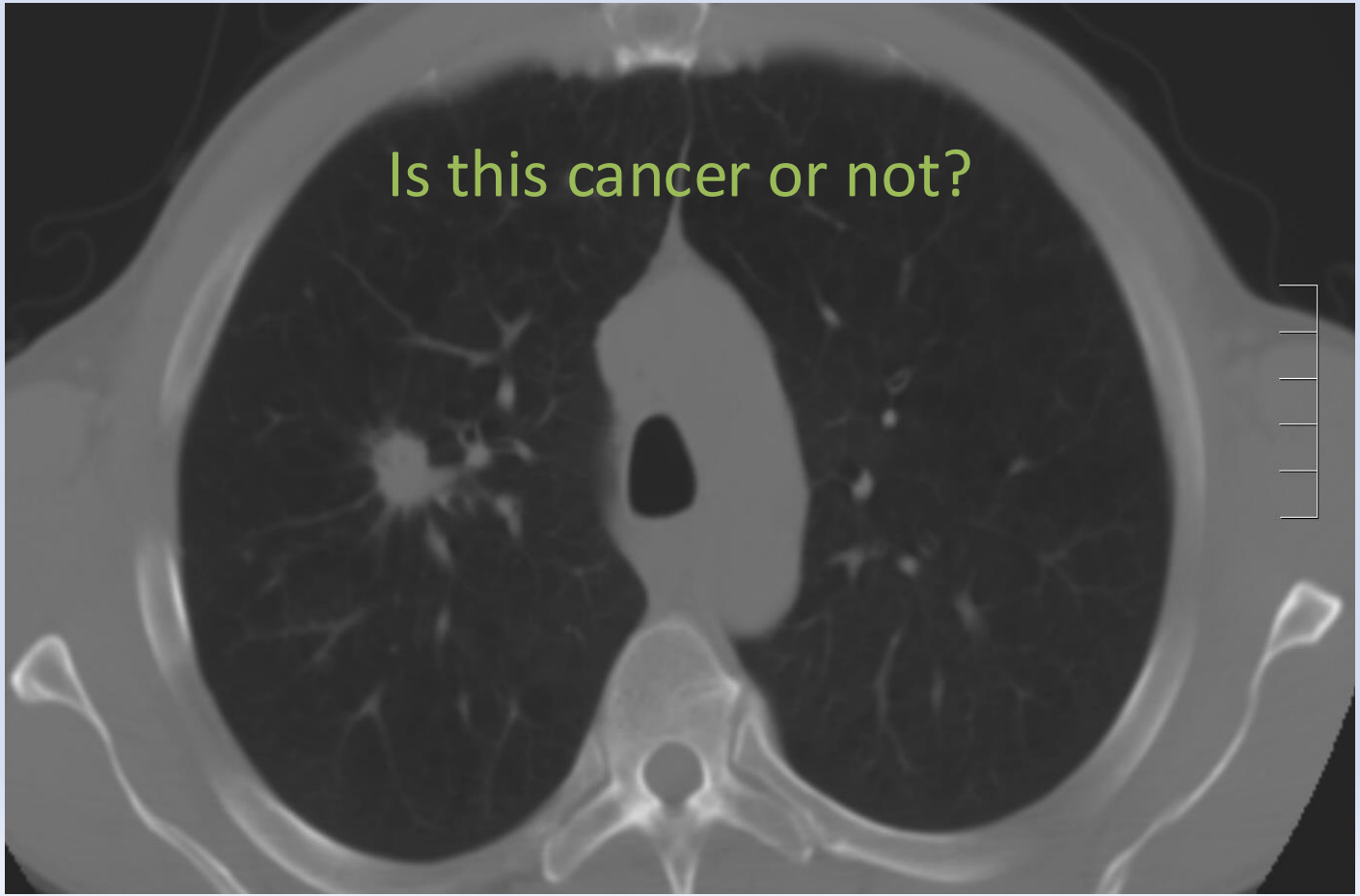
Incidental Pulmonary Nodule Programs (IPNs) – What are Best Practices Diagnosis and Monitoring

Gerard A. Silvestri, MD, MS, Master FCCP
Hillenbrand Professor of Thoracic Oncology
Medical University of South Carolina, Charleston

Overview

- Epidemiology
- Scope of the problem
- Prediction models represent a simple solution
- How to track
- Summary

What is the problem?



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!”

