, unmatched controls: 93%	**Screening** / Early diagnosis	No
DELFI-LUNG (Delfi Diagnostics, Inc)	Blood: cfDNA fragmentation pattern	Enrolling prospective study- 15,000 LCS pt	Varies based on multiple analytic cohorts	Enrichment of high-risk **screening** cohort / symptomatic lung cancer / Rule-in nodule biomarker	No / NCT05306288 (CASCADE-LUNG for LCS) / NCT04825834 (DELFI-L101 for Nodule Clin validation)
RespiraGene (Synergenz)	Oral swab: 20 SNPs + clinical			Enrichment of high risk **screening** cohort Smoking cessation for high risk (GeTSS)	**No**

Sears, Mazzone. Clin Chest Med. 2020

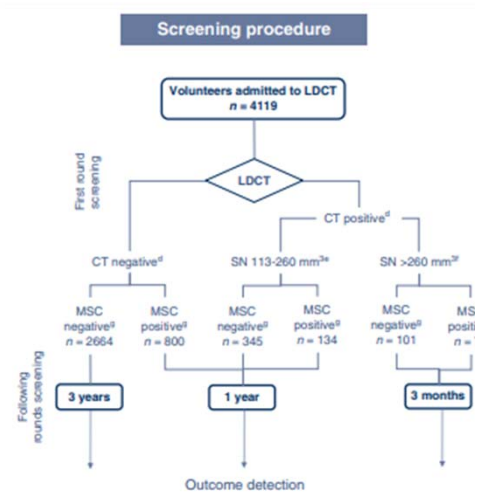
Fahrmann et al. J Clin Oncol. 2022

Nichols et al. BMC Res Notes. 2017

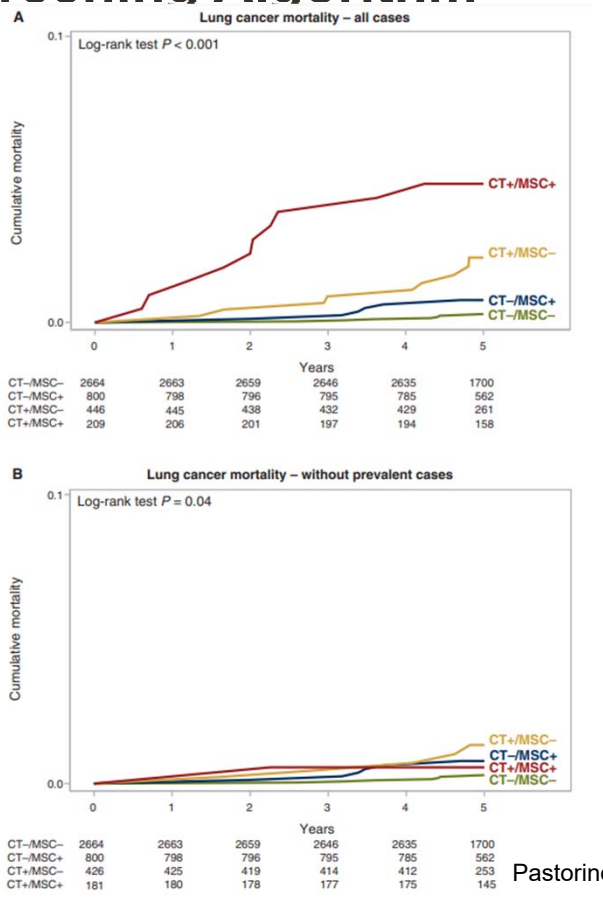
Mathios et al. Nature Communications. 2021

Biomarker-Driven Lung Cancer Screening Algorithm

bioMILD Trial



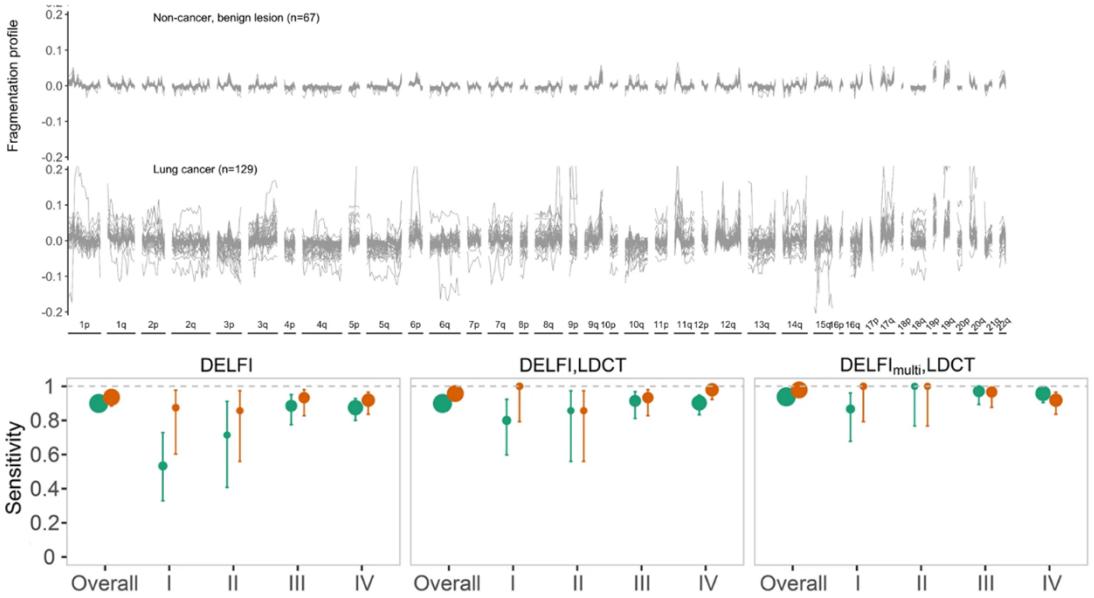
119 lung cancers (2.9%)
72 (60.5%) Stage I NSCLC

