2nd Annual
FLASCO LUNG SCREENING SUMMIT
Challenges of Early Lung Cancer Detection:
From CT Screening to Blood Biomarkers
MAY 20-21, 2022
Margaritaville Beach Resort, Hollywood, FL

How to Complement Biomarker Testing with Diagnostic Imaging

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Incidental and Screen-Detected Nodule Management

DISTINCT POPULATIONS REQUIRE DIFFERENT CLINICAL APPROACHES

INCIDENTAL NODULES

>1.6 million

found annually in the US[2]

Symptoms

Chest X-ray & Other Imaging

Mayo Calculator (23%*) & VA Model (54%*)
*prevalence of cancer

Fleischner Guidelines & CHEST (ACCP) Guidelines

SCREEN-DETECTED NODULES

~75 thousand

detected annually in the US[1,3]

LDCT Screening Program

Only **~4.2%** of screen-eligible (**8M**) patients were screened in 2018[4]

Brock Calculator (3-5%*)
*prevalence of cancer

ACR guidelines (Lung-RADS) & NCCN screen-detected nodule guidelines

1. Pham et al. ASCO Annual Meeting, Chicago, 2018.
2. Gould et al. AJRCCM. 2015; 192(10).
3. NLST Research Team. NEJM. 2011; 365: 395-409.
4. The 2019 State of Lung Cancer report (lung.org/solc)

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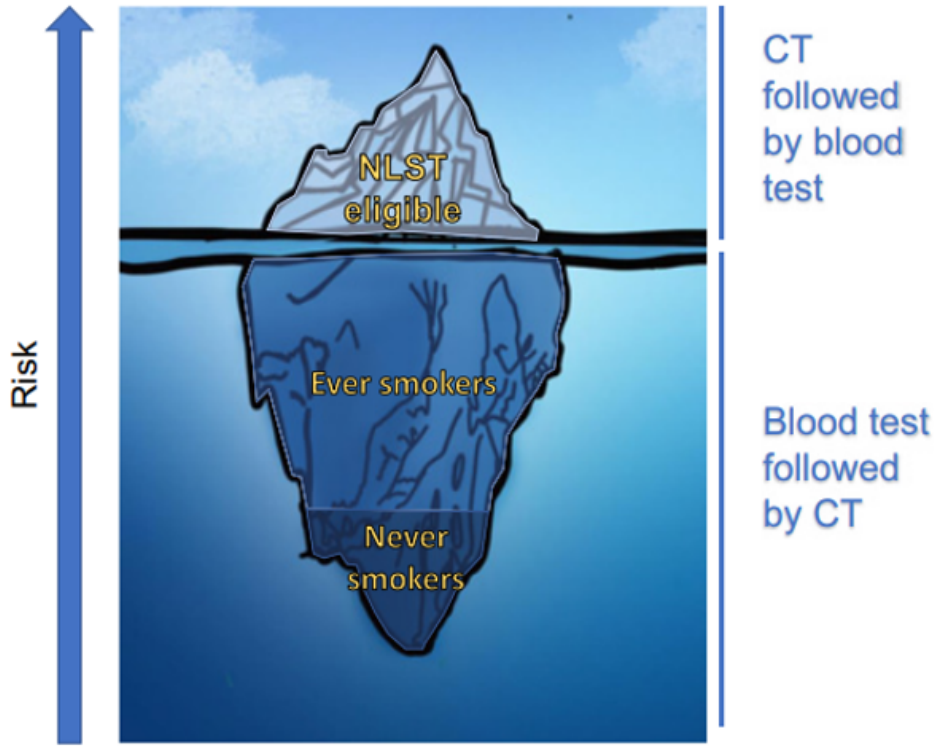
Why do we need biomarkers to help us at screening? Or maybe for early diagnosis?

- 2% of the U.S. population undergoes CT of the chest yearly for various reasons.
- Pulmonary nodules are incidentally found on 24%–31% of these CTs.
- Despite research to better classify and stratify pulmonary nodules (e.g., risk calculators and radiographic characteristics), the diagnostic workflow usually ends in:
  - watchful waiting
  - PET imaging
  - invasive procedures (biopsy/surgery).
- Hence, there is a substantial need for biomarkers that could accurately discriminate benign lesions from early cancers at the time of imaging.

Why do we need biomarkers to help us at screening? Or maybe for early diagnosis?



- Bulk of cases of lung cancer are not only ***not detected by screening***, but ***occur in patients not eligible for screening***.
- Approximately 4% of NLST-eligible patients undergo screening!!
- **IF** all NLST-eligible patients underwent screening, only 27% of lung cancers would be detected, similar to the portion of an iceberg seen above water.
- The other 73% of lung cancers occur in those ineligible for screening:
  - ✓ Those with only a light smoking history
  - ✓ Those who have quit > 15 years ago
  - ✓ Those who have never smoked.
- Biomarkers in high-risk individuals ***can decrease the rate of false positives after CT-based screening***.
- Biomarkers in lower-risk individuals ***can be used to identify patients at higher risk who may benefit from screening***.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020. Published OnlineFirst October 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0865.

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Detected nodules on CT…

- A biomarker role will be to classify the nodule risk.

- An effective biomarker used in combination with a clinical nodule risk score (e.g., Lung-RADS criteria, McWilliams, Swensen).

- A biomarker may be of utility:
  - in the setting of CT screening
  - in the workup of incidentally discovered lung nodules

- Most progress has been done in this diagnostic setting (3 approved tests available).

- Two tests are blood-based and the other performed on airway epithelial brushings collected during bronchoscopy.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020.

Source of Biomarkers:

- Biomarkers may be generated from cancer cells, the tumor microenvironment, or the host response to cancer.
- Factors related to lung carcinogenesis have been studied as diagnostic and prognostic biomarkers (e.g. apoptosis, cellular adhesion, cellular growth, and tumor proliferation).
- Epigenetic markers (e.g., DNA methylation, miRNAs, nucleosome remodeling, and histone modifications) have also been studied.
- Biomarkers can come from whole blood, serum, plasma, bronchial brushings, and sputum (any body fluid).

Blood-based biomarkers

Advantages:

-relative noninvasive nature of blood draws

-well-established laboratory pipelines for isolation

-analyses of various assays from plasma, exosomes, circulating nucleic acids and circulating cells.

Two tests, mostly intended for classification of indeterminate pulmonary nodules (IPN), are currently available.

Early Cancer Detection Test-Lung (EarlyCDT-Lung)

- EarlyCDT-Lung: 7-autoantibody panel (7-Ab Panel)
- First developed in 2010; extensively validated in seven different cohorts.
- This panel consisted of autoantibodies against p53, CAGE, NY-ESO-1 (*CTAG1B*), SOX2, GBU4–5, HuD, and MAGE-A4,
- Good performance in classifying indeterminate pulmonary nodules
- Sensitivity 41%; Specificity 90%.
- A cost effectiveness study indicated that the use of EarlyCDT-Lung in patients presenting with nodules of approximately 8-30 mm is around $24,000 per quality-of-life adjusted life year gained.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020.

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Integrated model (XL2 test)

Prospectively validated in the PANOPTIC study

Best performance in a subgroup with clinician-assessed pretest probability of cancer (pCA) < 50%.

In this subgroup of patients (n=178): Sensitivity 97%; Specificity 44%; NPV of 98% (and a LR− of 0.07).

This panel helps identifying low-risk pulmonary nodules ("rule out").

It outperforms PET/CT, physician estimates, and lung nodule risk scores.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020.

Airway gene expression classifier (Bronchial genomic classifier)

- An estimated 250,000 patients undergo a bronchoscopy for suspected lung cancer each year; 40% of them produce inconclusive results.
- Inconclusive results often lead to risky and expensive invasive procedures: transthoracic needle biopsy (TTNB) and surgical lung biopsy (SLB).
- TTNB has a 15% to 25% risk of collapsed lung and SLBs can cost more than $20,000.
- AEGIS-1 and AEGIS-2 prospective trials were conducted; enrolled patients undergoing bronchoscopy for suspicion of lung cancer.
- In patients with an intermediate pretest probability and a negative bronchoscopy (who had cancer prevalence of 41%), the classifier had a 91% NPV.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020.

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Airway gene expression classifier (Bronchial genomic classifier)

- In a combined group (AEGIS trials) of low and intermediate probability patients with nodules < 3 cm, sensitivity was 88% with a NPV 94%.
- Combining bronchoscopy and the classifier produced a LR- 0.06; this produces a post-test probability of <10% in patients with pretest probabilities of up to 66%.
- Negative classifier + non-diagnostic bronchoscopy and an intermediate probability of cancer = allow physicians to avoid unnecessary invasive procedures.
- Medicare approval in 2017.

