Lung Nodule Management – a Practical Guide

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Disclosures

- Investor/advisor – Oatmeal health
- Consulting/grants/ad boards/travel – Qure.ai, Sanofi, Penumbra, Noah Medical, Intuitive surgical, Biodesix
- Pace of change & updates

Outline

- Nodule program structure
- Referral patterns & sources
- Biopsy or not
- Biopsy options
- Treatment overview
- BONUS - Role of AI

Outline

- **Nodule program structure**
- **Referral patterns & sources**
- Biopsy or not
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- Treatment overview
- BONUS - Role of AI

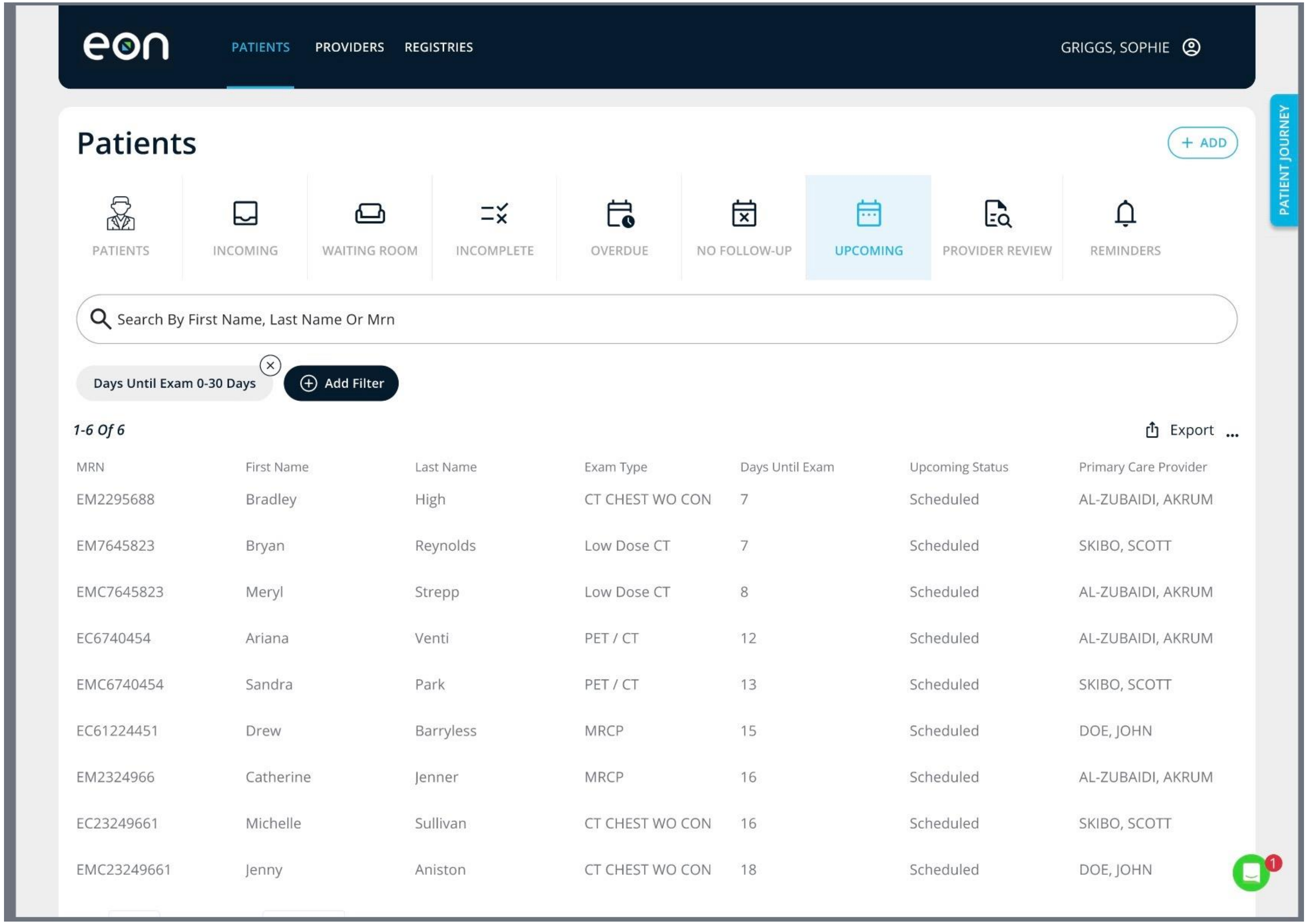
Nodule program structure

- Incidental
- Screen detected
- Which nodules enter the referral que?
  - L-RADS
  - Fleischner guidelines
- Where do they ‘land’?
  - Nodule board – virtual multi-disciplinary review
  - Nodule clinic – IP/TS – routine consultation

Nodule program structure

- Nodule management software?
- Excel sheet?

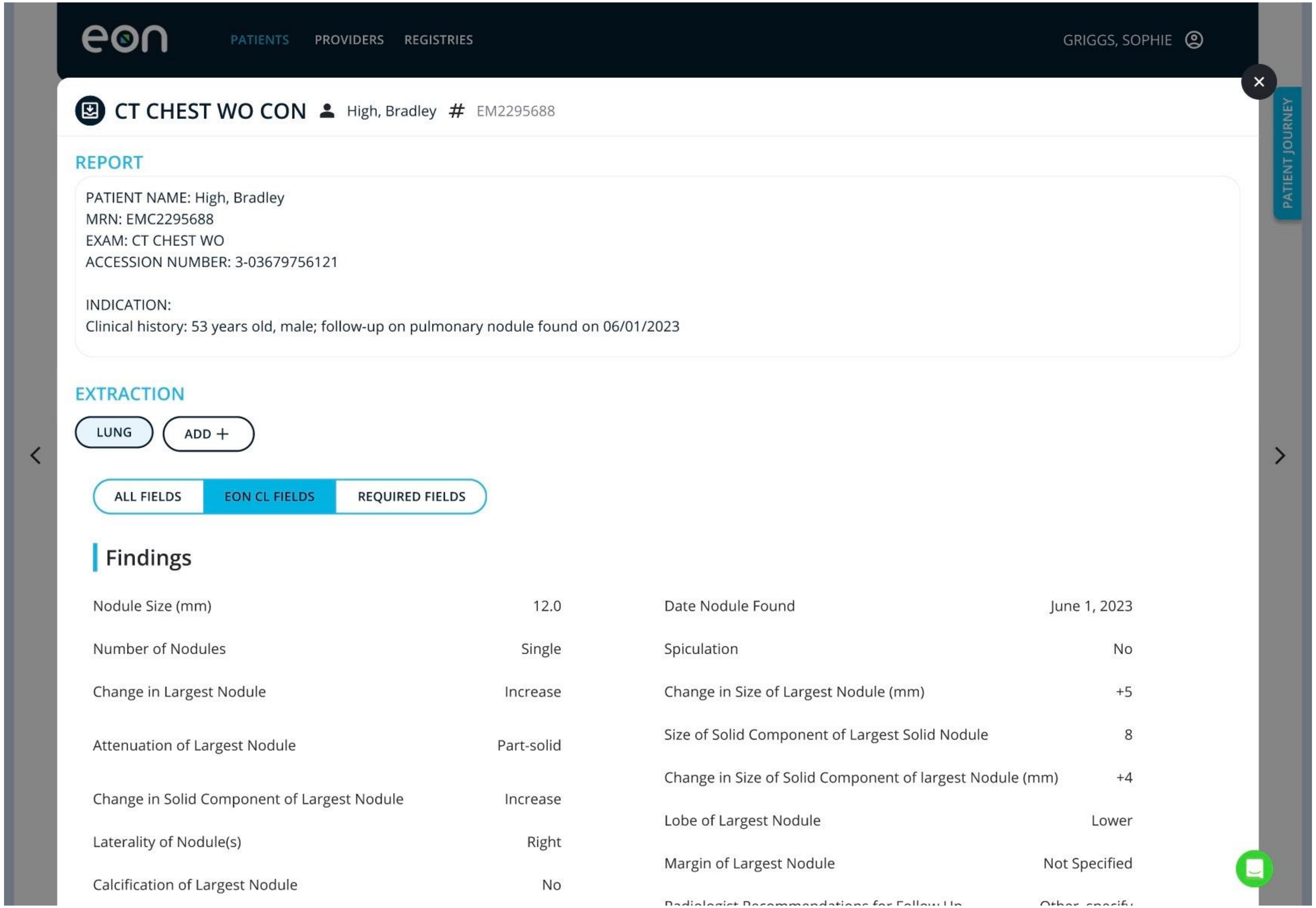
My practice – dashboard



MRN	First Name	Last Name	Exam Type	Days Until Exam	Upcoming Status	Primary Care Provider
EM2295688	Bradley	High	CT CHEST WO CON	7	Scheduled	AL-ZUBAIDI, AKRUM
EM7645823	Bryan	Reynolds	Low Dose CT	7	Scheduled	SKIBO, SCOTT
EMC7645823	Meryl	Strepp	Low Dose CT	8	Scheduled	AL-ZUBAIDI, AKRUM
EC6740454	Ariana	Venti	PET / CT	12	Scheduled	AL-ZUBAIDI, AKRUM
EMC6740454	Sandra	Park	PET / CT	13	Scheduled	SKIBO, SCOTT
EC61224451	Drew	Barryless	MRCP	15	Scheduled	DOE, JOHN
EM2324966	Catherine	Jenner	MRCP	16	Scheduled	AL-ZUBAIDI, AKRUM
EC23249661	Michelle	Sullivan	CT CHEST WO CON	16	Scheduled	SKIBO, SCOTT
EMC23249661	Jenny	Aniston	CT CHEST WO CON	18	Scheduled	DOE, JOHN

Courtsey Scott Skibo

My practice – CT findings



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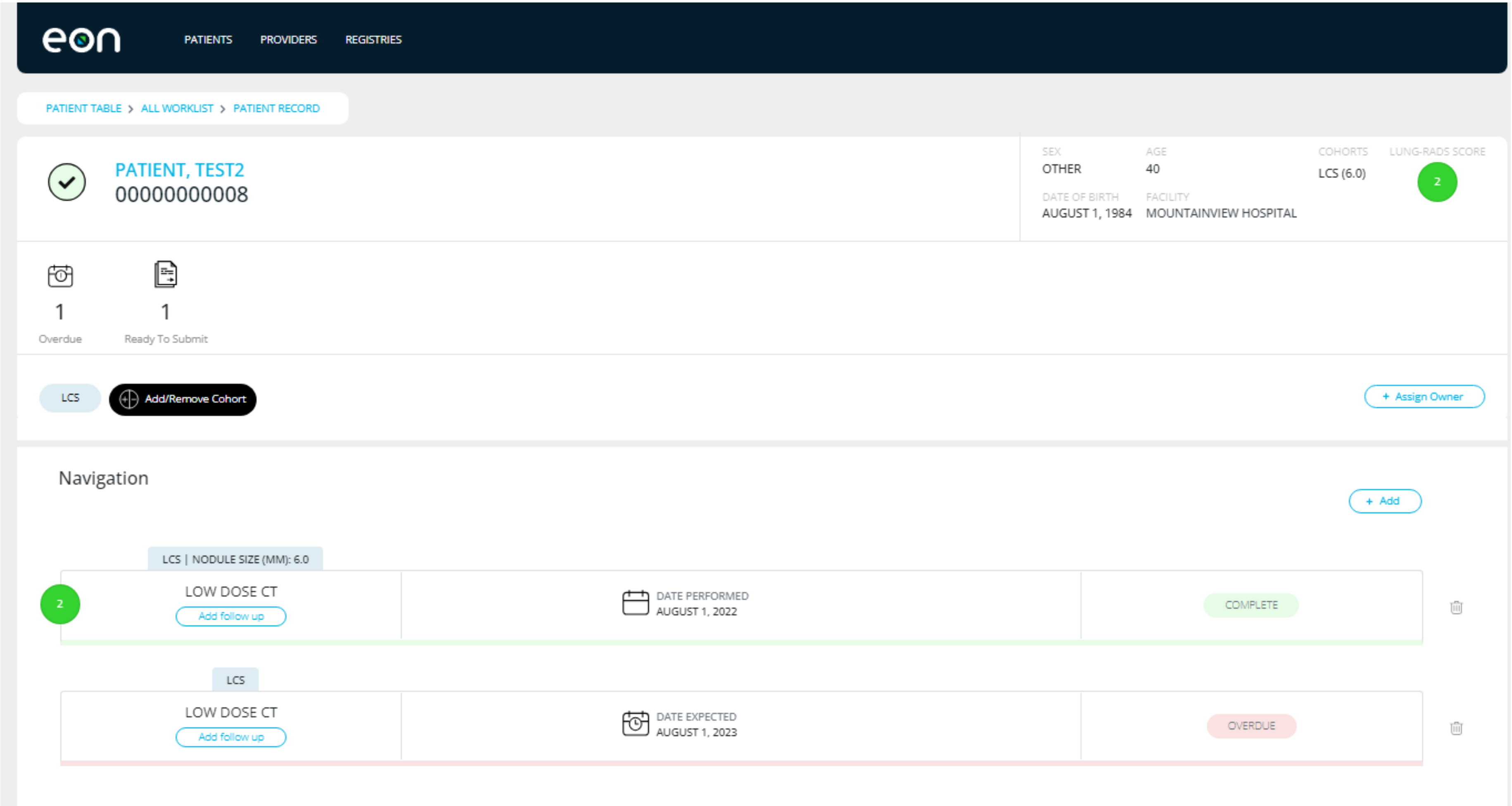
My practice – patient work list



Courtsey Raycil Jones

Fleischner society guidelines

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 in low-risk patients (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	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).

Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. MacMahon et al. https://pubs.rsna.org/doi/10.1148/radiol.2017161659

Fleischner society guidelines

B: Subsolid Nodules*

Nodule Type	Size		Comments
	<6 mm (<100 mm³)	≥6 mm (>100 mm³)	
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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L-RADS

Lung-RADS	Category Descriptor	Findings	Management
0	**Incomplete** Estimated Population Prevalence: ~ 1%	Prior chest CT examination being located for comparison (see note 9)	Comparison to prior chest CT;
		Part or all oflungs cannot be evaluated	Additional lung cancer screening CT imaging needed;
		Findings suggestive of an inflammatory or infectious process (see note 10)	1-3 month LDCT
1	**Negative** Estimated Population Prevalence: 39%	**No lung nodules OR**	12-month screening LDCT
		Nodule with benign features: • Complete, central, popcorn, or concentric ring calcifications **OR** • Fat-containing	
2	**Benign** - Based on imaging features or indolent behavior Estimated Population Prevalence: 45%	**Juxtapleural nodule:** • < 10 mm (524 mm³) mean diameter at baseline or new **AND** • Solid; smooth margins; and oval, lentiform, or triangular shape	
		Solid nodule: • < 6 mm (< 113 mm³) at baseline **OR** • New < 4 mm (< 34 mm³)	
		Part solid nodule: • < 6 mm total mean diameter (< 113 mm³) at baseline	
		Non solid nodule (GGN): • < 30 mm (< 14,137 mm³) at baseline, new, or growing **OR** • ≥ 30 mm (≥ 14,137 mm³) stable or slowly growing (see note 7)	
		Airway nodule, subsegmental - at baseline, new, or stable (see note 11)	
		Category 3 lesion that is stable or decreased in size at 6-month follow-up CT **OR** Category 4B lesion proven to be benign in etiology following appropriate diagnostic workup	
3	**Probably Benign** - Based on imaging features or behavior Estimated Population Prevalence: 9%	**Solid nodule:** • ≥ 6 to < 8 mm (≥ 113 to < 268 mm³) at baseline **OR** • New 4 mm to < 6 mm (34 to < 113 mm³)	6-month LDCT
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm³) with solid component < 6 mm (< 113 mm³) at baseline **OR** • New < 6 mm total mean diameter (< 113 mm³)	
		Non solid nodule (GGN): • ≥ 30 mm (≥ 14,137 mm³) at baseline or new	
		Atypical pulmonary cyst: (see note 12) • Growing cystic component (mean diameter) of a thick-walled cyst	
		Category 4A lesion that is stable or decreased in size at 3-month follow-up CT (excluding airway nodules)	

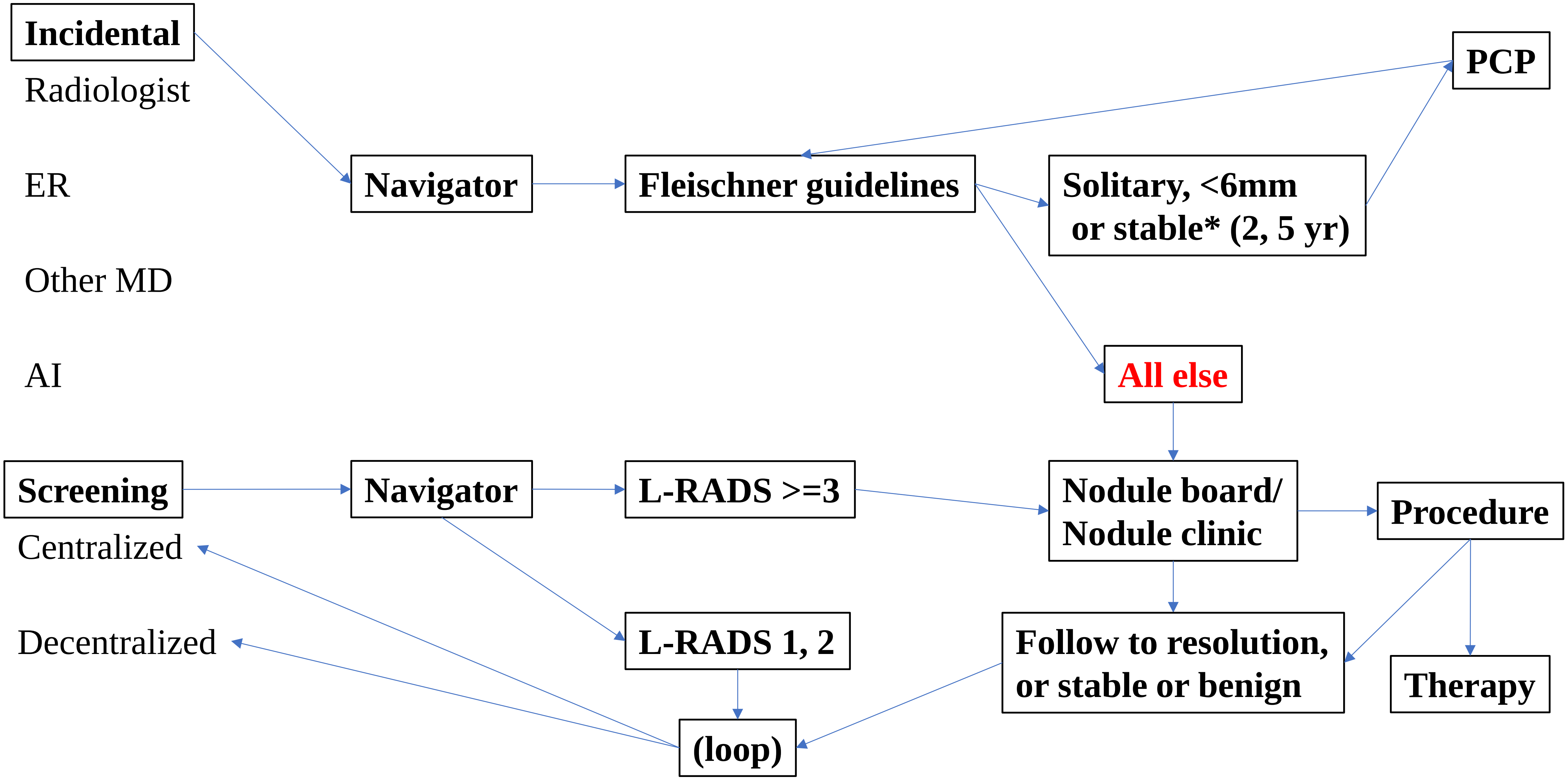
https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf

L-RADS

4A	**Suspicious** Estimated Population Prevalence: 4%	**Solid nodule:** • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm^3) at baseline **OR** • Growing < 8 mm (< 268 mm^3) **OR** • New 6 to < 8 mm (113 to < 268 mm^3)	3-month LDCT; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** • New or growing < 4 mm (< 34 mm^3) solid component	
		Airway nodule, segmental or more proximal - at baseline (see note 11)	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst **OR** • Multilocular cyst at baseline **OR** • Thin- or thick-walled cyst that becomes multilocular	
4B	**Very Suspicious** Estimated Population Prevalence: 2%	**Airway nodule**, segmental or more proximal - stable or growing (see note 11)	Referral for further clinical evaluation
		Solid nodule: • ≥ 15 mm (≥ 1767 mm^3) at baseline **OR** • New or growing ≥ 8 mm (≥ 268 mm^3)	Diagnostic chest CT with or without contrast; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component; tissue sampling; and/or referral for further clinical evaluation Management depends on clinical evaluation, patient preference, and the probability of malignancy (see note 13)
		Part solid nodule: • Solid component ≥ 8 mm (≥ 268 mm^3) at baseline **OR** • New or growing ≥ 4 mm (≥ 34 mm^3) solid component	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst with growing wall thickness/nodularity **OR** • Growing multilocular cyst (mean diameter) **OR** • Multilocular cyst with increased loculation or new/increased opacity (nodular, ground glass, or consolidation)	
		Slow growing solid or part solid nodule that demonstrates growth over multiple screening exams (see note 8)	
4X	Estimated Population Prevalence: < 1%	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion for lung cancer (see note 14)	
S	**Significant or Potentially Significant** Estimated Population Prevalence: 10%	**Modifier:** May add to category 0-4 for clinically significant or potentially clinically significant findings unrelated to lung cancer (see note 15)	As appropriate to the specific finding

https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf

Nodule program structure



Referral patterns & sources

- Incidental
  - Radiology
  - ER
  - Other MD
  - Self
  - AI

- Screen detected
  - Centralized (hub and spoke)
  - Decentralized (each one do one)

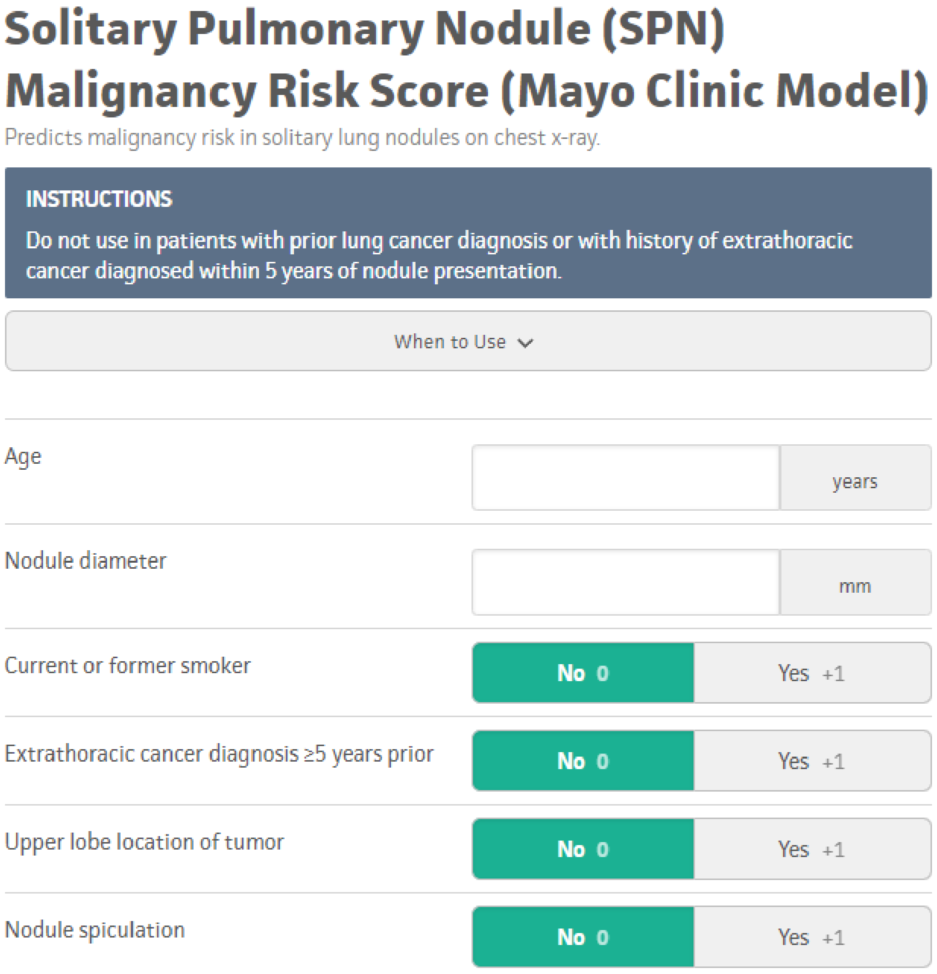
- Logistics
  - Automated
  - Manual

Outline

- Nodule program structure
- Referral patterns & sources
- **Biopsy or not**
- Biopsy options
- Treatment overview
- BONUS – Future role of AI

Biopsy or not

- Utilize all available information to **judge malignant potential**
  - Patient characteristics
    - Age
    - Smoking
    - Cancer history – personal, family
  - Nodule characteristics
    - Location
    - Size
    - Shape
    - Growth/Volume doubling time
    - PET scan – nodule, nodes, distant spread
  - Blood based testing
    - Integrated classifier
    - Infectious serologies
  - AI



