Lung Cancer Biomarkers for Diagnosis and Treatment

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Disclosure of Conflict of Interest

Charles A. Powell:

The speaker is a consultant for:

- **Astra Zeneca**
- **Daiichi-Sankyo**
- **Johnson and Johnson**

Objectives:

1. *Upon completion of this learning activity, participants should be able to determine the probability of lung cancer in a patient with a lung nodule by integrating risk information from clinical data and from imaging studies.*

2. *Upon completion of this learning activity, participants should be able to* use clinical evidence to acquire specimens for biomarker analysis and to interpret biomarker results in the settings of lung cancer screening, nodule evaluation, and lung tumor testing.

Biomarker

A **characteristic** that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention;

A **biological molecule** found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Source: www.fda.gov

Molecular Biomarker Premise

Molecular Biomarkers will provide clinically useful information that supplements data presently available for clinical decision making

Molecular Biomarker Evaluation

AMERICAN THORACIC SOCIETY DOCUMENTS

Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use?

An Official American Thoracic Society Policy Statement: Executive Summary

Peter J. Mazzone, Catherine Rufatto Sears, Doug A. Arenberg, Mina Gaga, Michael K. Gould, Pierre P. Massion, Vish S. Nair, Charles A. Powell, Gerard A. Silvestri, Anil Vachani, and Renda Soylemez Wiener; on behalf of the ATS Assembly on Thoracic Oncology

THIS OFFICIAL POLICY STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED JULY 2017

Am J Respir Crit Care Med Vol 196, Iss 7, pp 911–919, Oct 1, 2017

Clinical Lung Cancer Prediction Models

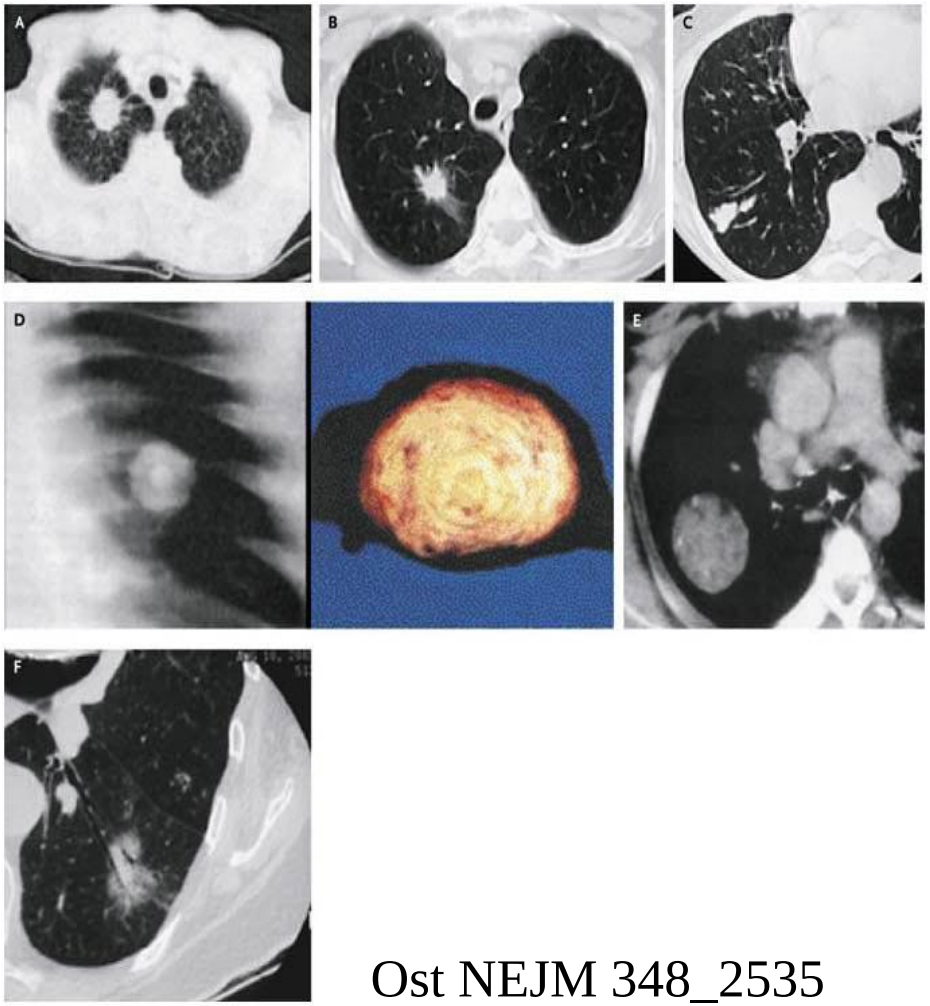
TABLE 2] Available Clinical Lung Cancer Risk Prediction Models[7-11]

First Author	Bach[7]	Spitz[8]	Cassidy[9]	Tammemägi[10]	Hoggart[11]
Source	Caret	MDA	LLP	PLCO	EPIC
Subjects	18,172	3,852	1,736	115,185	169,035
	10-60 cpd	N/F/C smokers	N/F/C smokers	Healthy population	F/C smokers
	25-55 y				
Age, y	50-75	20-80	20-80	55-74	35-65
Variables	Age	Age	Age	Age	Age
	Asbestos	Dust	Asbestos	BMI	Smoking
	Sex	Emphysema	Family history	Chest radiograph	
	Smoking	Family history	Pneumonia	COPD	
		Sex	Prior cancer	Education	
		Smoking	Sex	Family history	
			Smoking	Smoking	

