The Diagnostic Evaluation Of Pulmonary Nodules

Gerard A. Silvestri, MD, MS
Hillenbrand Professor in Thoracic Oncology
Medical University of South Carolina
Charleston, SC
Email: Silvestri @musc.edu

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Disclosures

- NOTE: All are Research Funding only
  - Patient Centered Outcomes Research Institute
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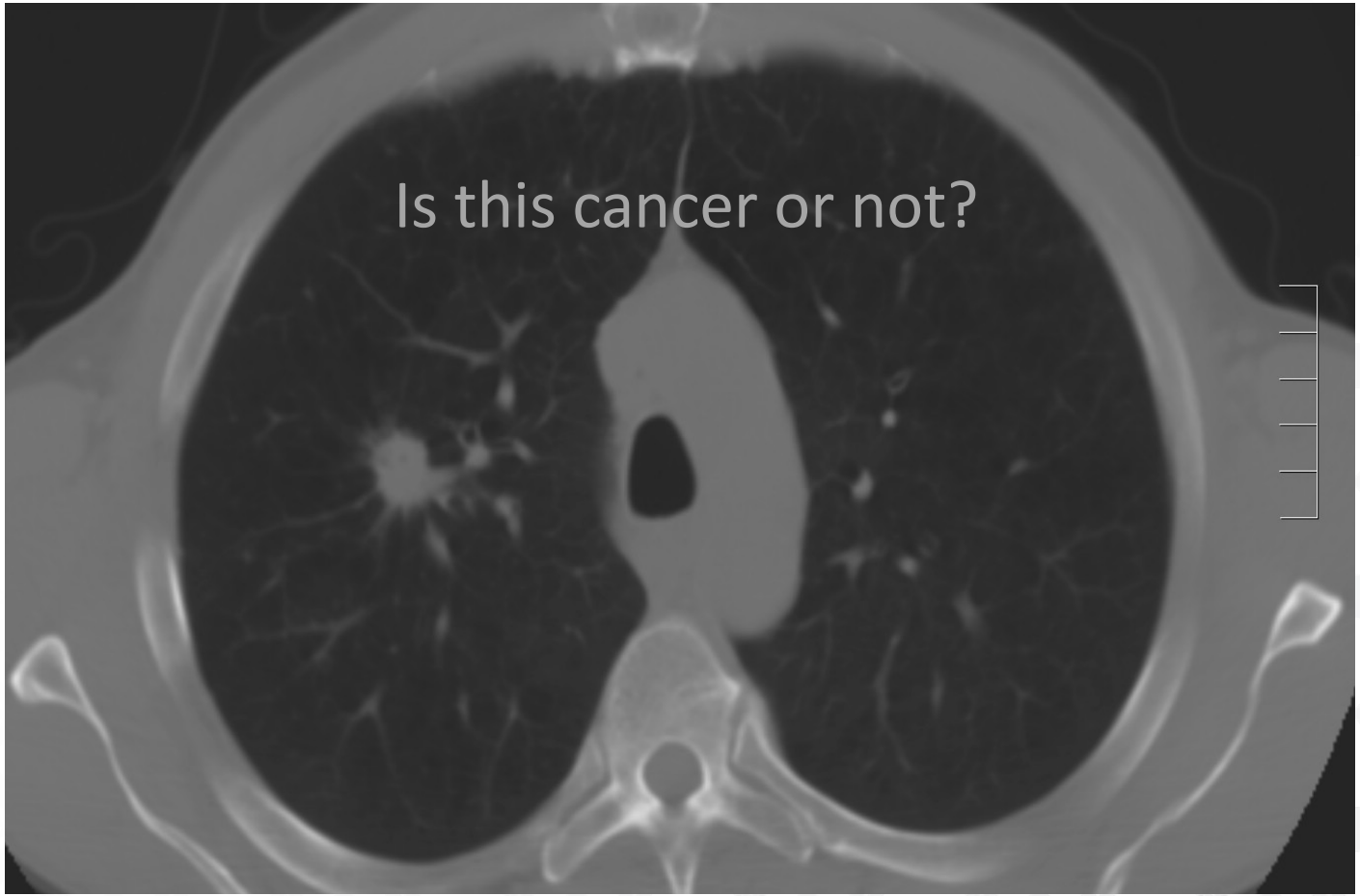
  - Auris Medical
  - Boston scientific Corporation
  - Exact Sciences
  - Integrated Diagnostics/Biodesix
  - Olympus America
  - Oncimmune
  - Oncocyte
  - Prolung
  - Veracyte
  - Veran

When it comes right down to it, what is the singular question we are attempting to answer?

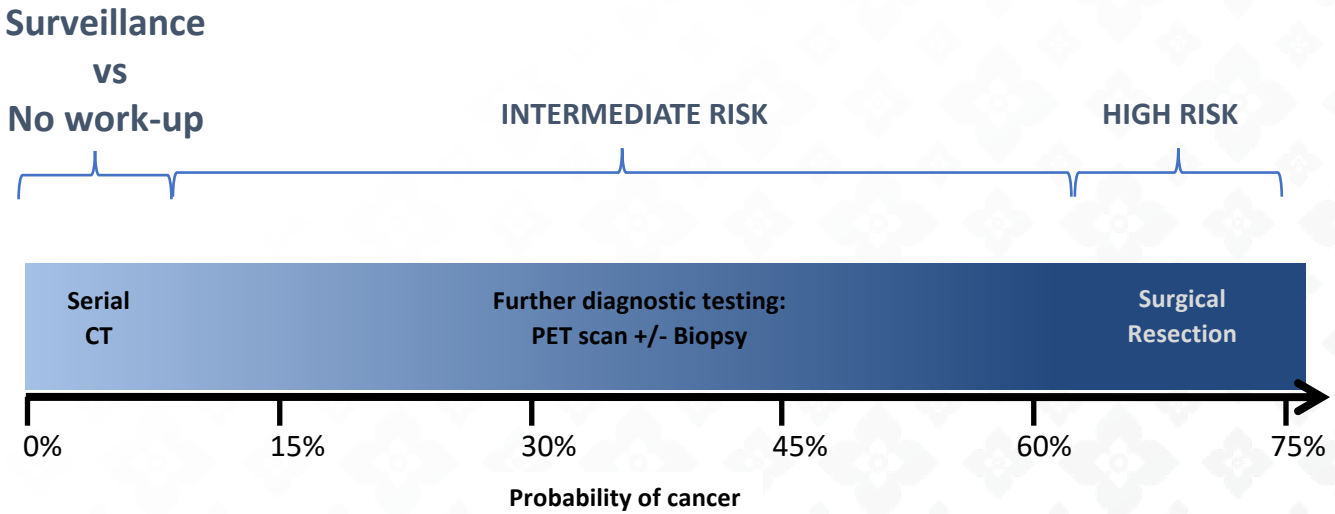

Is this cancer or not?