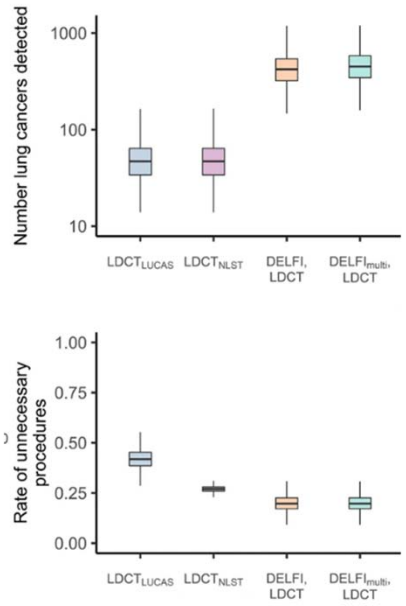


Pastorino et al. Ann Oncol. 2022

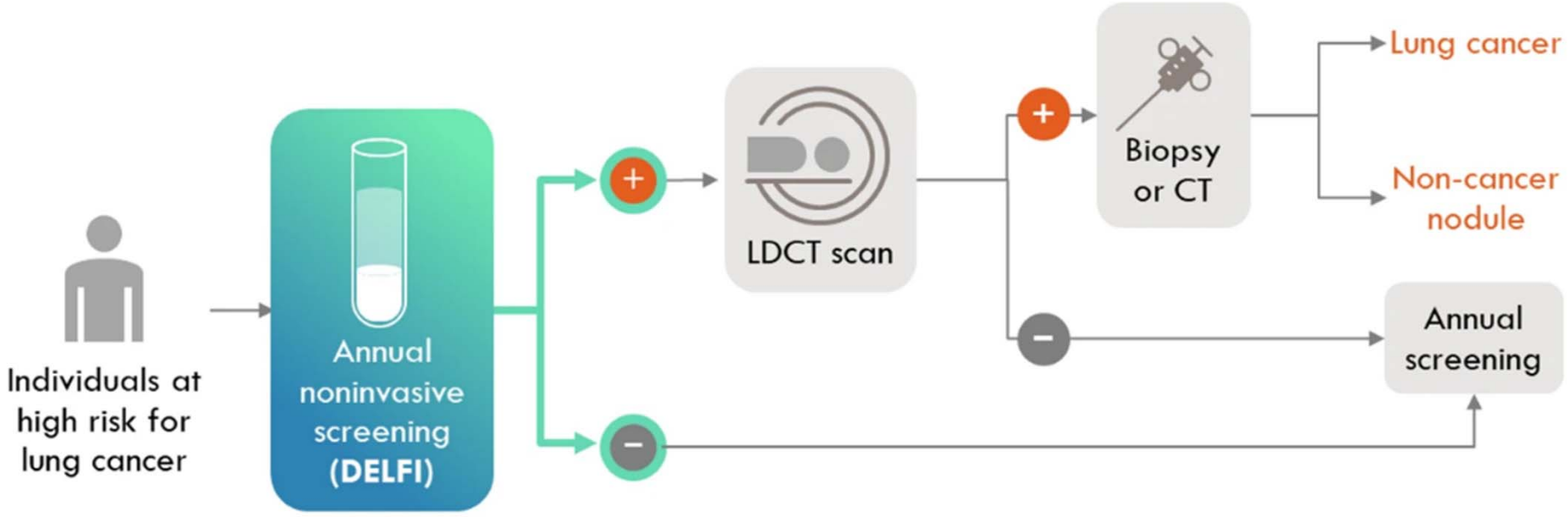
Combining Biomarkers with LCS Estimates and Risk Stratification Models

DELFI-LUNG





Mathios et al. Nature Communications. 2021

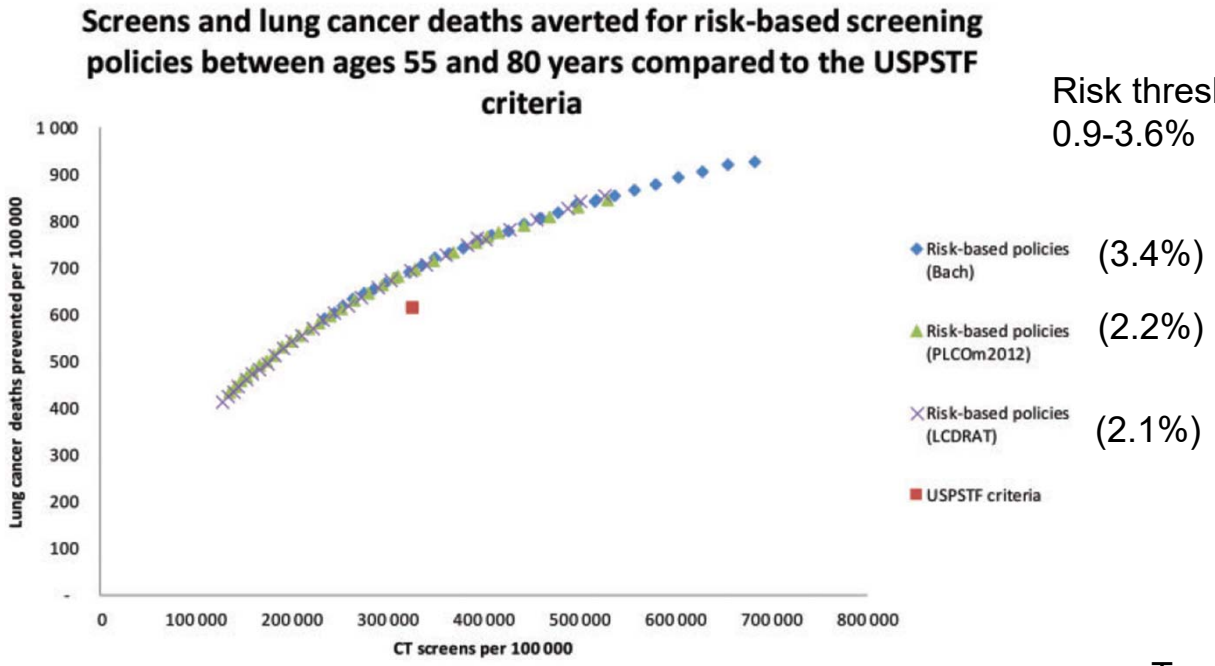

Individuals at high risk for lung cancer
Annual noninvasive screening (DELFI)
+
−
LDCT scan
+
−
Biopsy or CT
Lung cancer
Non-cancer nodule
Annual screening

Lung Cancer Risk Assessment Models (Gold Standard?)