Ostrin EJ et al. Cancer Epidemiol Biomarkers Prev; 29(12) December 2020.

The Current State of Nodule Management

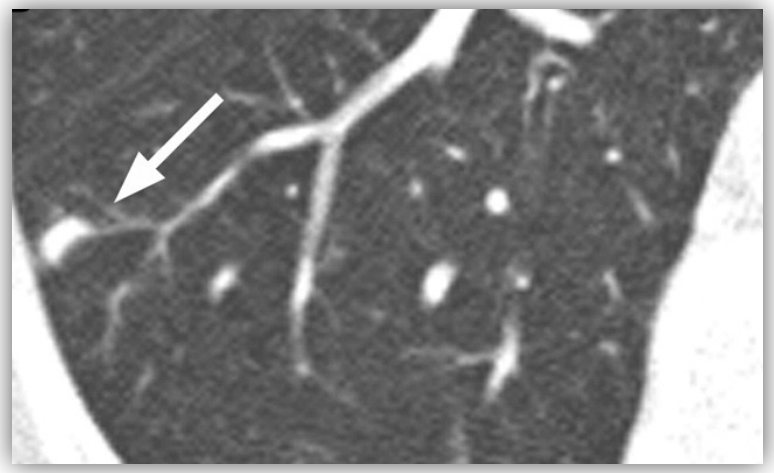
What Would Be Your Next Step For These Patients?

CT SURVEILLANCE? PET SCAN? BIOPSY? SURGERY?

Patient 1

CT scan of patient who was asymptomatic with a 28 mm solid nodule located in the upper lobe.

Patient 2



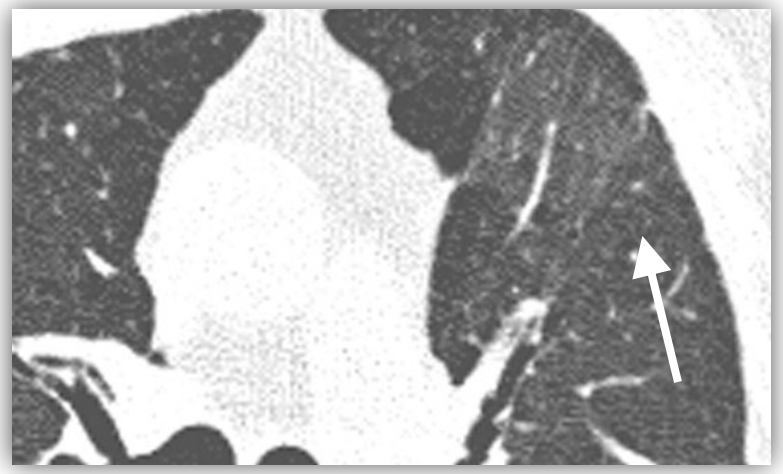
CT scan of 9mm solid nodule in the lower lobe.

Manos D, et al. CARJ. 2014; 65(2): 121-134.

What Would Your Next Step Be For These Patients?

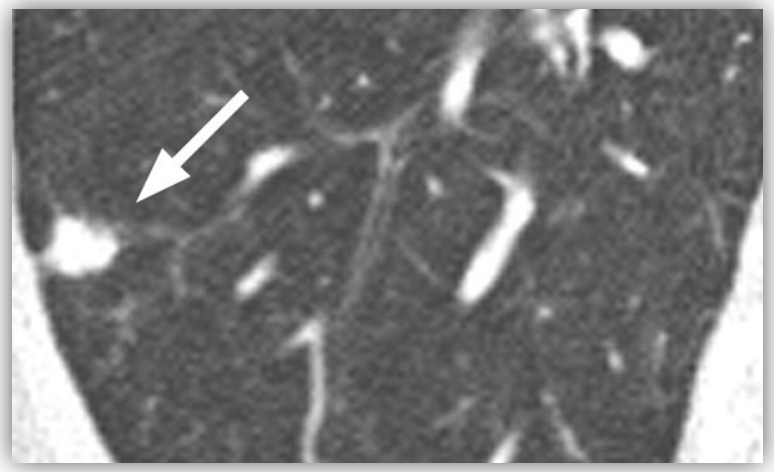
CT SURVEILLANCE? PET SCAN? BIOPSY? SURGERY?

Patient 1



Follow-up CT scan 8 weeks later showed near complete resolution.

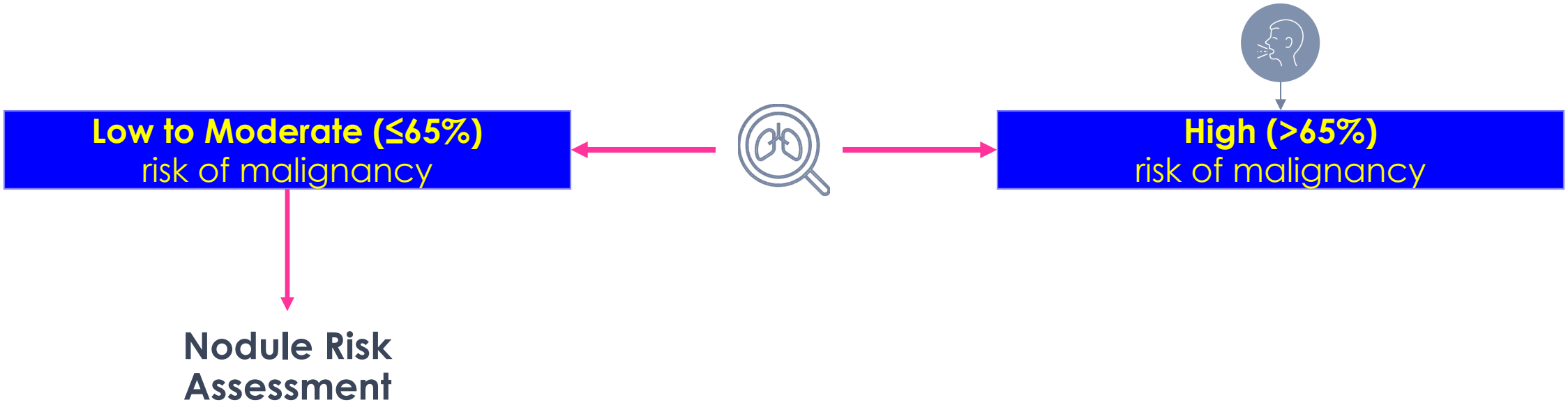
Patient 2



26 months after initial detection, the nodule showed progressive enlargement and was resected to reveal stage IA adenocarcinoma.

Manos D, et al. CARJ. 2014; 65(2): 121-134.

LUNG NODULE IDENTIFIED



Nodule Risk Assessment test (Proteomic test)

This test consists of two blood-based proteomic tests:

- 7-Ab Panel (higher risk of malignancy)– "rule in"
- Integrated Model (XL2) [lower risk of malignancy] – " rule out"

This test helps physicians to reclassify risk of cancer and aid in stratifying patients into distinct nodule management pathways: either intervention or surveillance.

LUNG NODULE IDENTIFIED

Patient presents with symptoms

Low to Moderate (≤65%) risk of malignancy

High (>65%) risk of malignancy

LUNG CANCER DIAGNOSIS

Nodule Risk Assessment

Integrated Model Test (proteomic test)

