Lung Cancer Priorities

Christine Argento, MD, FCCP, D-AABIP
Director of Bronchoscopy
Interventional Pulmonology
Associate Professor of Medicine
Johns Hopkins University

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Disclosures

- I consult and serve as education faculty:
  - Olympus
  - Biodesix
  - Cook
  - Boston Scientific
  - Intuitive

Overview

- Lung Cancer History and Statistics
- Risk Factors
- Lung Cancer Screening
- Diagnosis and Biomarker Testing

Once a rare disease…“Mountain Sickness”

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The 20th Century

PRIMARY
MALIGNANT GROWTHS
OF THE
LUNGS AND BRONCHI

A PATHOLOGICAL
AND CLINICAL STUDY

BY
I. ADLER, A.M., M.D.,
Professor Emeritus at the New York Polyclinic, Consulting Physician to the German, Beth-Israel, Mor Moriah, and Peoples Hospitals, and Montefiore Home and Hospital

'Oportet omnia signa contemplari'

LONGMANS, GREEN, AND CO.
FOURTH AVENUE & 30TH STREET, NEW YORK
LONDON, BOMBAY, AND CALCUTTA
1912

CHAPTER I

INTRODUCTORY

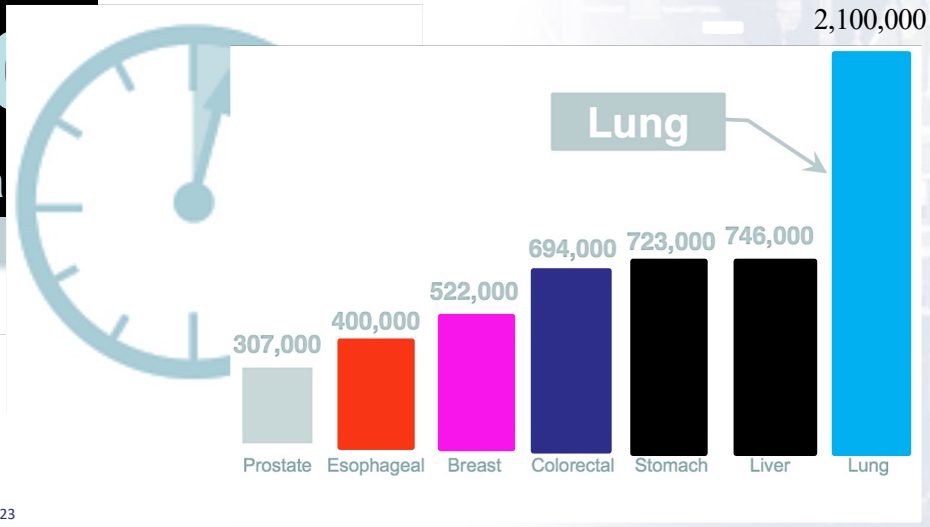
IS it worth while to write a monograph on the subject of primary malignant tumors of the lung? In the course of the last two centuries an ever-increasing literature has accumulated around this subject. But this literature is without

Our Why

Every 2.2 minutes someone is diagnosed with lung cancer

2,100,000

new diagnoses globa



American Cancer Society. *Cancer Facts & Figures 2018* Atlanta: American Cancer Society; 2023

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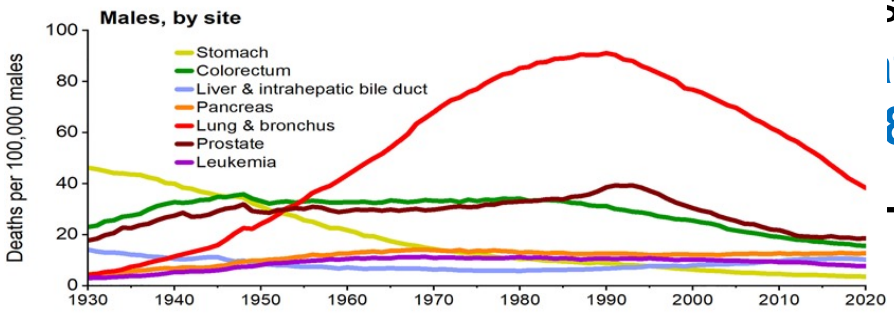
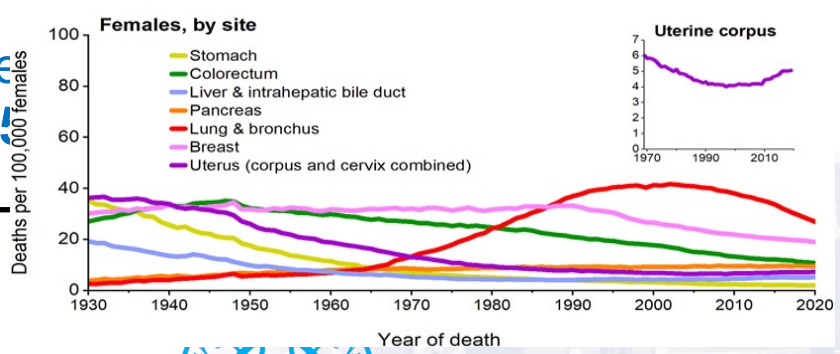
Non-Small Cell Lung Cancer (NSCLC) Background

2023 estimates of lung cancer incidence, mortality:





5-year relative survival rate (NSCLC)

8%

5-year survival rate for distant disease (NSCLC)

From 2011 to 2020, overall lung cancer mortality rates **declined by ~4% per year**

NCI. Cancer Stat Facts: Lung and Bronchus Cancer. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed 10/20/2023. American Cancer Society. Lung Cancer Survival Rates. https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html. Accessed 10/20/2023. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Jun 8; Accessed 10/19/2023].

Siegel, CA A Cancer J Clinicians, 2023:73:17-48

A Few Surprising Facts

~65% of all new lung cancer diagnoses are among people who have never smoked or are former smokers

~10-20% of new lung cancer cases are among never-smokers.

~ 25% women diagnosed are never smokers

1 in 16 women (both who did and did not smoke) will be diagnosed with lung cancer in their lifetimes

2X more black than white men will be diagnosed with lung cancer if all risk factors are equal

Siegel RL et al CA Cancer J Clin 2023; Siegal DA et al JAMA Oncol 2021

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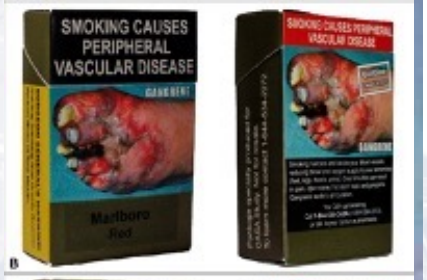

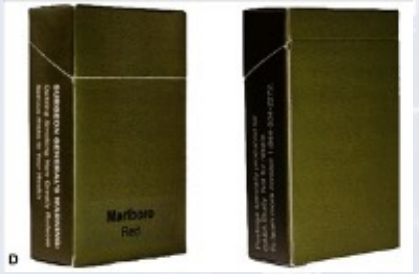

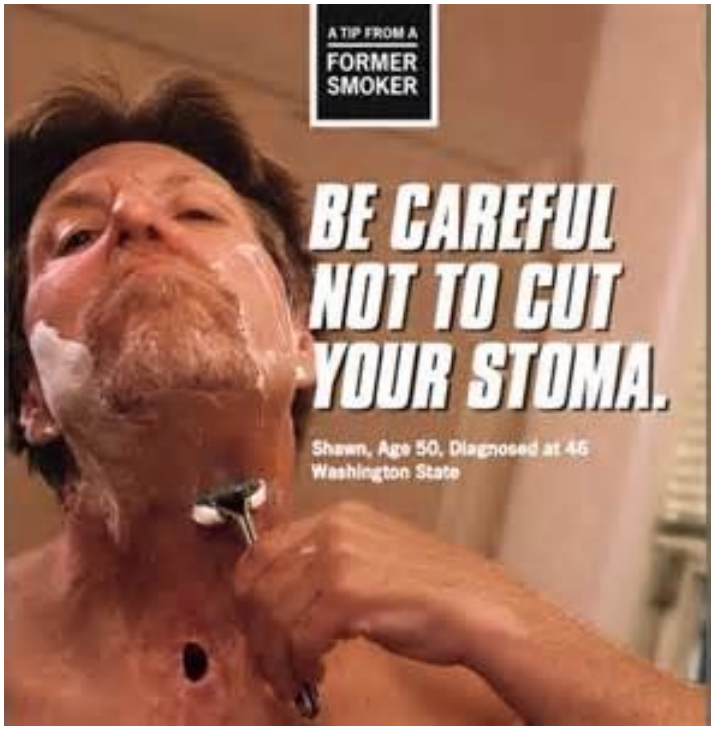

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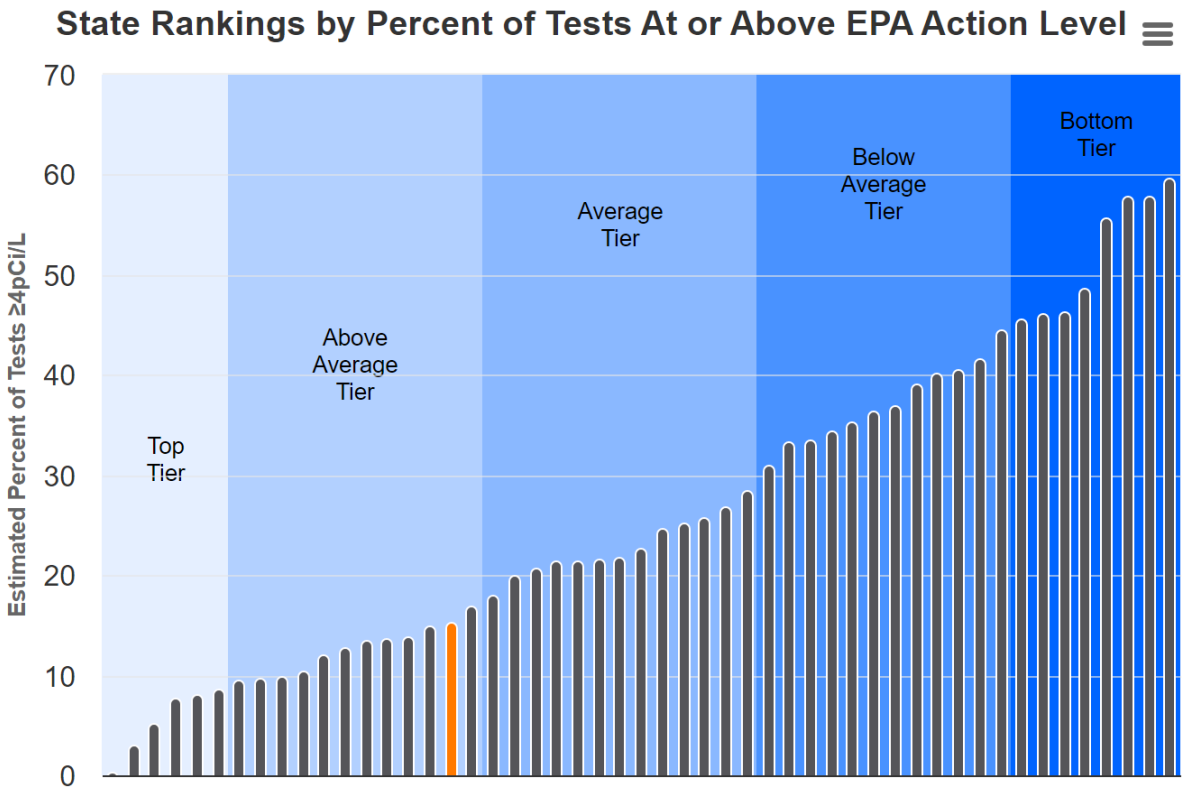
Radon