	PLCOm 2012*	Bach Model	LLP*	LCDRAT	Kovalchik Model	TSCE Models	Knote Model	Hunt Model
Source	PLCO	CARET	LLP	PLCO	PLCO	NHS, HPFS	CPS-I/II (ACS) +/- NHS	HUNT2
Factors	Age* Race/ethnicity BMI Education Prior CA Smoking* Family History COPD	Age Sex Smoking	Age* Sex* Prior CA Smoking*	Age Sex Race/ethnicity BMI Education Smoking FH Emphysema	Age BMI Smoking FH Emphysema	Age Sex Smoking	Age Race/ethnicity Smoking	Age BMI Smoking Daily cough

*Included in Simplified models

Modeling- Risk Based Screening



Risk thresholds
0.9-3.6%

(3.4%)

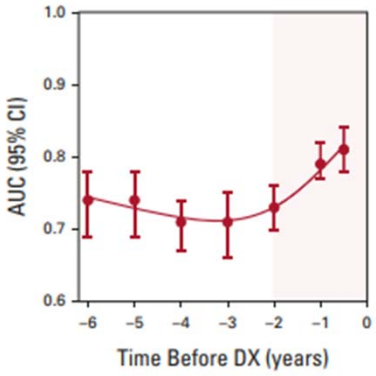
(2.2%)

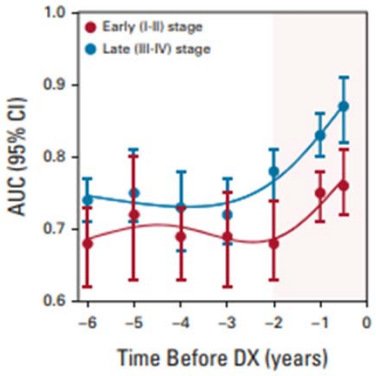
(2.1%)

Ten Haaf et al. JNCI. 2020

Combining Biomarkers with LCS Estimates and Risk Stratification Models

4MP + PLCO2012





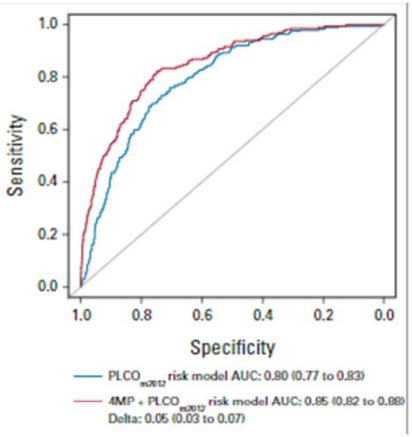


TABLE 2. Accuracy Performances in the Validation Set for the 4MP, $PLCO_{m2012}$, and the Combined Model of 4MP Plus $PLCO_{m2012}$ at Fixed Thresholds of ≥ 1.7% and ≥ 1% 6-Year Risk, to be Comparable With USPSTF2013 and USPSTF2021 Criteria in ESIA10+

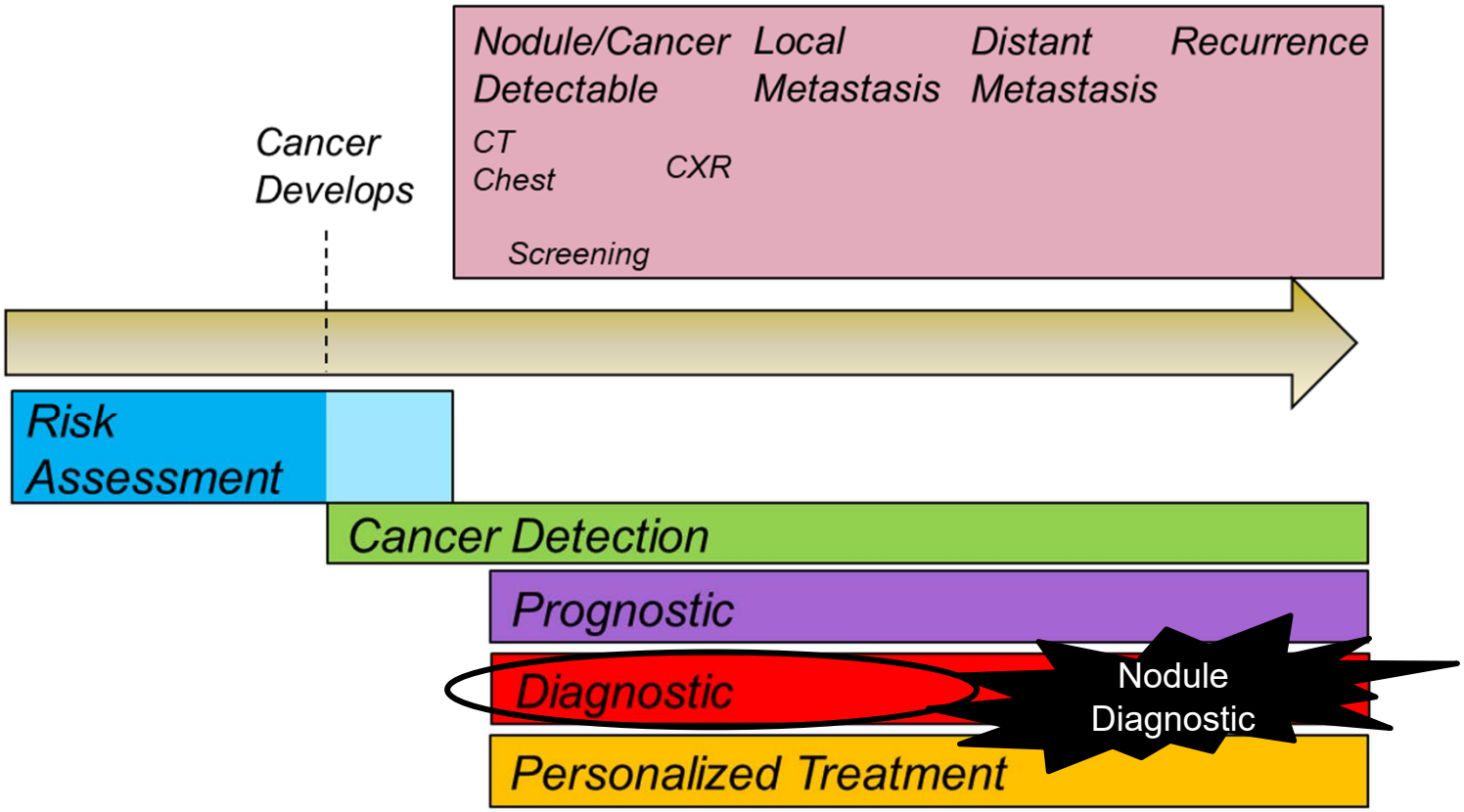
Criteria	N1[a]	N0	1-Year Sensitivity[b]	Specificity	1-Year TP[c]	FP[c]
≥ 1.7% risk threshold						
USPSTF2013[d]	119	32,243	0.716	0.564	85	14,061
4MP[e]	119	32,243	0.824	0.632	98	11,866
$PLCO_{m2012}$[f]	119	32,243	0.776	0.654	93	11,145
Combined 4MP + $PLCO_{m2012}$ model[g]	119	32,243	0.835	0.693	100	9,905
≥ 1.0% risk threshold						
USPSTF2021[d]	119	32,243	0.785	0.493	94	16,356
4MP[e]	119	32,243	0.915	0.454	109	17,591
$PLCO_{m2012}$[f]	119	32,243	0.920	0.466	110	17,224
Combined 4MP + $PLCO_{m2012}$ model[g]	119	32,243	0.884	0.562	105	14,122