Identify **likely benign** nodules

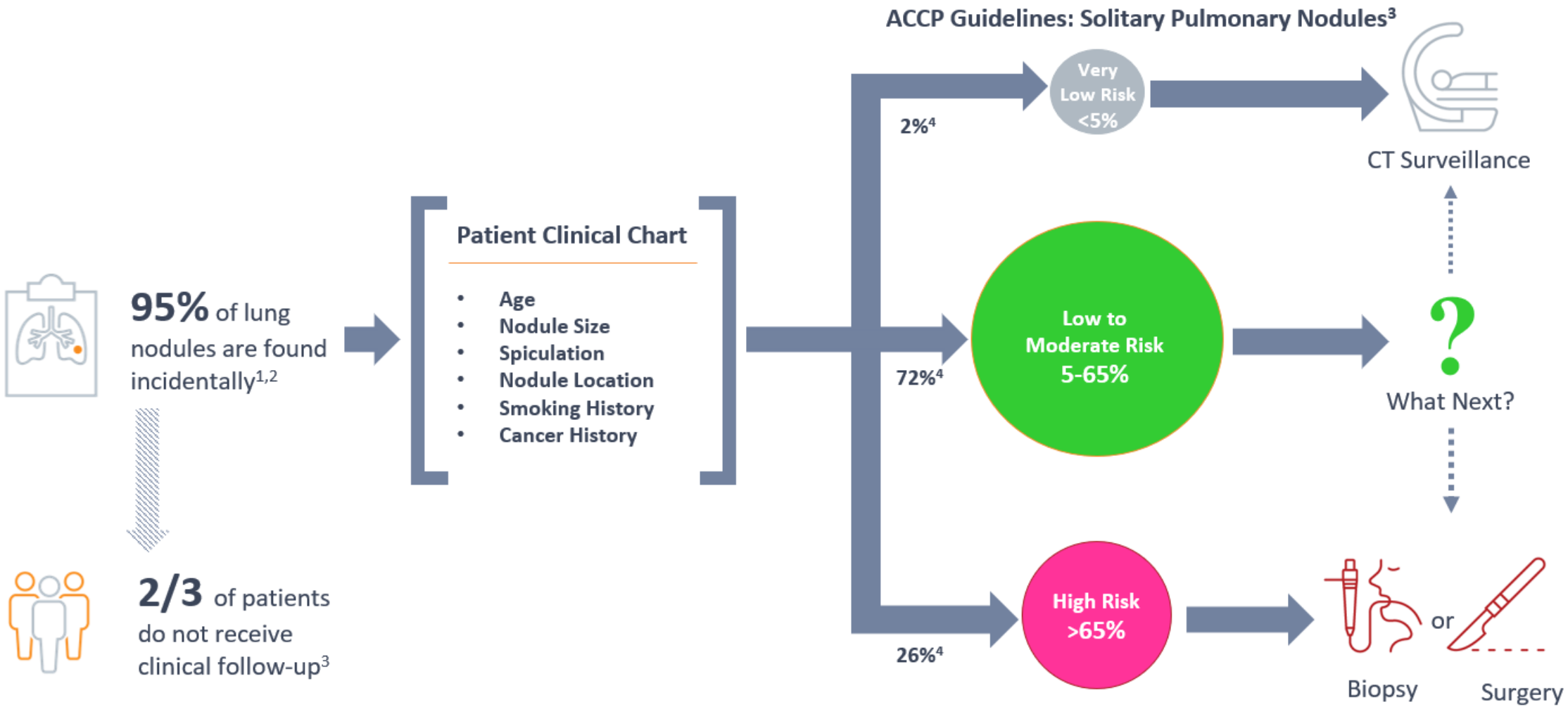
CT surveillance or standard of care

7-Ab Panel Lung Test (proteomic test)

Identify **likely malignant** nodules

Biopsy, surgery or standard of care

Unmet Need in Incidental Lung Nodule Management



1. *Pham et al. ASCO Annual Meeting, Chicago, 2018.*
2. *Gould et al. AJRCCM. 2015; 192(10).*
3. *Pyenson et al. JHEOR, 2019; 6(3): 118-129.*
4. *Silvestri et al. CHEST. 2018; 154(3):491-500. (PANOPTIC)*

Standard of Care in the PANOPTIC Study

Low to Moderate Risk Nodules are often managed aggressively to confirm diagnosis. [5-65%]

17%

of patients sent to **CT surveillance** have **malignant** nodules

38%

of **biopsies** are performed on **benign** nodules

20%

of **surgeries** are performed on **benign** nodules

Data from the PANOPTIC study, in the low to moderate risk population as assessed by the Solitary Pulmonary Nodule (SPN) Calculator. PANOPTIC was a prospective, observational study across 33 academic and community sites[1].

1. Silvestri et al. CHEST. 2018; 154(3):491-500. (PANOPTIC)

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Reclassifying The Risk… and reduce uncertainty:

Proteomic Test

INTENDED FOR PATIENTS:

- ≥40 years of age
- 8–30 mm nodule
- ≤65% risk of malignancy by Solitary Pulmonary Nodule (SPN) Calculator[5]
- No previous diagnosis of cancer

Very Low Risk <5%

Low to Moderate Risk 5-65%

High Risk >65%

7-Ab Panel Proteomic Test

If SPN calculator risk of malignancy ≤50%

Integrated Model XL2 Test

Identifies patients who may benefit from CT surveillance

CT Surveillance

Assess post-test risk of malignancy

Identifies patients who may benefit from timely intervention with results in **one day.**

Biopsy Surgery

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7-Ab Panel Blood-Based Test

Designed to help physicians identify patients with **LIKELY MALIGNANT** lung nodules.

The 7-Ab Panel test measures autoantibodies to tumor-associated antigens to help you detect lung cancer across histologies and stages [1,2]

- ☑ Non-Small Cell Stage I
- ☑ Non-Small Cell Stage II
- ☑ Non-Small Cell Stage III/IV
- ☑ Small Cell Limited-stage Disease
- ☑ Small Cell Extensive-stage Disease

Reflects the performance of the High Level result [3]

$0 out of pocket for Medicaid; covered by Medicare beneficiaries.

1. Massion et al. JTO. 2017; 12(3): 578-584.
2. Chapman et al. Tumor Biol. 2012; 33(5): 1319–1326.
3. Healey et al. JCT. 2017; 8(5): 506-517.

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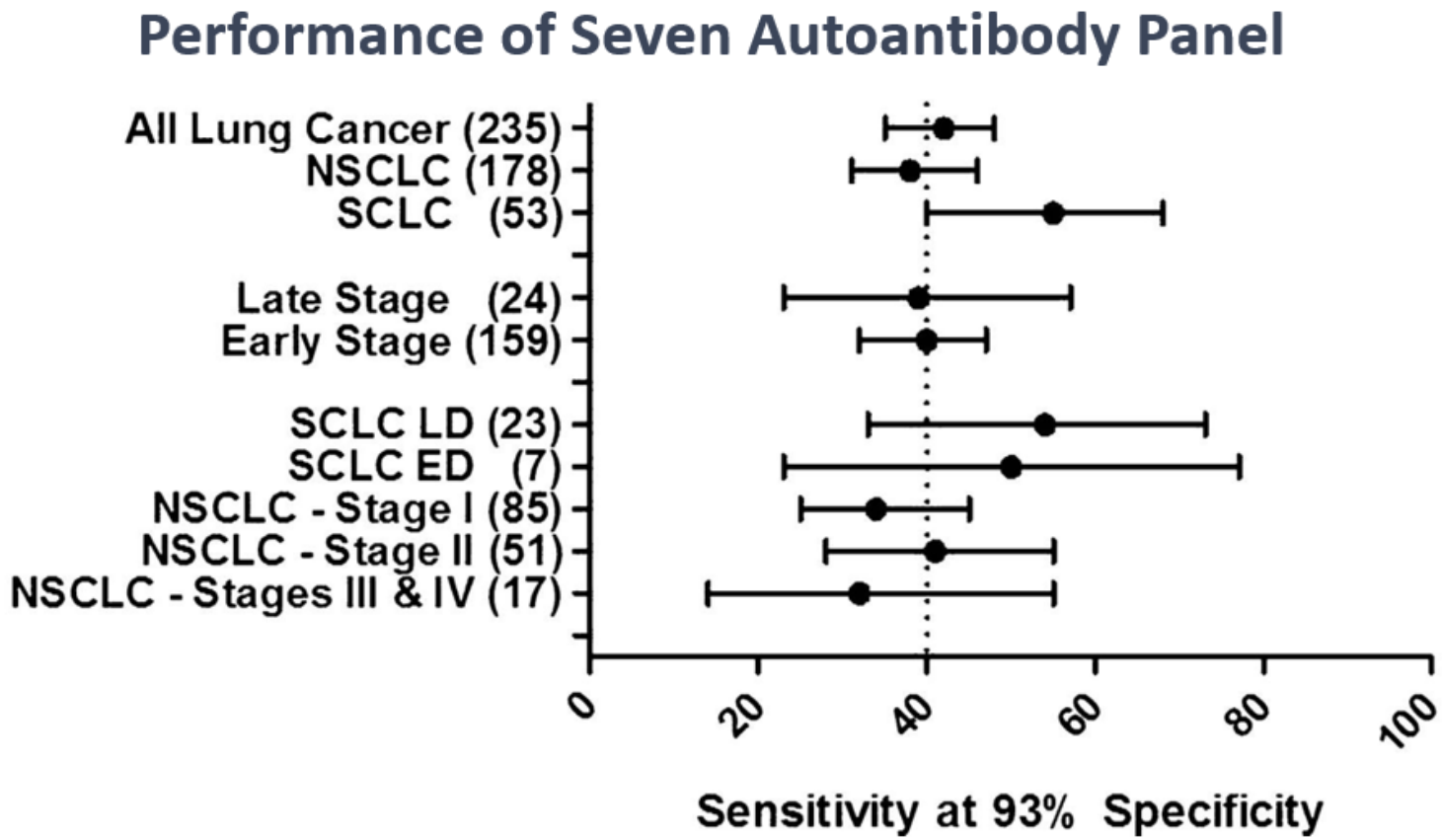
7-Ab Panel Proteomic Test Performance in Lung Cancer

Data from validation of 7 autoantibody panel.