- Decay product of uranium-238 and radium-226
  - Widely distributed in rock, soil, groundwater
  - Associated with an increased risk of lung cancer
  - Interactive effect with cigarette smoking
- 2nd most important cause of lung cancer in the USA
  - Implicated in 26% of lung cancer in never-smokers
  - Implicated in 13.4% of lung cancers overall (co-carcinogenic with cigarette exposure)

Beir-VI report, Washington DC National Academy Press 1999
EPA Assessment of Risks from Radon in Homes. Office of Radiation and Indoor Air United States Environmental Protection Agency. . Washington, DC 204602003

Prevention



Radon:

- In Delaware, **15.4%** of radon tests results were at or above the action level recommended by EPA.
- It ranks **17th** among all states, placing it in the **above average tier**.

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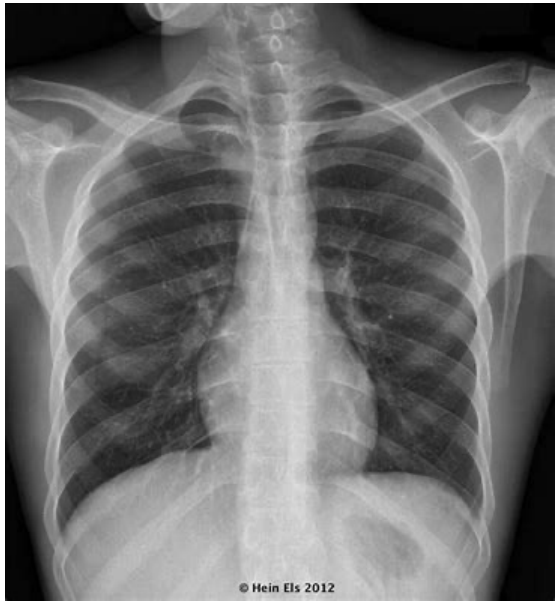
Lung Screening

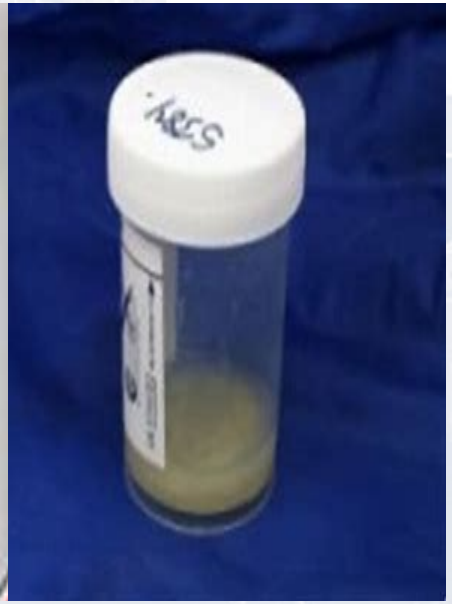
- Cancer screening is a test to check for disease in someone who does not have any symptoms

- Goal of screening is to find cancer early when it is more treatable and even curable

Lung Screening

- Not a new concept





Journal of Occ Med and Tox 2014.9:14

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Lung Screening

- National Lung Screening Trial (NLST)
  - 53,454 persons at high risk for lung cancer
  - 33 U.S. medical centers
  - August 2002 – April 2004
- **> 25%** of the low dose CT group had a positive finding
  - **96.4%** false positive
  - **20%** relative risk reduction in mortality from lung cancer
  - **6.9%** all-cause mortality reduction
  - Number needed to screen **320**

N Engl J Med 2011; 365:395-409

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NELSON Trial

Table 3. Lung-Cancer Stage and Histologic Type of All First-Detected Lung Cancers in Male Participants at 10 Years of Follow-up or on December 31, 2015.*

Variable	Screening Group			Control Group
	Screening-Detected Lung Cancer (N=203)†	Non–Screening-Detected Lung Cancer (N=141)	Any Lung Cancer (N=344)	Any Lung Cancer (N=304)
	number of participants (percent)			
Stage				
IA	95 (46.8)	10 (7.1)	105 (30.5)	21 (6.9)
IB	24 (11.8)	10 (7.1)	34 (9.9)	20 (6.6)
IIA	8 (3.9)	4 (2.8)	12 (3.5)	13 (4.3)
IIB	11 (5.4)	6 (4.3)	17 (4.9)	17 (5.6)
IIIA	20 (9.9)	14 (9.9)	34 (9.9)	43 (14.1)
IIIB	13 (6.4)	14 (9.9)	27 (7.8)	34 (11.2)
IV	19 (9.4)	73 (51.8)	92 (26.7)	139 (45.7)
Unknown	13 (6.4)	10 (7.1)	23 (6.7)	17 (5.6)
Histologic type‡				
Adenocarcinoma	123 (60.6)	56 (39.7)	179 (52.0)	133 (43.8)
Squamous-cell carcinoma	39 (19.2)	38 (27.0)	77 (22.4)	94 (30.9)
Small-cell carcinoma	13 (6.4)	27 (19.1)	40 (11.6)	46 (15.1)
NSCLC	8 (3.9)	8 (5.7)	16 (4.7)	13 (4.3)
Other	20 (9.9)	12 (8.5)	32 (9.3)	18 (5.9)

N Engl J Med 2020;382:503-13.

Number Needed to Screen (NNS) to Prevent 1 Death and Compliance with Screening

	Colon cancer	Cervical cancer	Breast cancer	Lung cancer (2015)
Compliance (%)	68.8%	80.0%	70.0%	5.9%
NNS	1,250	1,140	781	320

- ASCO daily news (Lung Cancer Screening Remains Poor. Here's How to Increase Rates and Save Lives (ascopubs.org)

Lopez-Olivo MA, Maki KG, Choi NJ, et al. Patient Adherence to Screening for Lung Cancer in the US: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(11):e2025102. Published 2020 Nov 2.

-**Gates TJ**. Screening for cancer: evaluating the evidence. *Am Fam Physician*. 2001;63(3):513-522.

-**Richardson A**. Screening and the number needed to treat. *J Med Screen*. 2001;8(3):125-127.

-**De Koning H, Van Der Aalst C, Ten Haaf K, et al**. Effects of volume CT lung cancer screening: Mortality results of the NELSON randomized-controlled population based trial. 2018 World Conference on Lung Cancer. Abstract PL02.05.

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Following NLST

- In 2012 and 2013 our guidelines recommended lung cancer screening
  - 55-74 years old
  - 30 pack year smoking history
  - Currently smoking or if they have quit smoking, it has been within 15 years

- 8 million people in the US qualify for Lung Cancer Screening

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Updated Screening Criteria 2021

- Age 50-80 years
- 20 pack year smoking history
- Currently smoking or having quit within the last 15 years

15 million eligible compared to the 8 million previously

Women are under-represented
41% NLST and 16% NELSON
Results suggest LDCT screening for lung cancer in women → larger reduction in lung cancer mortality

BMJ 2017;356:j347
NEJM 2011 Aug; 365(5): 395-409

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American Cancer Society®

How many more people will be eligible for lung cancer screening with the new ACS guideline?

- Presently about **14.3 million** people are eligible for screening under the 2021 USPSTF recommendation (**32%** of those who ever smoked)
- The 2023 ACS guideline increases the number to **19.2 million** (**43%** of those who ever smoked)

Lung cancer diagnosis and mortality beyond 15 years since quit in individuals with a 20+ pack-year history: A systematic review

Karli K. Kondo PhD[1,2] | Basmah Rahman MPH[1] | Chelsea K. Ayers MPH[3] | Rose Relevo MLIS, MSMI[1] | Jessica C. Griffin MS[1] | Michael T. Halpern MD, PhD, MPH[4]

- Rates of lung cancer diagnosis (incidence) and mortality remain elevated in people who formerly smoked at ALL TIME POINTS compared to those who never smoked
- Will need to examine impact of smoking of different duration and different intensities

CA Cancer J Clin 2024 Jan-Feb;74(1):84-114.

Observational Studies are Identifying a Substantial Number of Lung Cancer Cases Who Do Not Meet Screening Eligibility Because of YSQ

Lifetime Smoking History and Risk of Lung Cancer: Results From the Framingham Heart Study

Hilary A. Tindle, Meredith Stevenson Duncan, Robert A. Greevy, Ramachandran S. Vasan, Suman Kundu, Pierre P. Massion, Matthew S. Freiberg

- **"Notably, only about half of lung cancer cases among former and current smoking persons did not meet the current screening eligibility criteria at the time of diagnosis, including 41% who formerly smoked but had more than 15 YSQ.**

Conclusion

Persons who formerly smoked retain significant life-long risk of lung cancer. The logic for including YSQ smoking as a criterion for lung cancer screening eligibility must be reexamined.

Tindle, et al. JNCI 2018; DOI: 10.1093/jnci/djy041

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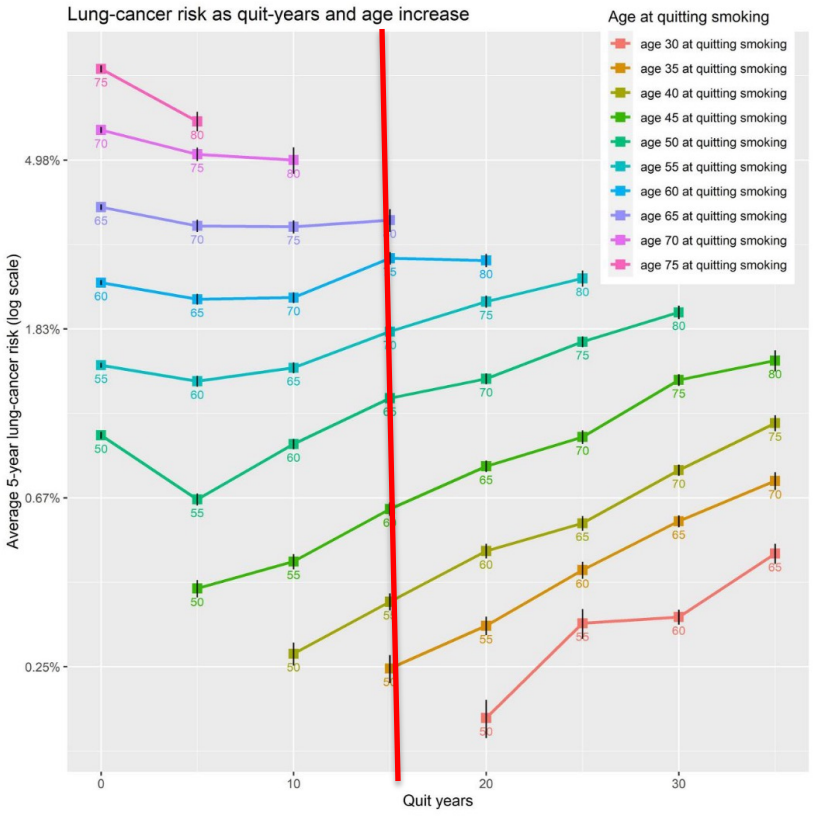

- People who formerly smoked, lung cancer risk remains elevated even after they quit

Cancer 2024 Jan;130(2):201-215

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Who Supports Lung Cancer Screening?