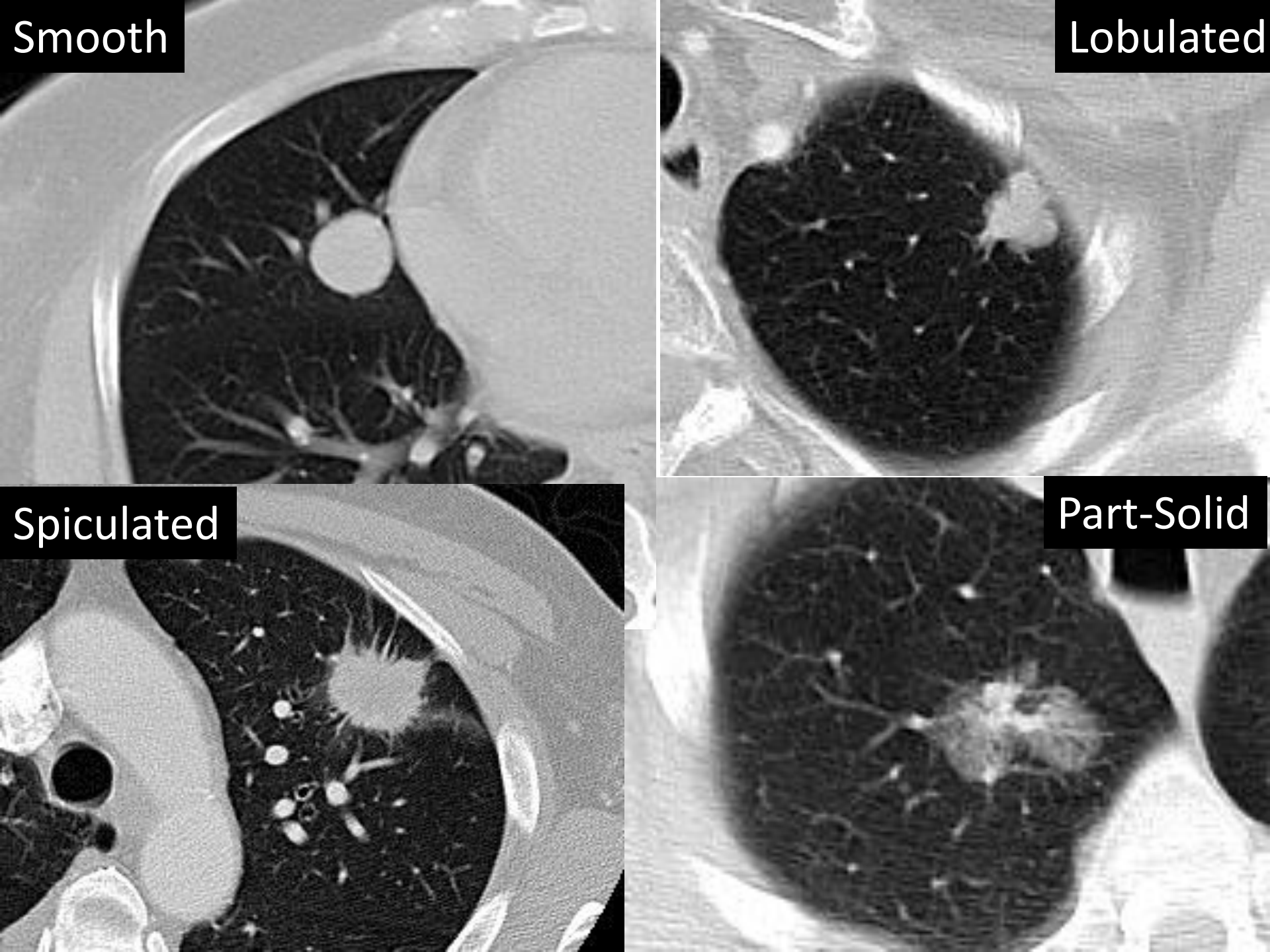
C = current; Caret = Carotene and Retinol Efficacy Trial; cpd = cigarettes per day; EPIC = European Prospective Investigation into Cancer and Nutrition; F = former; LLP = Liverpool Lung Project; MDA = MD Anderson; N = never; PLCO = Prostate, Lung, Colorectal, Ovarian Screening Trial.

Mazzone, Powell et al. Chest 2015: 147: 295.

Is this nodule malignant?



Ost NEJM 348_2535


Smooth
Lobulated
Spiculated
Part-Solid

Lung-RADS version 1 Nodule Management Algorithm for Screen Detected Nodules

Category	Category Descriptor	Category	Findings	Management	Probability of Malignancy	Estimated Population Prevalence
Incomplete	-	0	prior chest CT examination(s) being located for comparison part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative	No nodules and definitely benign nodules	1	no lung nodules nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	solid nodule(s): < 6 mm new < 4 mm part solid nodule(s): < 6 mm total diameter on baseline screening non solid nodule(s) (GGN): < 20 mm OR ≥ 20 mm and unchanged or slowly growing category 3 or 4 nodules unchanged for ≥ 3 months			
Probably Benign	Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	solid nodule(s): ≥ 6 to < 8 mm at baseline OR new 4 mm to < 6 mm part solid nodule(s) ≥ 6 mm total diameter with solid component < 6 mm OR new < 6 mm total diameter non solid nodule(s) (GGN) ≥ 20 mm on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	solid nodule(s): ≥ 8 to < 15 mm at baseline OR growing < 8 mm OR new 6 to < 8 mm part solid nodule(s: ≥ 6 mm with solid component ≥ 6 mm to < 8 mm OR with a new or growing < 4 mm solid component endobronchial nodule	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component	5-15%	2%
		4B	solid nodule(s) ≥ 15 mm OR new or growing, and ≥ 8 mm part solid nodule(s) with: a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component	chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm solid component.	> 15%	2%
		4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			

Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017[1]

Heber MacMahon, MB, BCh
David P. Naidich, MD
Jin Mo Goo, MD, PhD
Kyung Soo Lee, MD, PhD
Ann N. C. Leung, MD
John R. Mayo, MD
Atul C. Mehta, MB, BS
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Geoffrey D. Rubin, MD
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William D. Travis, MD
Paul E. Van Schil, MD, PhD
Alexander A. Bankier, MD, PhD

The Fleischner Society Guidelines for management of solid nodules were published in 2005, and separate guidelines for subsolid nodules were issued in 2013. Since then, new information has become available; therefore, the guidelines have been revised to reflect current thinking on nodule management. The revised guidelines incorporate several substantive changes that reflect current thinking on the management of small nodules. The minimum threshold size for routine follow-up has been increased, and recommended follow-up intervals are now given as a range rather than as a precise time period to give radiologists, clinicians, and patients greater discretion to accommodate individual risk factors and preferences. The guidelines for solid and subsolid nodules have been combined in one simplified table, and specific recommendations have been included for multiple nodules. These guidelines represent the consensus of the Fleischner Society, and as such, they

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

A: Solid Nodules*

Nodule Type	Size: <6 mm (<100 mm³)	Size: 6–8 mm (100–250 mm³)	Size: >8 mm (>250 mm³)	Comments
Single				
Low risk†	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	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 at 3 months, PET/CT, or tissue sampling	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).

B: Subsolid Nodules*

Nodule Type	Size: <6 mm (<100 mm³)	Size: ≥6 mm (>100 mm³)	Comments
Single			
Ground glass	No routine follow-up	CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules < 6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).
Part solid	No routine follow-up	CT at 3–6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years.	In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A-4C)
Multiple	CT at 3–6 months. If stable, consider CT at 2 and 4 years.	CT at 3–6 months. Subsequent management based on the most suspicious nodule(s).	Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A).

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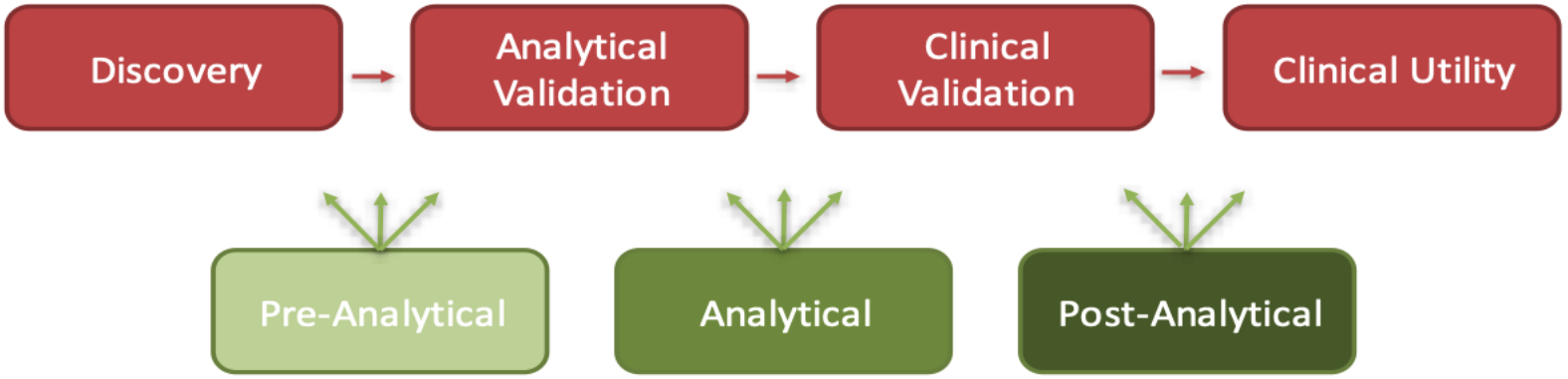
Molecular Biomarkers in Lung Cancer

- Risk Prediction
- Cancer Detection
- Diagnosis
- Treatment



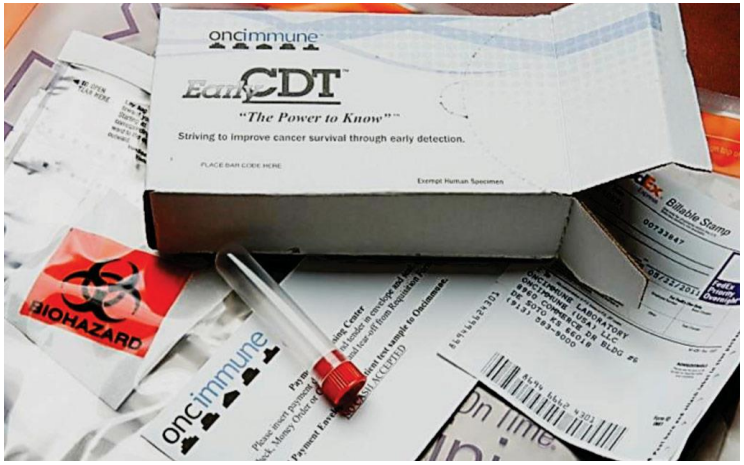
Biomarker categories, definitions, and clinical applications.