[Solitary Pulmonary Nodule (SPN) Malignancy Risk Score (Mayo Clinic Model) (mdcalc.com)]

Nodule characteristics - hamartoma

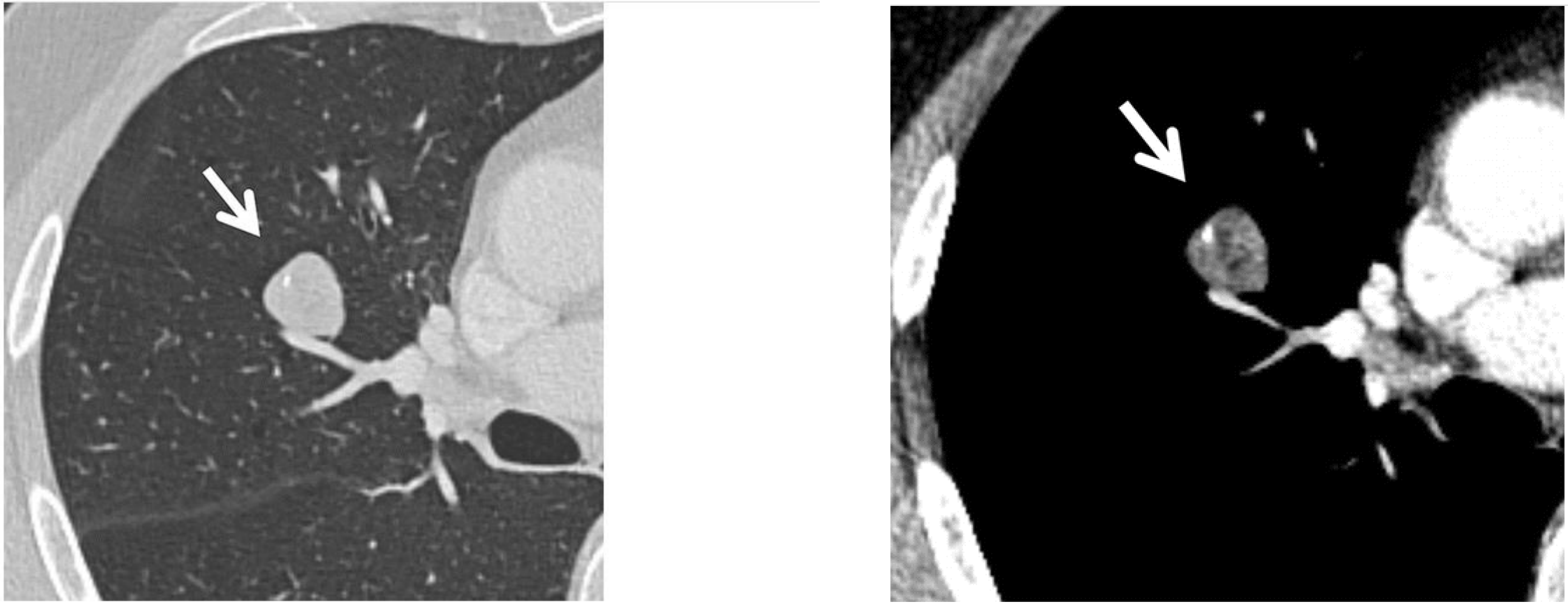
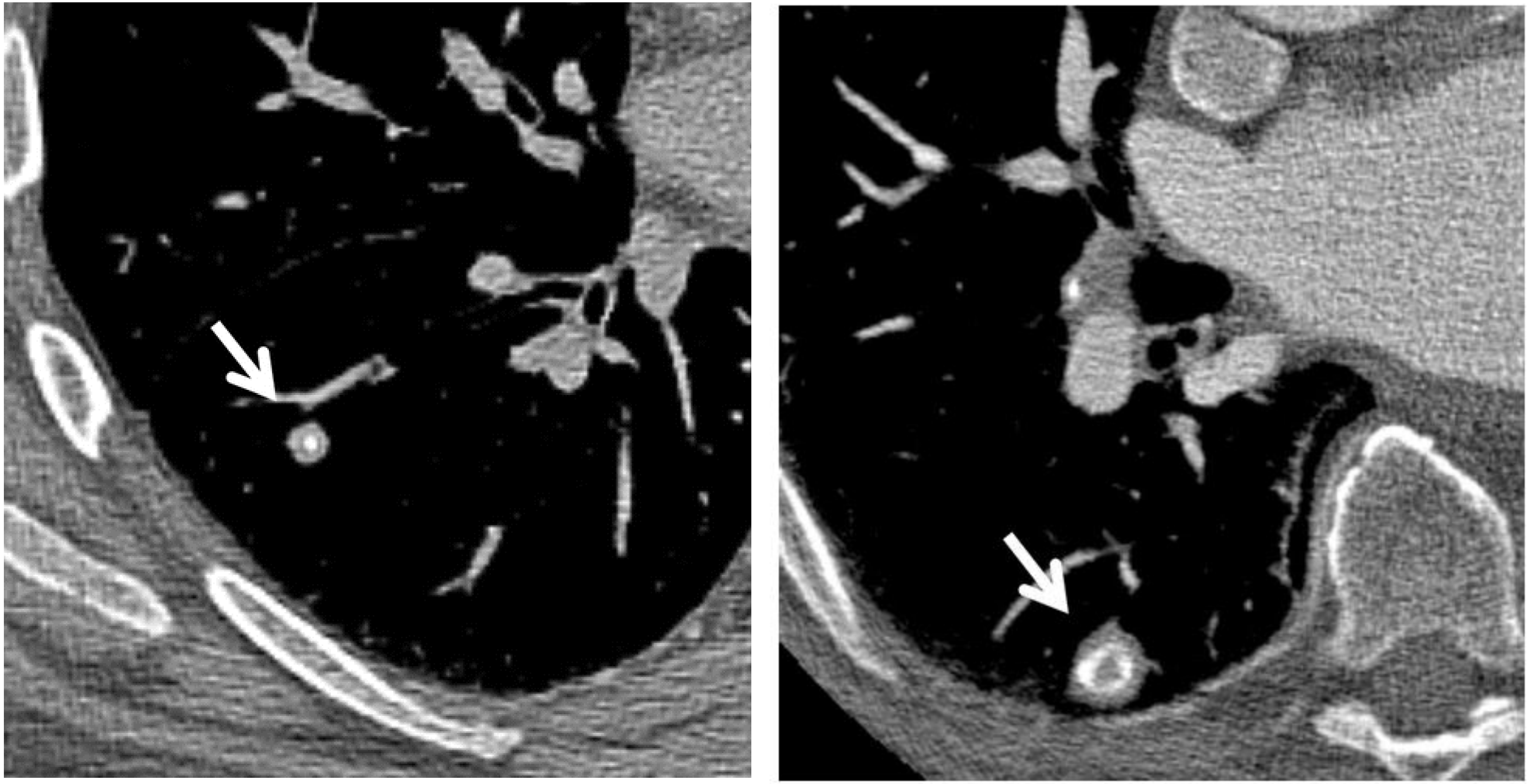


Figure 1a: (a) Lung window and **(b)** soft-tissue window 1-mm transverse CT sections show a smoothly marginated solid nodule (arrow) with internal fat and calcification, consistent with a hamartoma. No further CT follow-up is recommended for such findings.

Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. MacMahon et al. https://pubs.rsna.org/doi/10.1148/radiol.2017161659

Nodule characteristics - granuloma



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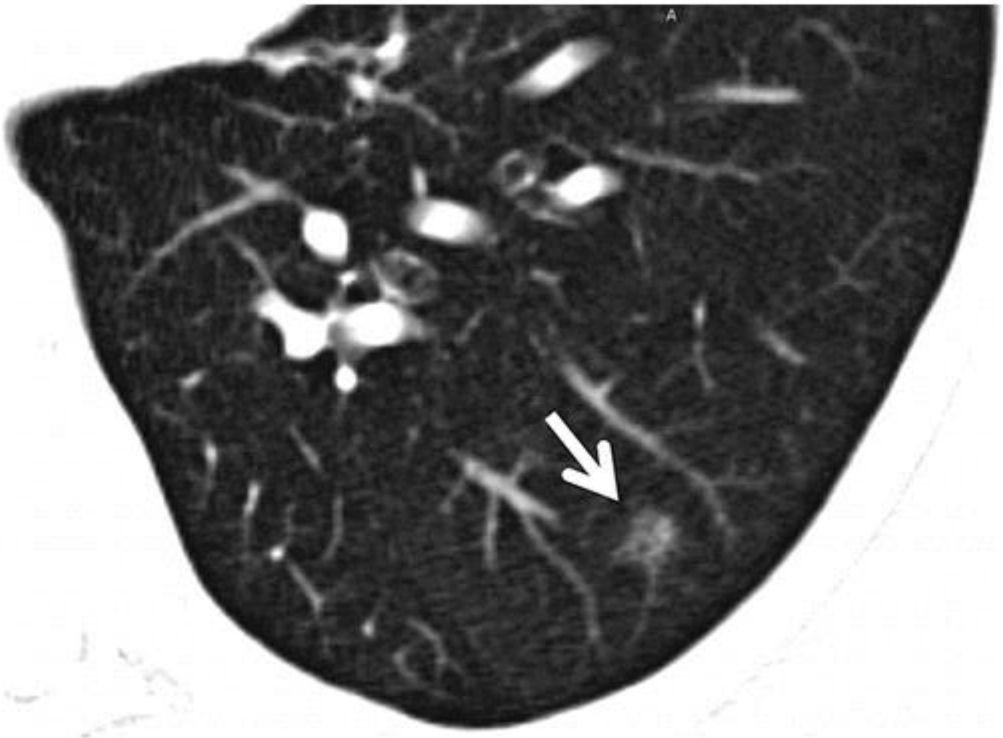
Nodule characteristics – ground glass opacity



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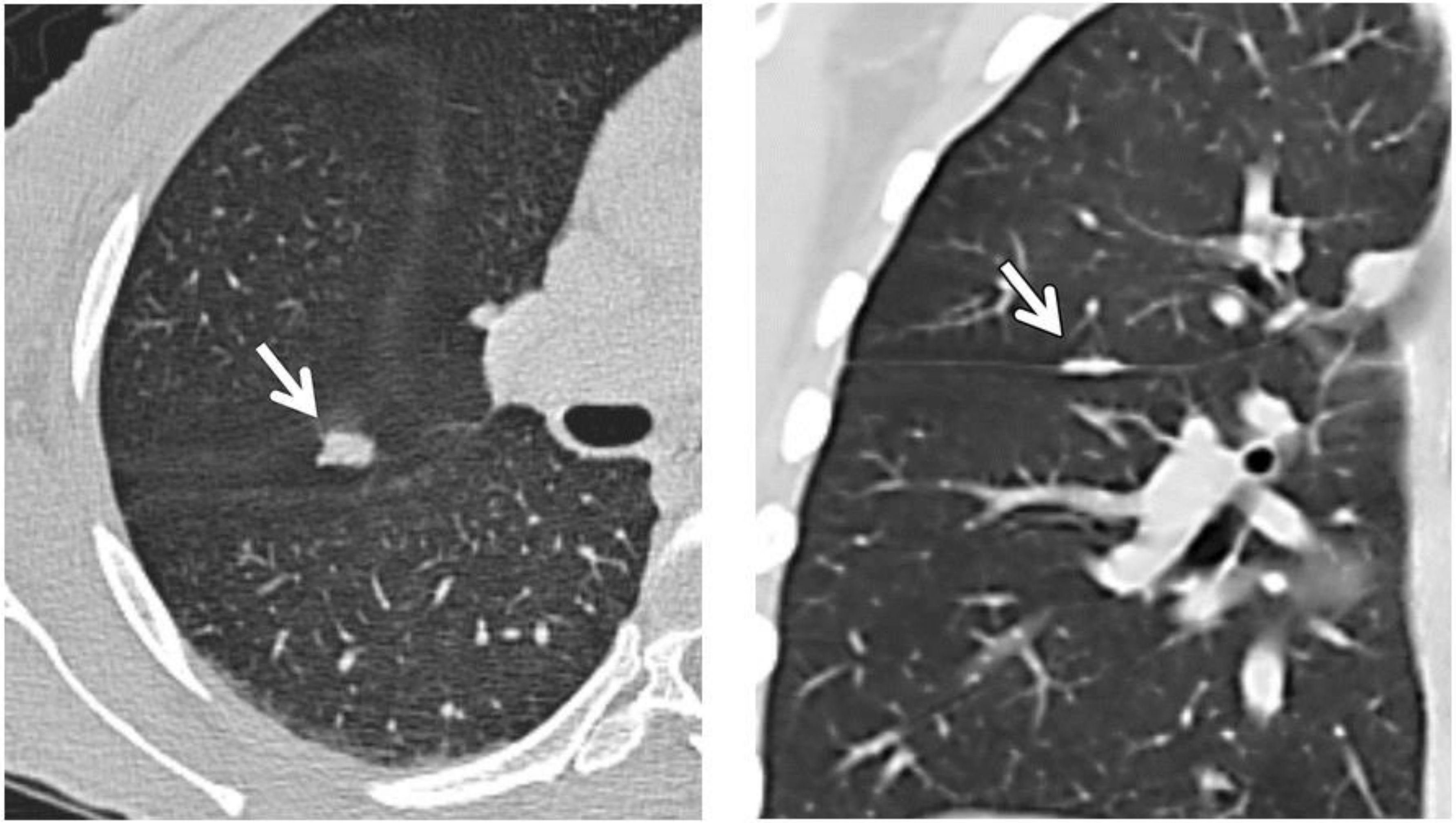
Nodule characteristics – intra-parenchymal lymph node