- US Preventive Services Task Force (2021)
- National Comprehensive Cancer Network (2022)
- American Academy of Family Physicians (2021)
- Centers for Medicare/Medicaid (2022)
- American Cancer Society (2023)
- American Society of Clinical Oncology (2019)
- American College of Chest Physicians (2018)
- American Association of Thoracic Surgery
- Canadian Task for on Periodic Heath Examination (2016)

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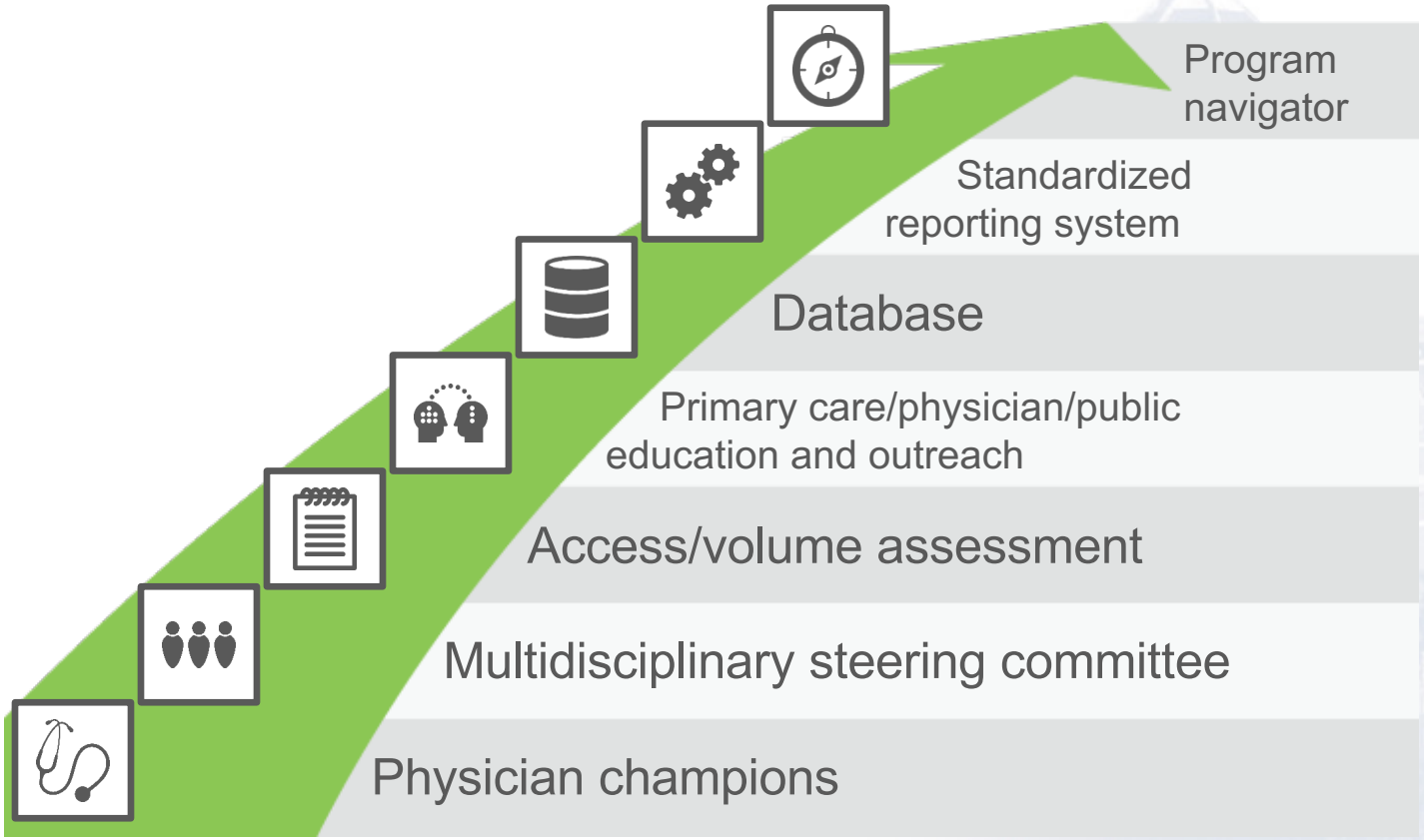
What Does Lung Screening Entail?

Key Lung Screening Program Elements



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Shared Decision Making

Harms of the screening test
Risks of invasive procedures for benign disease
Overtreatment for indolent disease
VS.
Benefits of early detection

Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: What does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681-692. Doi: 10.1016/S0277.9536(96)00221-3.
Alston C, Berger ZD, Brownlee S, et al. Shared decision-making strategies for best care: Patient Decision Aids. Discussion paper, Institute of Medicine. 2014. http://nam.edu/perspectives-2014-shared-decision-making-strategies-for-best-care-patient-decision-aids/
Stacey D, Legare F, Col NF, et al. Decision aids for people facing health treatments or screening decisions. Cochrane Data Base Syst Rev. 2014;1. Doi: 10.10.1002/14651858.CD001431.pub4.

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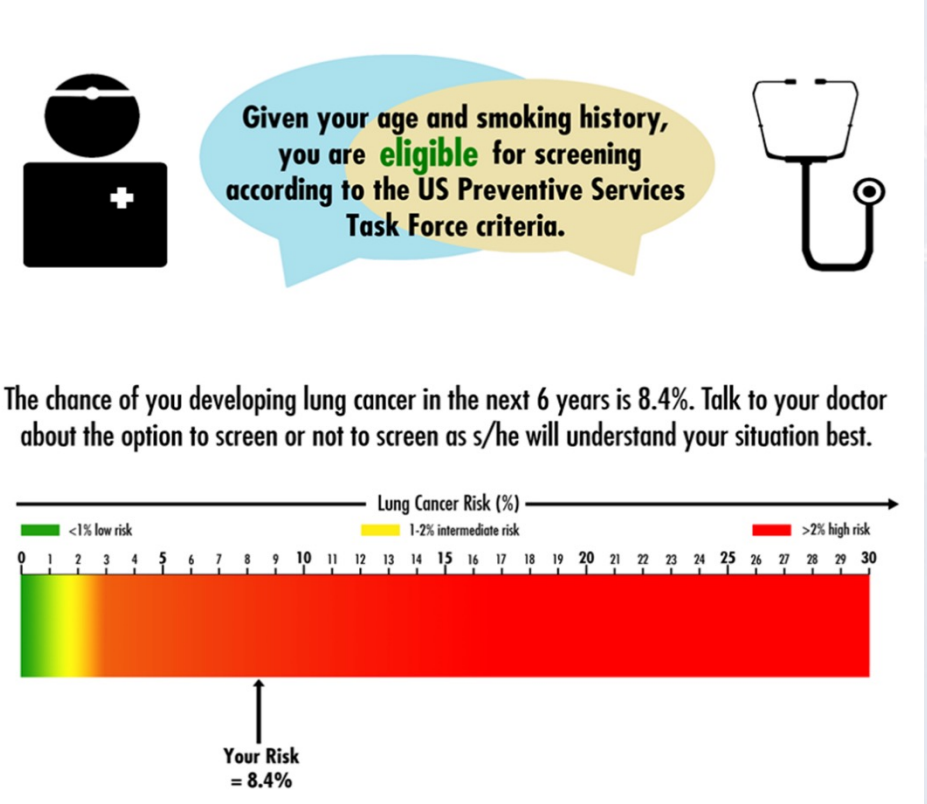
Example lung cancer risk calculator



http://www.shouldiscreen.com/lung-cancer-risk-calculator-1/

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How Well Do We Do with Cancer Screening?

- 2021 National Health Interview Survey screening for eligible patients:
  - Breast: 75.7%
  - Cervical : 75.2%
  - Colorectal: 72.2%

- American Lung Association 2022 report:
  - **Lung cancer: 5.8% of eligible patients are screened**

Sabatino, et al. Prev Chronic Dis 2023

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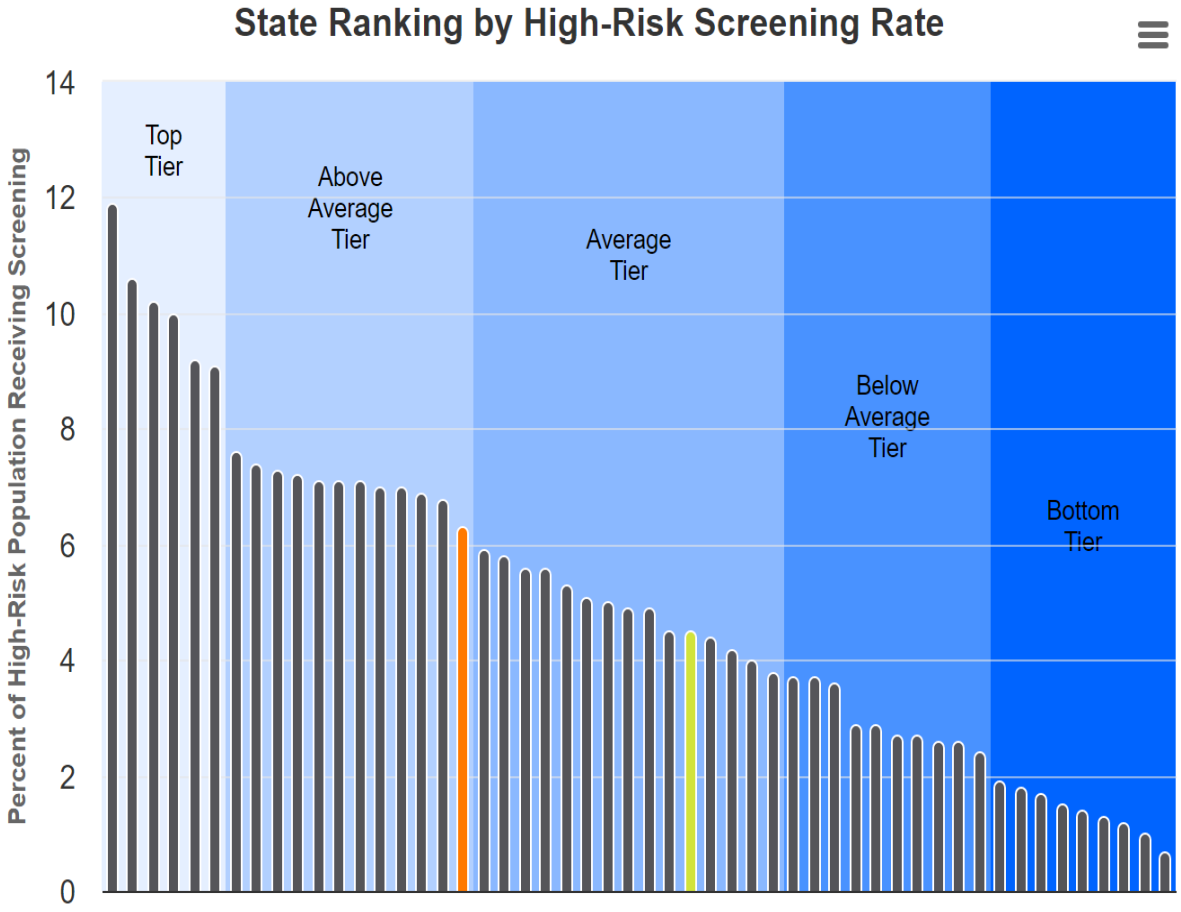
Screening