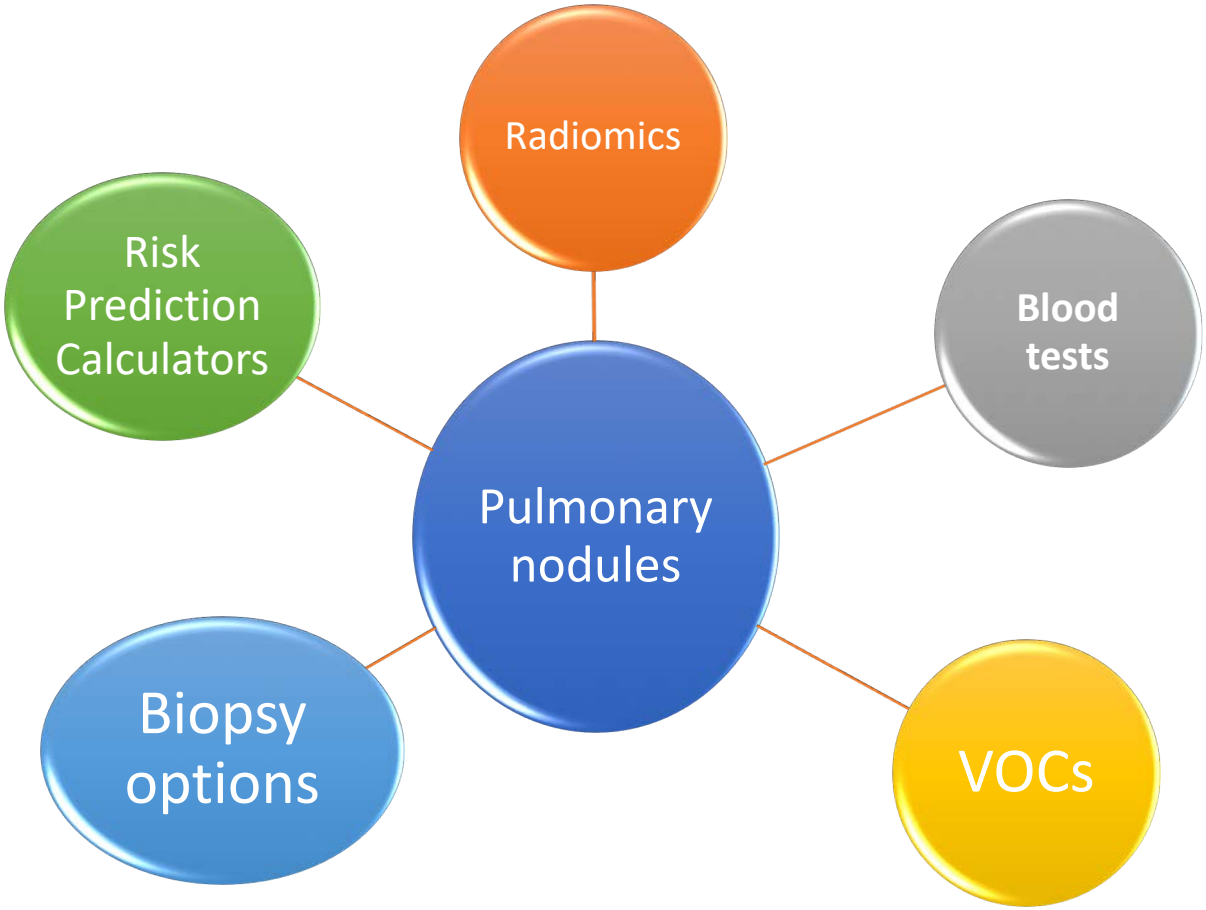
Management Alternatives

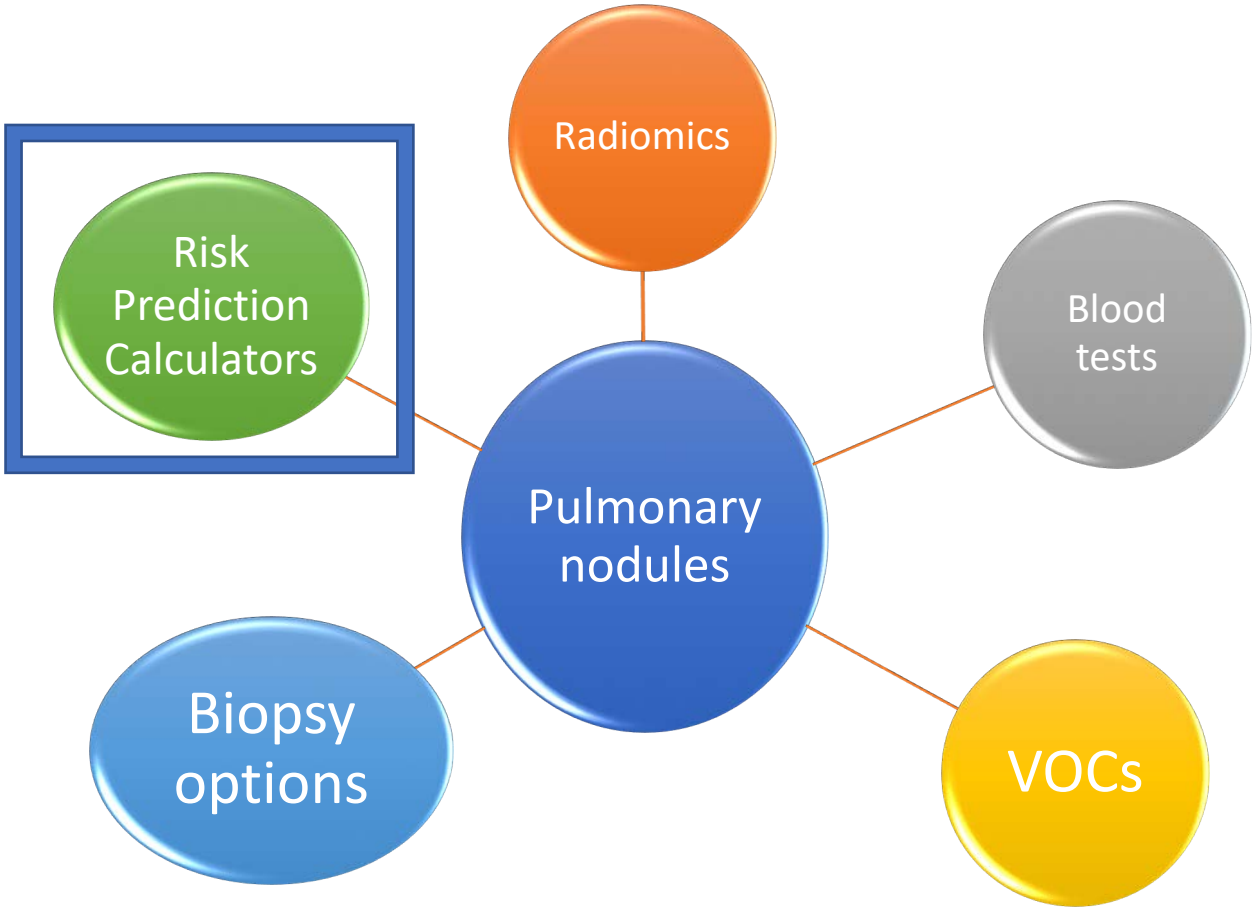
- Surgery
  - “When in doubt, cut it out”
- Biopsy
  - “When cancer is the answer, tissue is the issue”
- Wait and watch
  - “Don’t just do something…stand there!”

For any nodule

First step: Assess likelihood of malignancy
Clinical judgment vs. risk calculator




Radiomics
Risk Prediction Calculators
Blood tests
Pulmonary nodules
Biopsy options
VOCs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ARS Question 1

A 70 year old female with a 1 pack per day smoking history for 50 years presents with a 1.4 cm spiculated nodule in the Right upper Lobe. She has family history of cancer.

The probability that this nodule is cancer is?