Biomarker Category	Biomarker Definition	Study Definitions	Clinical Applications	Example
Risk prediction	Biomarker assesses the *probability of cancer* developing and being diagnosed over time.	Target condition: Diagnosis of lung cancer after a defined period of time. Target population: Individuals **without** symptoms, signs, or current imaging evidence of lung cancer.	Risk mitigation Screening	BRCA2 mutation
Cancer detection	Cancer is *present but has not been detected*. The patient may or may not have symptoms; biomarker identifies the presence of cancer.	Target condition: Undetected lung cancer. Target population: Individuals **with or without** symptoms or signs of the presence of lung cancer.	Screening Symptom evaluation	Cologuard
Diagnosis	A nodule, mass, or other imaging finding is known to be present but has not been diagnosed; biomarker assesses the probability that the finding is malignant.	Target condition: Indeterminate lung nodule, mass. Target population: Individuals with abnormal chest imaging.	Evaluation of a lung nodule, mass, or other imaging finding	Percepta Early CDT-Lung Nodify XL2
Treatment	A cancer is diagnosed; biomarker assesses prognosis or response to therapy	Target condition: Lung Cancer Target population: Individuals with lung cancer diagnosis prior to treatment	Targeted therapy	EGFR, ALK, ROS1, BRAF, NTRK, MET RET NGS IHC: PD-L1

Adopted from: Mazzone, Sears. Powell, et al. Standards for Evaluating Molecular Biomarkers of Lung Cancer Risk, Early Detection, and Lung Nodule Management: When is the Biomarker Ready for Clinical Use?

Early CDT Lung
Serum Autoantibody Panel

- **CAGE**
- **P53**
- **SOX-2**
- **NY-ESO-1**
- **GBU4-5**
- **HuD**
- **MAGE A4**



- Sensitivity 41%, Specificity 87%
- Cost effectiveness: 8 – 30 mm nodules- $24,000 QALY
- Not yet evaluated in lung cancer screening cohorts

Ostrin EJ et al, 2020,10.1158/1055-9965

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer

Table 3. Performance of Bronchoscopy and the Classifier, Stratified According to the Pretest Probability of Cancer.*

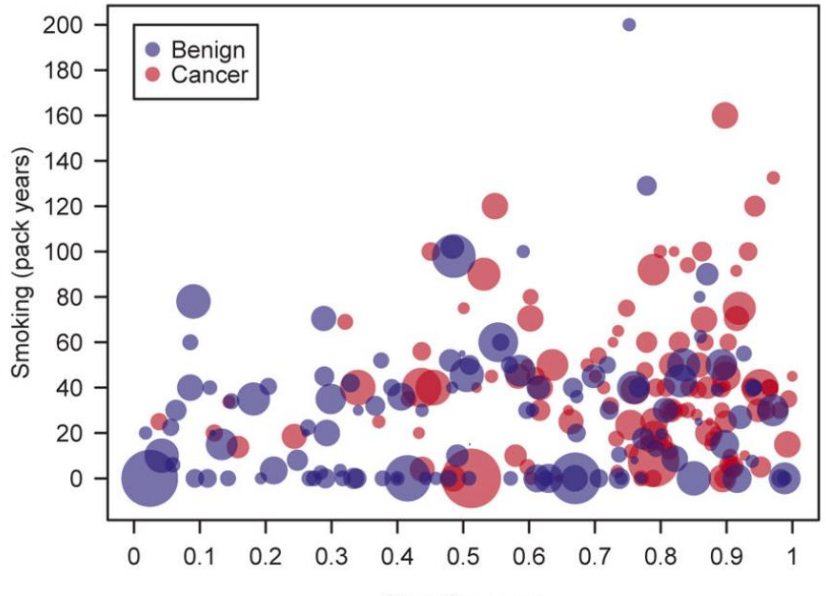
Variable	Low Pretest Probability of Cancer (N=62)	Intermediate Pretest Probability of Cancer (N=101)	High Pretest Probability of Cancer (N=426)	Unknown Pretest Probability of Cancer (N=50)
Patients with lung cancer — no. (%)	3 (5)	41 (41)	405 (95)	38 (76)
Patients with benign lesions — no. (%)	59 (95)	60 (59)	21 (5)	12 (24)
Bronchoscopy performance				
Sensitivity — % (95% CI)	33 (1–91)	41 (26–58)	79 (74–82)	82 (66–92)
Patients with nondiagnostic bronchoscopic examination — no. (%)†	61 (98)	84 (83)	108 (25)	19 (38)
Classifier performance				
Sensitivity — % (95% CI)‡	100 (16–100)	88 (68–97)	89 (80–94)	100 (59–100)
Specificity — % (95% CI)§	56 (42–69)	48 (35–62)	29 (11–52)	33 (10–65)
Negative predictive value — % (95% CI)¶	100 (89–100)	91 (75–98)	38 (15–65)	100 (40–100)
Positive predictive value — % (95% CI)¶	7 (1–24)	40 (27–55)	84 (75–91)	47 (21–73)
Combined classifier and bronchoscopy sensitivity — % (95% CI)	100 (29–100)	93 (80–98)	98 (96–99)	97 (91–100)

Percepta

- 23 gene-expression classifier improved the diagnostic performance of bronchoscopy for the detection of lung cancer.
- In intermediate-risk patients with a nondiagnostic bronchoscopic examination, a negative classifier score provides support for a more conservative diagnostic approach.

NEJM 2015; 373:243.