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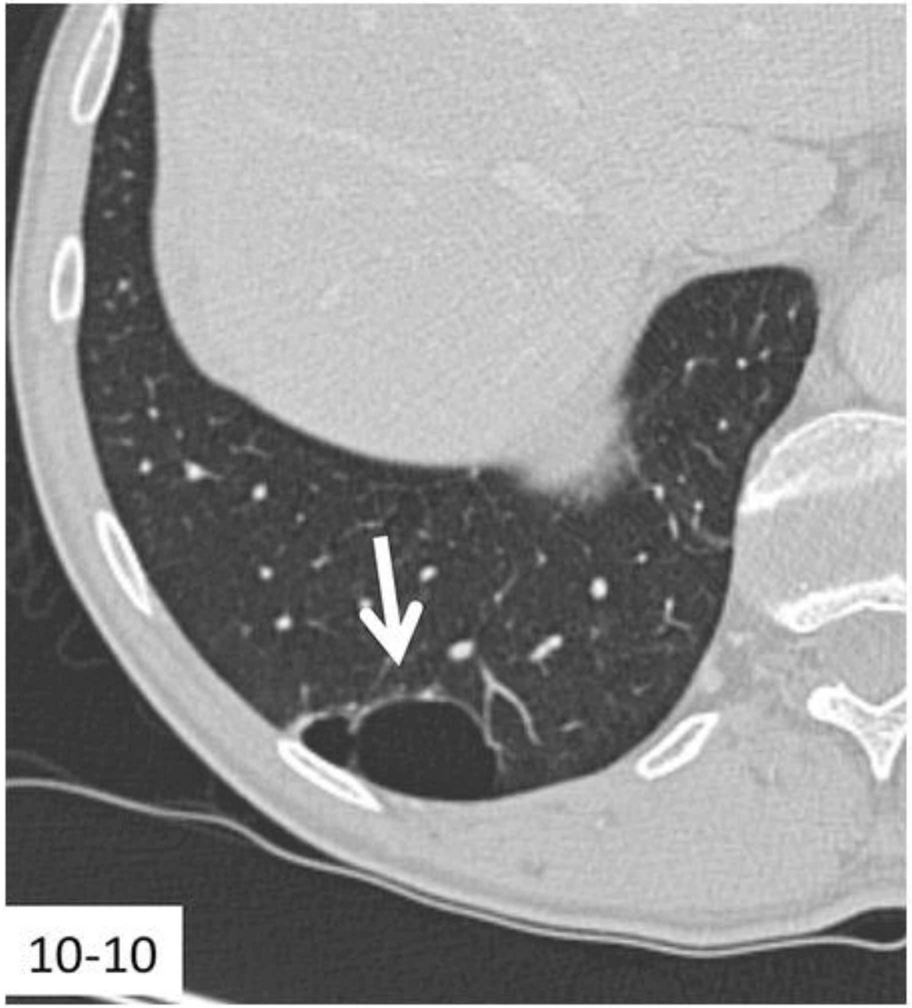
Nodule characteristics – adenocarcinoma



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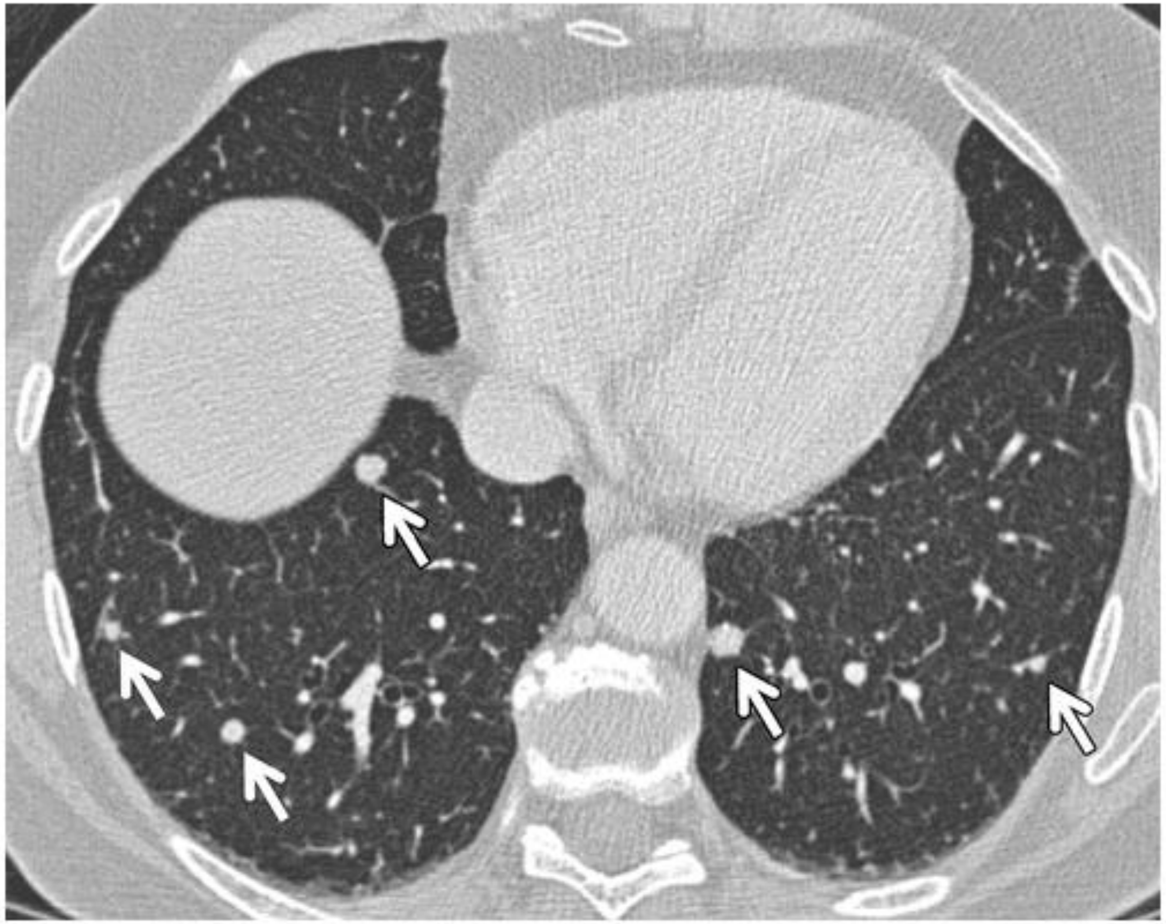
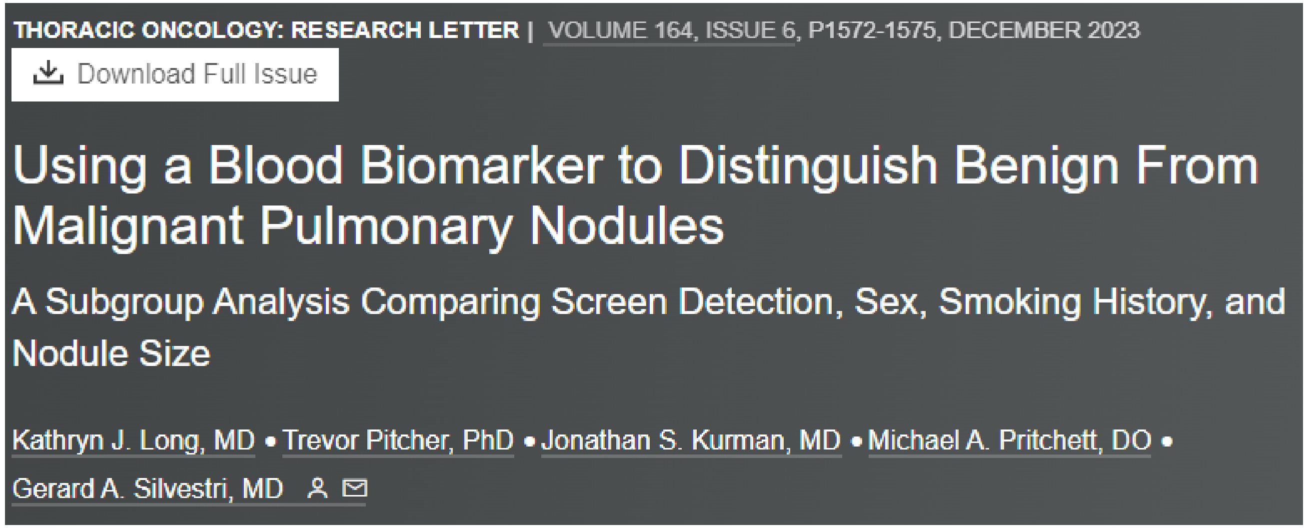
Nodule characteristics – metastatic disease



Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. MacMahon et al. https://pubs.rsna.org/doi/10.1148/radiol.2017161659

Integrated classifier – blood test to judge cancer risk

- Rule-out biomarker
- Reduce procedures for benign nodules
- Combines 2 proteins (LG3BP, C163A) and
  5 clinical/imaging factors
  (age, smoking status, nodule size, spiculation/not, location)
- Identifies benign nodules with 98% NPV
- Equally strong performance in males and females
- AI backed development – ML based error correction, prevent over-fitting, data boosting



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Using a Blood Biomarker to Distinguish Benign From Malignant Pulmonary Nodules

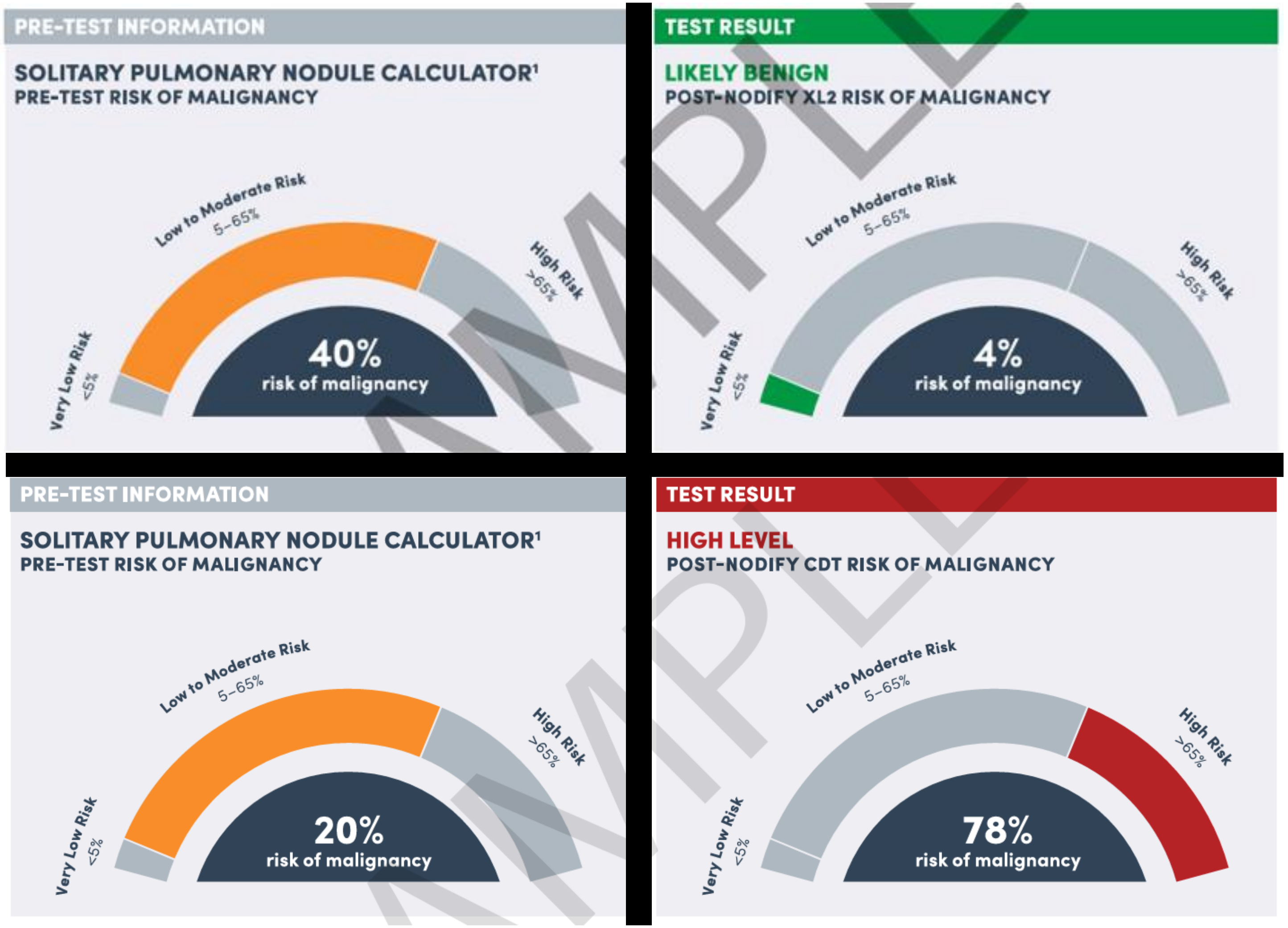
A Subgroup Analysis Comparing Screen Detection, Sex, Smoking History, and Nodule Size