Fahrmann et al. J Clin Oncol. 2022

Complementing Diagnostic Imaging
with Biomarker Testing

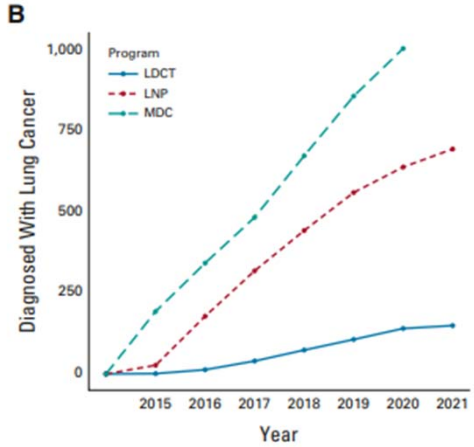
Biomarkers for Nodule Risk Assessment

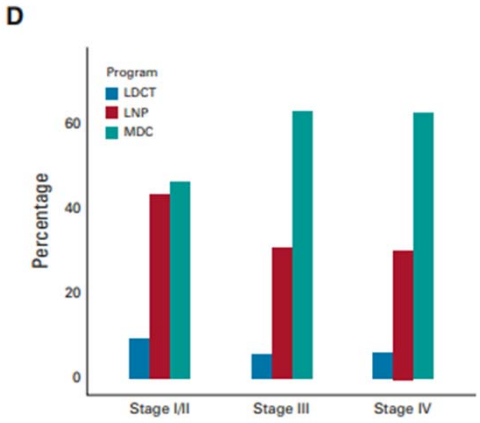
INDIANA UNIVERSITY MELVIN AND BREN SIMON COMPREHENSIVE CANCER CENTER


Nodule/Cancer Detectable
Local Metastasis
Distant Metastasis
Recurrence
CT Chest
CXR
Screening
Cancer Develops
Risk Assessment
Cancer Detection
Prognostic
Diagnostic
Personalized Treatment
Nodule Diagnostic

Problem… Pulmnary Nodules are Common

>1,600,000 incidental lung nodules/year…. And growing!





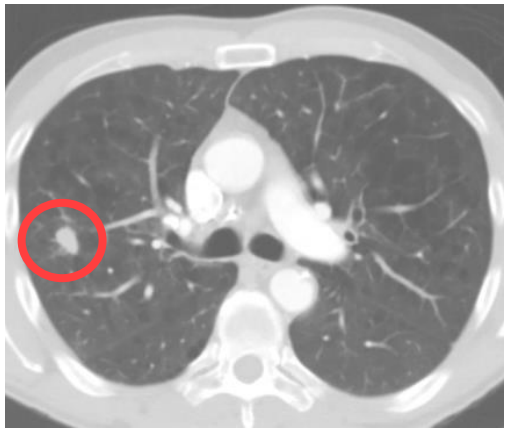
Most (Early) Lung Cancers are Detected Incidentally!

Gould et al. Am J Resp Crit Care Med, 2015;192(10)
Smith-Bindman et al. JAMA 2019;322(9):843-859

Osarogiagbon et al. J Clin Oncol 2022;40:2094-2105.