1. < 5%
2. Somewhere between 5% and 65%
3. > 65%
4. The probability of cancer can’t be calculated given the information provided

Question 1

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1. < 5%
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3. **> 65%**
4. The probability of cancer can't be calculated given the information provided

SPN Management

- Pre-test probability of cancer and management recommendations

  - **Low < 5% risk of cancer**
    - Serial CT's
  - **Intermediate is 5 – 60%**
    - Consider PET, TTNA, Bronch
  - **High is > 60%**
    - Excisional biopsy with frozen section

Solitary Pulmonary Nodule
Differential Diagnosis: Benign SPN

- Non-specific or healed granulomas (25%)
- Infectious granulomas (15%)
- Benign neoplasms (15%)
  - Hamartoma
  - Lipoma, fibroma, countless others (rare)
- Others: lung abscess, pseudotumor, round atelectasis, AVM, infarct, mucoid impaction, hematoma, rheumatoid nodule, Wegener's

Differential Diagnosis: Malignancy in a pulmonary nodule

- Adenocarcinoma (~50%)
  - Bronchoalveolar cell carcinoma (~5%)
- Squamous cell carcinoma (~20%)
- Solitary metastasis (~10%)
- Undifferentiated NSCLC (~10%)
- Small cell carcinoma (<2%)

Current Model Used To Predict Cancer in Nodules

- Six independent predictors of malignancy in SPN
  - **Patient characteristics:**
  - **Age,**
  - **Smoking status**
  - **History of extrathoracic malignancy**
  - **Nodule characteristics:**
  - **Diameter**
  - **Spiculation**
  - **Upper lobe location**

George Box: "All models are wrong but some are useful"

Swensen et al. Arch Intern Med 1997;157:849

Predictors of Cancer in Screen Detected nodules

	OR	P Value
Older age	1.03 (.99-1.07)	0.16
female sex	1.82 (1.1-3.0)	0.02
family hx of lung cancer	1.83 (.83-2.17)	0.23
Emphysema	1.34 (.78-2.3)	0.29
larger nodule size	2.06 (1.3-2.5)	<0.001
Upper lobe	1.93 (1.1-3.3)	0.02
higher nodule count	0.92 (.85-1.00)	0.049
Spiculation	2.187 (1.16-4.05)	0.02

AUC >.90

N Engl J Med 2013;369:910-9.

CT: Size Matters

Size	% malignant
• 2-5 mm	1%
• 6-10 mm	24%
• 11-20 mm	33%
• 21-45 mm	80%

Henschke et al. Lancet 1999;354:9-105.

CT: Edge Characteristics

Border type	LR
1. Smooth	0.2
2. Lobulated	0.5
3. Spiculated	5.0
4. Corona radiata	14

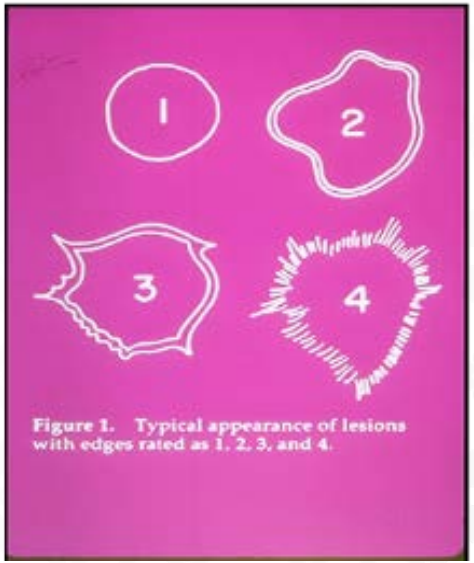


Figure 1. Typical appearance of lesions with edges rated as 1, 2, 3, and 4.

Siegelman et al. Radiology 1986;160:307

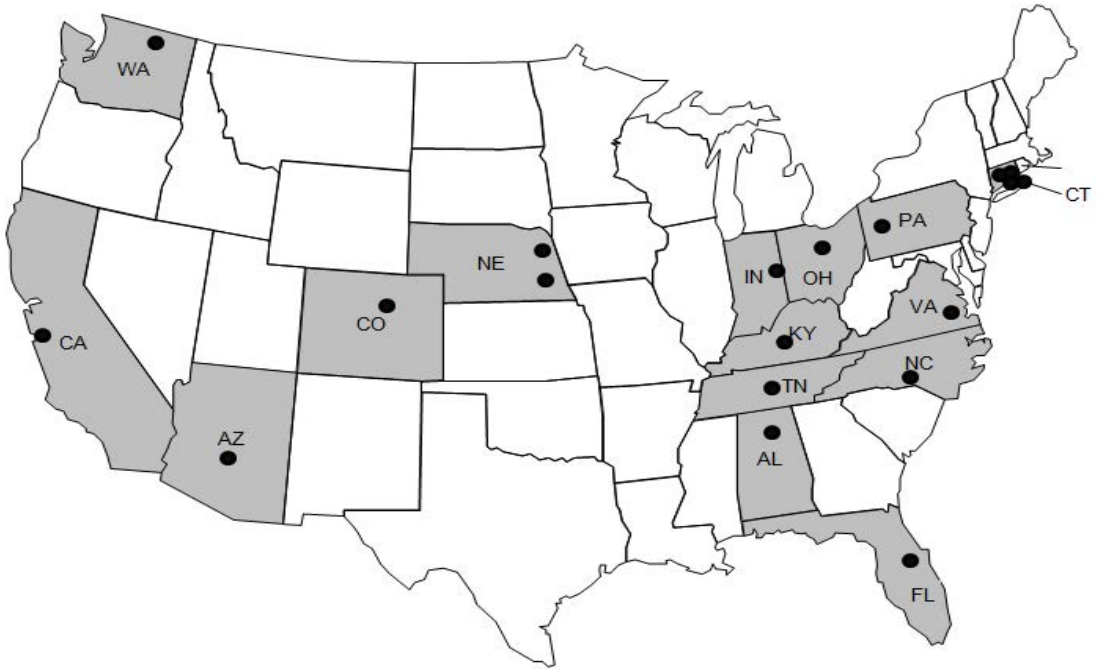
CHEST

Management of Pulmonary Nodules by Community Pulmonologists

A Multicenter Observational Study

Nichole T. Tanner, MD, MSCR; Jyoti Aggarwal, MHS; Michael K. Gould, MD; Paul Kearney, PhD; Gregory Diette, MD, MHS; Anil Vachani, MD; Kenneth C. Fang, MD; and Gerard A. Silvestri, MD

PODCAST



33 Geographically Diverse Outpatient Pulmonary Clinics

Chest 2015:148(6):1405-14

Diagnosis and procedure use categorized by nodule pretest probability for cancer

N=377	Low Risk < 5% n=36	Intermediate Risk >5 to <65% n=300	High Risk >65%	
Outcome				
Benign	36 (100%)		(55%)	<0.0001
Malignant			18 (45%)	<0.0001
Most In…		…ized		
	20 (56%)	141 (47%)	14 (34%)	0.1548
Biopsy	10 (28%)	95 (32%)	20 (49%)	0.0711
Surgery	6 (17%)	64 (21%)	7 (17%)	0.6878