Epidemiology

- **Incidentally detected nodules**
- **29% of all scans positive for nodule (4-30 mm)**
- **Estimated 1.5 million nodules detected/year in US**
- **Prevalence of malignancy**
  - 5% of all incidental nodules at 2 yrs
  - Up to 10% for nodules >8mm
  - 25% in patients referred to a pulmonologist
  - >70% for patients referred to a thoracic surgeon

Gould et al. AJRCCM 2015
Vachani et al. CHEST 2022
Tanner et al. CHEST 2015
Godfrey et al. 2023

Epidemiology

- 4000 IPN's identified every day
- 95% of all pulmonary nodules are benign
- The frequency of nodules is higher in individuals undergoing imaging in fungal endemic areas
- NLST – 96% of all positive scans are false positive and three -quarters have some form of diagnostic follow-up

Am J Respir Crit Care Med 2015;192(10): p1208
Ann Am Thorac Soc 2016;13(9): p1568
N Engl J Med 2011; 365: p395

Surgery for Benign Disease
22% Overall

Study	Surgical procedure	Surgical procedure with benign result
NLST	673	164 (24.4%)
Dépiscan	9	3 (33.3%)
DANTE	90	17 (18.9%)
DLCST	25	7 (28%)
NELSON	NR	61
ITALUNG	38	4 (10.5%)
MILD	45	4 **(8.9%)**
LUSI	NR	NR
UKLS	39	4 (10.3%)
LSS	46	18 **(39.1%)**

Mazzone et al. Chest Guidelines 2021

Too much and too little care

- Retrospective cohort from 15 VA hospitals

Results:

- 47% of patients received care inconsistent with guidelines
  - 17.8% over-evaluation
  - 26.9% under-evaluation
- 15% of patients underwent invasive procedures
  - 41% of these did not have cancer
  - 30% of patients who underwent surgical resection did not have cancer

- 5% of patients had no follow-up

Weiner JAMA 2014

Does it Matter Whether The Nodule is Screen Detected or Not?

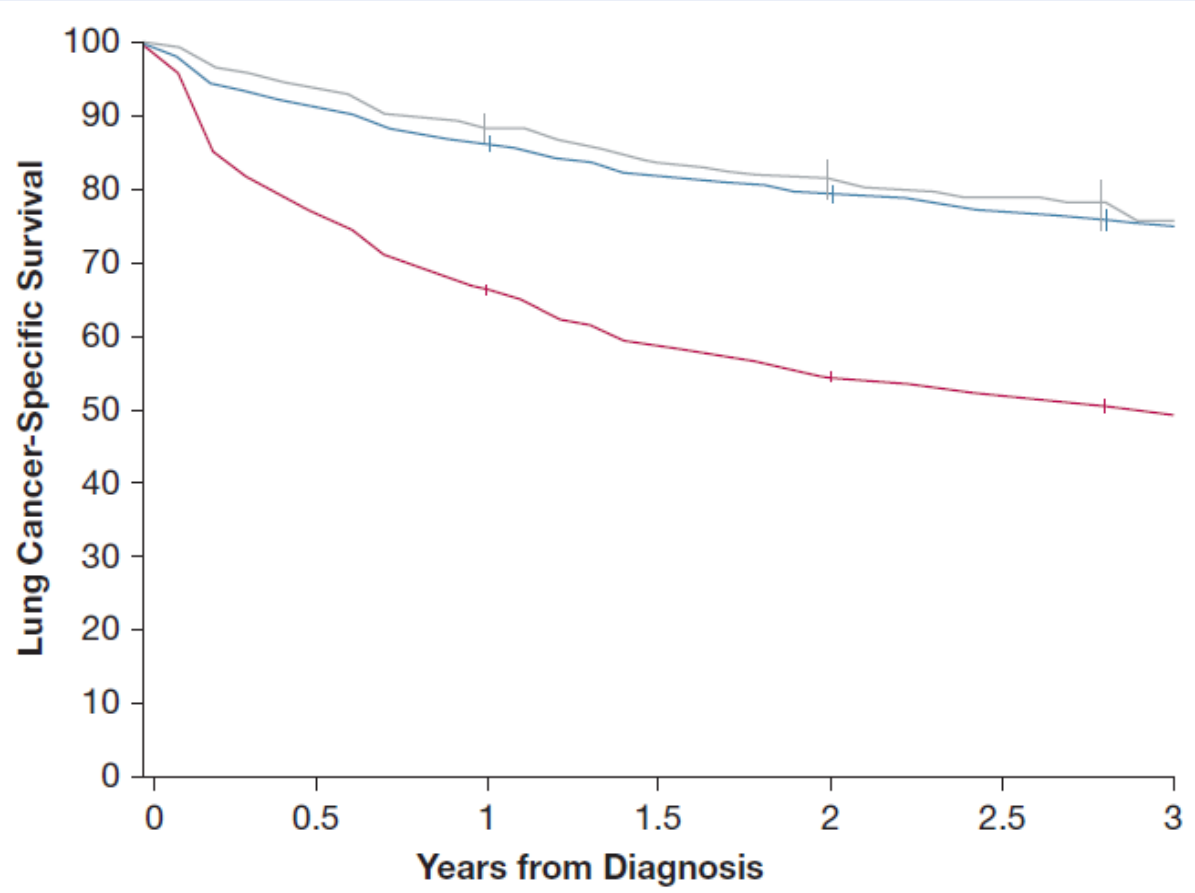
- Assessed the **relative proportion of early-stage lung cancer diagnosed after reporting of PNs** vs through low-dose CT (LDCT) scan screening?
- **Seer Medicare Cohort**
  - Patients in the lung cancer cohort were classified by **whether they had undergone LDCT scan screening, whether they had a diagnosis of PN,** or neither within 18 months before diagnosis.
  - Compared cancer stage and survival across groups.