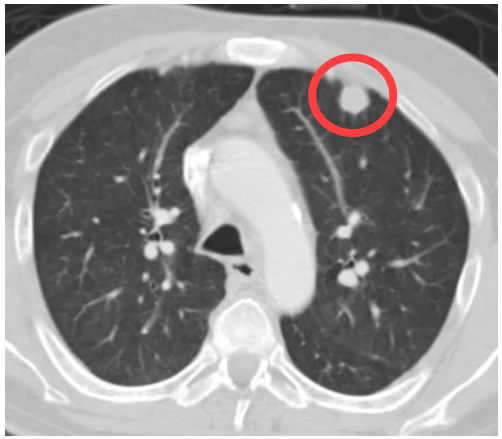
Pulmonary Nodule Diagnostic Biomarkers

62-Year-Old Male Smoker



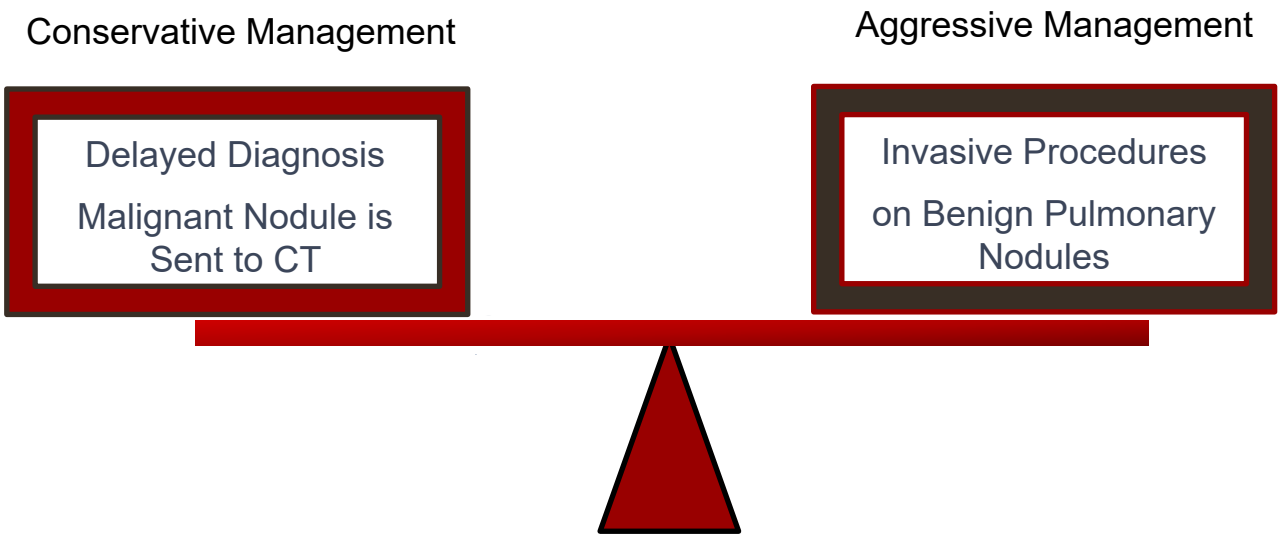
LUNG CANCER

54-Year-Old Male Smoker

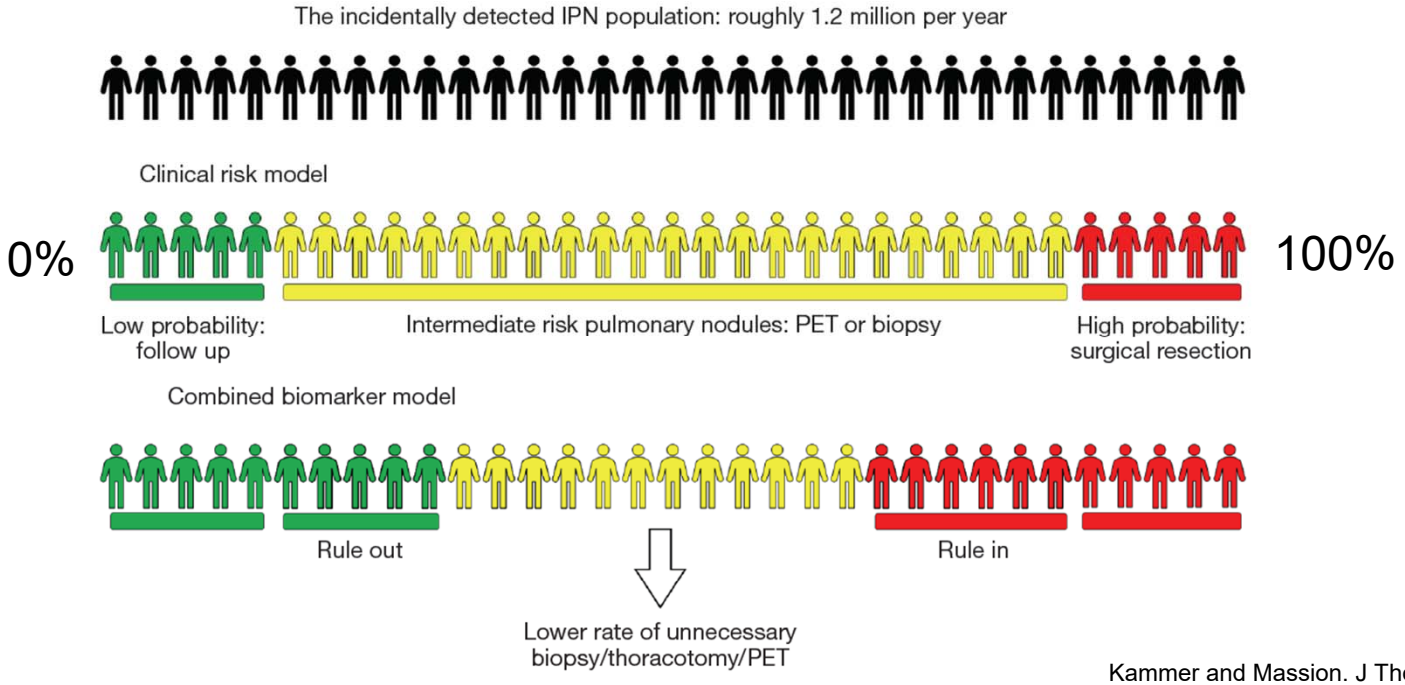


HISTOPLASMOSIS

The Lung Nodule Biomarker: Goal



Problem: Intermediate Risk Nodules



Kammer and Massion. J Thorac Dis. 2020

Commercially Available Nodule Management Biomarkers*

	Measurement	Validation Cohort	Sens/Spec	Proposed Use	Availability/ Clinical Utility
Nodify CDT (Biodesix)	Blood auto-antibody panel: ELISA	Patients: 1613 Cancers: 61	Sens: 37% Spec: 91%	**Nodule management** (intermed. risk) • Positive = aggressive management	Yes / No clinical utility trial
Nodify XL2 (Biodesix)	Plasma Protein: MRM Mass Spectrometry + 5 Clinical characteristics (Mayo)	PANOPTIC: Patients: 392 (178*) Cancers: 29	Sens 97% Spec: 44%	**Nodule management** (low-intermed risk) Pretest Probability Cancer < 50% • Negative = radiologic surveillance	Yes/**Clinical utility trials initiated** (ALTITUDE) NCT04171492
Percepta GSC (Veracyte)	Bronchial epithelial cells: mRNA/gene expression profile	AEGIS-1/AEGIS-2 Patients: 639 Cancers: 487	Sens: 88% Spec: 47%	**Nodules** (intermed risk) undergoing bronchoscopy • Negative = radiologic surveillance	Yes / Clinical Utility extrapolated
Percepta Nasal Swab (Veracyte)	Nasal epithelial cells: mRNA/gene expression + clinical risk factors	AEGIS-2 Patients: 130 Cancers: 66	Sens: 91% Spec: 52%	**Nodules** (intermediate risk) • Negative = radiologic surveillance	Yes/ No clinical utility trial
REVEAL (MagArray)	Blood tumor mRNA by Nanostring (Biochip) + clinical	Patients: 97 Cancers: 51	Sens: 94% Spec: 33%	**Nodules** (intermediate risk) • Low score = radiologic surveillance	Yes/ No clinical utility trial

Large clinical validation/registry studies ongoing - LungLB (LungLifeAI), DELFI, GRAIL, DetermaDx Lung, bioAffinity, 4-MP, many multi-cancer platforms

Sears, Mazzone. Clin Chest Med. 2020. Trivedi et al. Biomed Research Clin Practice. 2018. Kossenkov et al. Cancer Res. 2019. Ostrin et al. J Thorac Oncol. 2021. Mazzone et al. J Clin Oncol. 2021 (abst, 8551)

Trend: Pan-Cancer Biomarkers Galleri (GRAIL)

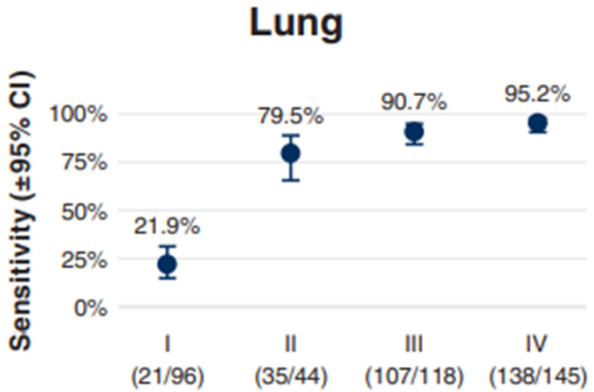
Targeted Genome Methylation Assay using cfDNA