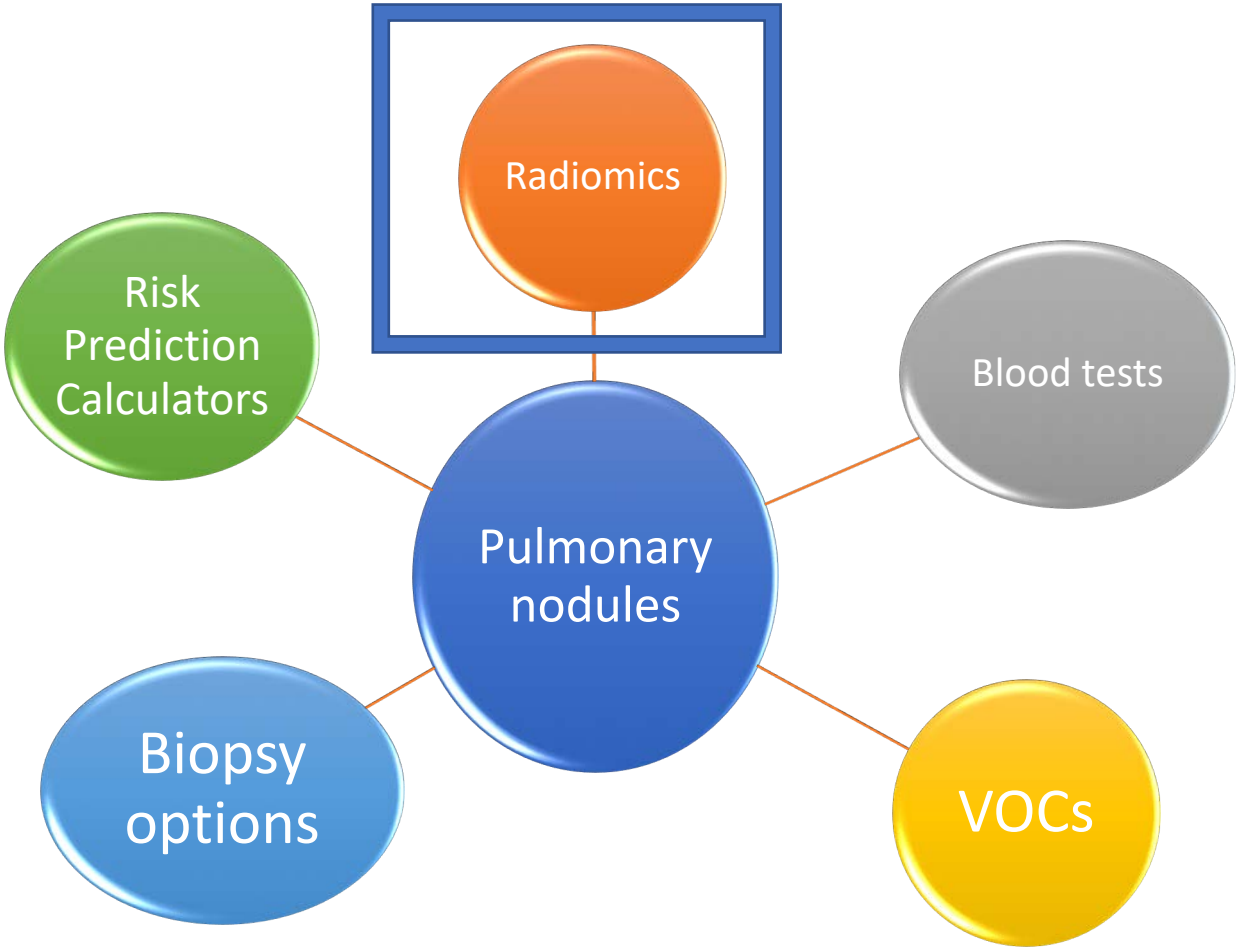
Surgery for BENIGN DISEASE = 35%

Tanner et al. *Chest* 2015:148(6):1405-14

Nodules in the community

- 25% of patients presenting to pulmonologists ultimately have cancer
- 44% of very low risk patients (pCA <0.05) underwent an invasive procedure for a benign nodule
- There was no difference in the rate of surgical resection for nodules based on pretest probability of cancer
  - Possible explanations:
    - Pulmonologists do not routinely consider pCA
    - They unaware that guidelines exist for nodule management
    - They choose not to follow them guidelines

Tanner NT, et al. Chest.2015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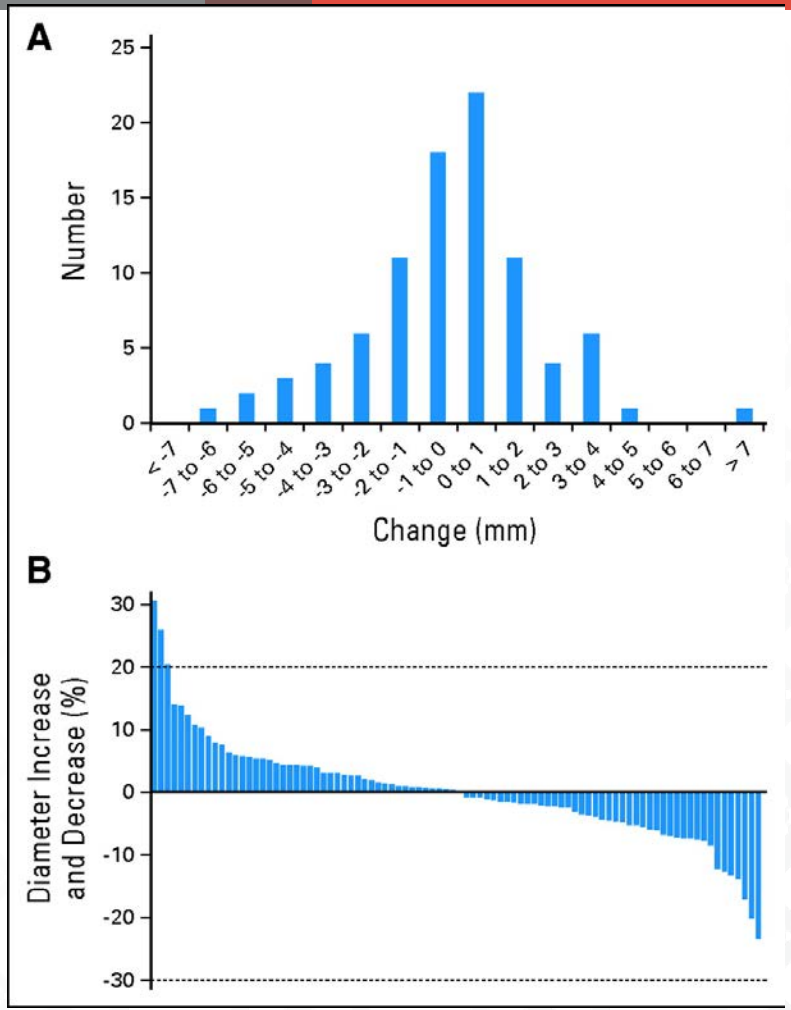
Variability of Tumor Measurement on Repeat CT within 15 minutes

- 33 patients with NSCLC
- Repeat CT within 15 min.
- 57% 1mm different
- 33% 2mm different
- 23% shrinkage
- 33% growth.