Nodify Xpresys Lung 2 : Blood Proteomic Assay



www.ScienceTranslationalMedicine.org 16 October 2013 Vol 5 Issue 207 207ra142

2 plasma proteins LG3BP and C163A and 5 Clinical Risk Factors

PANOPTIC

685 patients with 6 – 30 mm nodules

Post Hoc Analysis of 178 patients with pre-test probability cancer < 50%

Sensitivity 97%, Specificity 44%, NPV 98%

CHEST 2018; 154(3):491-500

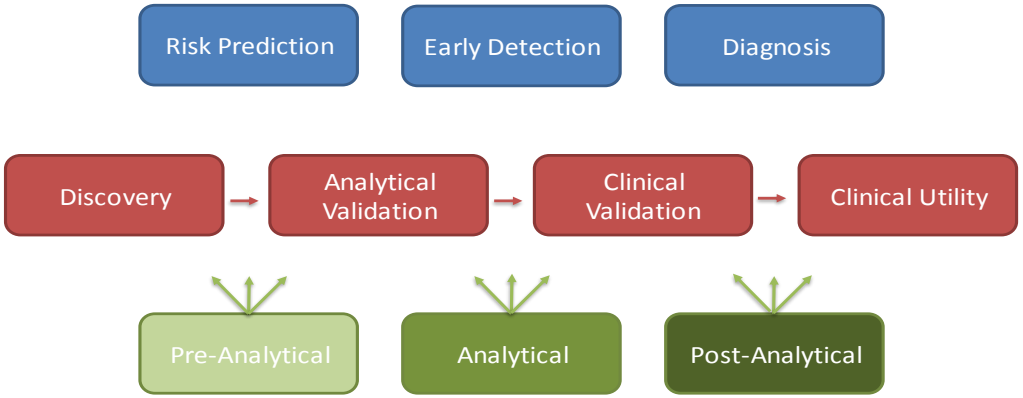
Evidence for a molecular biomarker to be considered clinically useful in the context of Lung nodule management

To be considered clinically useful, a clinically validated molecular biomarker used to assist with lung nodule management must lead to:

- Earlier diagnosis of malignant nodules without substantially increasing the number of procedures for benign disease, or
- Fewer procedures for benign disease without substantially delaying the diagnosis of malignant nodules.

Mazzone, Sears., et al. Standards for Evaluating Molecular Biomarkers of Lung Cancer Risk, Early Detection, and Lung Nodule Management: When is the Biomarker Ready for Clinical Use?

Molecular Biomarkers in Lung Cancer



1. Trial Design elements of Target Condition and Target Population are determined by Biomarker Category
2. Several Biomarkers have shown promising performance in clinical validation studies
3. Evidence for Clinical Utility Awaits outcomes of ongoing studies

Biomarkers in Advanced Lung Cancer: Targeted Therapy & Immunotherapy

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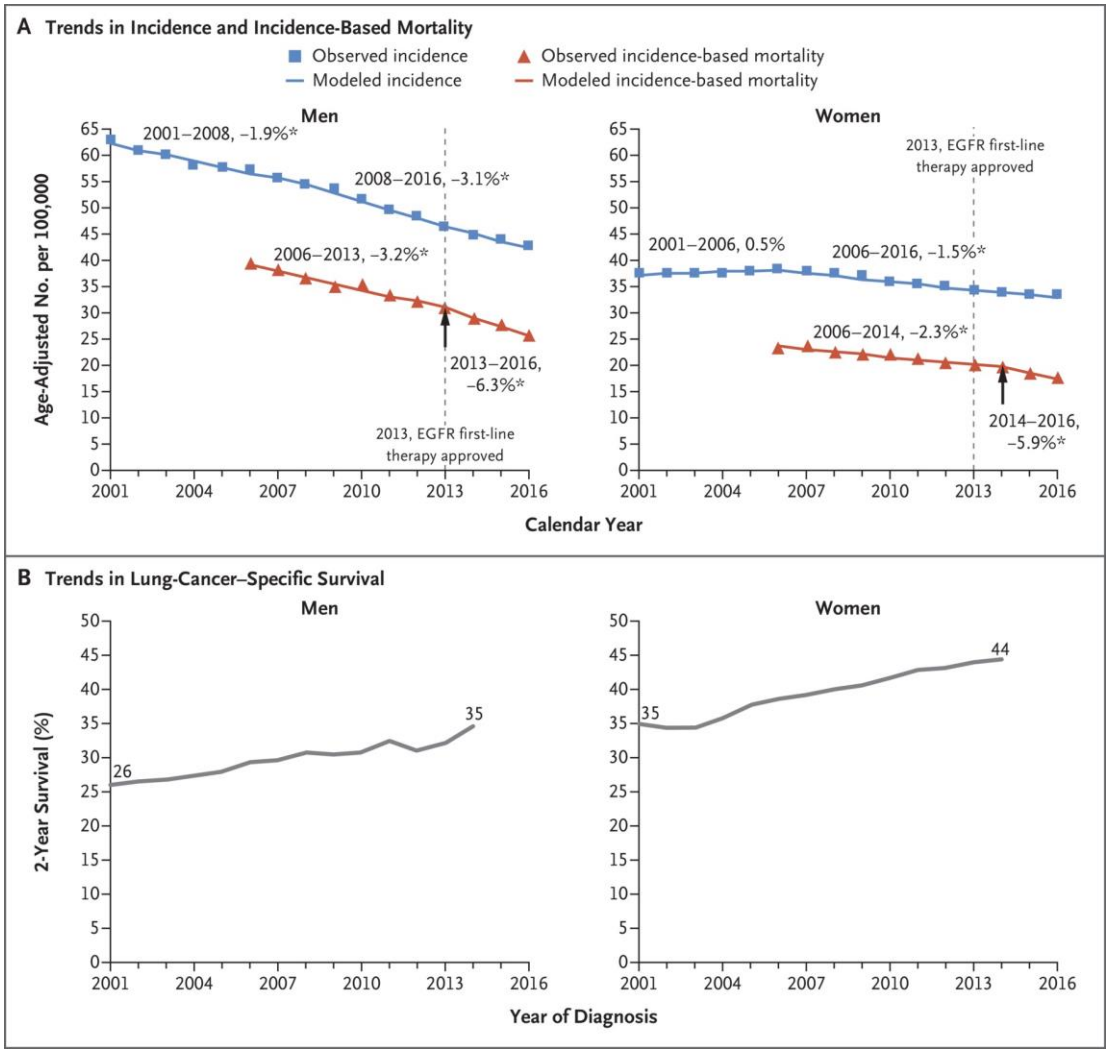
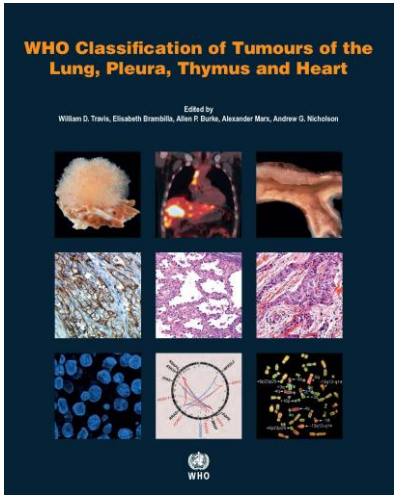
Non–Small-Cell Lung-Cancer (NSCLC) Incidence, Incidence-Based Mortality, and Survival Trends among Men and Women.