Kathryn J. Long, MD • Trevor Pitcher, PhD • Jonathan S. Kurman, MD • Michael A. Pritchett, DO • Gerard A. Silvestri, MD

AI <> blood – my practice

Pre-test risk

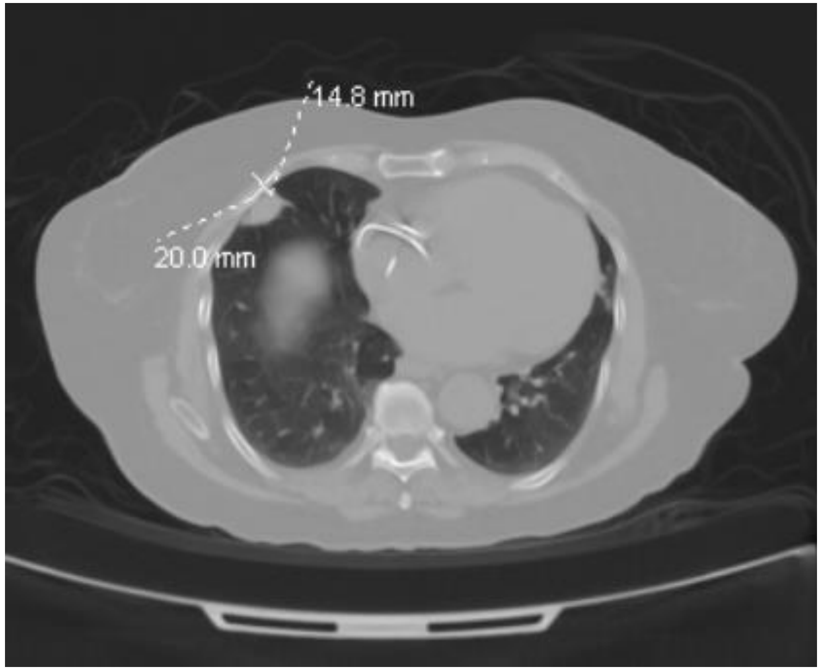
Post-test risk

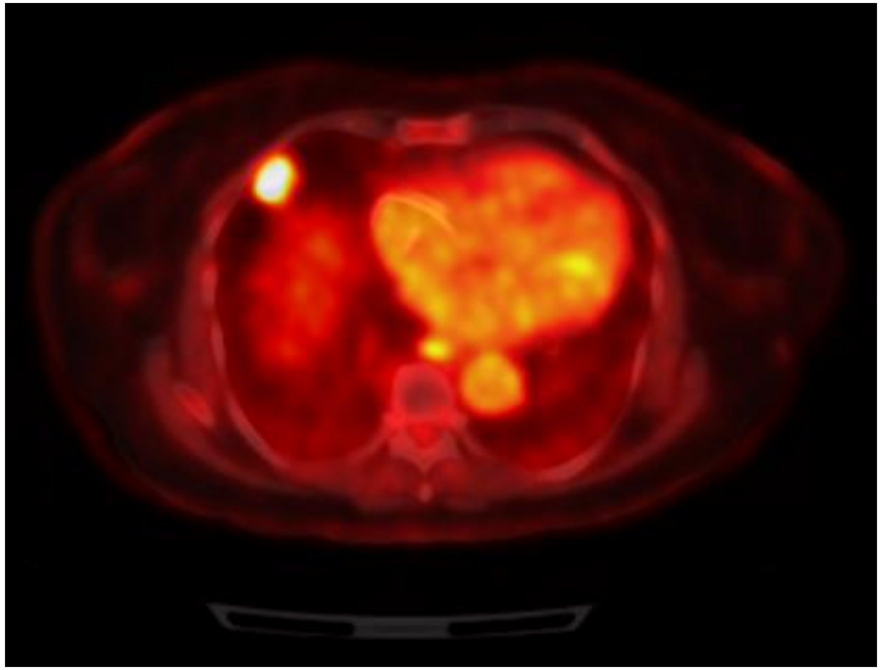


Pre-test risk

Post-test risk

AI <> blood – my practice

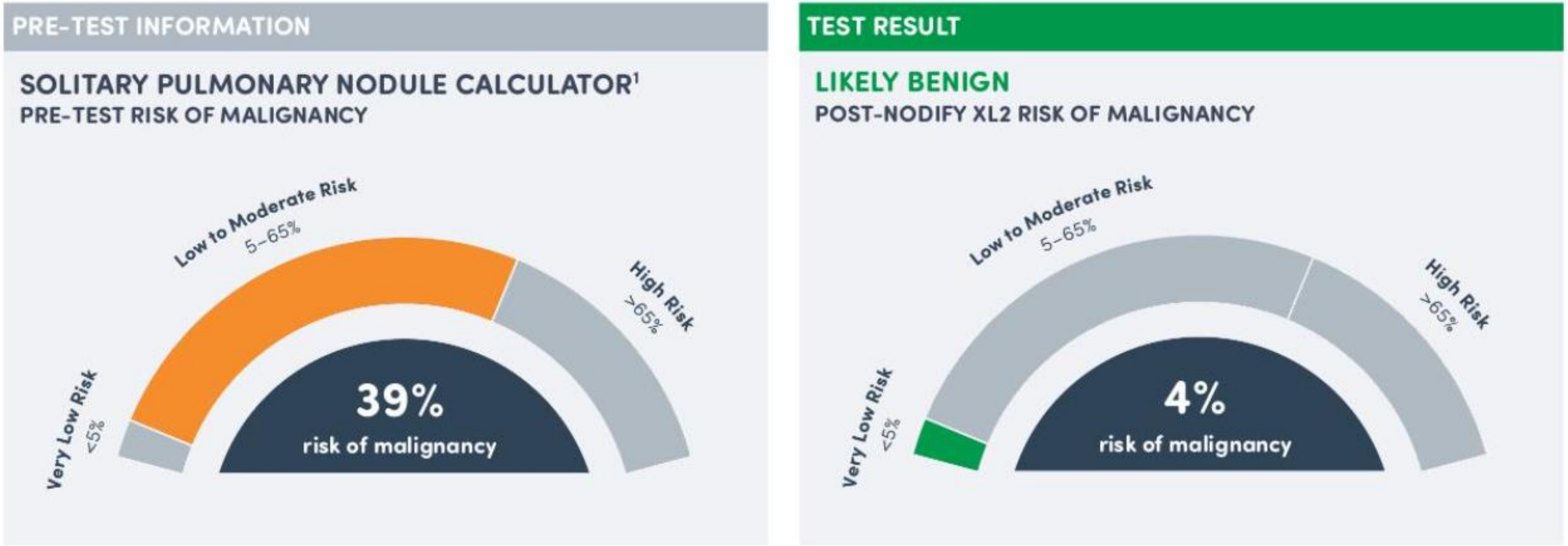




IMPRESSION:

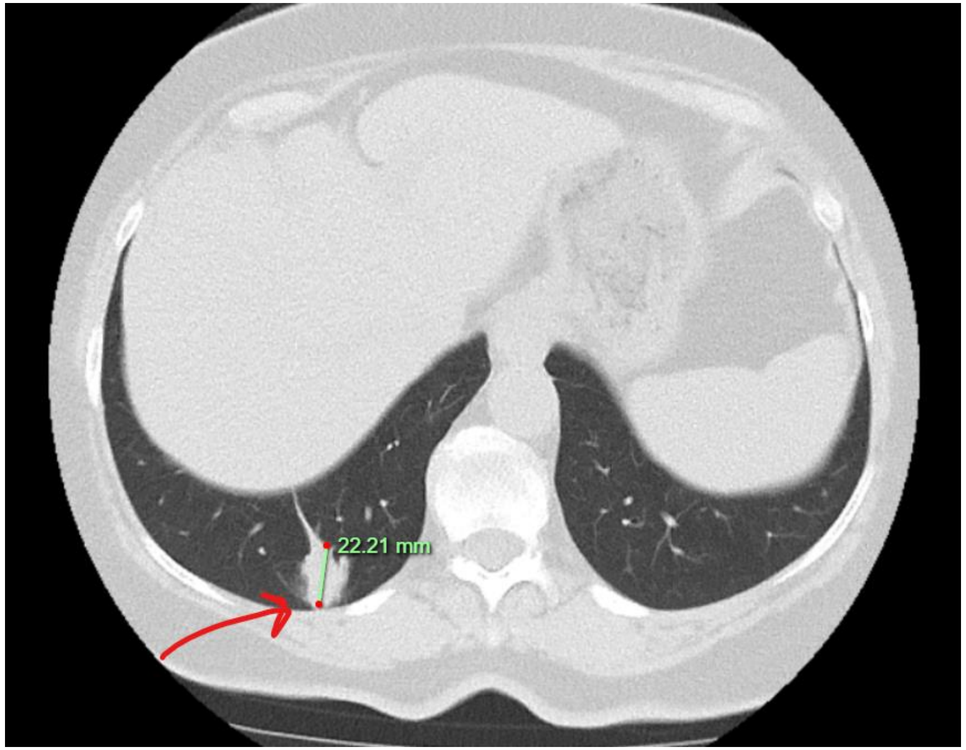
FDG avid right middle lobe pulmonary nodule should be considered malignant (likely a primary lung malignancy) until proven otherwise. Amenable to CT-guided percutaneous biopsy.

Things I think about



- No more scans?
- Ignore and biopsy? (but the AI said it's okay!?!)
- Trust, but verify.