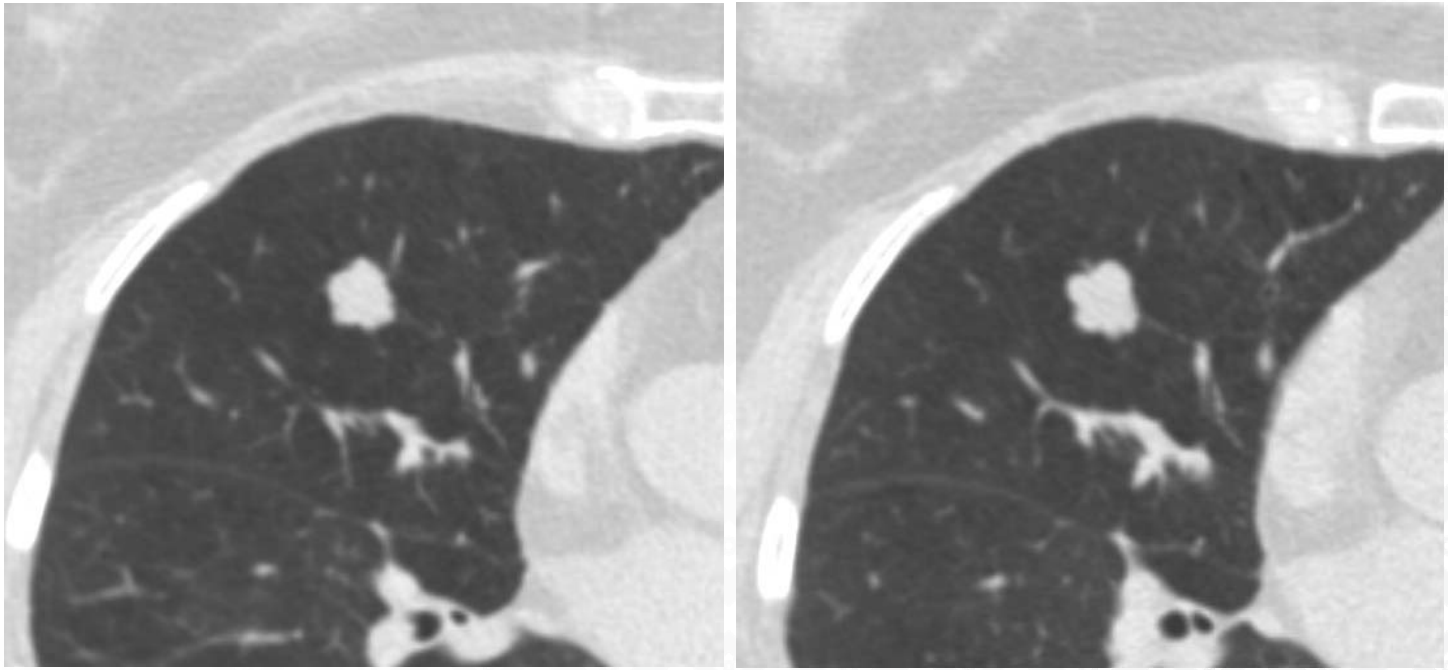
- JCO 2011, 29:311



JOURNAL OF CLINICAL ONCOLOGY

Oxnard G R et al. JCO 2011;29:3114-3119

Standard Curser Measurements



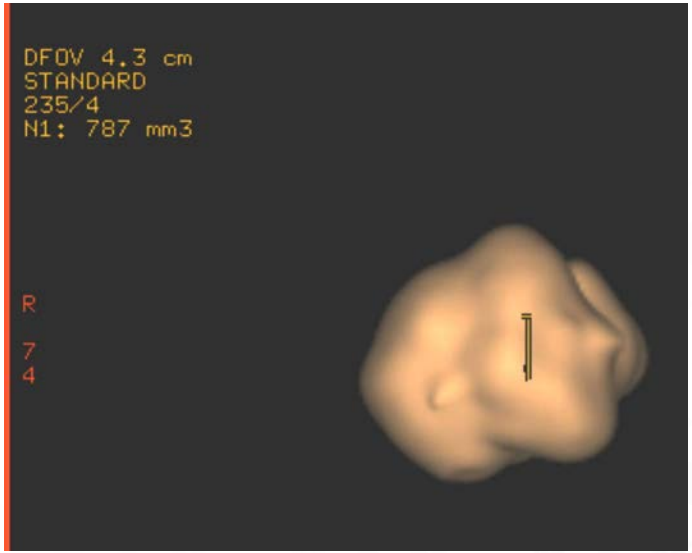
3/05

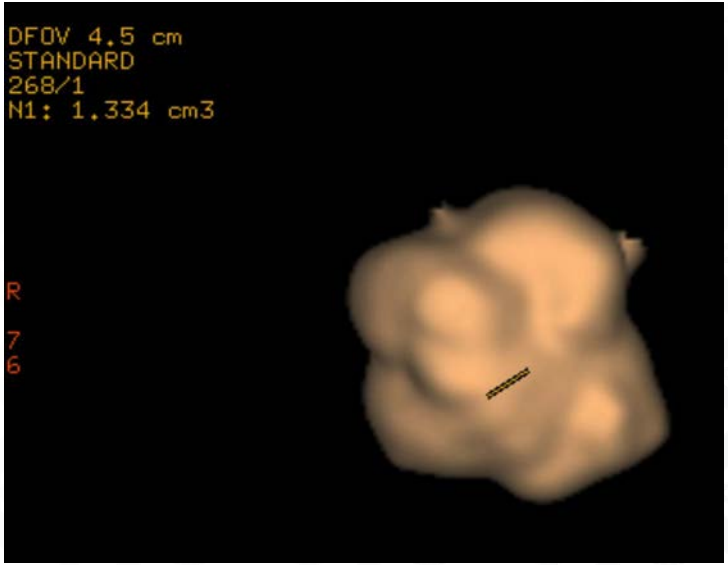
1.3 cm

9/05

1.5 cm

Volumetrics





3/05

1.3 cm

787 mm^3

9/05

1.5 cm

1.334 mm^3

ORIGINAL ARTICLE

NEJM 2009

Management of Lung Nodules Detected by Volume CT Scanning

Rob J. van Klaveren, M.D., Ph.D., Matthijs Oudkerk, M.D., Ph.D.,

- Definition of negative baseline screen
  - No nodule (49%)
  - Calcified nodule or volume <50 mm3 (~30%)
  - Indeterminate: volume 50 to 500 mm3 (19%)
  - 95% of the indeterminate patients had nodules that resolved at 3 months, had no growth (<25% increase), or had VDT ≥400 days
- Sensitivity for lung cancer 94.6%
- NPV= 99.7% (7,341/7,361)
- Reduced false positives from 30% to 2%