Howlader N et al. N Engl J Med 2020;383:640-649

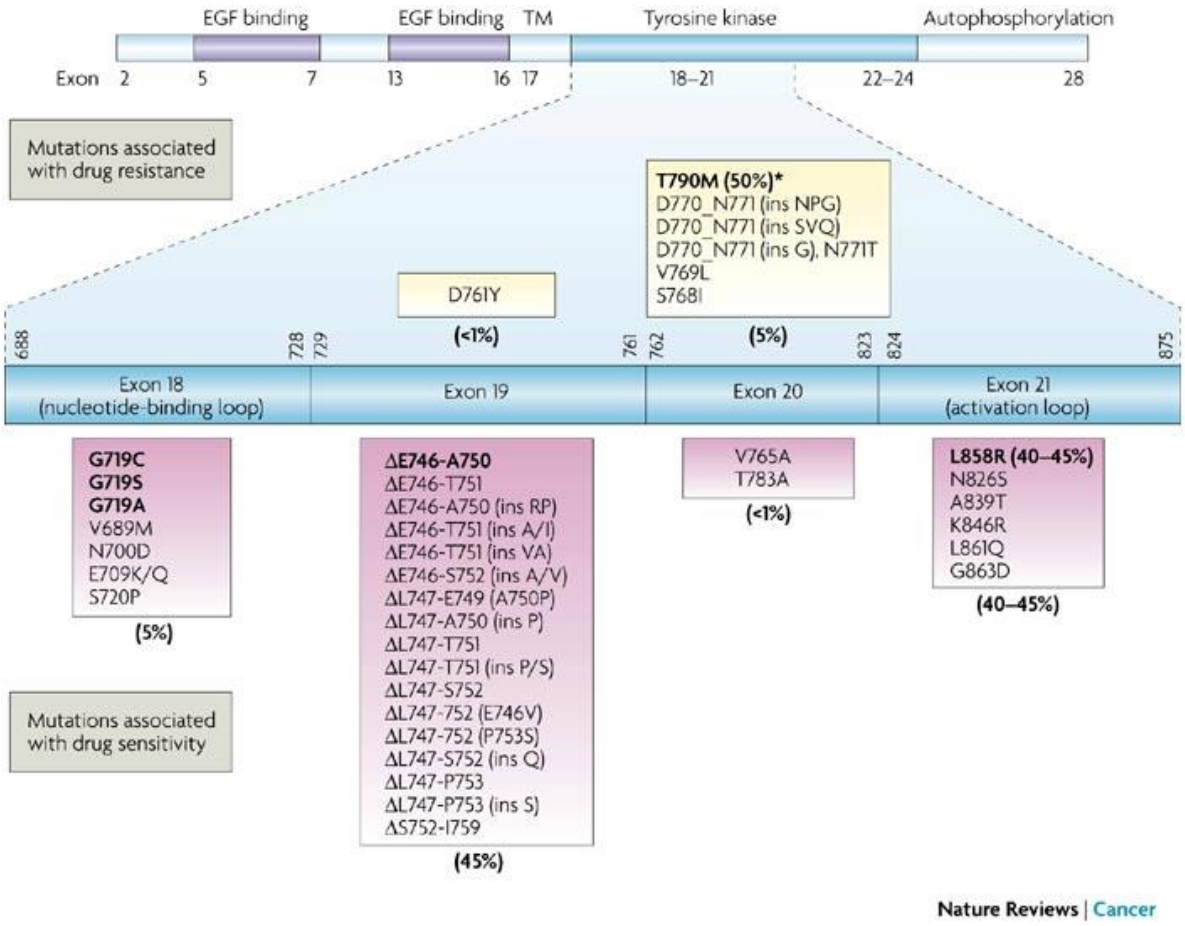
Major Genetic Changes in Lung Cancer



Alterations	Small cell carcinoma (%)	Adenocarcinoma (%)	Squamous cell carcinoma (%)
Mutation			
BRAF	0%	< 5%	0%
EGFR Caucasian	< 1%	10–20%	< 1%
Asian	< 5%	35–45%	< 5%
ERBB2/HER2	0%	< 5%	0%
KRAS Caucasian	< 1%	15–35%	< 5%
Asian	< 1%	5–10%	< 5%
PIK3CA	< 5%	< 5%	5–15%
RB	> 90%	5–15%	5–15%
TP53	> 90%	30–40%	50–80%
Amplification			
EGFR	< 1%	5–10%	10%
ERBB2/HER2	< 1%	< 5%	< 1%