Pinsky, CHEST 23.

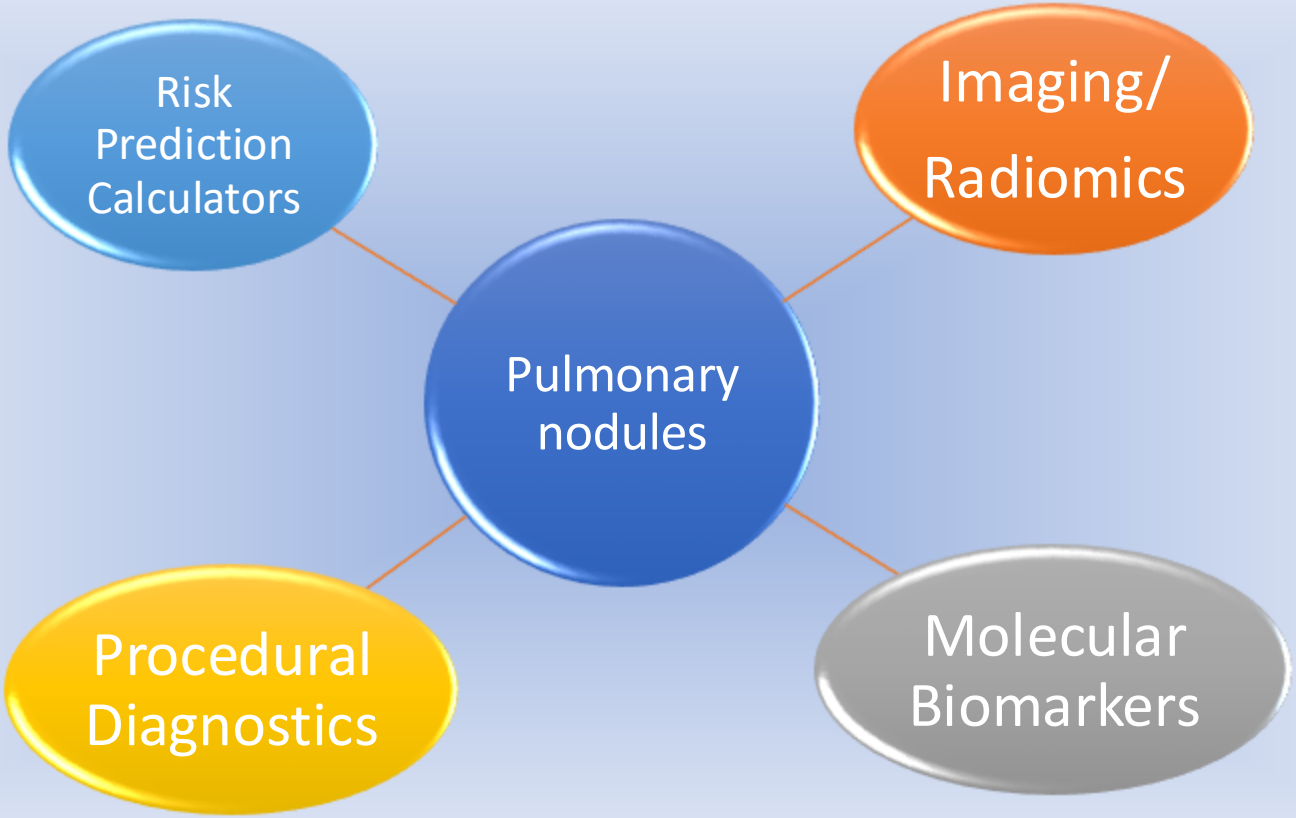
Diagnosis

	PN Group (6942)	LDCT Group (1271)	Reference (35981)
Women (%)	**56.8**	51.1	48.4
Adenocarcinoma (%)	**52.4**	45.2	43.6
Squamous cell (%)	21.1	26.8	23.6
Localized (%)	**58.1**	50.3	24.4
Distant (%)	19.1	19.1	51.6
Stage I (%)	**58.5**	51.0	23.0
Stage IV (%)	18.0	17.4	48.8