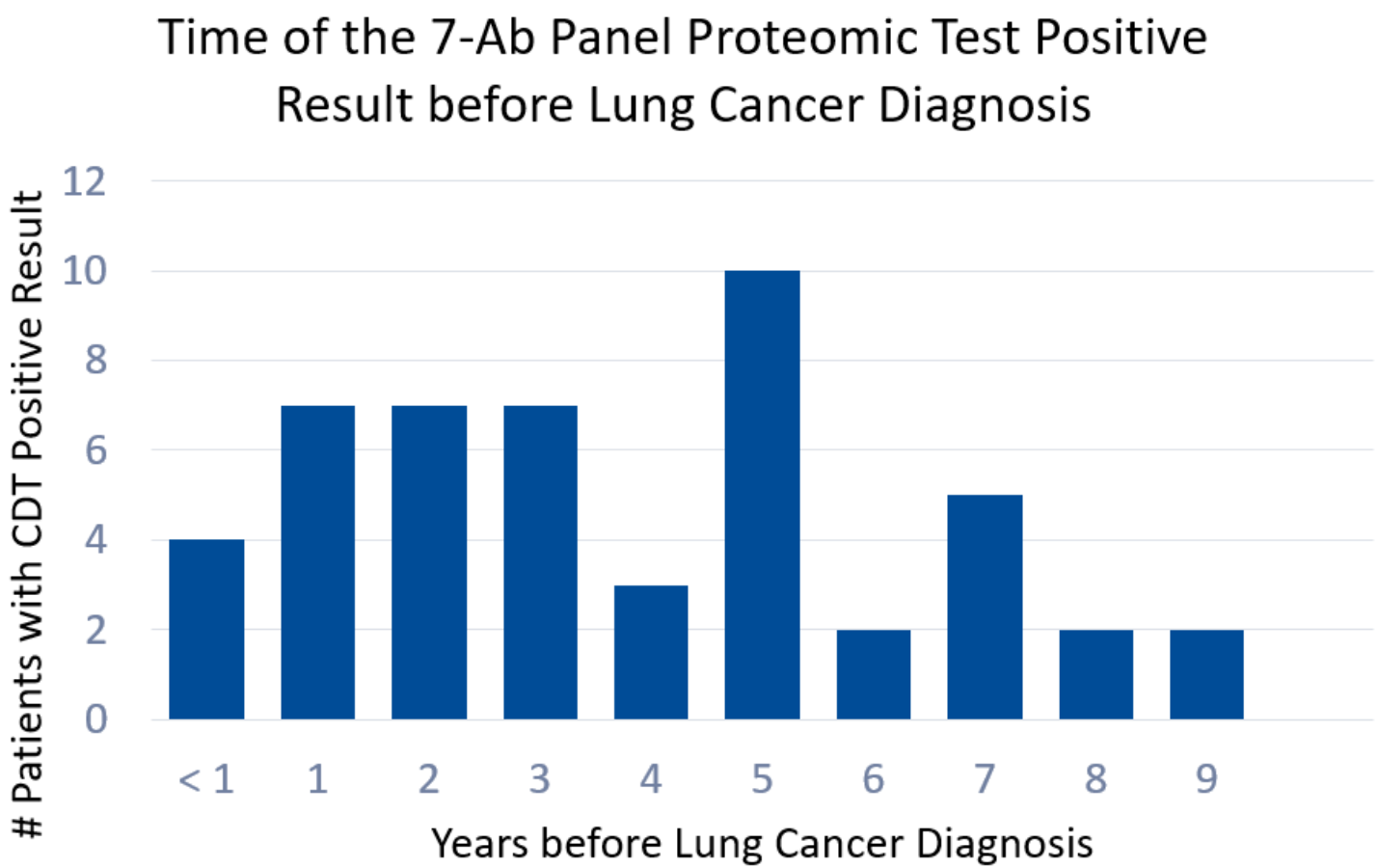
- P53
- CAGE
- NY-ESO-1
- GBU4-5
- MAGE A4
- SOX2
- HuD



Chapman et al. Tumour Biol. 2012; 33(5): 1319-1326.

7-Ab Panel Proteomic Test

Elevated levels detected average of 4 years before lung cancer diagnosis.



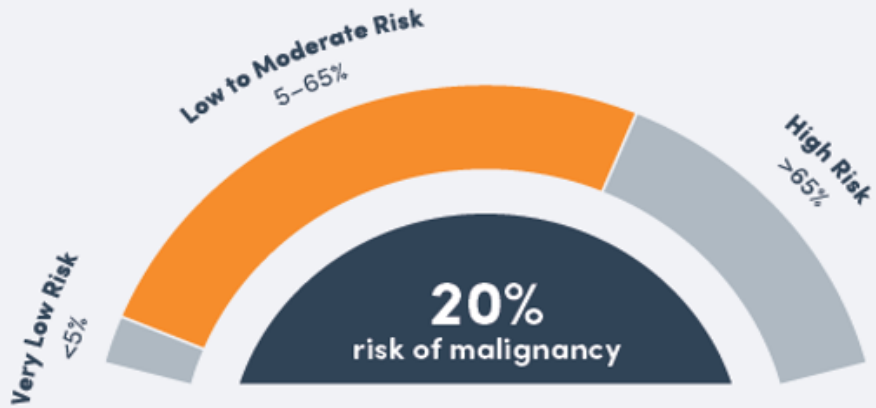
- Analysis of lung cancer subgroup (n=142) from the UKCTOCS study.
- Blood samples from each patient were collected annually over a 9-year period.
- 35% (n=49) of the lung cancer subgroup had a positive 7-Ab Panel result in at least one of the blood samples.
- Detection lead time up to 9 years before lung cancer diagnosis.

Jett et al. World Conference on Lung Cancer, Yokohama, Japan. 2017.

Example on 7-Ab Panel Proteomic Test Result:

PRE-TEST INFORMATION

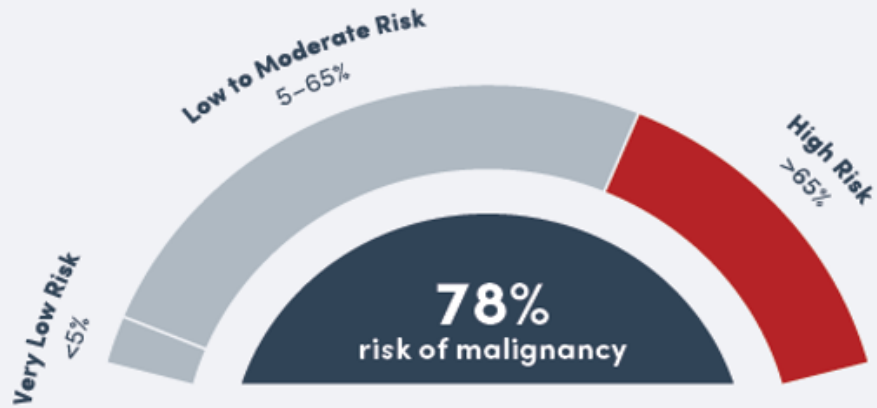
SOLITARY PULMONARY NODULE CALCULATOR[1]
PRE-TEST RISK OF MALIGNANCY



Nodule Size (mm): 13	Nodule Location: Other
Spiculation: Yes	Smoking History: Current/Former
Age (years): 50	History of Cancer: No History of Cancer

TEST RESULT

HIGH LEVEL
Post- 7-Ab Panel Proteomic Test risk of malignancy



INTERPRETATION OF RESULTS

Patients with a High Level 7-Ab Panel Proteomic Test result have a higher risk of malignancy than predicted by clinical factors alone. This result does not definitely mean that the patient has lung cancer.

The post- 7-Ab Panel Proteomic Test risk of malignancy was calculated based on the performance of the High Level 7-Ab Panel Proteomic Test result in the clinical validation study.[2]

1. Swenson et al. Arch Intern Med. 1997; 157(8): 849-855.
2. Healey et al. JCT. 2017; 8(5): 506-517.
3. Gould et al. CHEST. 2013; 143(3): e93S-e120S.