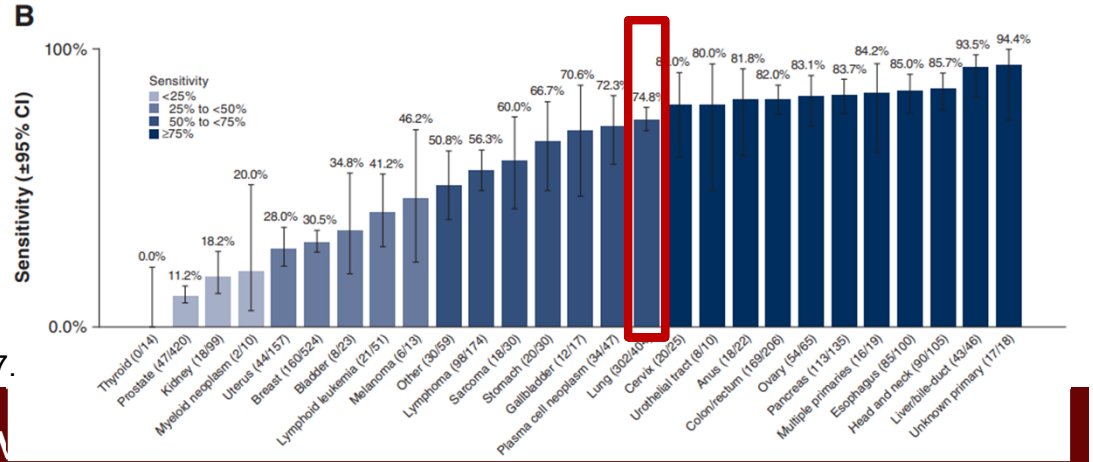
Prospective collection/retrospective analysis (CCGA)

- 15,254 patients (8584 cancer, 6670 non-cancer)
- 142 sites in N. America
- Clinical validation on 5309 participants

Sens: 51.5% (75% Lung Cancer)

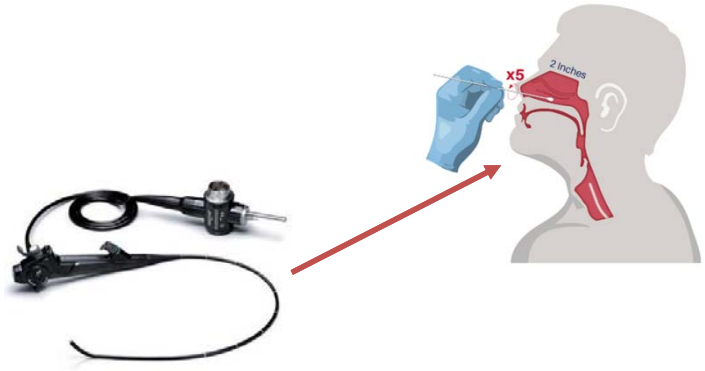
Spec: 99.5%





Klein et al. Annals Oncol. 2021;32(9):1167-1177.

Trend = Less Invasive Percepta - (AEGIS-1 and -2)



Bronchial airway cells, mRNA gene panel

Low-intermediate risk nodule/non-dx bronchoscopy

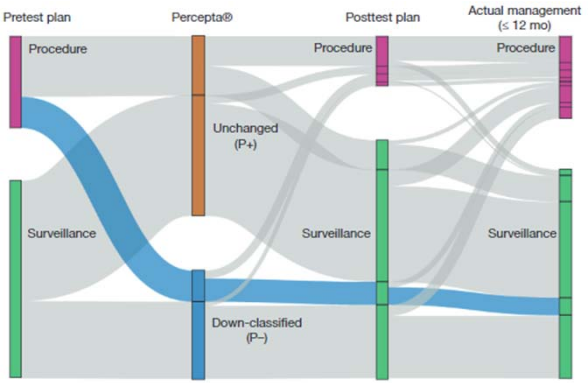
“Rule-Out” Biomarker

Registry = of 34% down-classified,

78% had change in clinical practice

Est. 74% decrease planned procedures (initially)

Cost: predicted cost-effective (ICER $15,052/QALY)[1]

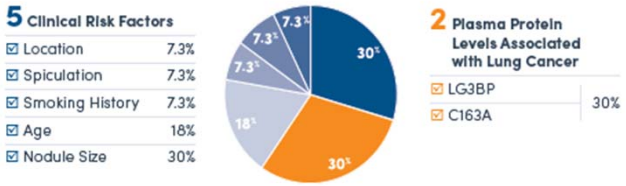


Silvestri et al. NEJM 2015; 373:243-251.
[2]Lee et al. CHEST. 2021; 159(1):401-412 3Mazzone et al. J Clin Oncol. 2021 (abst, 8551)

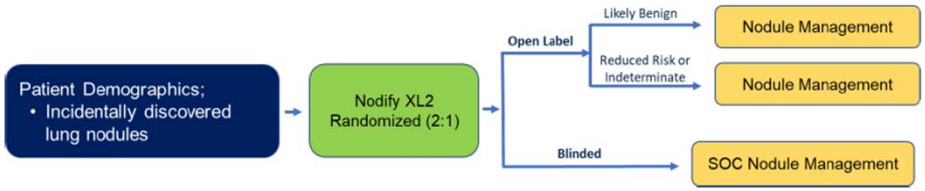
Trend: Confirming Clinical Utility
Nodify XL2 - ALTITUDE Study

Low-intermediate risk incidental nodule
"Rule-Out" Biomarker, blood, MRM proteomics