Pinsky, CHEST 23.



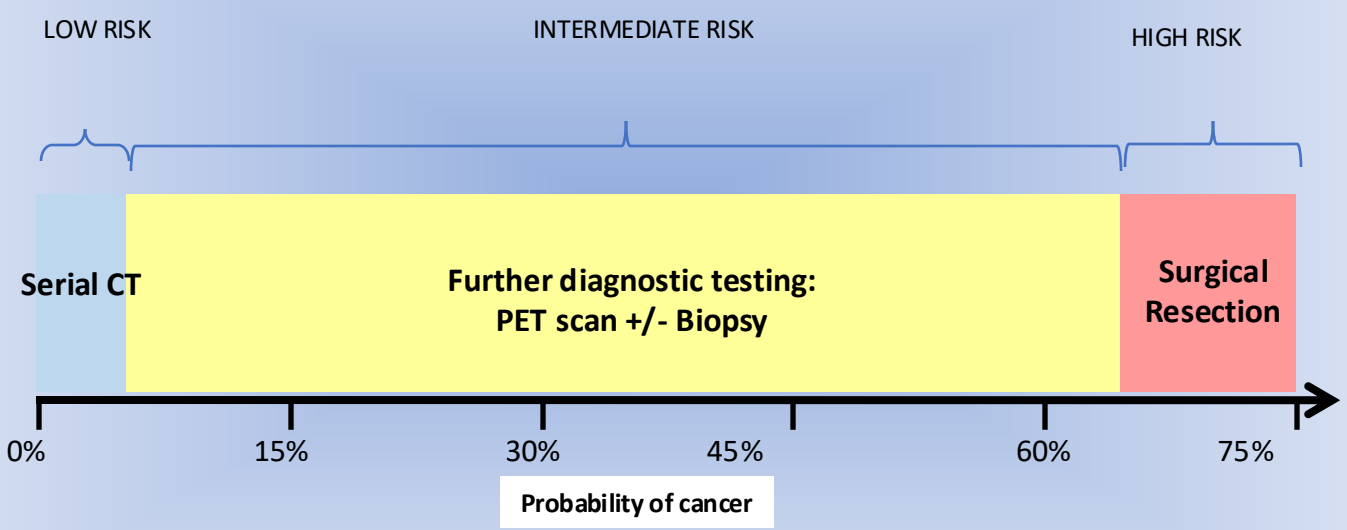
Pinsky, CHEST 23.


Risk Prediction Calculators
Imaging/ Radiomics
Pulmonary nodules
Procedural Diagnostics
Molecular Biomarkers

The Solution

- Assessing pre-test probability for malignancy
- Making a clinical decision based on the pCA
- Follow Guidelines