Risk categories are according to the American College of Chest Physicians (ACCP) guidelines for incidental lung nodules[3].

Integrated Model (XL2) Blood-based test

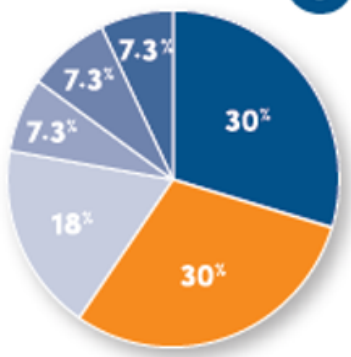
Designed to help physicians identify patients with LIKELY BENIGN lung nodules.

The XL2 protein levels were found to be as important as nodule size in predicting risk of malignancy

97% Sensitivity

98% NPV

Reflects the median performance of Integrated Model XL2 test in the PANOPTIC study



5 Clinical Risk Factors

☑ Location	7.3%
☑ Spiculation	7.3%
☑ Smoking History	7.3%
☑ Age	18%
☑ Nodule Size	30%

2 Plasma Protein Levels Associated with Lung Cancer

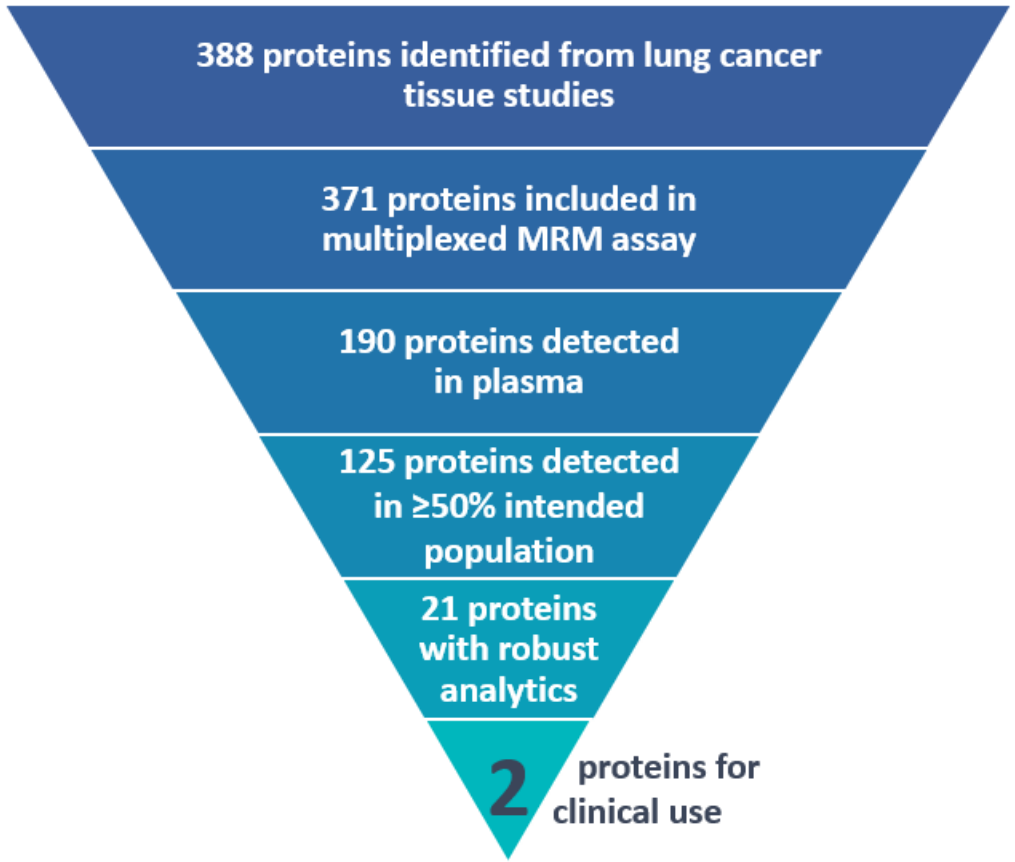
☑ LG3BP	30%
☑ C163A	

1. Springmeyer et al. ATS Conference, San Diego, CA. 2018.
2. Silvestri et al. CHEST. 2018; 154(3): 491-500. (PANOPTIC)

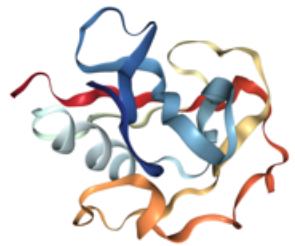
XL2 Test Discovery

LG3BP:C163A performed better than all other protein ratios evaluated.

Discovery[1,2]: Systems Biology Approach



LG3BP

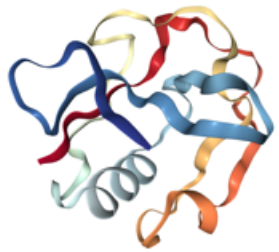


Source: RCSB 1BY2

- Galectin-3 Binding Protein (Gal-3BP)
- Also known as Mac-2 binding protein
- Elevated blood levels reported in patients with **LUNG CANCER**[3]

XL2 MEASURES LG3BP:C163 RATIO

C163A



Source: RCSB 5HRJ

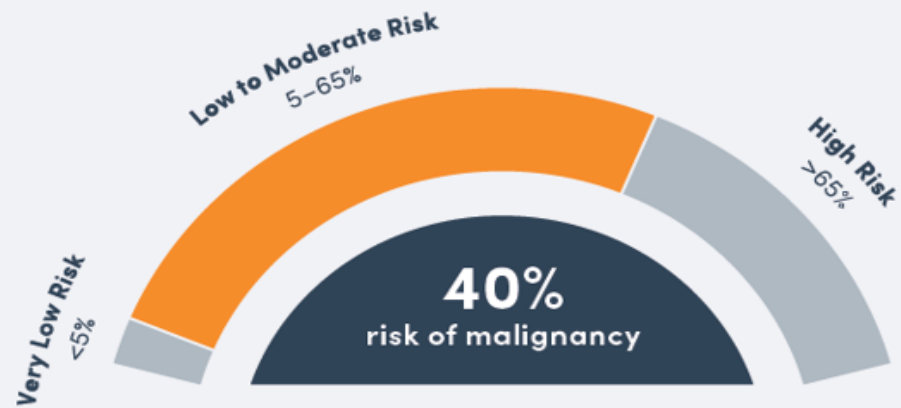
- Hemoglobin scavenger receptor
- Also known as soluble CD163
- C163A is shed from macrophages during **INFLAMMATION**[4]

1. *Li et al. Sci Transl Med. 2013; 5: 207ra142*
2. *Kearney et al. ATS Conference. 2018*
3. *Sun et al. Mol Cell Proteomics. 2013; 12(2): 395-406*
4. *Yu et al. Adv Cancer Res. 2015; 128: 309-364*

Example on XL2 test result:

PRE-TEST INFORMATION

SOLITARY PULMONARY NODULE CALCULATOR[1]
PRE-TEST RISK OF MALIGNANCY

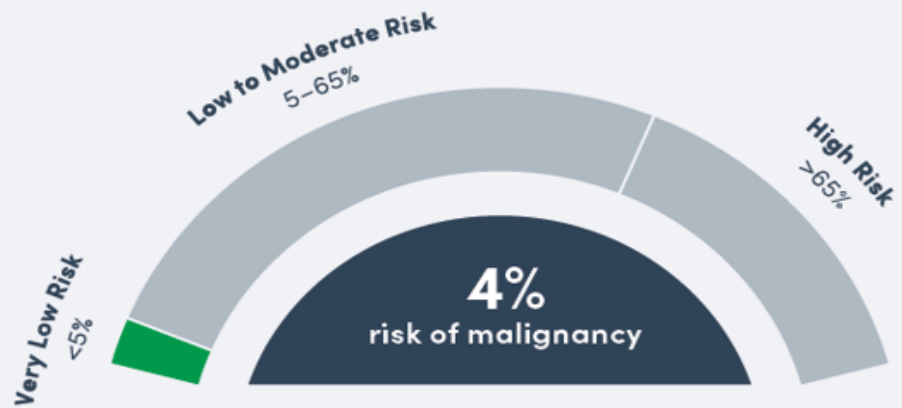


Nodule Size (mm): 14	Nodule Location: Upper
Spiculation: Yes	Smoking History: Current/Former
Age (years): 52	History of Cancer: No History of Cancer

TEST RESULT

LIKELY BENIGN

POST- XL2 RISK OF MALIGNACY



INTERPRETATION OF RESULTS

Patients with a Likely Benign XL2 test result have a high probability of having a benign nodule.