Screening for High Risk:

- In Delaware, **6.3%** of those at high risk were screened, which was **significantly higher** than the national rate of 4.5%.
- It ranks **18th** among all states, placing it in the **above average tier**.
- Actual screening rates may be higher in states with large, regional managed care providers that did not share screening data.

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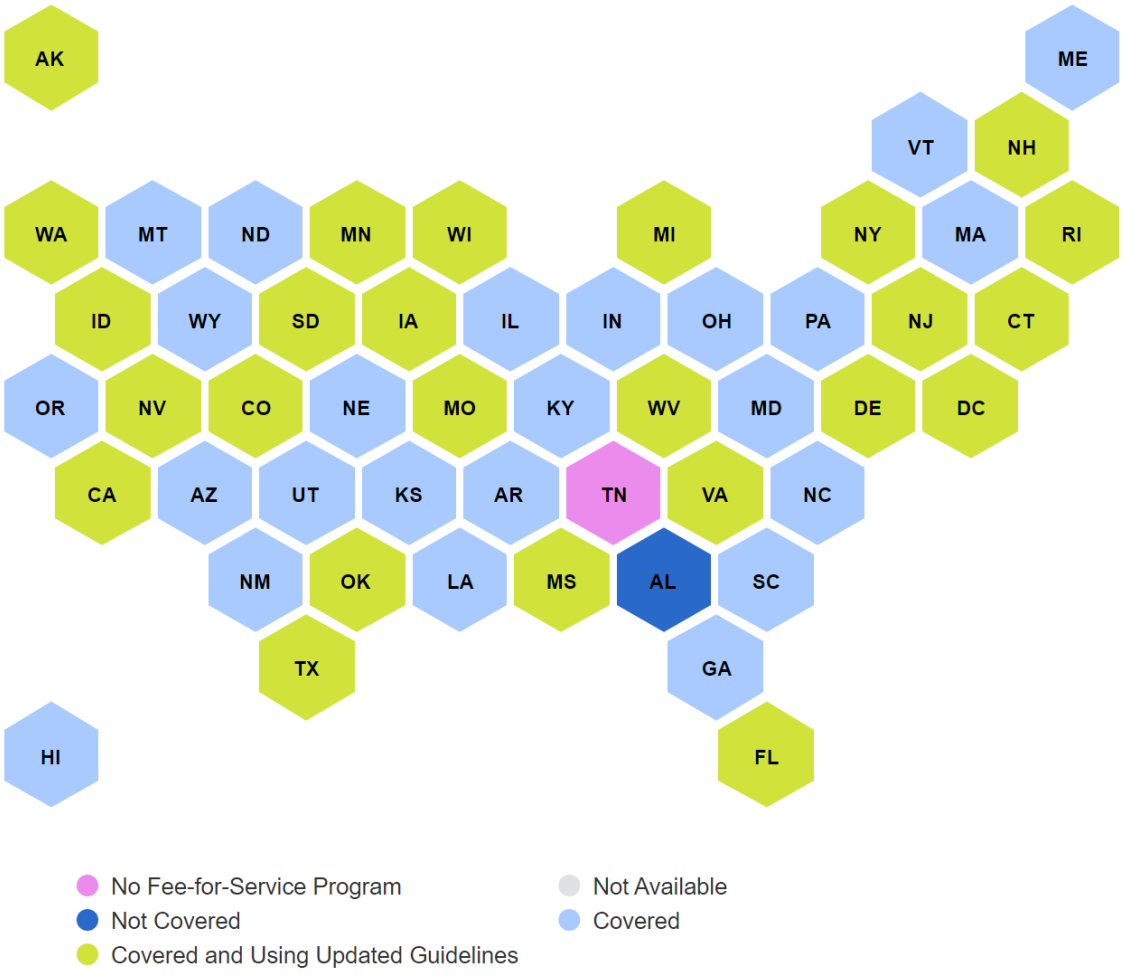
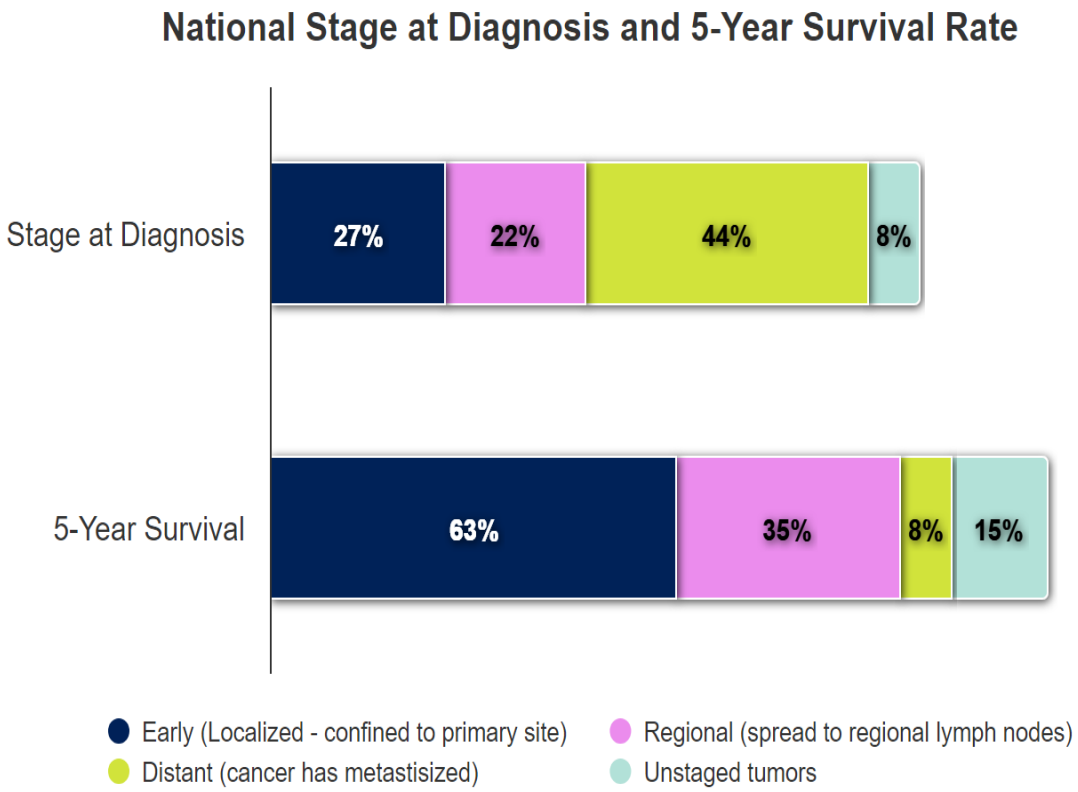
Coverage of Lung Cancer Screening in State Medicaid Fee-for-Service Programs



Medicaid Coverage:

- Delaware was one of the 49 states whose Medicaid fee-for-service programs covered lung cancer screening as of October 2023.
- In addition, their program used recommended guidelines for determining eligibility and did not require prior authorization or copays.

Stage and 5 Year Survival Rate



Early Diagnosis:

- **28.4%** of cases are caught at an early stage, which is **significantly higher** than the national rate of 26.6%.
- It ranks **10th** among the 47 states with data on diagnosis at an early stage, placing it in the **above average tier**.
- Over the last five years, the early diagnosis rate in Delaware did not change significantly.

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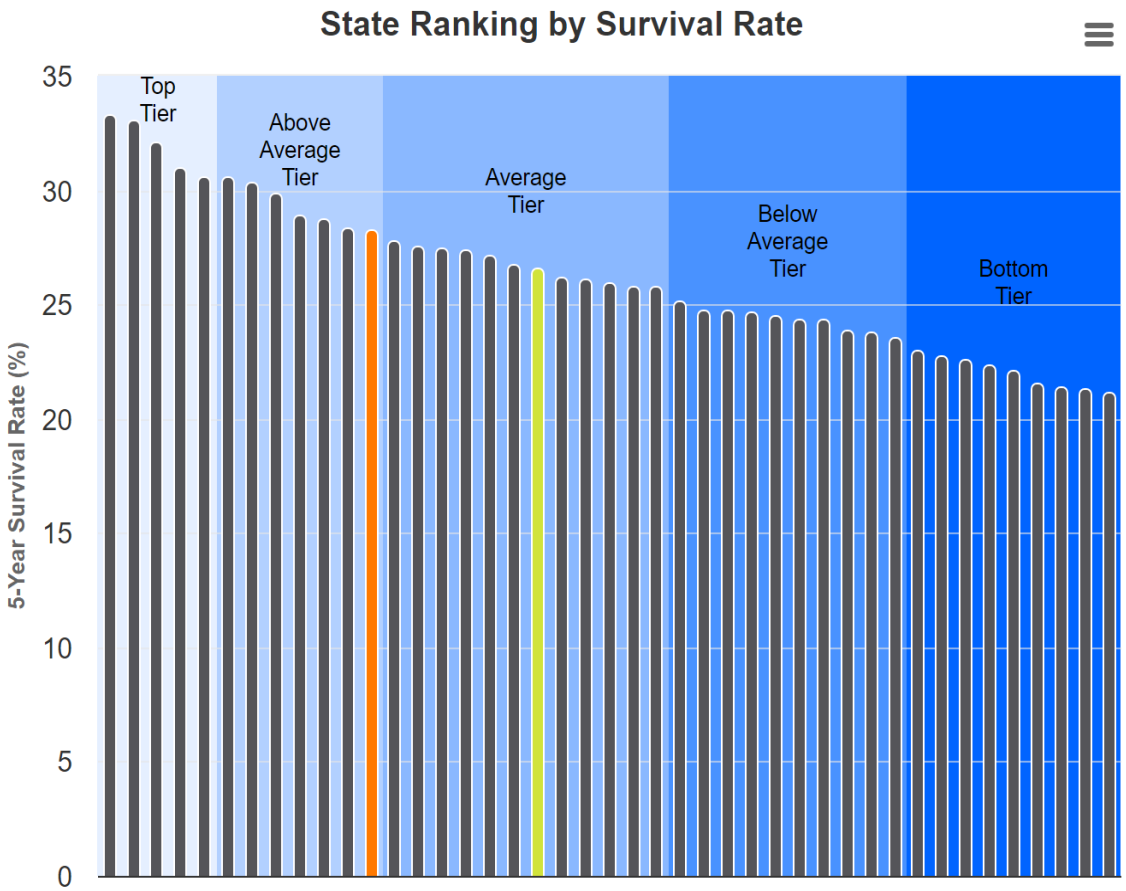
Lung Cancer Survival



5-Year Survival Rate:

- The percent of people alive five years after being diagnosed with lung cancer (the survival rate) in Delaware is **28.3%**, which is not significantly different than the national rate of 26.6%
- It ranks **12th** among the 42 states with survival data, placing it in the **average tier**.
- Over the last five years, the survival rate in Delaware **improved** by **31%**.