Fleischner Society Guidelines 2017

Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

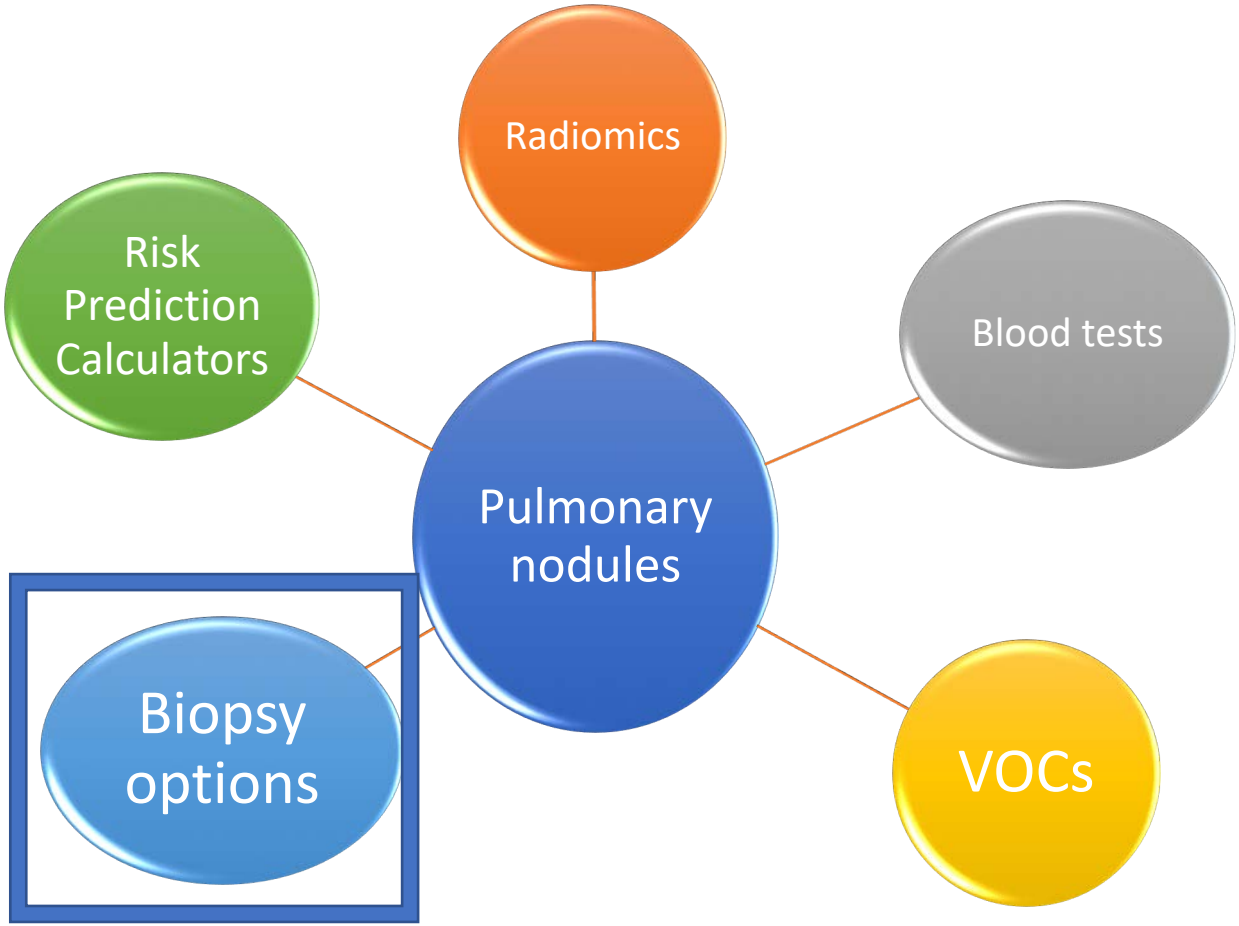
A: Solid Nodules*

Nodule Type	Size: <6 mm (<100 mm^3)	Size: 6–8 mm (100–250 mm^3)	Size: >8 mm (>250 mm^3)	Comments
Single				
Low risk†	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT, PET/CT, or tissue sampling at 3 months	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
High risk†	Optional CT at 12 months	CT at 6–12 months, then CT at 18–24 months	Consider CT, PET/CT, or tissue sampling at 3 months	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
Multiple				
Low risk†	No routine follow-up	CT at 3–6 months, then consider CT at 18–24 months	CT at 3–6 months, then consider CT at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
High risk†	Optional CT at 12 months	CT at 3–6 months, then at 18–24 months	CT at 3–6 months, then at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).

FDG-PET Imaging

- Non-invasive, functional imaging test
- FDG accumulates in metabolically active tumor cells
- Sensitivity ~72-95%, specificity ~83%
- False negative results:
  - Small nodules <8 mm to 10 mm
  - Well-differentiated adenocarcinoma, BAC, carcinoid
- False positive results:
  - Granulomatous infection/inflammation

Lowe and Naunheim. Thorax 1998;53:703-12.
Wahidi et al. Chest 2007.
Gould et al, Chest 2013
Cronin.Radiology,2008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Transthoracic Needle Aspiration

11 studies with data about accuracy in SPN:

- Median sensitivity 90% (range 65% to 94%)
- Median specificity 100% (range 96% to 100%)
- Specificity assumed to be 100% in some studies
- Non-diagnostic results 5x more common in benign than malignant nodules, but non-diagnostic biopsy does not rule out malignancy
- Median probability of PTX 15% (range 15% to 43%)
- ~6% required chest tube (range 4% to 18%)

Gould et al. Chest 2013, Weiner et al, Ann Intern Med 2015

Transthoracic Needle Aspiration

ACCP recs: In patients with an indeterminate SPN (10 mm) it is appropriate to perform a TTNA or bronchoscopy in the following circumstances:

- when clinical pre-test probability and findings on imaging tests are discordant, for example, when the pre-test probability of cancer is high and the lesion is not hypermetabolic by PET
- when a benign diagnosis requiring specific medical treatment is suspected
- when a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.
- Patient non operative and need tissue to treat

Yield of Bronchoscopy for Lung Cancer

Study	Sites/Patients	Yield/Sensitivity
2013 ACCP Guidelines	35 studies 4,507 patients	Central lesions – 88%
	34 studies 5,742 patients	Peripheral lesions – 78%
	10 studies 1,367 patients	< 2cm – 34% > 2cm – 63%
2012 Meta-analysis	39 studies 3,004 patients	Overall – 70% > 2cm – 82% < 2cm – 61%

Rivera et al. *CHEST* 2013
Wang Memoli et al. *CHEST 2012*

Yield of Bronchoscopy for Lung Cancer

Study	Sites/Patients	Yield/Sensitivity
2015 AQuIRE registry	15 sites 531 patients	Flexible bronchoscopy – 64% Radial EBUS – 57% EMN – 39%
2015 AEGIS study	28 sites 639 patients	Overall – 53% for diagnosis of cancer
2018 Multicenter RCT standard bronchoscope with fluoroscopy (SB-F) vs thin bronchoscope with radial EBUS (TB-EBUS)	5 sites 221 patients	Overall – 44% SB-F – 37% TB-EBUS – 49% > 3cm – 57%

Ost et al. *AJRCCM*, 2015
Silvestri et al. *NEJM*, 2015
Tanner et al. *CHEST*, 2018

The NEW ENGLAND JOURNAL of MEDICINE

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*

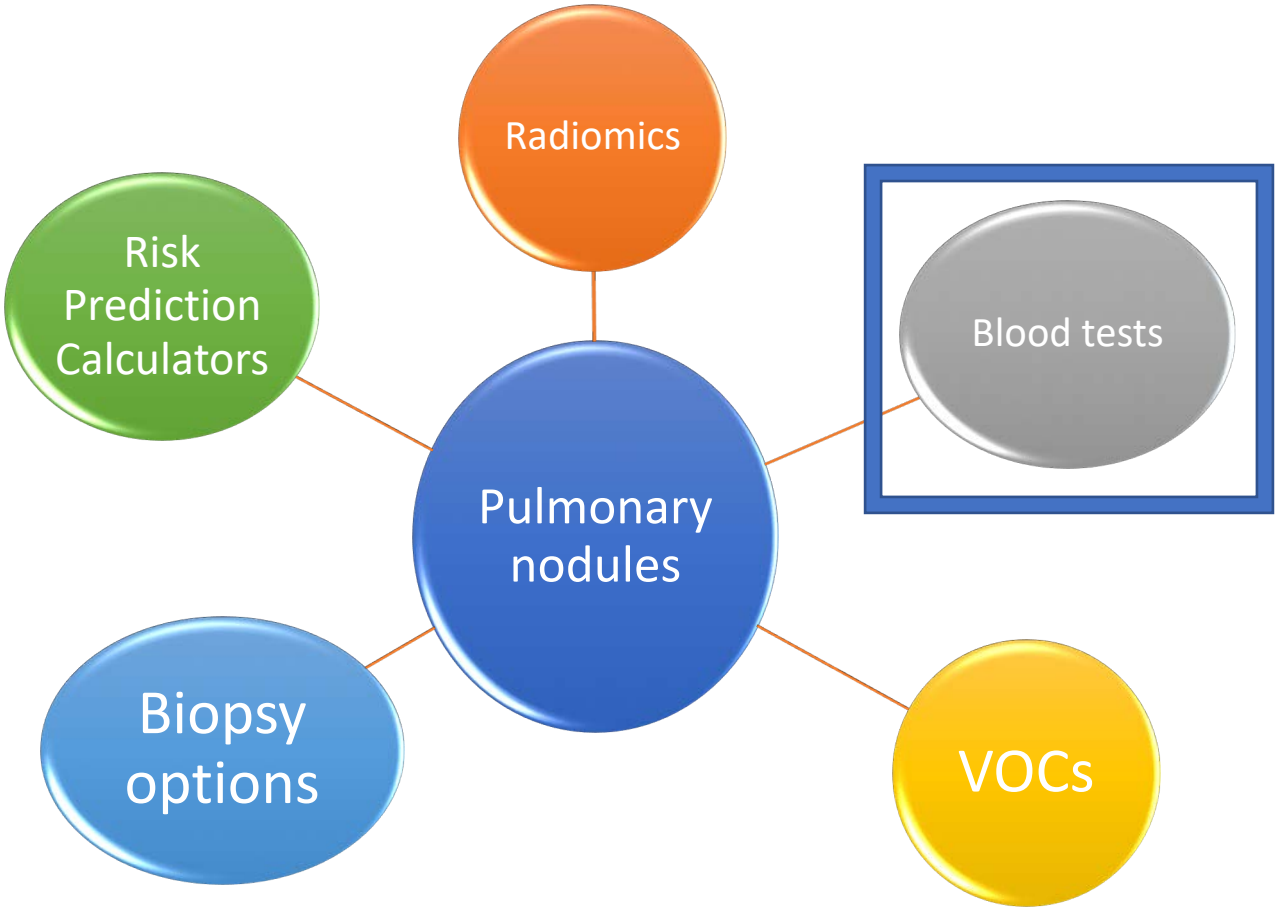
- Rationale: Bronchoscopy is often non-diagnostic in patients with pulmonary lesions leading to additional invasive testing.