The post- XL2 risk of malignancy was calculated based on the performance of the XL2 98% NPV Likely Benign test result in the PANOPTIC clinical validation study.[2]

Risk categories are according to the American College of Chest Physicians (ACCP) guidelines for incidental lung nodules[3].

1. Swenson et al. Arch Intern Med. 1997; 157(8): 849-855.
2. Silvestri et al. CHEST. 2018; 154(3): 491-500. (PANOPTIC)
3. Gould et al. CHEST. 2013; 143(3): e93S-e120S.

Test Case

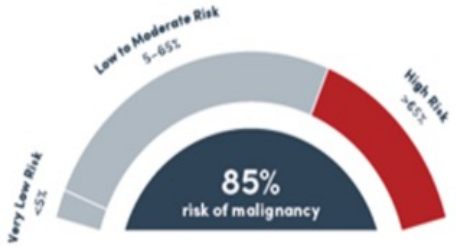
Testing Strategy Results & Interpretation

Nodule Risk Assessment Test results are presented as an **individualized risk of malignancy** to support shared decision making and help reduce patient anxiety.

Nodule Risk Assessment

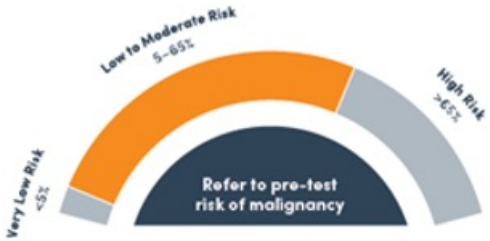
7-Ab Panel Proteomic Test is performed first

If 7-Ab Panel Proteomic Test Positive



The patient has a High-Level result and 85% post- 7-Ab Panel Proteomic Test risk of malignancy. The XL2 test will not be performed in this case.

If 7-Ab Panel Proteomic Test Negative



If 7-Ab Panel Proteomic Test is negative, XL2 will be performed

XL2 LIKELY BENIGN

This patient has a Likely Benign result and a 3% post- XL2 risk of malignancy.

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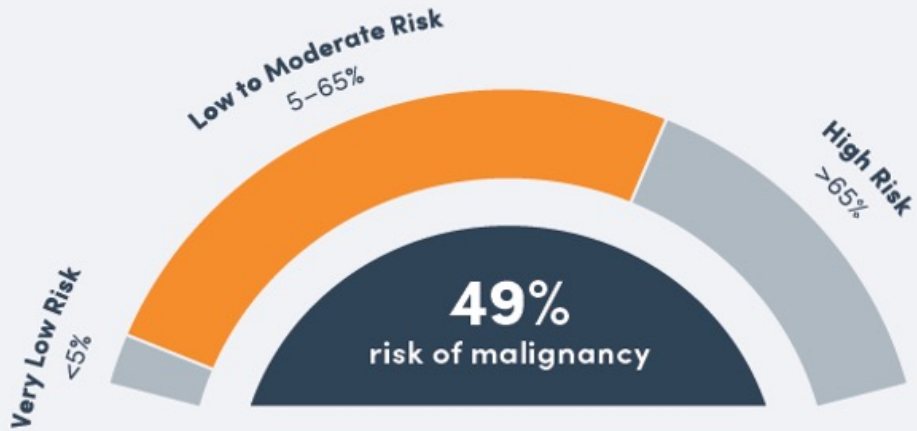
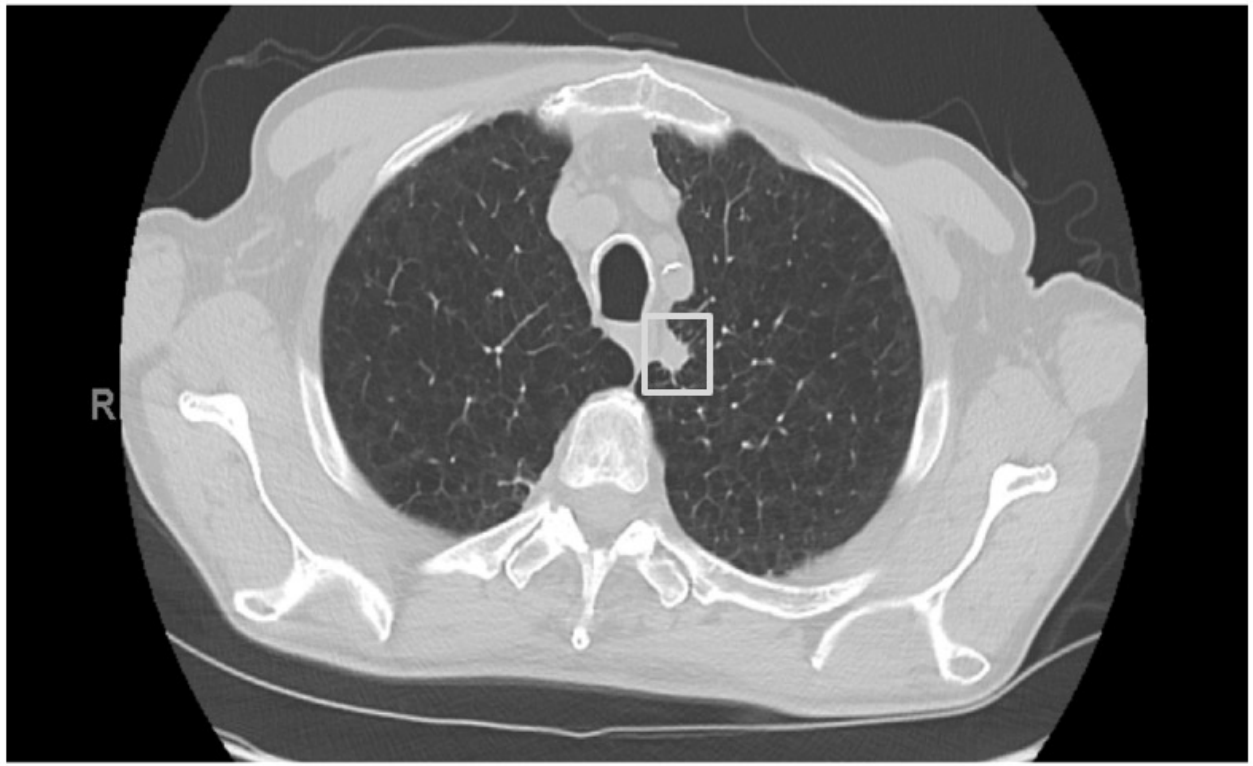
Patient 3

PRE-TEST INFORMATION

SOLITARY PULMONARY NODULE CALCULATOR[1]
PRE-TEST RISK OF MALIGNANCY



Nodule Size (mm): 10	Nodule Location: Upper
Spiculation: Yes	Smoking History: Current/Former
Age (years): 74	History of Cancer: No History of Cancer



Case study courtesy of Kyle Hogarth, MD, FCCP
Professor of Medicine, Section of Pulmonary and Critical Care Medicine
Director, Bronchoscopy, University of Chicago

SPN Malignancy Risk

Calculator

1.	Age?	..... years
2.	Smoker (current or previous)?	Yes or No
3.	Extra-thoracic cancer more than 5 years previous?	Yes or No
4.	Diameter?	..... mm
5.	Upper Lobe?	Yes or No
6.	Spiculated?	Yes or No

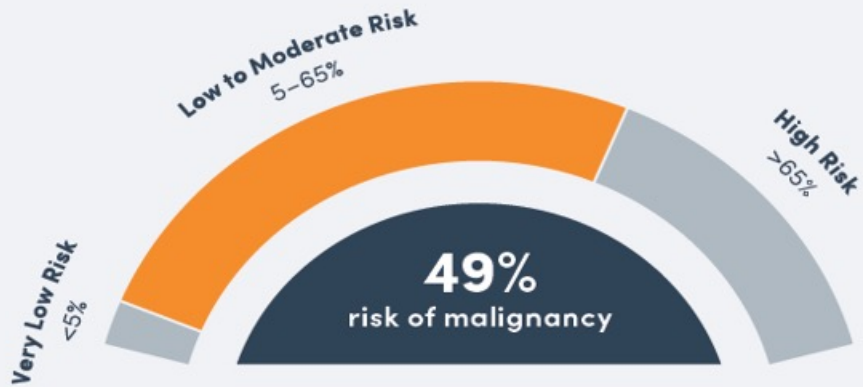
Mayo Clinic Model.