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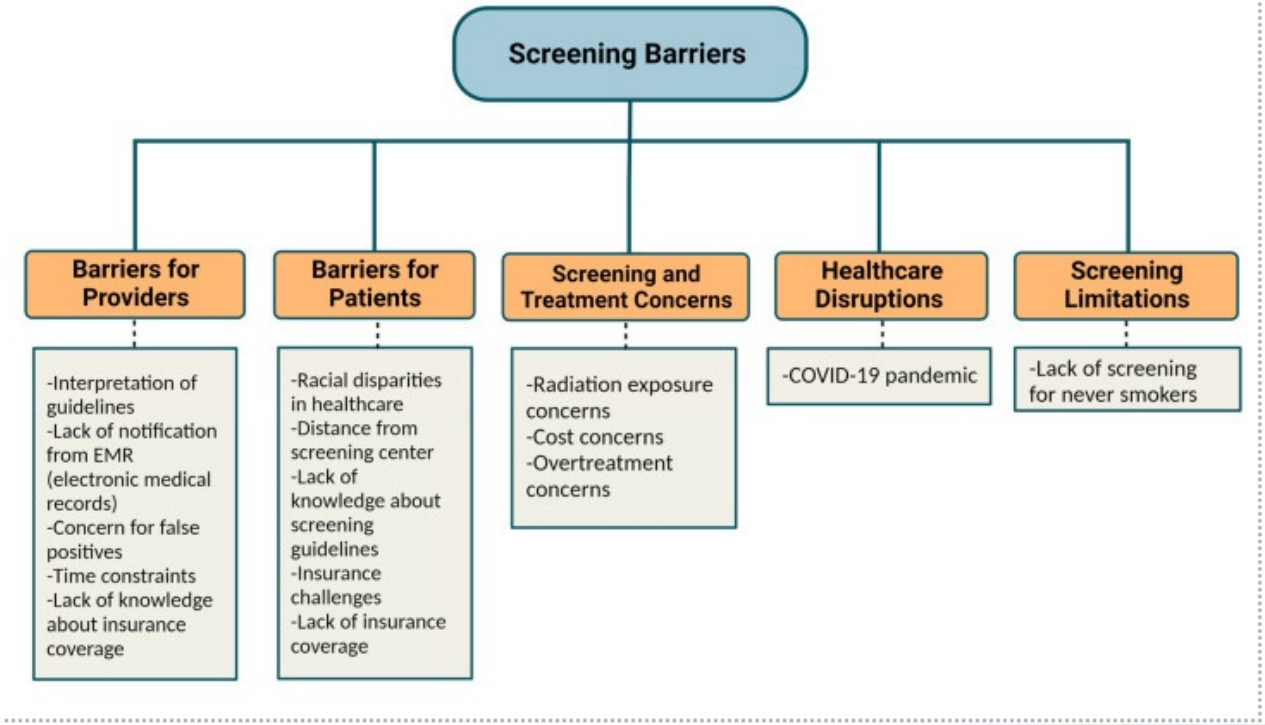
Challenges to Screening in Early-Stage Lung Cancer



Zarinshenas, Amini, et al. Cancers. March 2023

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JAMA Network Open

Research Letter | Surgery

Eligibility for Lung Cancer Screening Among Women Receiving Screening for Breast Cancer

Ashley L. Titan, MD; Ioana Baiu, MD, MPH; Doug Liou, MD; Natalie S. Lui, MD; Mark Berry, MD; Joseph Shrager, MD; Leah Backhus, MD, MPH

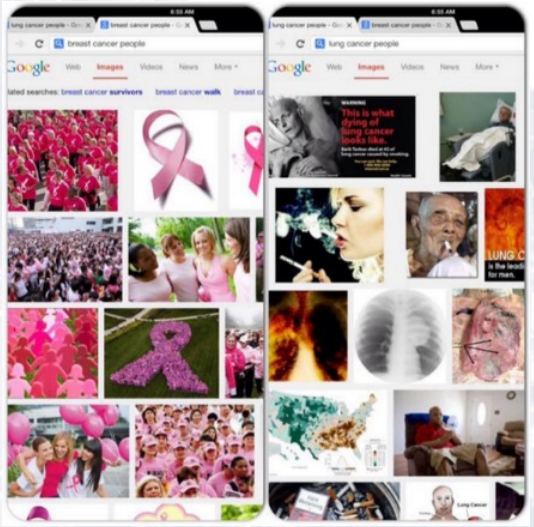
Table 2. Clinicians Ordering Lung Cancer Screening for Eligible Participants

Specialty	Clinicians, No. (%)		*P* value
	Ordered mammogram	Ordered LCS	
Primary care	30 (85.7)	21 (60.0)	<.001
Pulmonology	0	10 (28.6)	
Obstetrics and gynecology	3 (8.6)	0	
Other[a]	2 (5.7)	4 (11.4)	

JAMA Network Open. 2022;5(9):e2233840. doi:10.1001/jamanetworkopen.2022.33840

Lung Cancer Screening is Different Due to Stigma Associated with Smoking

- Many of those eligible don't get screened
  - Healthcare professionals and patients unaware of option for LCS
  - Former smokers especially unaware of their risk
  - Time constraints
  - Low use shared decision making in clinical practice
  - Stigma associated with smoking
  - Reimbursement
  - Who orders the screening test?
  - Misinformation
  - Terminology



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Physician Recommendation Primary Reason for Getting Screened

Baseline: Lung Screening and Lung Cancer Characteristics

	Usual Care (N=46)	Telephone Counseling (N=46)
Lung Screening history (% yes)	47.8%	39.1%
Primary reasons for screening		
Doctor recommendation	82.6%	82.2%
Peace of mind about lung cancer	80.4%	84.4%
Personal History of Cancer (e.g., skin, prostate, breast)	26.7%	26.7%
Family History of Lung Cancer	34.8%	44.4%
Perceived worry about developing LC (% very much/extremely)	45.6%	44.5%
Perceived risk about developing LC (% higher/much higher risk than others)	50%	48.9%

No significant group differences

JOURNAL ARTICLE

A qualitative study exploring patient motivations for screening for lung cancer

Joshua A Roth, Lisa Carter-Harris, Susan Brandzel, Diana S M Buist, Karen J Wernli

PloS One 2018, 13 (7): e0196758

BACKGROUND: Low-dose computed tomography (LDCT) of the chest for lung cancer screening of heavy smokers was given a 'B' rating by the U.S. Preventive Services Task Force (USPSTF) in 2013, and gained widespread insurance coverage in the U.S. in 2015. Lung cancer screening has since had low uptake. However, for those that do choose to screen, little is known about patient motivations for completing screening in real-world practice.

OBJECTIVE: To explore the motivations for screening-eligible patients to screen for lung cancer.

METHODS: Semi-structured qualitative interviews were conducted with 20 LDCT screen-completed men and women who were members of an integrated mixed-model healthcare system in Washington State. From June to September 2015, participants were recruited and individual interviews performed about motivations to screen for lung cancer. Audio-recorded interviews were transcribed and analyzed using inductive content analysis by three investigators.

RESULTS: Four primary themes emerged as motivations for completing LDCT lung cancer screening: 1) trust in the referring clinician; 2) early-detection benefit; 3) low or limited harm perception; and 4) friends or family with advanced cancer.

CONCLUSION: Participants in our study were primarily motivated to screen for lung cancer based on perceived benefit of early-detection, absence of safety concerns, and personal relationships. Our findings provide new insights about patient motivations to screen, and can potentially be used to improve lung cancer screening uptake and shared decision-making processes.

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Screening for Non-Smokers

- Taiwan Lung Cancer Screening for Never-Smoker Trial (TALENT)
  - Positive family history of lung cancer is a significant contributor to lung cancer risk in never-smokers
  - In Taiwan, 53% of lung cancer deaths occur in never-smokers
  - 12,011 never-smoking individuals aged 55 to 75 years with a high-risk feature (family history of lung cancer, history of chronic lung disease, cooking without ventilation, and cooking with high intensity of frying)
  - 73.8% of the study population were women
- Prevalence of lung cancer (6 year follow-up): 2.6%
- Patients with family history of lung cancer: 3.2%

Yang, P. JTO March 2021; 16 (3): S58

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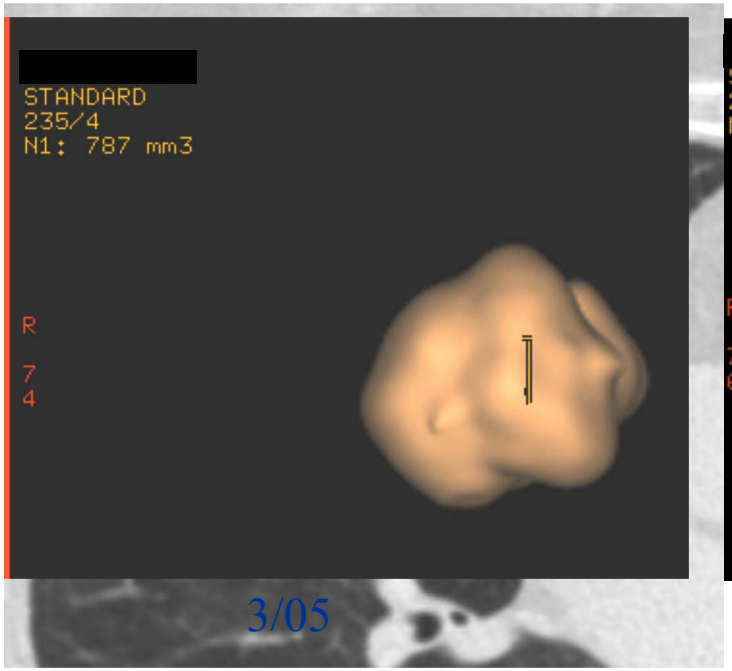
Volume Measurements