MET	< 1%	< 5%	< 5%
MYC	20–30%	5–10%	5–10%
FGFR1	< 1%	< 5%	15–25%
Gene rearrangement			
ALK	0%	5%	< 1%
RET	0%	1–2%	0%
ROS1	0%	1–2%	0%
NTRK1	0%	< 1%	0%
NRG1	0%	< 1%	0%

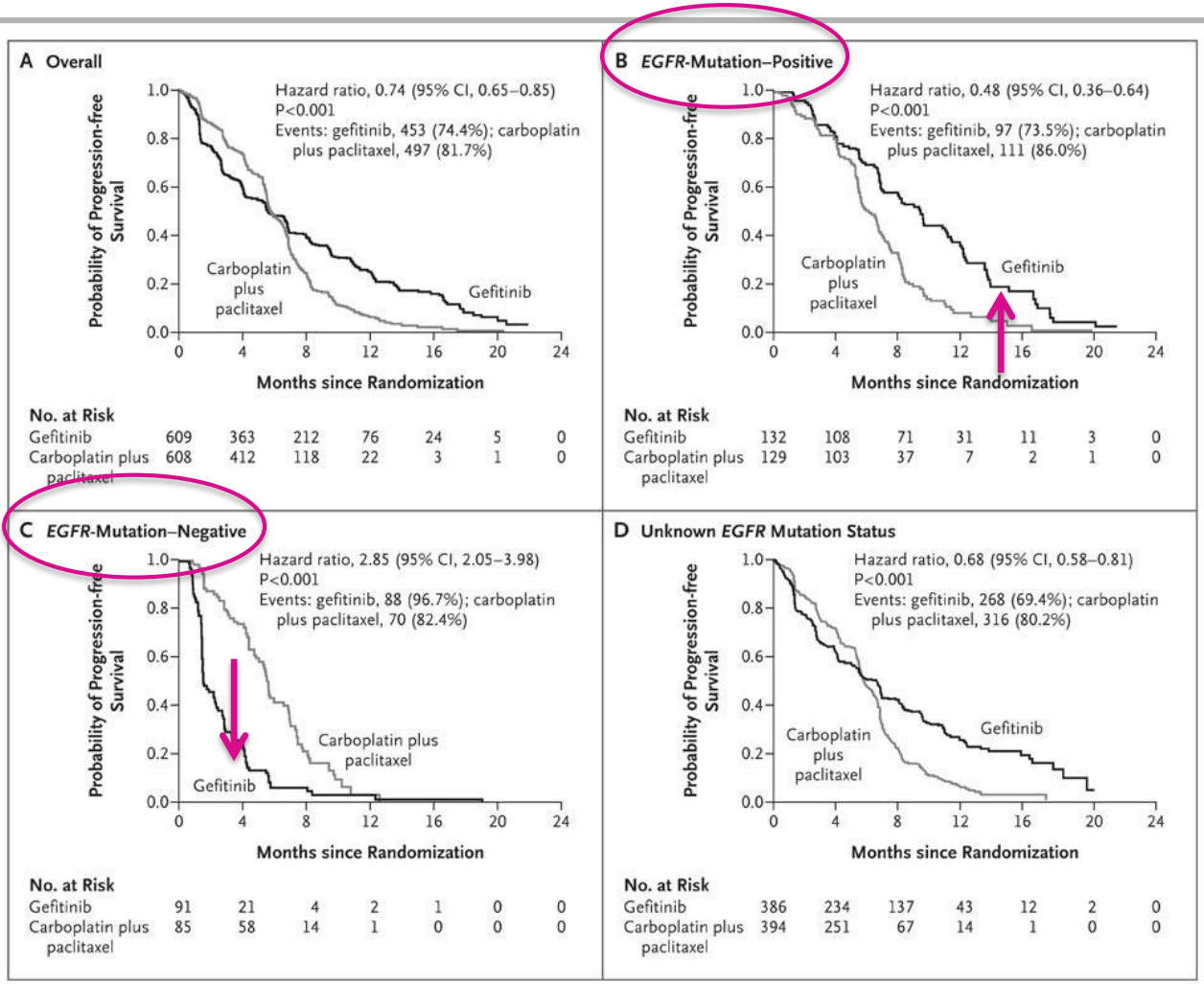
Lung Cancer Precision Medicine: EGFR Mutation Targeted Therapy

Response rate to TKI is 70% for EGFR mutant NSCLC



Sharma *et al. Nature Reviews Cancer* **7**, 169–181; 2007

EGFR Mutation Status Predicts Response to Tyrosine Kinase Inhibitor Therapy- Progression Free Survival The iPass Trial