- Objective: Evaluate the effectiveness of a bronchial-airway gene-expression classifier on the diagnostic performance of bronchoscopy.

Results

- N= 639
- Gene-expression classifier measured in epithelial cells collected from normal-appearing mainstem bronchus
- 43% of bronchoscopies non-diagnostic
- 35% with benign lesions underwent invasive procedures
- The combination of the classifier plus bronchoscopy had a sensitivity of 96% (95% CI, 93 to 98) in AEGIS-1 and 98% (95% CI, 96 to 99) in
- Independent of lesion size and location.
- In 101 patients with an intermediate pretest probability of cancer, the negative predictive value of the classifier was 91% (95% CI, 75 to 98) among patients with a non-diagnostic bronchoscopic examination

- **Silvestri, NEJM, 2015**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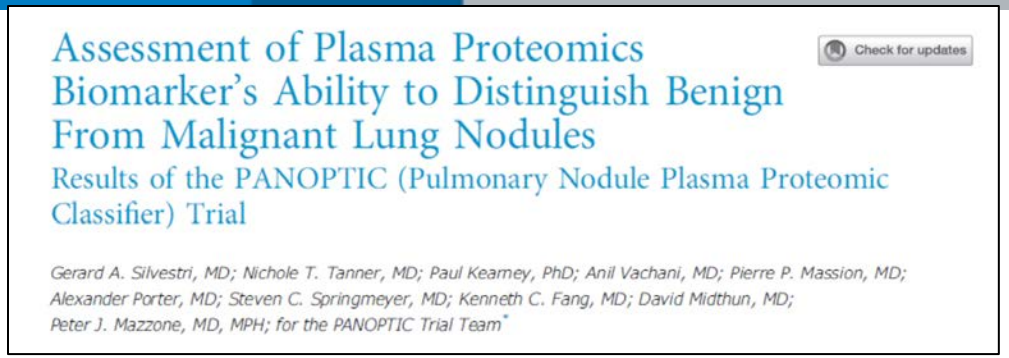


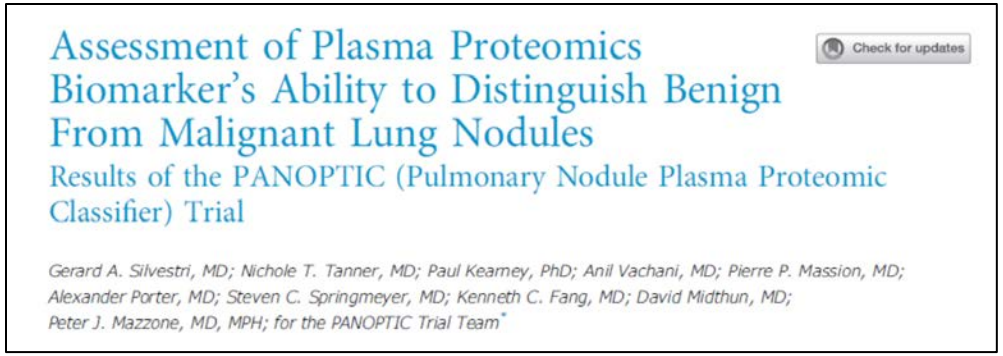
Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules

Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial

Gerard A. Silvestri, MD; Nichole T. Tanner, MD; Paul Kearney, PhD; Anil Vachani, MD; Pierre P. Massion, MD; Alexander Porter, MD; Steven C. Springmeyer, MD; Kenneth C. Fang, MD; David Midthun, MD; Peter J. Mazzone, MD, MPH; for the PANOPTIC Trial Team*

- Design: prospective, multi-center trial (33 North American sites), 685 patients
- Eligibility: Age ≥ 40 with new lung nodule ≥8mm and ≤30mm
- Methods: 2 plasma proteins, LG3BP and C163A, were integrated with a clinical risk prediction model to identify likely benign nodules
- Clinician assessment of nodule pre-test probability for malignancy was provided at enrollment

Silvestri, Chest 2018



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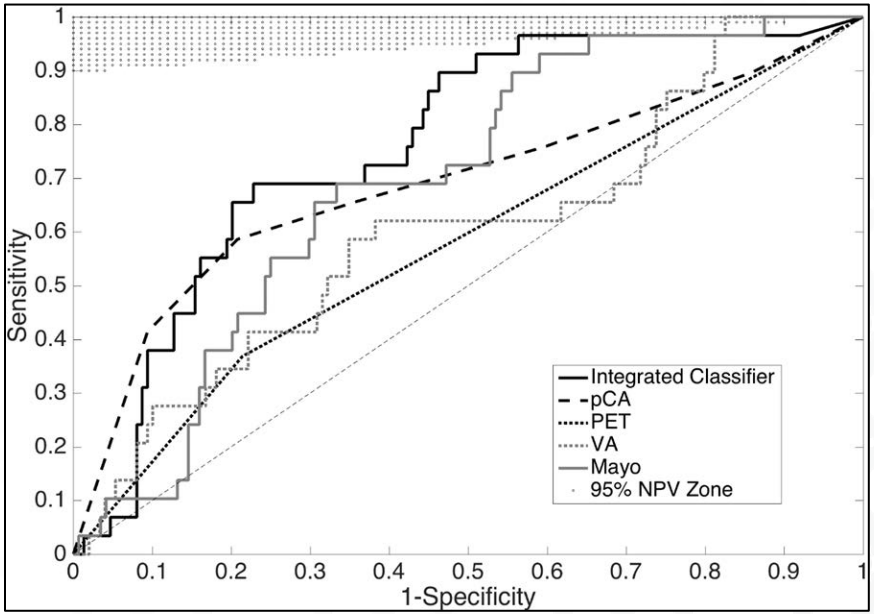
Results

- 178 patients had pCA ≤ 80%; prevalence of cancer was 16%
- The integrated classifier:
  - Sensitivity of 97%
  - Specificity 44%
- NPV 98% in distinguishing benign from malignant nodules
- Had results been used to direct care, 40% fewer procedures would have been done on benign nodules
  - 3% of malignant nodules would have been misclassified

Silvestri, Chest 2018

Comparison of AUCs for ROCs of lung nodule malignancy risk assessment tools relative to 95% NPV zone.