Assess likelihood of malignancy



Gould et al. CHEST 2013

Risk prediction models

Table 2. Validated Risk Prediction Models for Evaluation of Pulmonary Nodules

Risk prediction model	Mayo Clinic model[17]	Herder model[18]	VA model[19]	Brock University model[2]	Cleveland Clinic model[20]
Nodule detection	Incidental nodule on chest radiograph	Incidental nodule on chest radiograph and PET scan was performed for further evaluation	Incidental nodule seen on chest radiographic confirmed on CT imaging +/− PET scan	Nodules detected on LDCT as part of lung cancer screening program	Incidental nodules referred to biopsy or resection
% Of nodules that were malignant in the cohort used to develop the model	23	57	54	5.5	66.5
Model variables	Age Smoking history History of extrathoracic malignancy ≥5 y ago Nodule diameter Spiculation Upper lobe location	Mayo Clinic model + FDG-PET uptake	Age Smoking history Time since quitting smoking Nodule diameter	Age Sex Family history of lung cancer Emphysema Nodule Size Nodule type Location Nodule count	Age Smoking history Upper lobe location Solid and irregular/spiculated nodule edges Emphysema FDG-PET avidity History of cancer other than lung
Area under the curve	0.83	0.88	0.79	≥0.94	0.75-0.81 (C-index)

Mazzone PJ JAMA 2022

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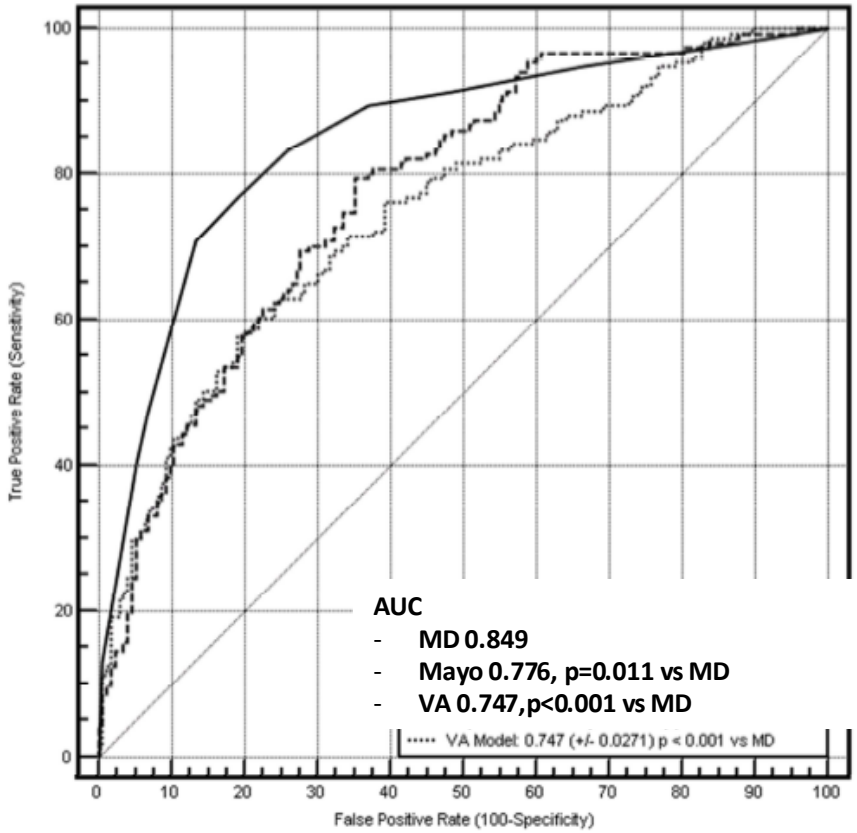
Physician and Model ROCs



Tanner, Silvestri Chest 2017

Diagnosis and procedure use categorized by nodule pretest probability for cancer

	Low Risk < 5% n=36	Intermediate Risk >5 to <65% n=300	High Risk >65% n=41	p-value
Outcome				
Benign	**36 (100%)**	**224 (75%)**	**23 (55%)**	**<0.0001**
Malignant	**0**	**76 (25%)**	**18 (45%)**	**<0.0001**
Most Invasive Procedure Utilized				
Surgery	**6 (17%)**	**64 (21%)**	**7 (17%)**	**0.6878**
Biopsy	**10 (28%)**	**95 (32%)**	**20 (49%)**	**0.0711**
Surveillance	**20 (56%)**	**141 (47%)**	**14 (34%)**	**0.1548**

Tanner NT, Silvestri Chest. 2015.