AI <> blood – my practice

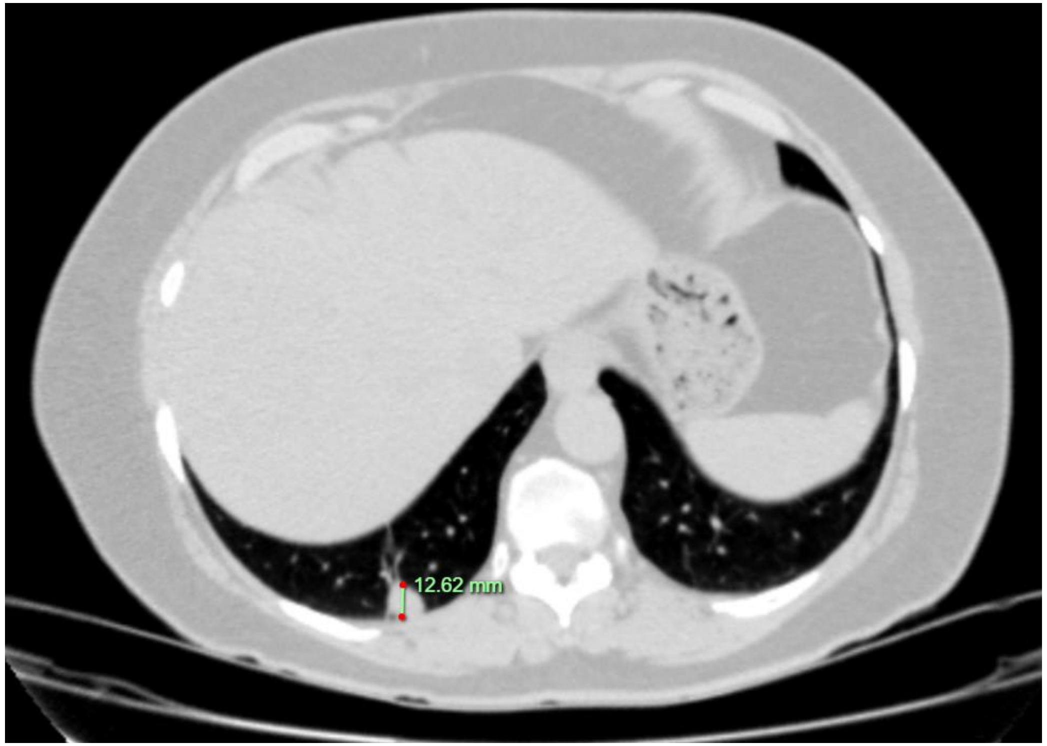


But

10 yr

Earlier

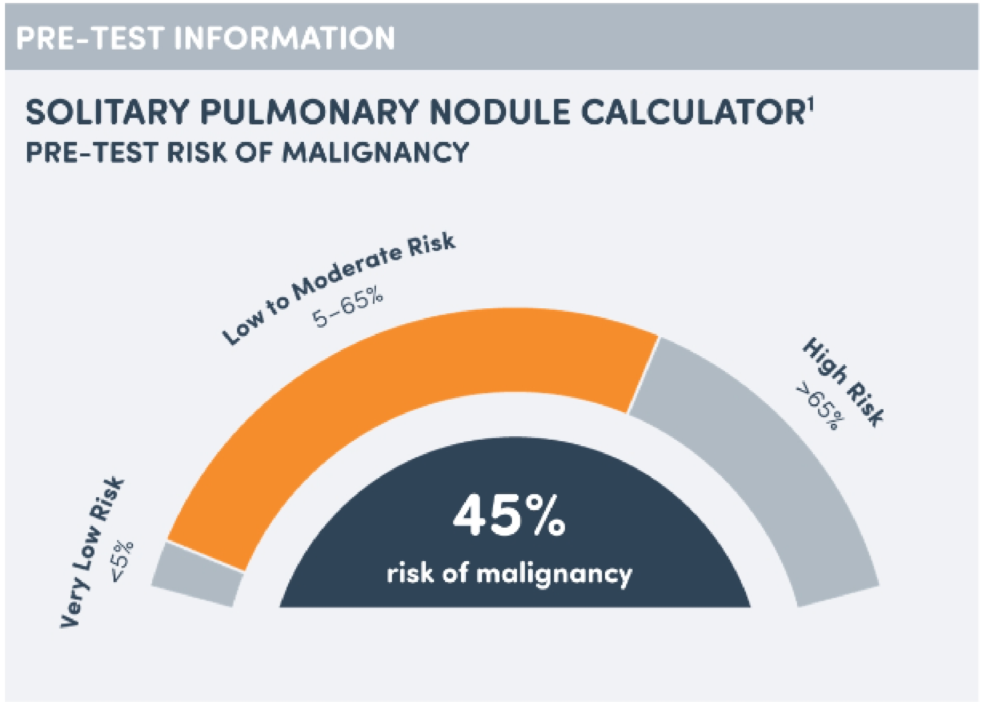
→

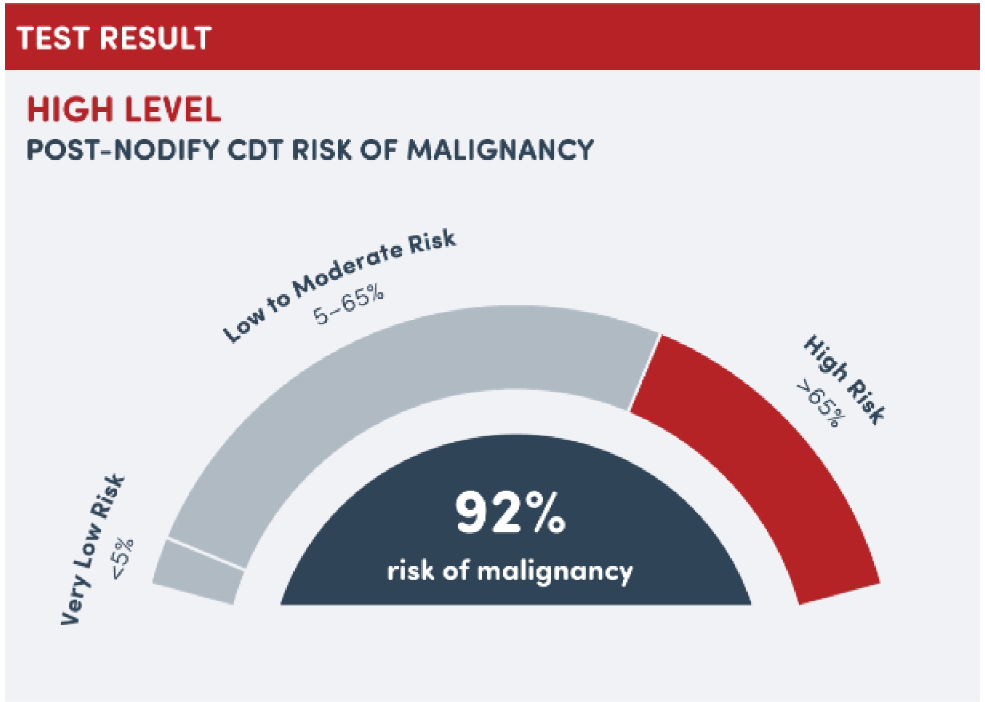


2.2 cm

1.2 cm

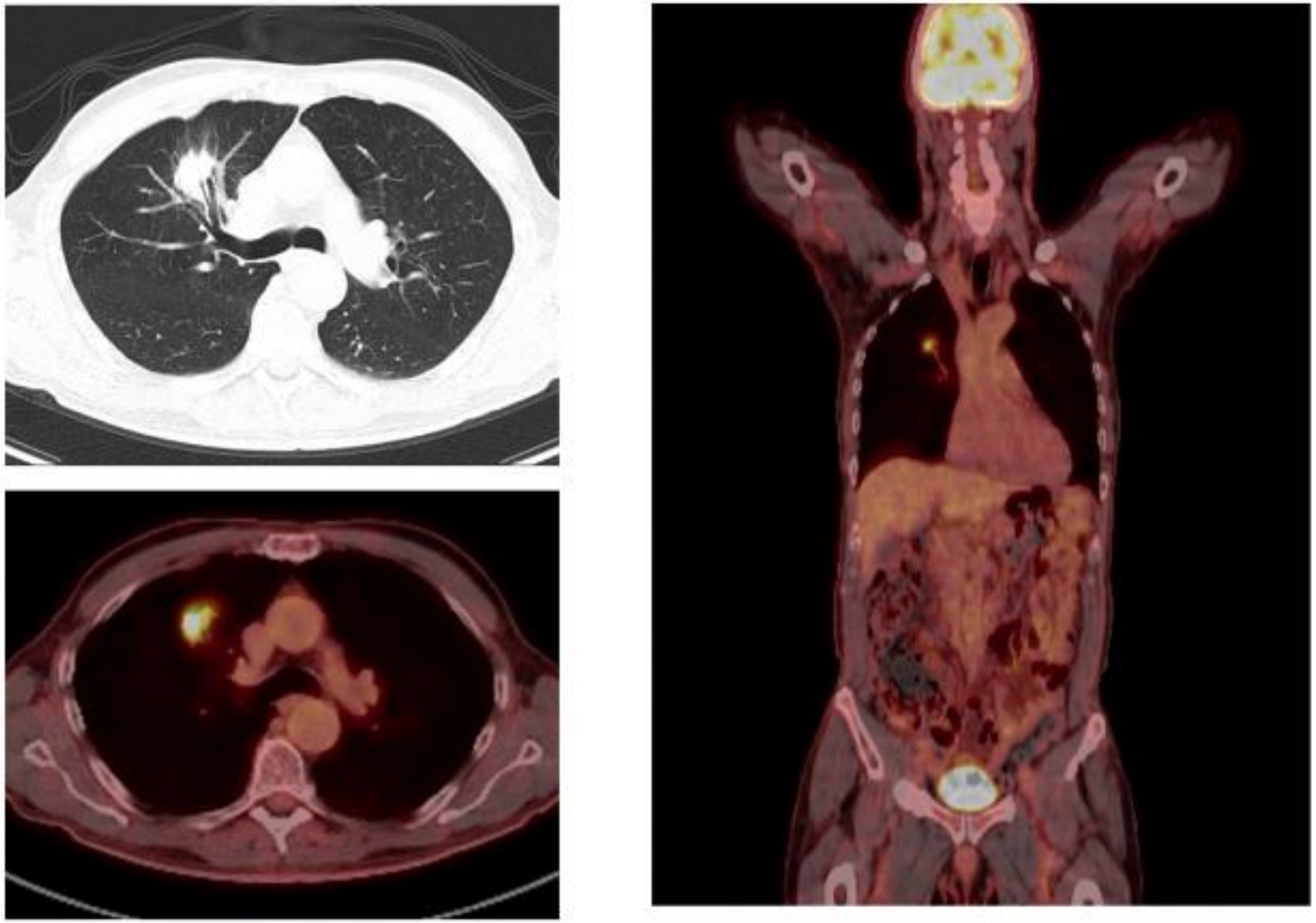
Things I think about





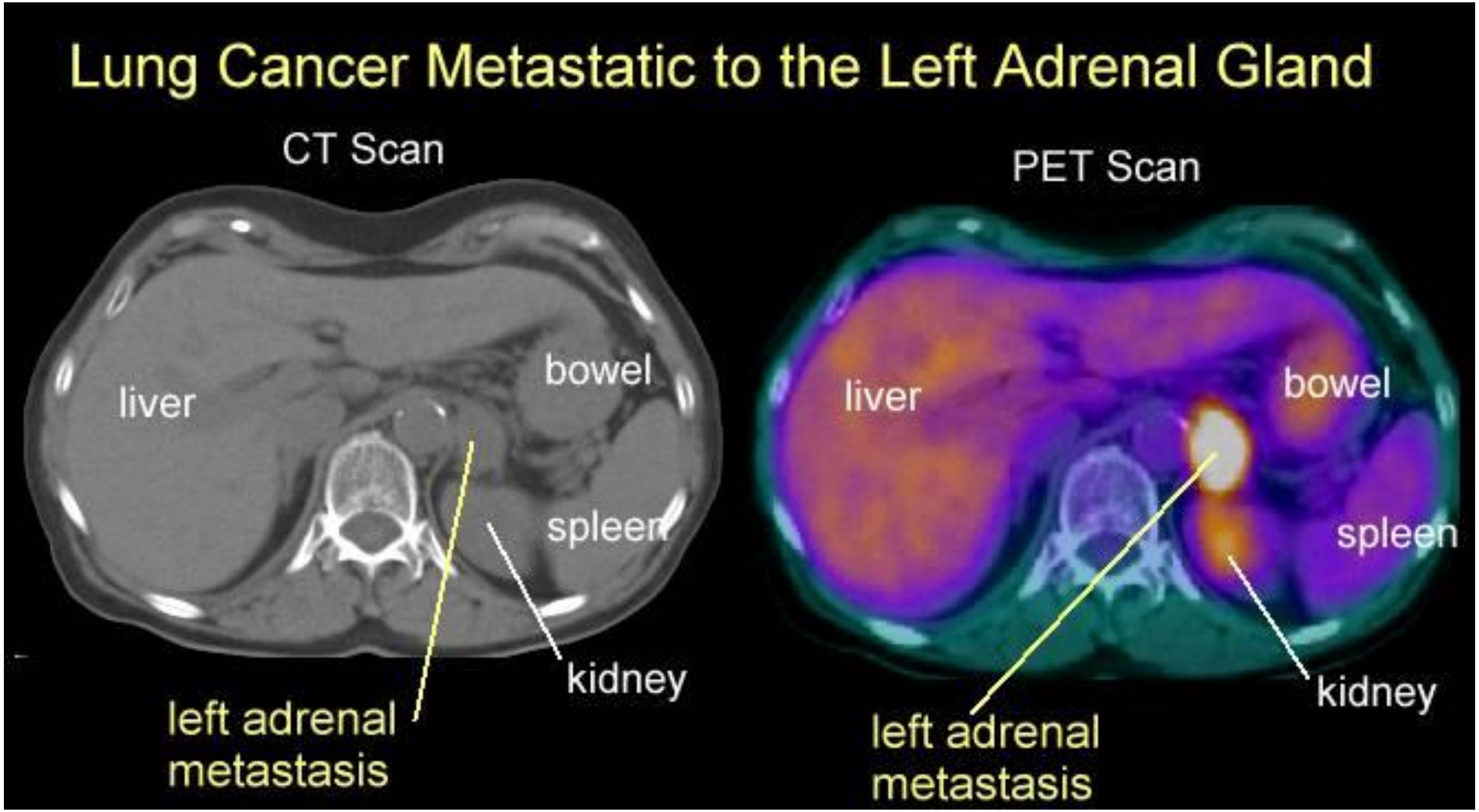
- One more scan? It’s a 10 yr interval without ‘spread’
- Biopsy? (Trust, but verify).
- Surgery?