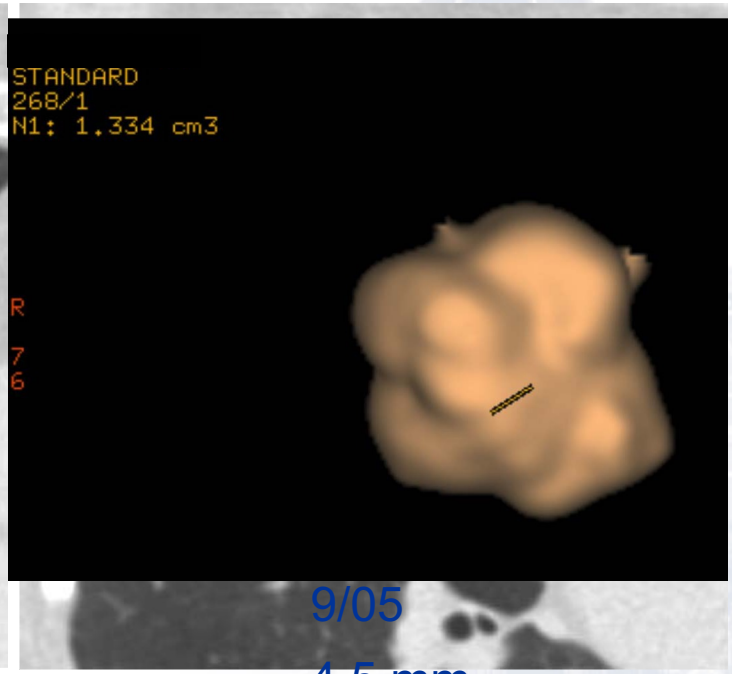
3/05

4.3 mm

3/05/22

787 mm^3

4.3 mm



9/05

4.5 mm

9/05/22

1.334 mm^3

4.5 mm

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AI might change everything

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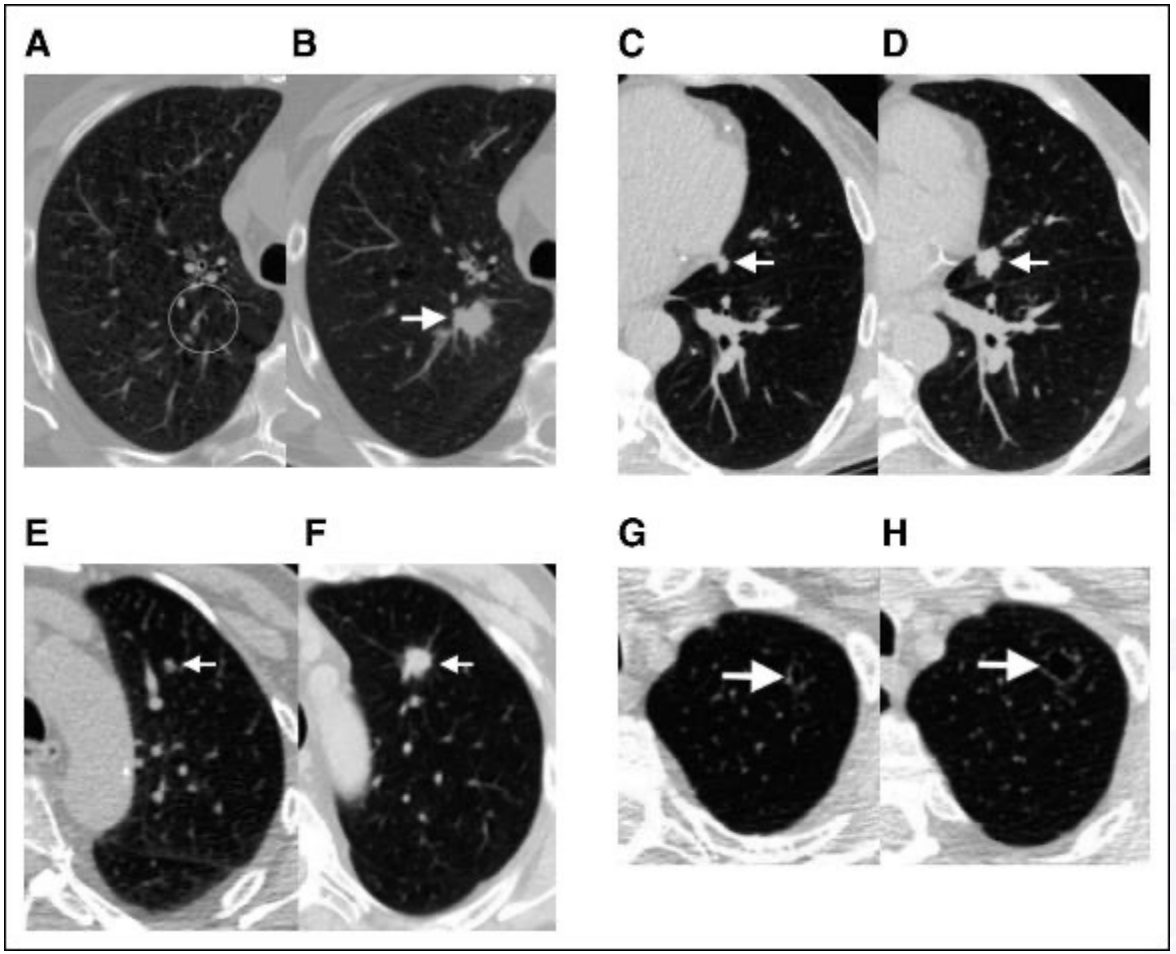
ORIGINAL REPORTS | Thoracic Oncology

Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography



- Benign appearing (Lung-RADS 1 or 2) nodules that were given high AI risk scores and ultimately found to be cancer

Mikhael PG, et al. J Clin Oncol. 2023 Apr 20;41(12):2191-2200.

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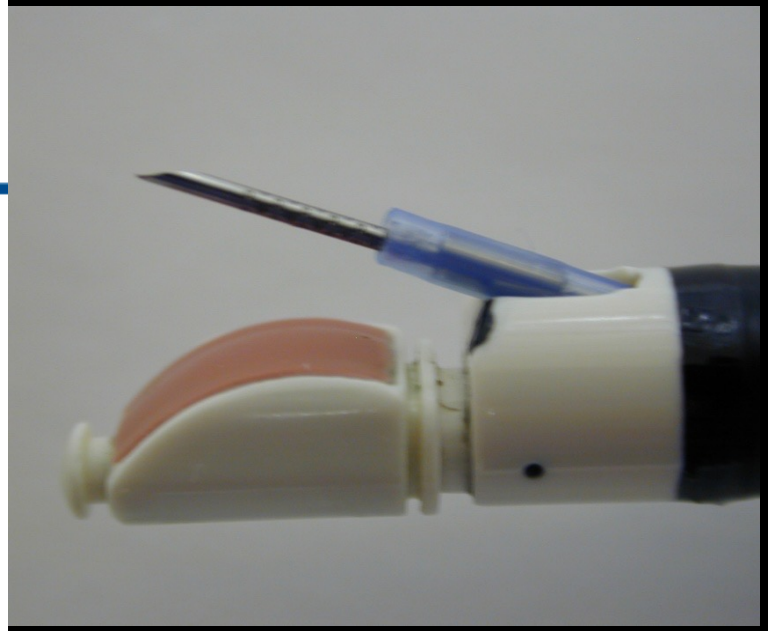