Mayo Model

- **Incidental nodules, originally developed on CXR/ validated on CT**
- **Independent predictors of malignancy**
- **Clinical**
  - **Older age (OR 1.04 for each year)**
  - **Current or former smoking (OR 2.2)**
  - **Hx of cancer > 5 years (OR 3.8)**
- **Radiographic**
  - **Nodule diameter (OR 1.14 for each mm)**
  - **Spiculation (OR 2.8)**
  - **Upper-lobe location (OR 2.2)**

Swensen S. et al, Arch Int Med 1997; 157:849-55

Examples

- 75 year old
- Current smoker
- 15 mm nodule
- Spiculated
- Upper lobe location
- No extrathoracic malignancy
- PET not performed
- pCA = **87.5%**

- 40 year old
- never smoker
- 15 mm
- non spiculated
- lower lobe location
- No extrathoracic malignancy
- PET not performed
- pCA = **3.4%**

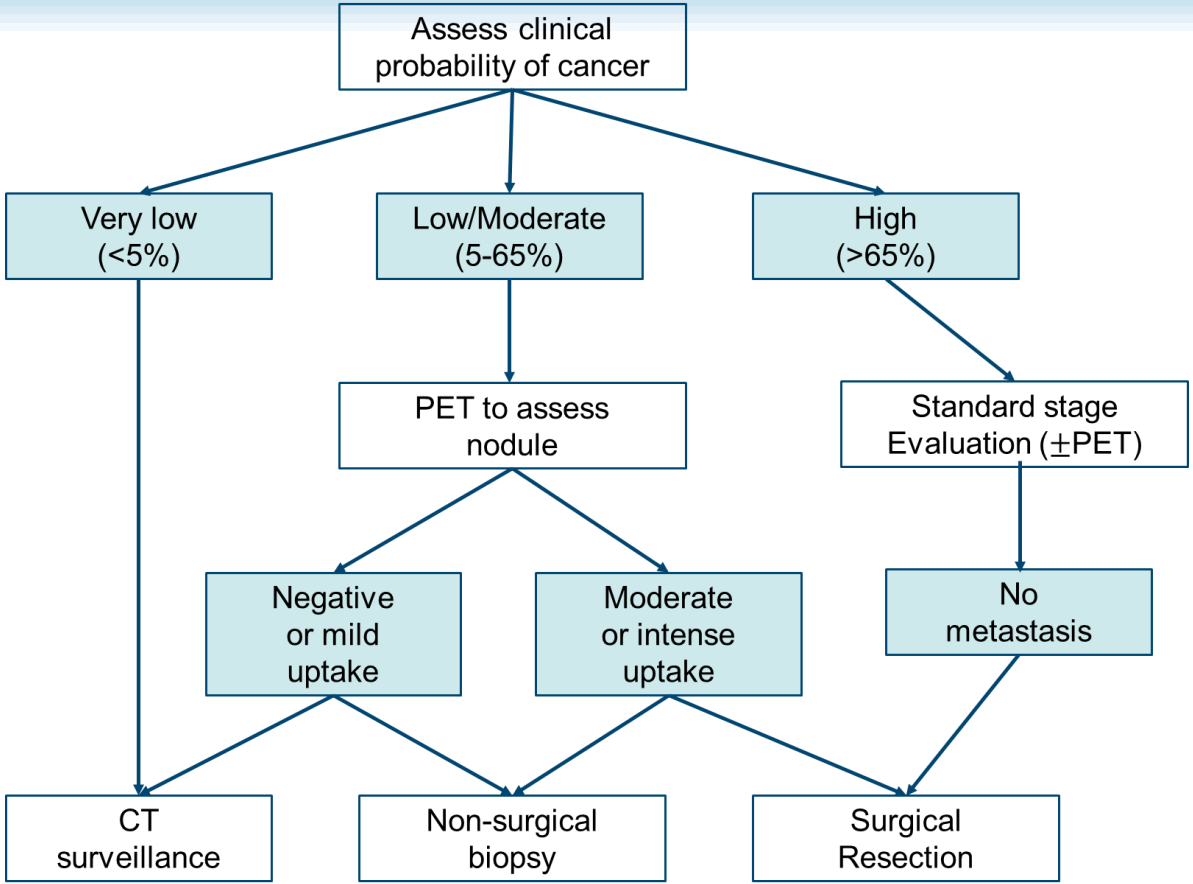
- https://www.mdcalc.com/calc/4057/solitary-pulmonary-nodule-spn-malignancy-risk-score-mayo-clinic-model

Accuracy of PET for Nodules: Meta-Analysis

- Literature Search 2000-2014
  - 70 studies: 10 in endemic areas for infectious lung disease
  - 60% of nodules were malignant
- **Sensitivity 89%: Specificity 75%**
  - Specificity **61%** (95%CI 49-72%) in infectious lung disease areas
- PET scans are NOT good radiographic biomarkers