CT with/without PET scan



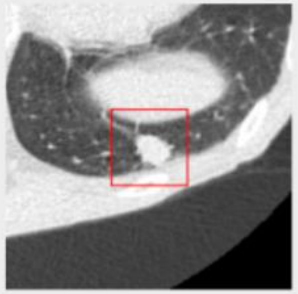
https://www.charterradiology.com/pet-ct/pulmonary-nodule-clinic/

CT with/without PET scan



https://www.aboutcancer.com/adrenal_sah_1007.jpg

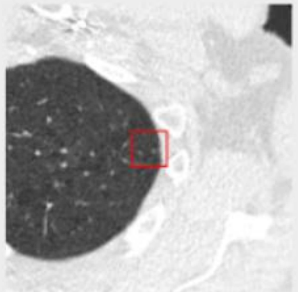
AI in imaging – my practice



Primary

Series	Primary, 4
Key slice	265
Lobe	left lower lobe
Diameter	16.6 x 12.5 mm
Mean Diam.	14.5 mm
Volume	3504 mm³
Type	Solid Nodule

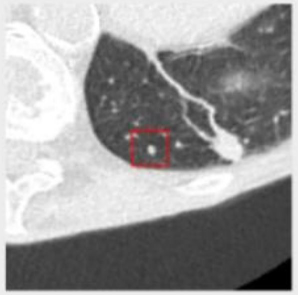
Good to know



Primary

Series	Primary, 4
Key slice	49
Lobe	left upper lobe
Diameter	7.6 x 2.4 mm
Mean Diam.	5.0 mm
Volume	30 mm³
Type	Solid Nodule

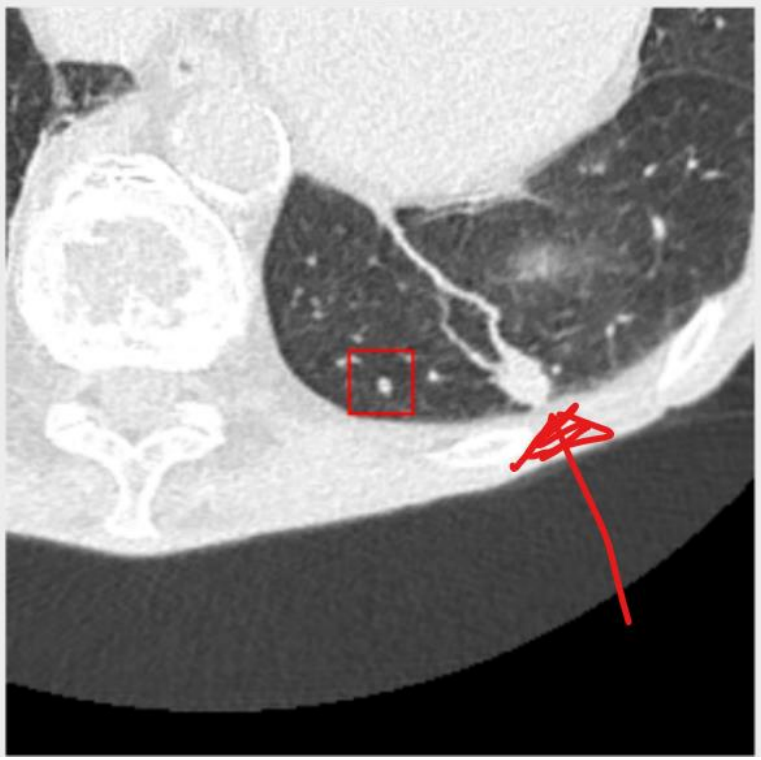
Meh



Primary

Series	Primary, 4
Key slice	259
Lobe	left lower lobe
Diameter	4.3 x 3.3 mm
Mean Diam.	3.8 mm
Volume	29 mm³
Type	Solid Nodule

The *other* one →



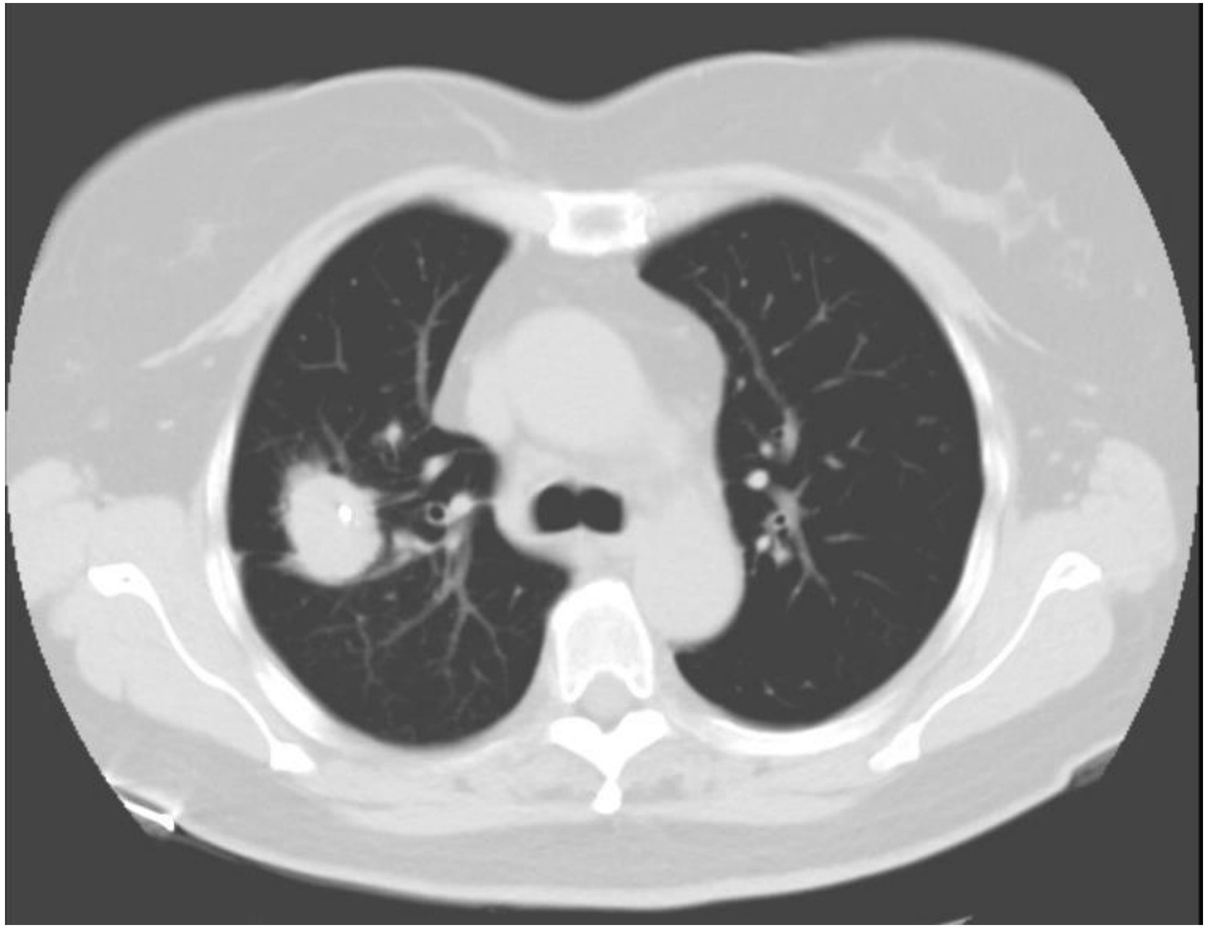
Outline

- Nodule program structure
- Referral patterns & sources
- Biopsy or not
- **Biopsy options**
- Treatment overview
- BONUS - Role of AI