Mok T et al. N Engl J Med 2009

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Neal I. Lindeman, MD,[a,*] Philip T. Cagle, MD,[d] Dara L. Aisner, MD, PhD,[e] Maria E. Arcila, MD,[f] Mary Beth Beasley, MD,[h] Eric H. Bernicker, MD,[c] Carol Colasacco, MLIS, SCT(ASCP),[i] Sanja Dacic, MD, PhD,[j] Fred R. Hirsch, MD, PhD,[k] Keith Kerr, MB, ChB,[l] David J. Kwiatkowski, MD, PhD,[b] Marc Ladanyi, MD,[g] Jan A. Nowak, MD, PhD,[m] Lynette Sholl, MD,[a] Robyn Temple-Smolkin, PhD,[n] Benjamin Solomon, MBBS, PhD,[o] Lesley H. Souter, PhD,[p] Erik Thunnissen, MD, PhD,[q] Ming S. Tsao, MD,[r] Christina B. Ventura, MPH, MT(ASCP),[i] Murry W. Wynes, PhD,[s] Yasushi Yatabe, MD, PhD[t]

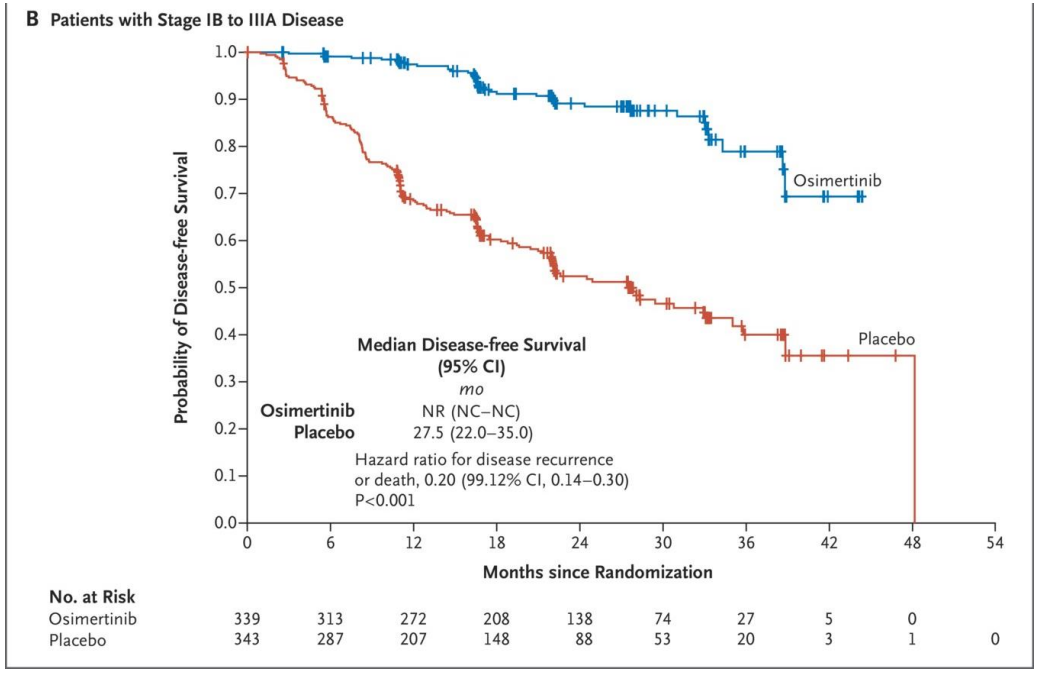
Journal of Thoracic Oncology Vol. 13 No. 3: 323-358

Targeted Therapy or Immunotherapy for Advanced Lung Cancer

Molecular Alteration	Agent-First Line Therapy
EGFR Mutation	Afatinib, Erlotinib, Dacomitinib, Osimertinib
ALK Rearrangement	Alectinib, Brigatinib, Ceritinib, Crizotinib
ROS1 Rearrangement	Ceritinib, Crizotinib, Entrectinib
BRAF V600E Mutation	Dabrafenib + Trametinib
NTRK Gene Fusion	Larotrectinib, Entrectinib
MET Exon 14 Mutation	Capmatinib, Crizotinib
RET Rearrangement	Selpercatinib, Pralsetinib, Cabozantinib
IMMUNOTHERAPY	
PD-L1 > 50%	Single Agent Pembrolizumab, Atezolizumab
PD-L1 > 1% (TMB)	Pembrolizumab single agent or Combination regimens with Nivolumab, Atezolizumab, Ipilimumab + platinum based chemotherapy

NCCN Guidelines v 8.2020

ADUARA: Osimertinib in Resected EGFR- Mutated *Early Stage* NSCLC



Wu Y-L et al. N Engl J Med 2020;383:1711-1723

- 682 Patients randomized to Osimertinib vs. Placebo following resection and adjuvant platinum-based chemotherapy
- 76% Stage II-IIA and 26% IB patients received adjuvant therapy
- In the overall population, 89% of the patients in the osimertinib group and 52% of those in the placebo group were alive and disease-free at 24 months

H.R. 0.20; 99.12% CI, 0.14 - 0.30; P<0.001.

Selecting Patients for Targeted Therapy

Advanced Lung Carcinoma

PD-L1 IHC

Molecular Testing-Tumor

Next Generation Sequencing (NGS)

or

Sequential sequencing of targeted mutations, followed by NGS

Key: Patients with targeted mutation in EGFR or ALK or BRAF respond better to targeted therapy compared to immunotherapy

Molecular Testing-Blood:

2 FDA approved tests for use when tumor material is insufficient or inaccessible for molecular testing, Guardant approved for use as initial test for diagnosis.