An online calculator is available at http://reference.medscape.com/calculator/solitary-pulmonary-nodule-risk.

Patient 3

PRE-TEST INFORMATION

SOLITARY PULMONARY NODULE CALCULATOR[1]
PRE-TEST RISK OF MALIGNANCY



Nodule Size (mm): 10	Nodule Location: Upper
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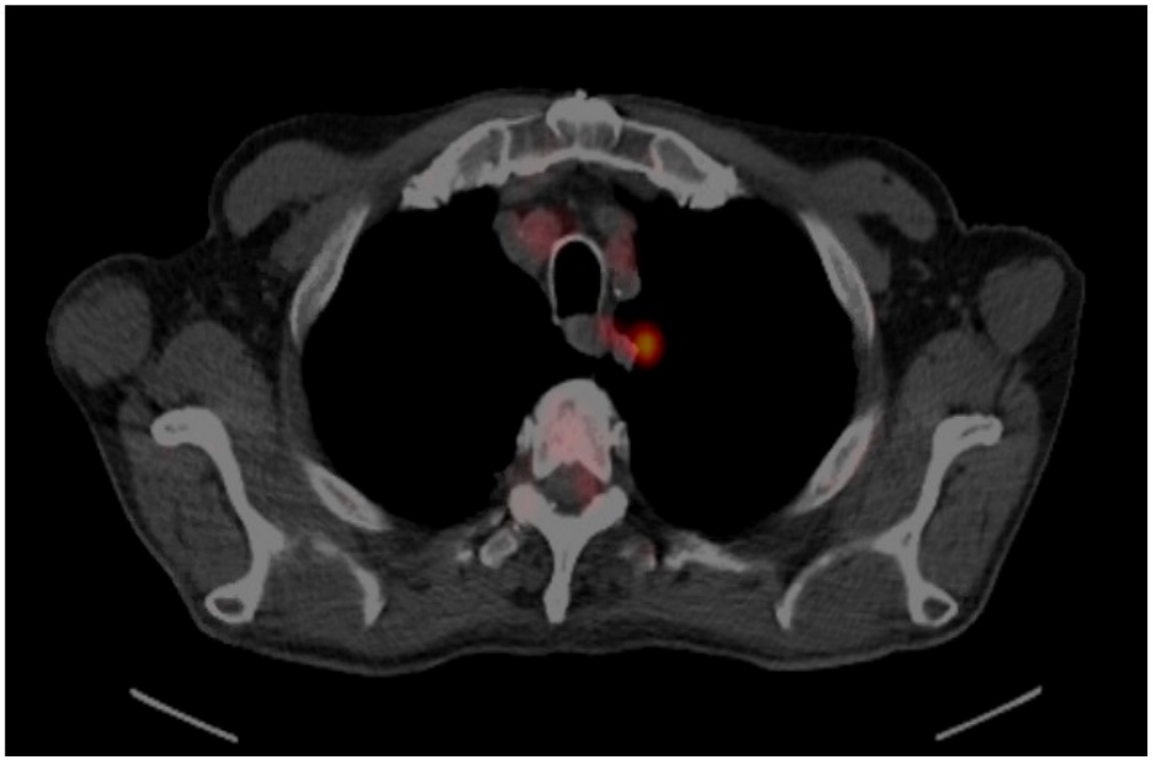


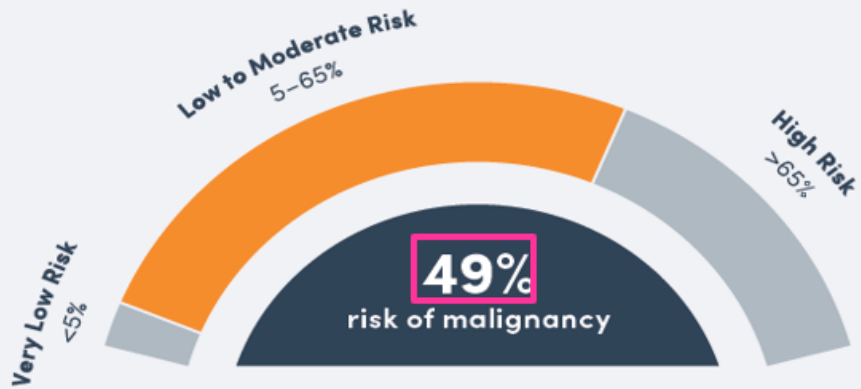
- PET scan completed with SUV of 7.0
- Nodule risk assessment test (XL2) was ordered.

Case study courtesy of Kyle Hogarth, MD, FCCP
Professor of Medicine, Section of Pulmonary and Critical Care Medicine
Director, Bronchoscopy, University of Chicago

Patient 3

PRE-TEST INFORMATION

SOLITARY PULMONARY NODULE CALCULATOR[1]
PRE-TEST RISK OF MALIGNANCY

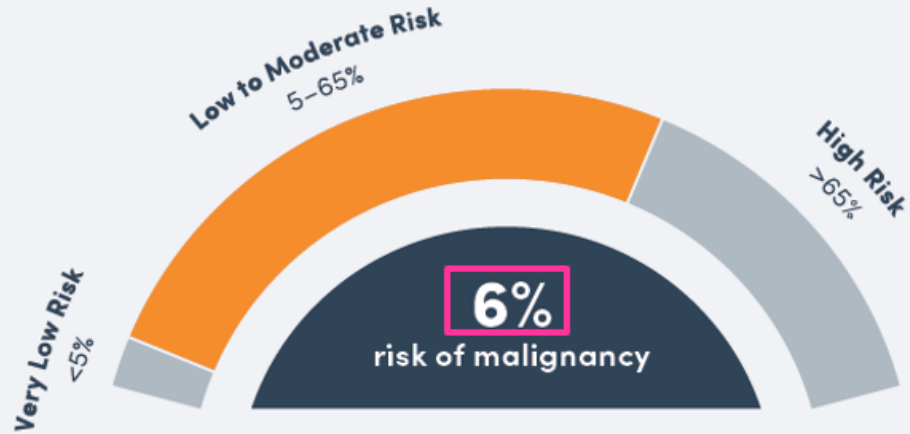


Nodule Size (mm): 10	Nodule Location: Upper
Spiculation: Yes	Smoking History: Current/Former
Age (years): 74	History of Cancer: No History of Cancer

TEST RESULT

LIKELY BENIGN

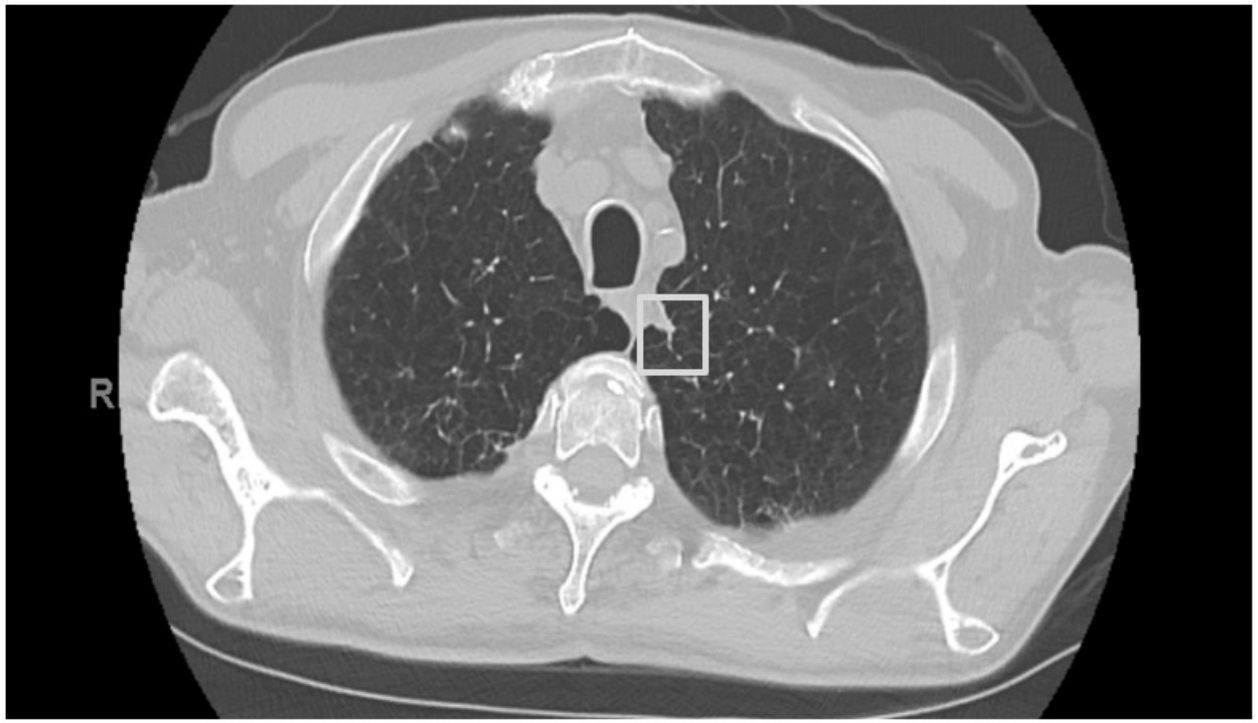
POST-INTEGRATED MODEL TEST FOR RISK OF MALIGNANCY



Patient with a likely benign post-integrated model (prospective validated in the PANOPTIC study) test have a high probability of having a benign nodule.