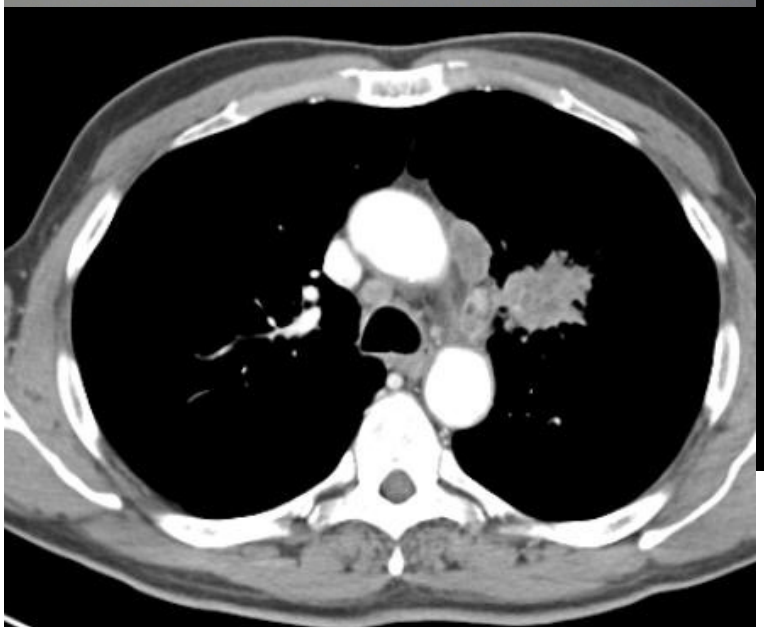

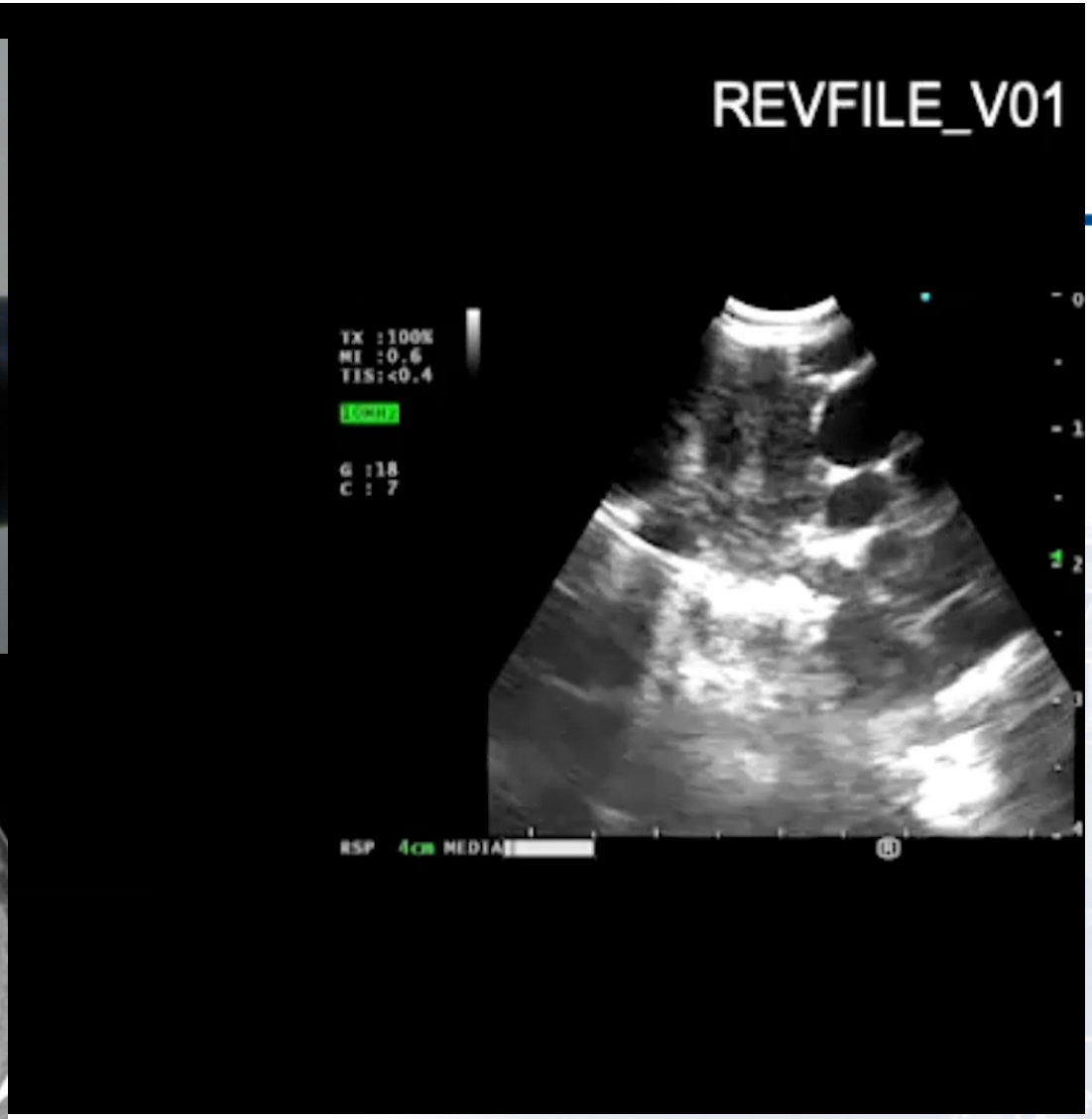

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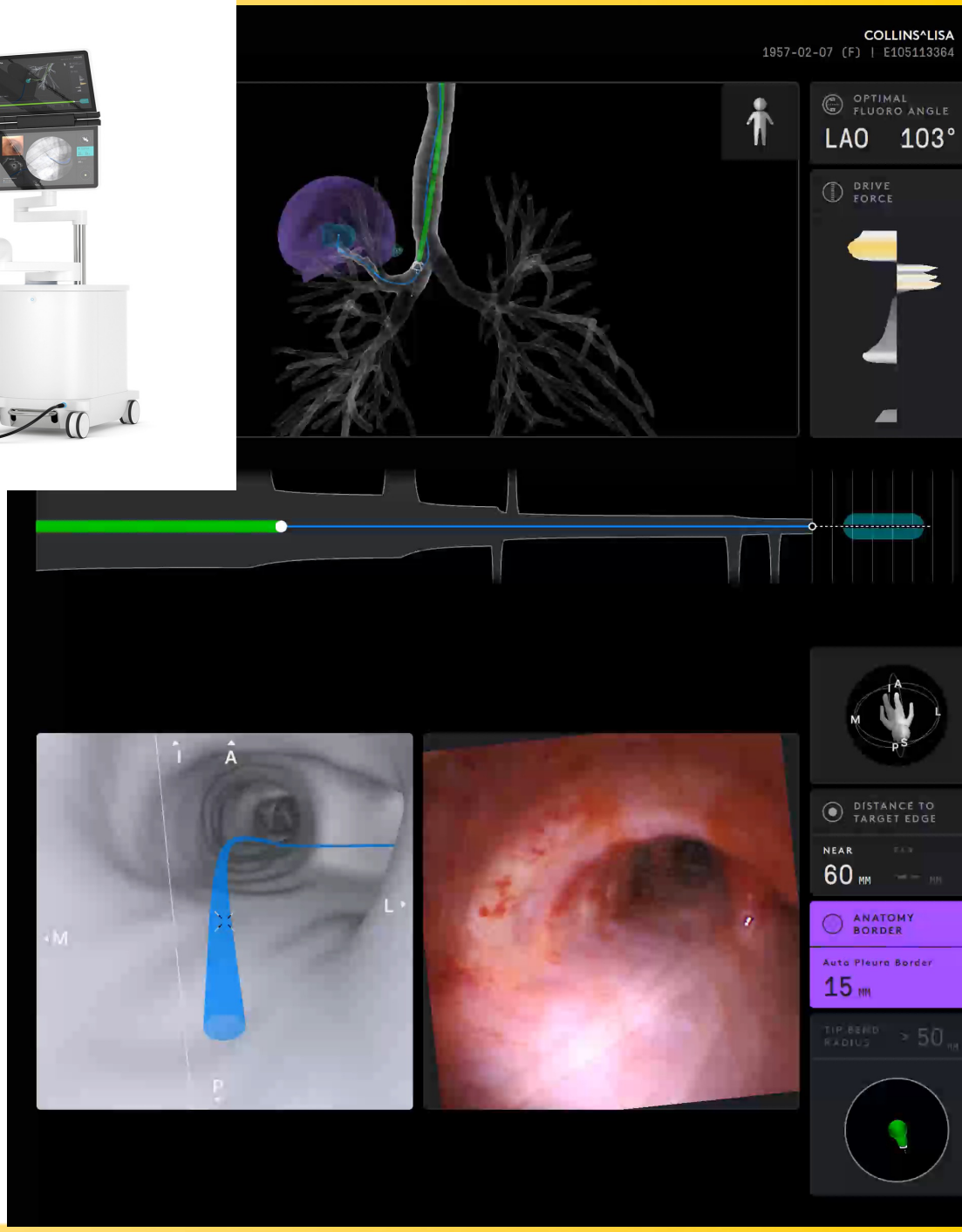
COLLINS^LISA
1957-02-07 (F) | E105113364
OPTIMAL FLUORO ANGLE
LAO 103°
DRIVE FORCE
I
A
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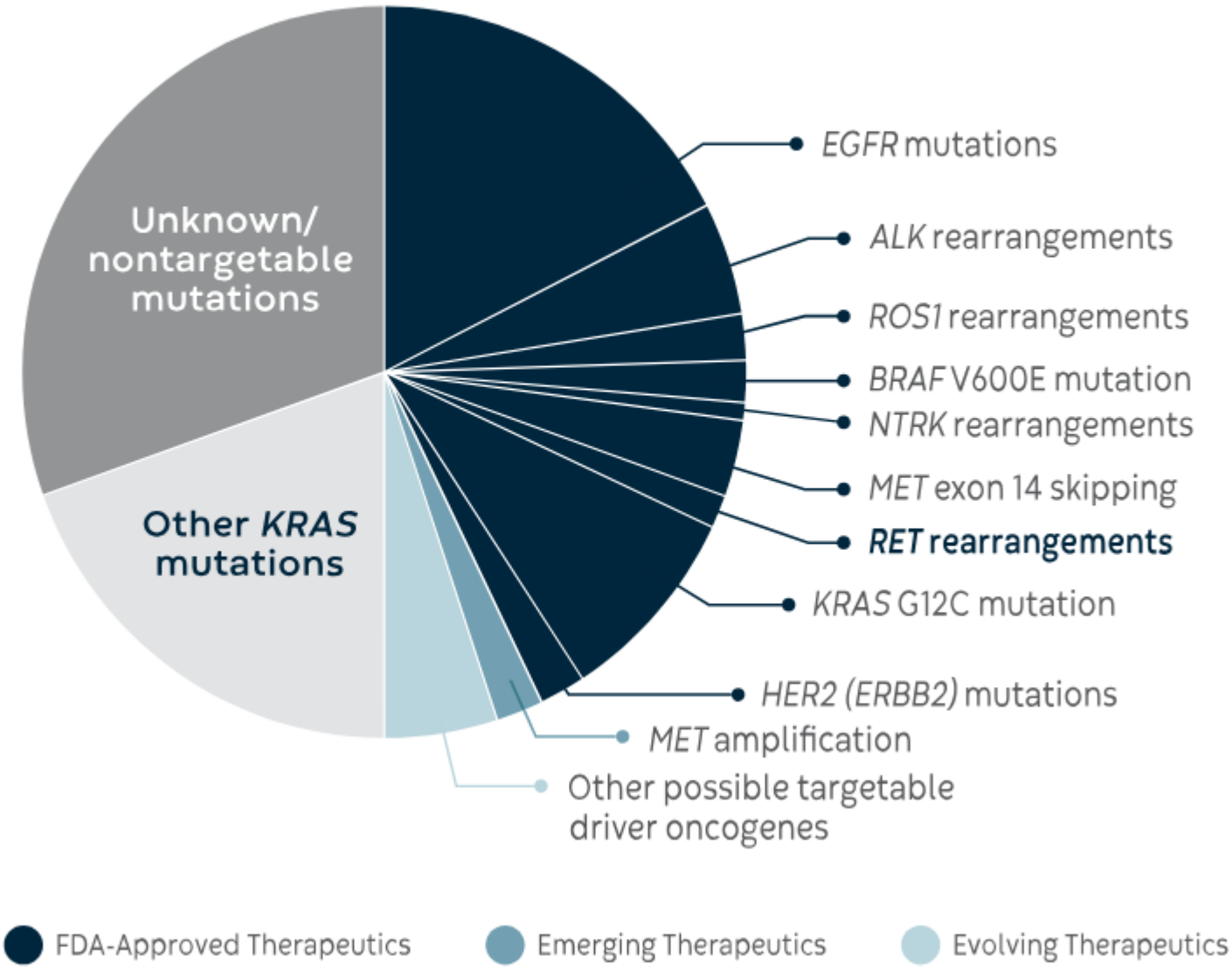
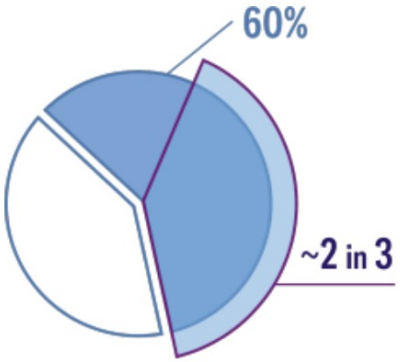
DISTANCE TO TARGET EDGE
NEAR
60 MM
ANATOMY BORDER
Auto Pleura Border
15 MM
TIP BEND RADIUS
> 50 MM