Nodify XL2 – Biomarker + Clinical Risk

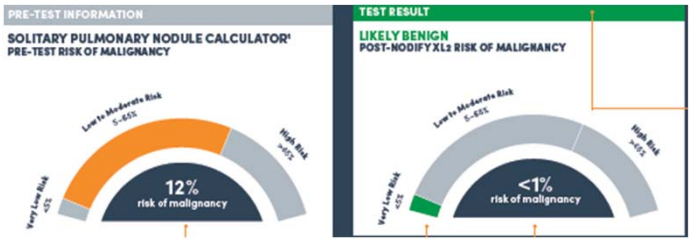


ALTITUDE – Clinical Utility Study



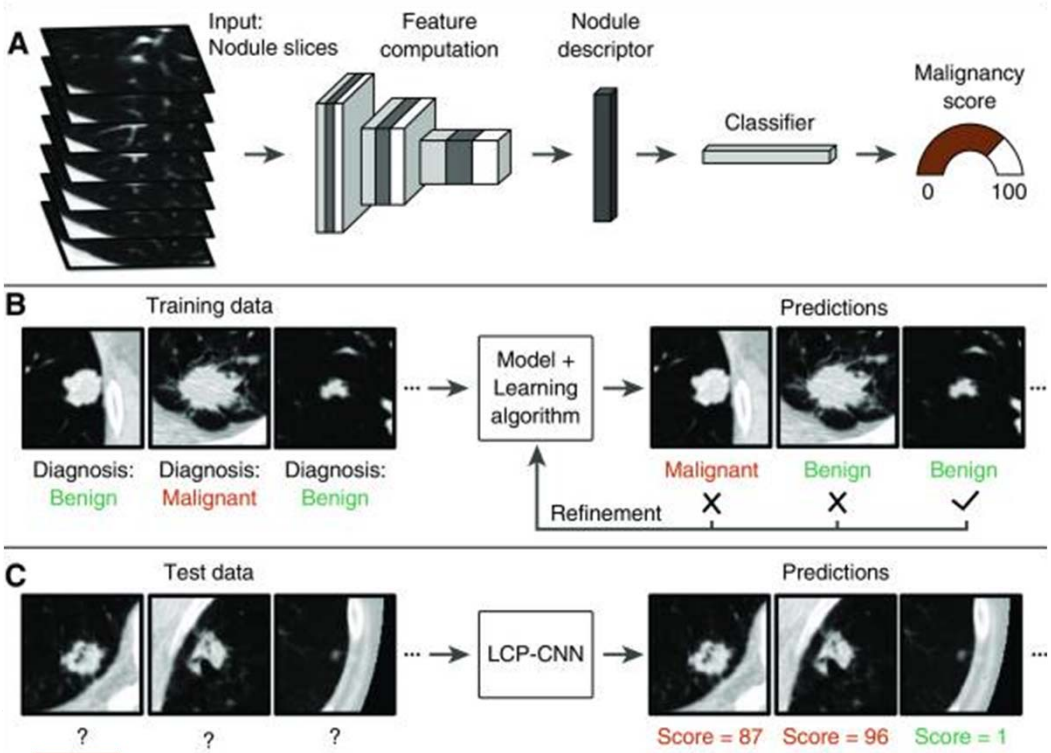
Results of Clinical Validation Study (PANOPTIC)

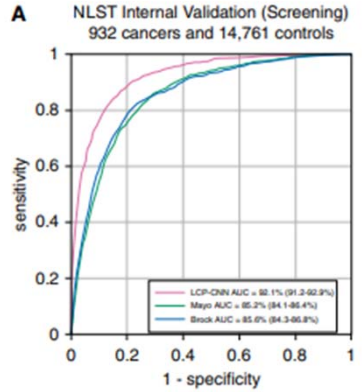
- Sensitivity: 97%. NPV 98%.
- Anticipated 47% fewer procedures on benign nodules (reclassified < 5% risk)

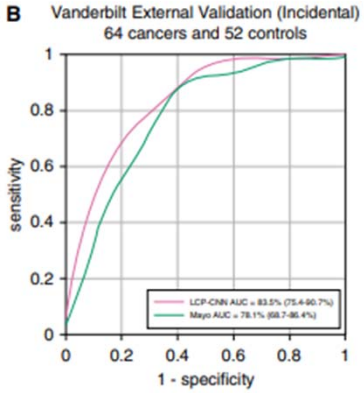


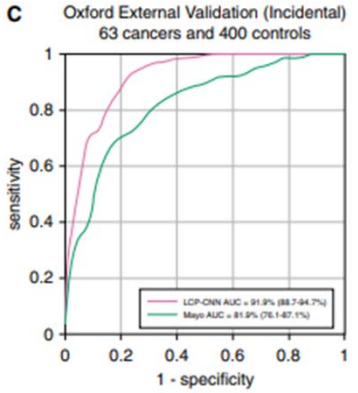
Silvestri et al. Chest 2018;154(3):491-500.

Trend – Radiomics based on Deep Learning Modeling
LCP-CNN for Nodule Risk Assessment