Case study courtesy of Kyle Hogarth, MD, FCCP
Professor of Medicine, Section of Pulmonary and Critical Care Medicine
Director, Bronchoscopy, University of Chicago

Patient 3

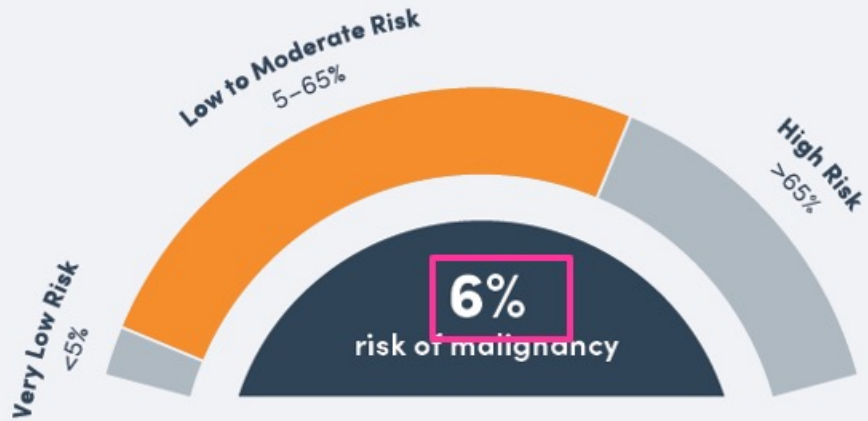


- 3-month follow-up CT scan demonstrated a reduction in size to 7mm
- Inflammatory or benign etiology indicated

TEST RESULT

LIKELY BENIGN

POST-INTEGRATED MODEL TEST FOR RISK OF MALIGNANCY



INTERPRETATION OF RESULTS

Patients with a Likely Benign XL2 test result have a high probability of having a benign nodule. This result does not definitely mean that the patient does not have lung cancer.

The post-Nodify XL2 risk of malignancy was calculated based on the performance of the 98% NPV Likely Benign Nodify XL2 test result in the PANOPTIC clinical validation study.[2]

Case study courtesy of Kyle Hogarth, MD, FCCP
Professor of Medicine, Section of Pulmonary and Critical Care Medicine
Director, Bronchoscopy, University of Chicago

Other Research Efforts in Development for early diagnosis/detection of lung cancer…

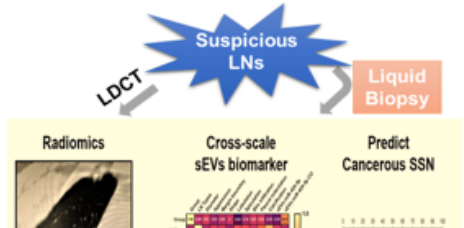
Small extracellular vesicle (sEVs)-- miRNAs

Background

Sub-solid nodule (SSN) is a common radiographic finding

Due to the possibility of malignancy, further evaluation is urgently needed for the prevention & management of lung cancer (LC)

We aims to identify small extracellular vesicles (sEVs) based biomarker integrated into radiomics-clinical features through cross-scale to differentiate the suspicious SSN & predict the risk of LC



Patel, N et al., J. Biomed. Nanotechnol. 2021, Vol. 17, No. 6

Methods

Enrolled patients with SSN including LC and Benign nodules (BN) & Healthy persons as a control to discover sEVs differentials expressed miRNAs (DEMs)

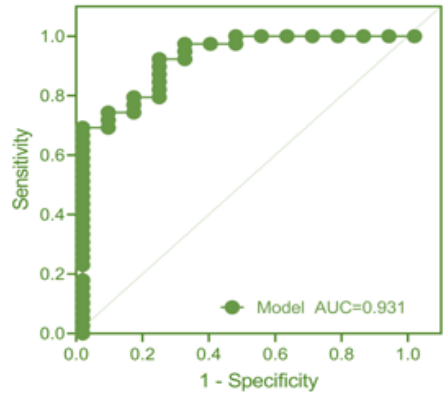
By next-generation sequencing (NGS) (n=9) & validation (n=103) by RT-qPCR

Through cross-scale integration of small-molecule biomarker & macro-imaging, prediction model developed by Logit & Logistic algorithms

Interpreted into an easy-to-use nomogram by Cox-proportional hazards modeling

Results

- 10 radiomics signs & 4 clinical features of SSN were merged with sEVs-miR-424-5p and obtained the correlation matrix of each sign
- The significant features were proceeded in multivariate logistic regression analysis to develop the cross-scale integrated modeling, which yielded a significantly higher AUC of 0.931 ($p<0.0001$)



sEVs-miR-424-5p could be a novel biomarker for distinguishing SSN of LC & BN populations

Its association with the cross-scale fusion of radiomics-clinical feature will provide great potential to be an errorless prediction of malignant SSN

Nishant Patel. 2021 WCLC, September 8-14, 2021.

FLORIDA PRECISION ONCOLOGY
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Plasma DNA Methylation (Gene signature?)

Positive rate of plasma DNA methylation in patients.

Genes	Lung cancer*	Non-lung cancer*
CDH13	66.7 (26/39)	27.3 (3/11)
WT1	30.8 (12/39)	0 (0/11)
CDKN2A	28.2 (11/39)	0 (0/11)
HOXA9	20.5 (8/39)	9.1 (1/11)
PITX2	28.2 (11/39)	9.1 (1/11)
CALCA	84.6 (33/39)	45.5 (5/11)
RASSF1A	41.0 (16/39)	0 (0/11)
DLEC1	41.0 (16/39)	0 (0/11)
All 8 genes	94.9 (37/39)	63.6 (7/11)

* % (number of methylation-positive cases/total number of cases).

Specificity and sensitivity of DNA methylation in diagnosis of lung cancer.

Genes	Sensitivity	Specificity	Cut-off values	Ranges of methylation	
				lung cancer	non-lung cancer
CDH13	31 (12/39)	91 (10/11)	18.0	0.000–75.513	0.000–26.912
WT1	31 (12/39)	100 (11/11)	0.0	0.000–181.576	0.000–0.000
CDKN2A	28 (11/39)	100 (11/11)	0.0	0.000–21.321	0.000–0.000
HOXA9	21 (8/39)	100 (11/11)	3.1	0.000–39.405	0.000–3.041
PITX2	28 (11/39)	100 (11/11)	2.0	0.000–19.059	0.000–1.811
CALCA	51 (20/39)	100 (11/11)	38.0	0.000–425.447	0.000–37.004
RASSF1A	41 (16/39)	100 (11/11)	0.0	0.000–19.059	0.000–0.000
DLEC1	41 (16/39)	100 (11/11)	0.0	0.000–24.146	0.000–0.000
All 8 genes	72 (28/39)	91 (10/11)	N/A	N/A	N/A

N/A – not applicable; % (number of methylation-positive cases/total number of cancer cases); specificity: % (number of methylation-negative cases/total number of benign cases).

Yang Z., et al. DNA methylation analysis of selected genes for the detection ofearly-stage lung cancer using circulating cell-free DNA. Adv Clin Exp Med. 2019;28(3):355-360.

Conclusion

- There is a need to improve the accuracy of lung cancer screening (beyond LDCT) to decrease over-diagnosis and morbidity.
- Blood-based biomarkers (e.g., 7-Ab Panel/XL2 proteomic tests) and airway gene expression classifier (updated test based on next-generation RNA transcriptome) are being used in clinical practice as adjuncts to LDCT in lung cancer screening.
- Other efforts to develop potential methods for early diagnosis of lung cancer include quantitative detection of plasma DNA methylation, sEVs by miRNAs, others.