Deppen et al JAMA 2014; 312:1227-36

Guidelines for nodule management



Gould Chest 2013

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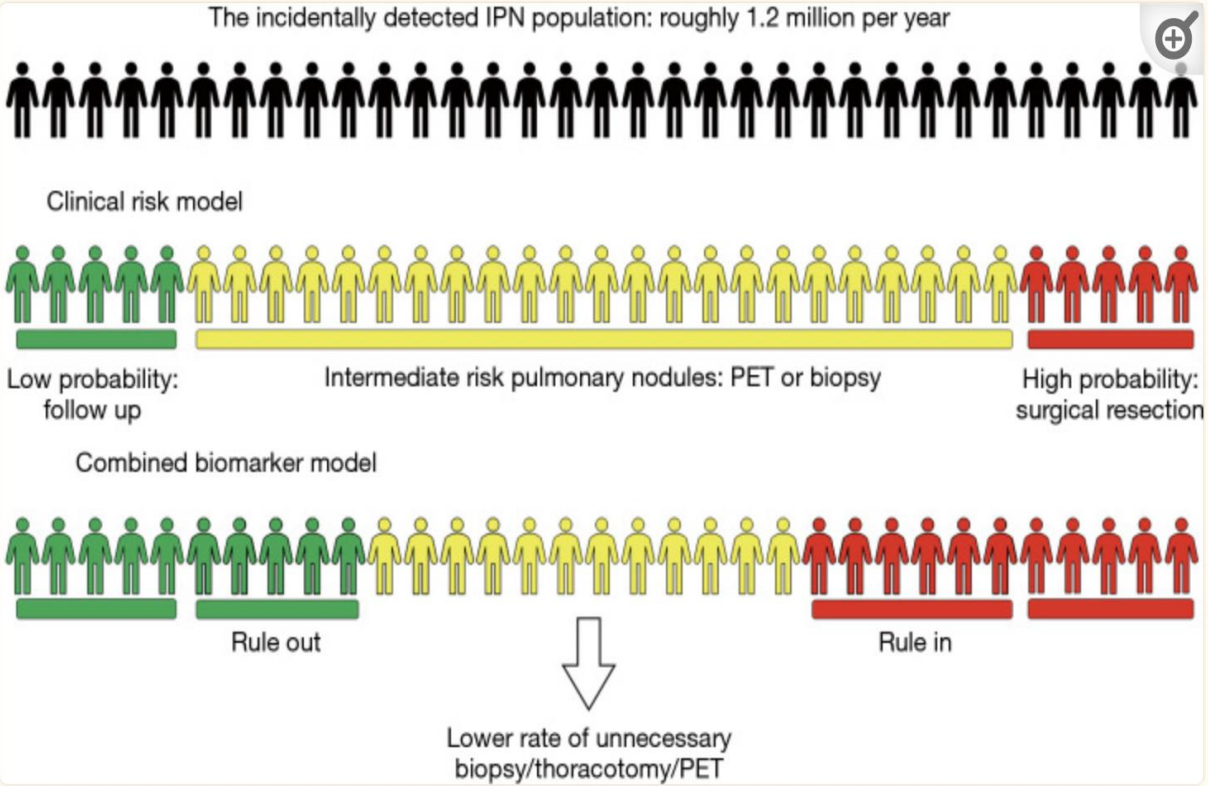
Biomarkers

- Biomarker – a characteristic used to measure and evaluate objectively normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention
- Clinically useful biomarker
  - ✓Prompt identification and treatment of those with cancer
  - ✓Avoidance of unnecessary diagnostic procedures in those without cancer

Role of a biomarker



8. Kammer MN, Maisson PP J Thorac Dis 2020

Conclusions

- Common Radiologic Problem with an Increasing incidence
- Management Decisions Often Based on Pre-test Probability of Malignancy
- However, need to use and trust either the models or your own clinical intuition and act accordingly
- Nodule tracking systems are necessary such that follow-up management occurs. APP's perfect for this role
- Answer probably comes with escaping from silos combining technologies and utilizing deep machine learning/Artificial intelligence.
- Importance of NGS/PDL-1 testing will take increasing role in nodule management as early stage disease now has a myriad of management alternatives (adjuvant, neoadjuvant, perioperative)