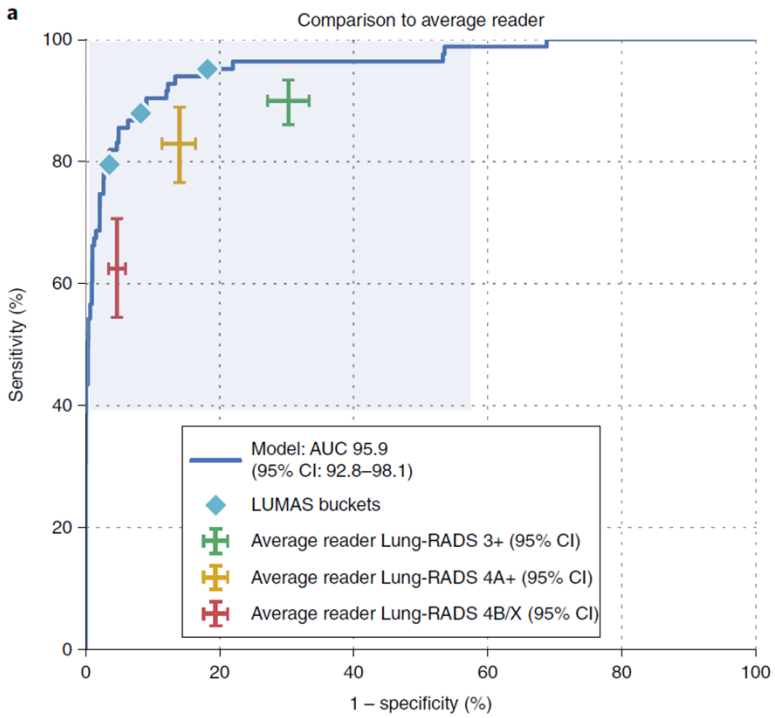


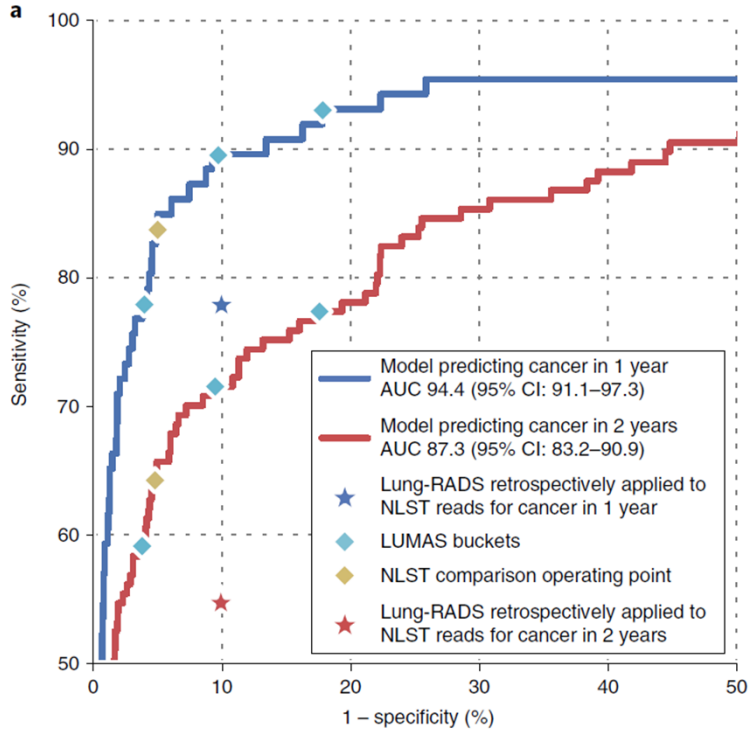




Massion et al. Am J Resp Crit Care Med. 2020;202(2):241-249

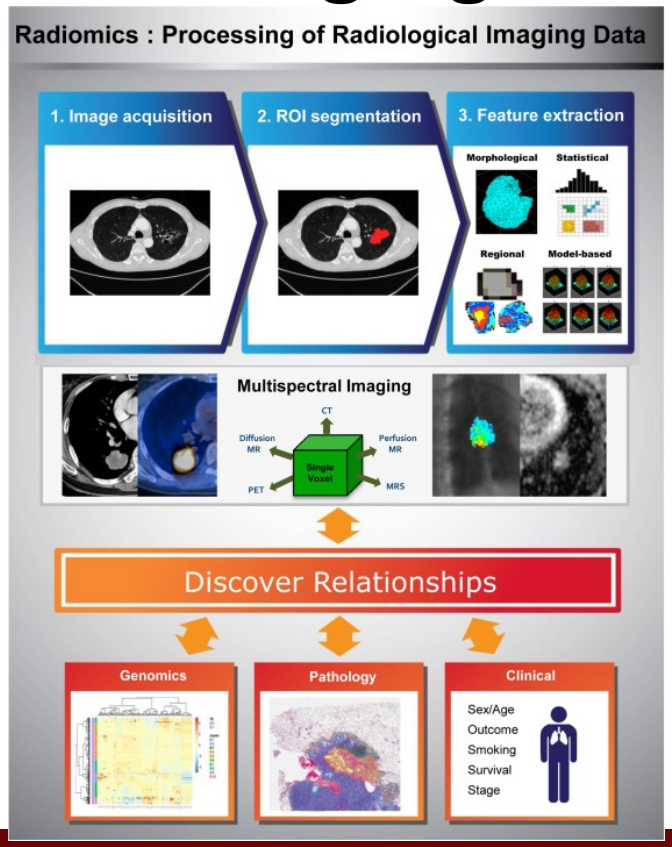
LCS: Radiomics vs Radiologists: LUMAS





Ardila et al. Nature Medicine. 2019

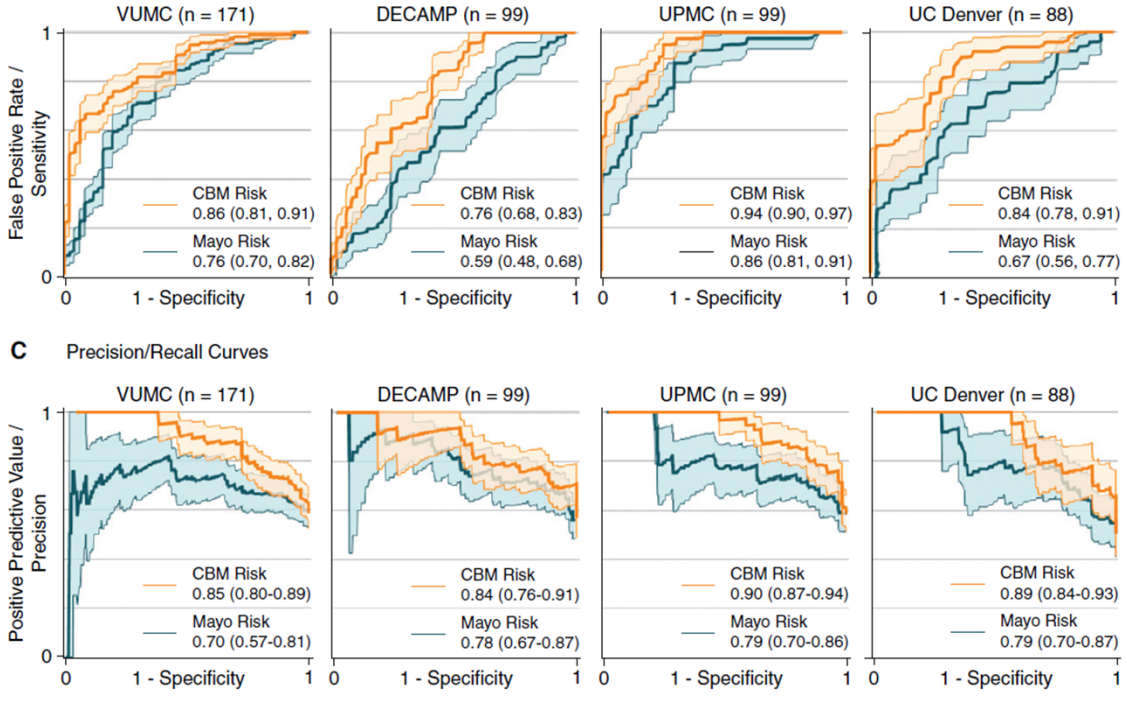
Radiomics and imaging biomarkers



Lee et al. European J Radiol. 2017;86:297-307

Trend: Combining Modalities for Nodule Diagosis Combined Blood, Imaging, Clinical Biomarkers (CBM)

Blood (CYFRA 21-1) + Risk Module (Mayo) + Radiomics (nodule machine learning)



Kammer et al. Am J Respir Crit Care Med. 2021.

Conclusions

- Rapid expansion of biomarkers in conjunction with imaging
  - Lung cancer screening/Earlier lung cancer diagnosis
  - Nodule risk assessment
- Increasing biomarker availability*
- Trends in early lung cancer diagnosis
  - Less invasive
  - Liquid biopsies
  - Prediction of utility
  - Clinical utility studies to determine if estimates predict usefulness in practice
  - Radiomics
  - Combining clinical, radiologic and biomarker characteristics to improve performance