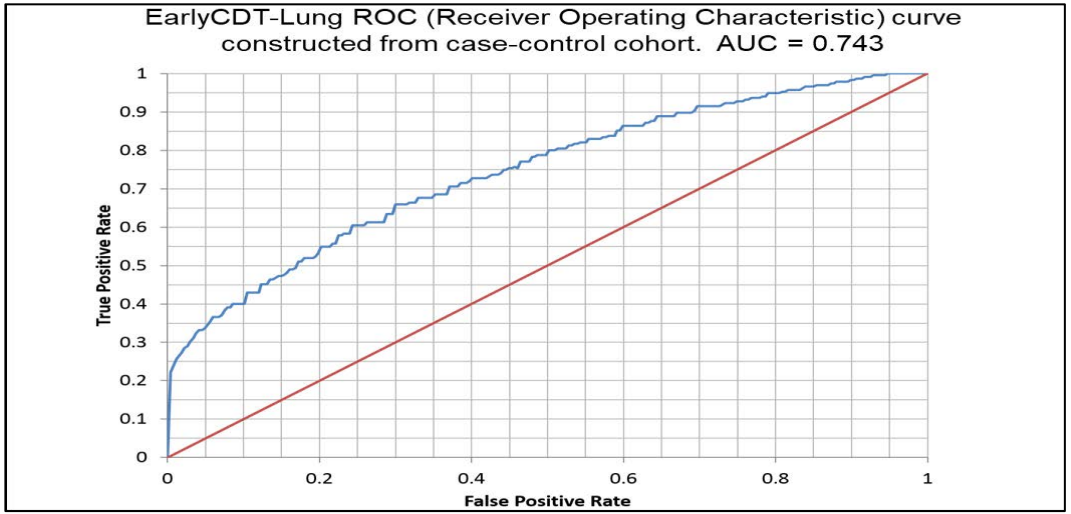


Silvestri, Chest 2018

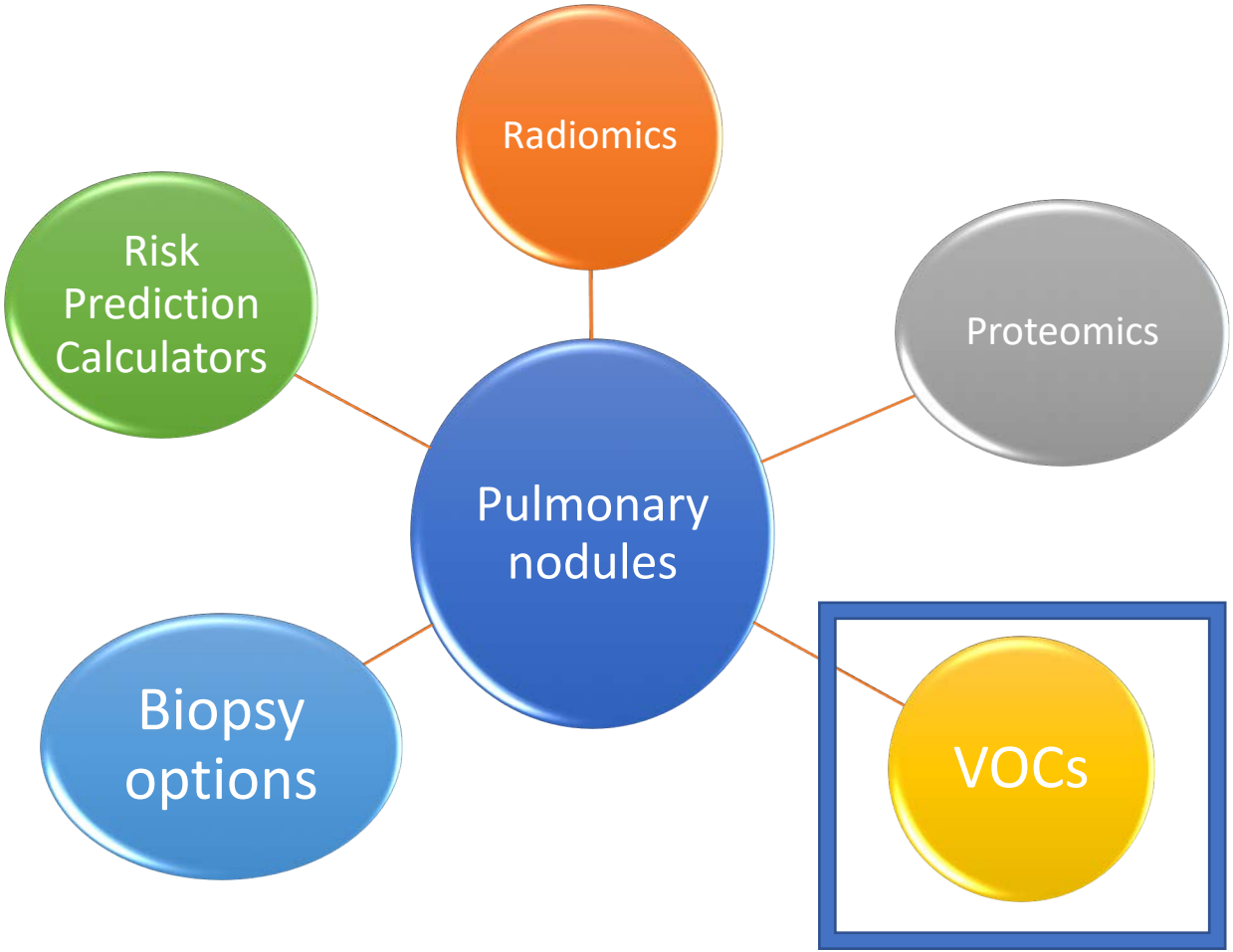
EarlyCDT®-Lung

Rule in Test: Early CDT Oncimmune

- **autoantibodies can aid early detection and nodule risk stratification in lung cancer patients**
  - **Absent or low concentrations in benign cohorts**
  - **7 panel ELISA**
  - **p53, NY-ESO-1, SOX2, HuD, GBU4-5, CAGE & MAGE A4**
  - **~40% sensitivity & 93% specificity for all stages of lung cancer**



Personal communication courtesy of Jim Jett, MD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Volatile Organic Compounds

- Origin
  - Endogenous (end-products of metabolic pathways)
  - Exogenous (contaminants from environment)
- VOCs detected in various lung diseases
  - Combination, rather than single
- Analyzers
  - Gas chromatography/mass spectrometry
  - Portable devices
  - Canine detection

Canine and Electronic Nose to Detect Lung Cancer

- Canine Detection:
- 3 studies with 280 subjects
  - Sensitivity range 71%-99%
  - Specificity range 82%-99%

- Electronic Nose:
- 7 studies with 30 subjects
  - Sensitivity range 7%-86%
  - Specificity range 72%-99%

- Dent et al, J Thorac Dis 2013

Conclusions

- Common Radiologic Problem with an Increasing incidence
- Multiple Imaging Strategies
- Multiple minimally invasive and surgical approaches
- Management Decisions Often Based on Pre-test Probability of Malignancy
- Biomarkers will help build physician confidence
- Bronchoscopy may not be as useful as we think
- Answer probably comes with escaping from silos Deep machine learning/ Artificial intelligence.