Unknown/ nontargetable mutations
Other KRAS mutations
EGFR mutations
ALK rearrangements
ROS1 rearrangements
BRAF V600E mutation
NTRK rearrangements
MET exon 14 skipping
RET rearrangements
KRAS G12C mutation
HER2 (ERBB2) mutations
MET amplification
Other possible targetable driver oncogenes
FDA-Approved Therapeutics
Emerging Therapeutics
Evolving Therapeutics

BIOMARKERS ARE COMMON IN NSCLC

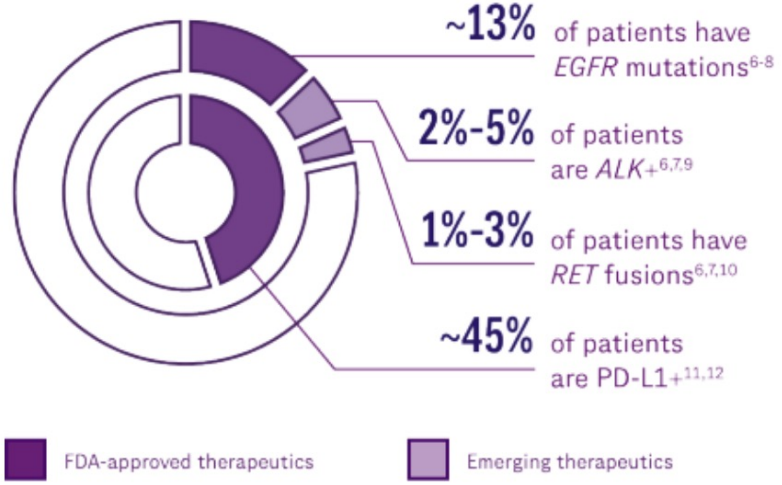
METASTATIC NSCLC (mNSCLC)
NONSQUAMOUS



MORE THAN 60%
of patients have oncogenic drivers—and of these patients, about 2 in 3 have an actionable biomarker[1-5a]

[a]Regardless of PD-L1 expression.

STAGES I-III NSCLC



Evolving biomarkers include:

- BRAF[13]
- MET[14]
- NTRK[13]
- ROS1[13]

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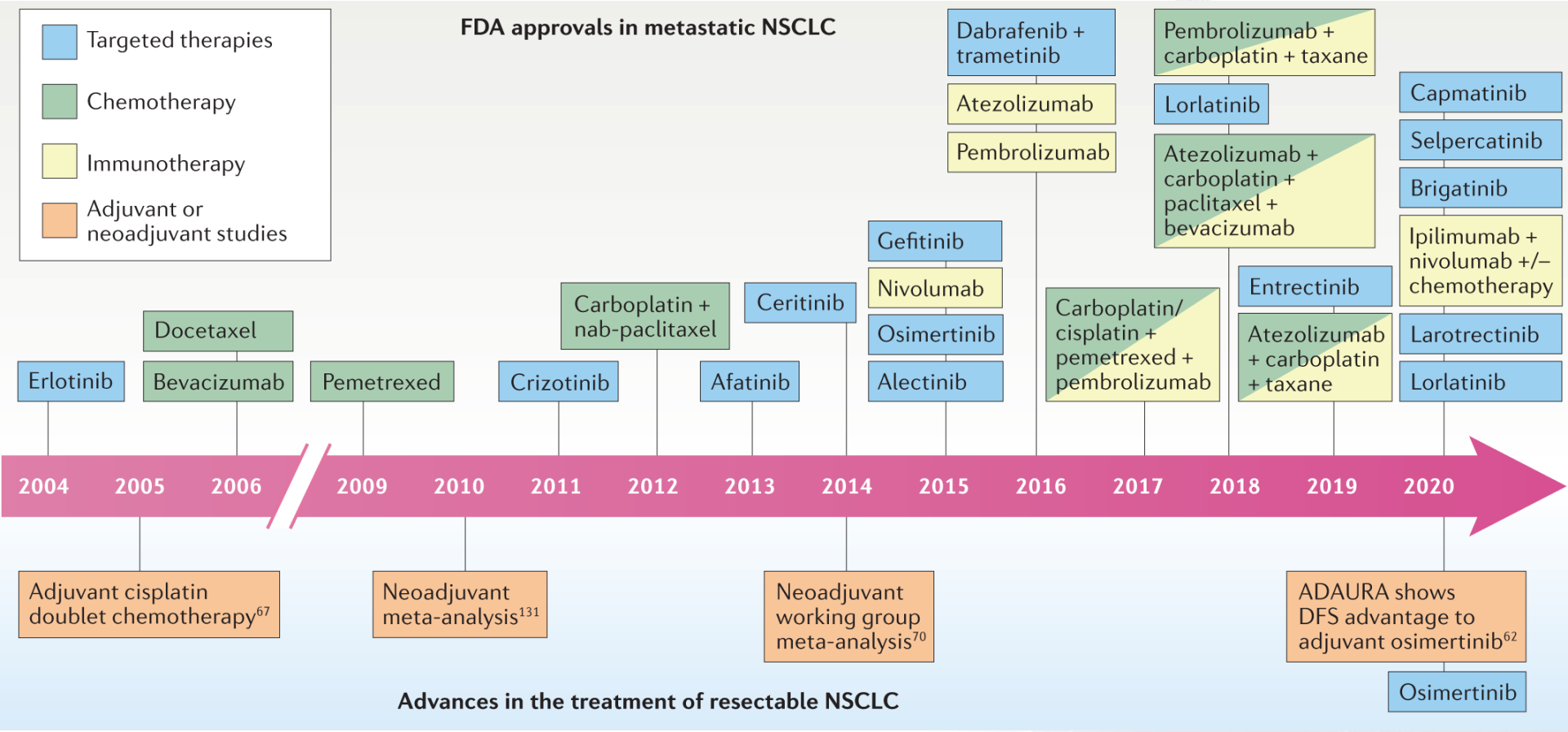
Targeted therapies
Chemotherapy
Immunotherapy
Adjuvant or neoadjuvant studies
FDA approvals in metastatic NSCLC
Erlotinib
Docetaxel
Bevacizumab
Pemetrexed
Crizotinib
Carboplatin + nab-paclitaxel
Afatinib
Ceritinib
Gefitinib
Nivolumab
Osimertinib
Alectinib
Dabrafenib + trametinib
Atezolizumab
Pembrolizumab
Carboplatin/ cisplatin + pemetrexed + pembrolizumab
Pembrolizumab + carboplatin + taxane
Lorlatinib
Atezolizumab + carboplatin + paclitaxel + bevacizumab
Entrectinib
Atezolizumab + carboplatin + taxane
Capmatinib
Selpercatinib
Brigatinib
Ipilimumab + nivolumab +/– chemotherapy
Larotrectinib
Lorlatinib
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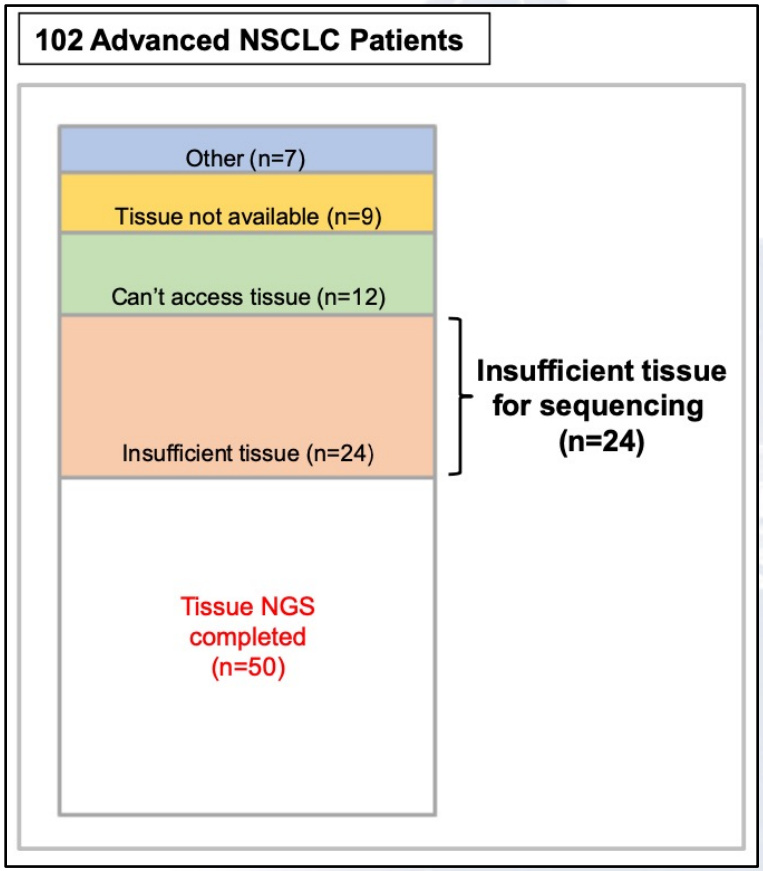
2020
Adjuvant cisplatin doublet chemotherapy[67]
Neoadjuvant meta-analysis[131]
Neoadjuvant working group meta-analysis[70]
ADAURA shows DFS advantage to adjuvant osimertinib[62]
Osimertinib
Advances in the treatment of resectable NSCLC

So what's the problem?

- Guidelines now advocate for mutation screening as standard of care
- Lung cancer diagnosis was historically obtained from solid tissue biopsy alone
- There are limitations with solid tissue sampling:
  - Invasiveness
  - May be difficult to obtain
  - Patients may require repeated invasive procedures following disease progression
  - May have insufficient tissue for detailed sequencing analysis



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Delaware

Rate of New Cases	Survival Rate	Early Diagnosis	Surgical Treatment	Lack of Treatment	Screening
Average	Above Average	Above Average	Average	Average	Above Average

Fee-For-Service Medicaid Coverage of Screening

Covered and Using Updated Guidelines

Highlighted Disparity

Black individuals in Delaware are least likely to be diagnosed early.

https://www.lung.org/research/state-of-lung-cancer/states/delaware

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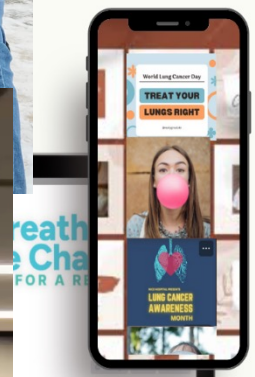
NATIONAL LUNG CANCER ROUNDTABLE



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Conclusions

- Creative programs can help with smoking cessation
- Early detection for lung cancer is possible with low dose CT screening AND WILL SAVE LIVES
- Many reasons why lung screening has not been well-adopted
- Risk factors such as family history, radon exposure, second hand smoke exposure may help to create a stratification score that will better identify who to screen
- Although lung cancer treatments are improving survival, biomarker testing is critical and under-utilized
- Blood assays to look for biomarkers
- Education, awareness and research efforts

Thank You
aargent1@jh.edu

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