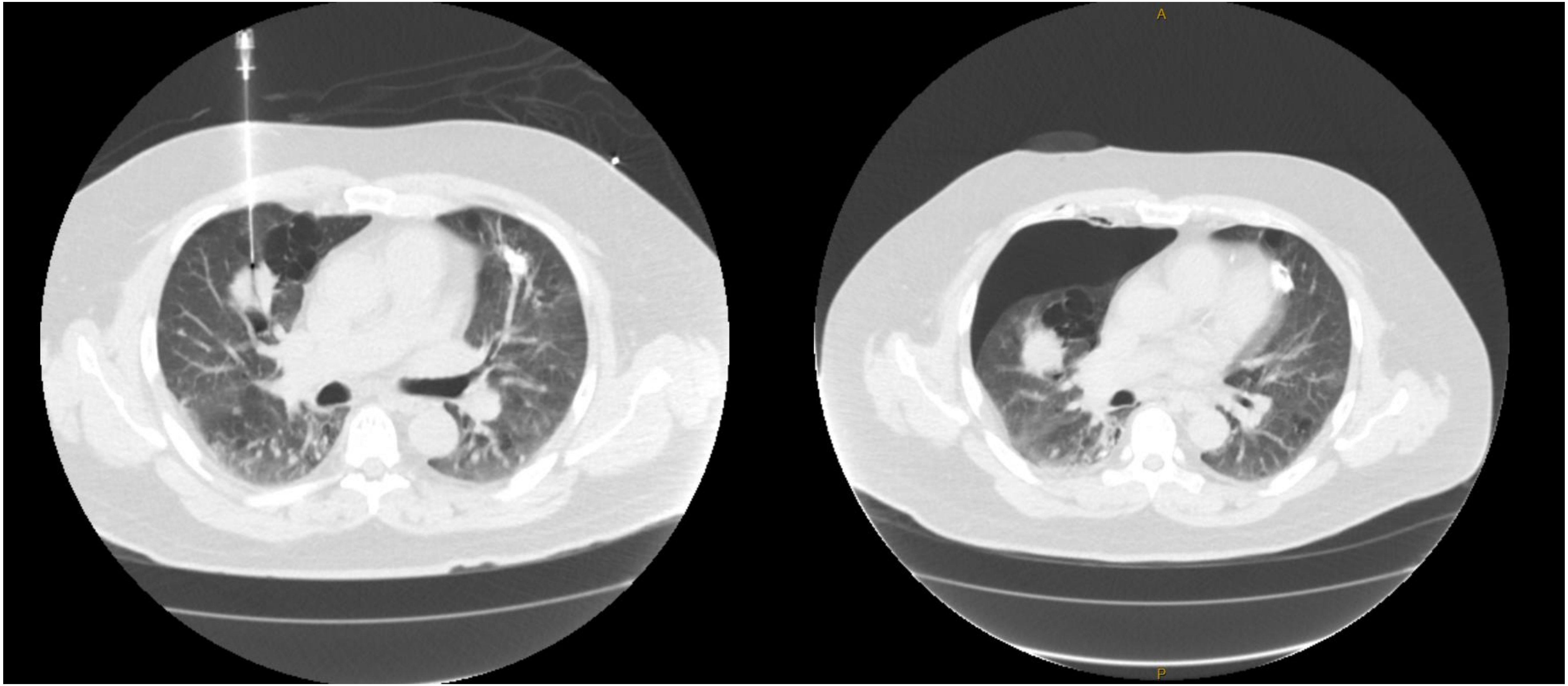
Biopsy options

- Can patient tolerate a biopsy?
  - Empiric radiation
  - Fiducial only

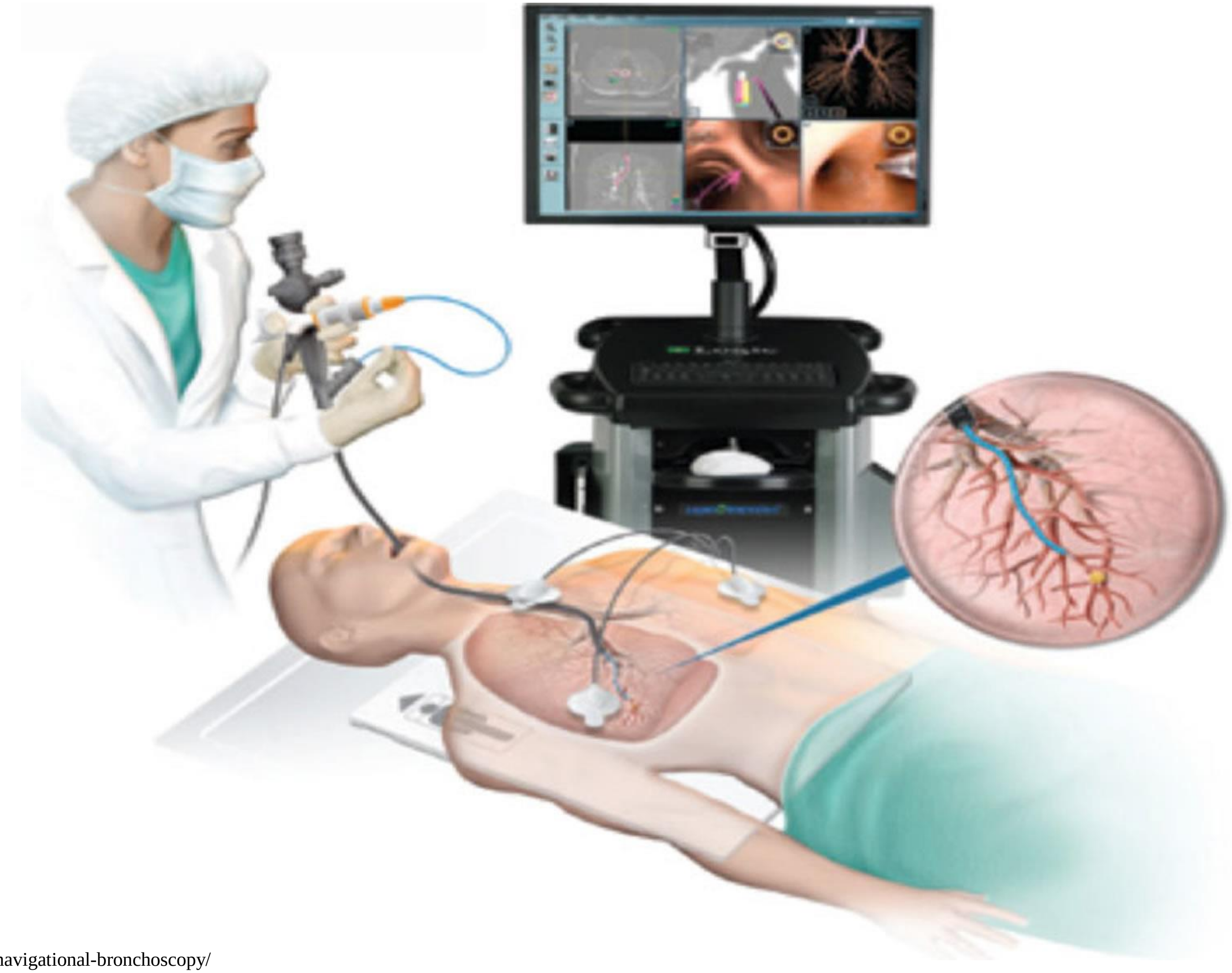
- Technique
  - Transthoracic
  - Bronchoscopic
    - Nodule
    - Nodes – sequence
    - Both
  - Surgical – open/VATS/RATS
  - Metastatic sites



Transthoracic needle biopsy

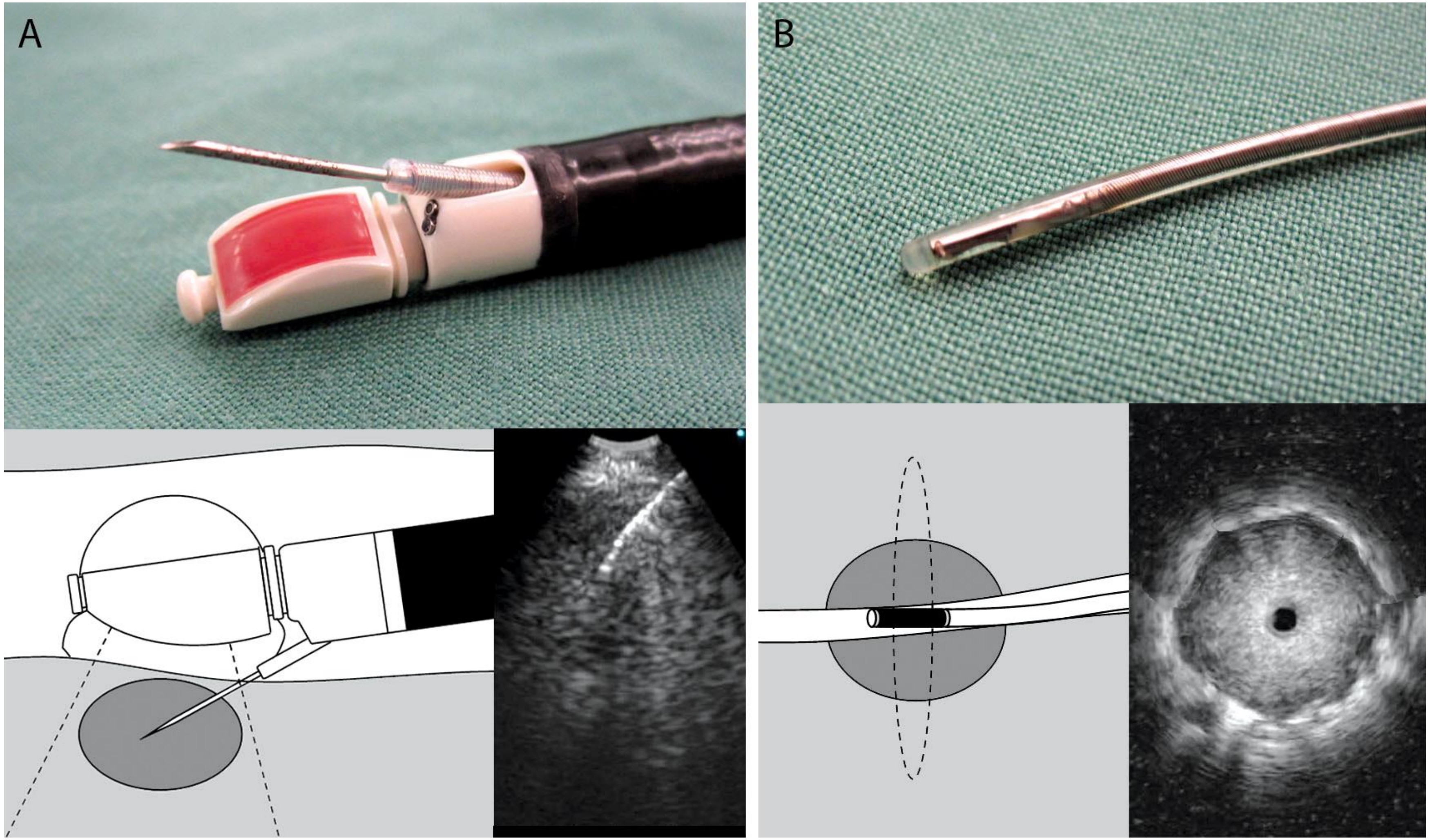


Bronchoscopy – ‘regular’



https://pulmonarypracticeassociates.com/navigational-bronchoscopy/

Bronchoscopy – EBUS (ultrasound)

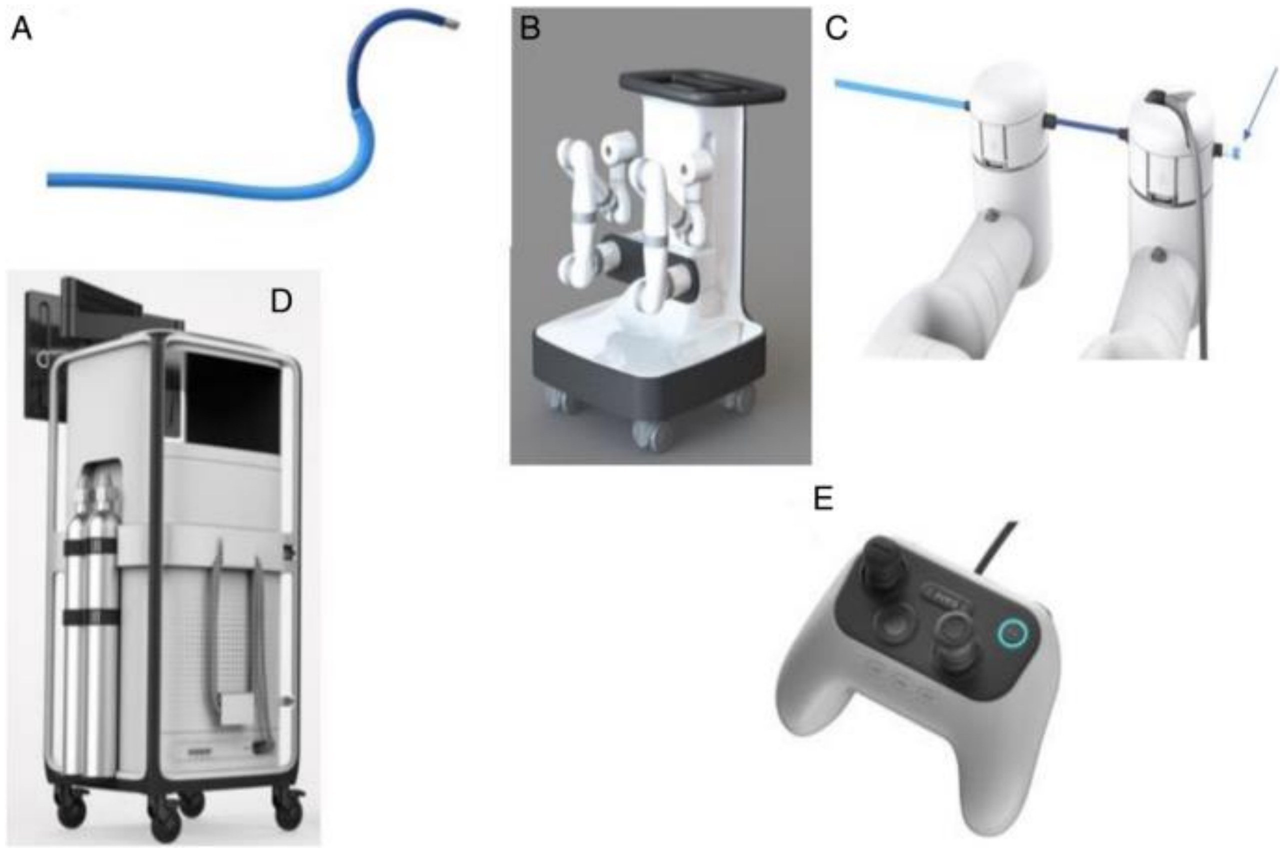


https://mforum.com.au/endobronchial-ultrasound/

Robotic-assisted bronchoscopy – Ion

https://ctsurgery.weillcornell.org/surgical-services/thoracic-surgery/interventional-pulmonology/robotic-bronchoscopy

Robotic-assisted bronchoscopy – Monarch



https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-019-0857-z

Robotic-assisted bronchoscopy – Galaxy

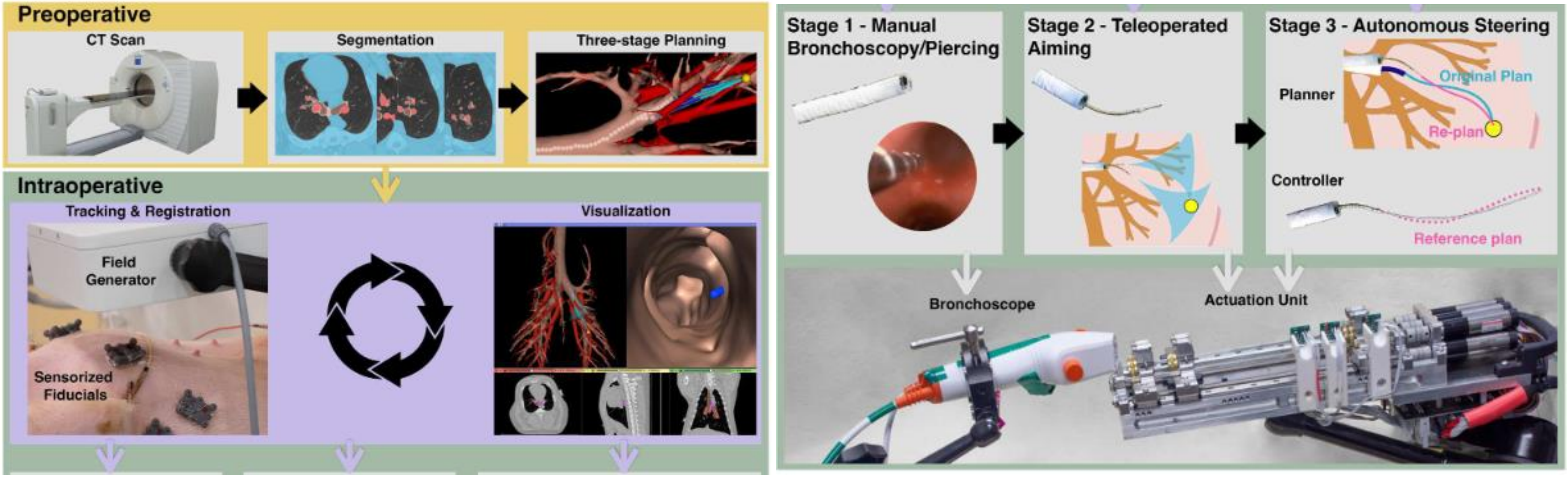
https://www.youtube.com/watch?app=desktop&v=l-nk3SEvpKQ

Future of biopsy?

Sci Robot. 2023 Sep 20;8(82):eadf7614. doi: 10.1126/scirobotics.adf7614. Epub 2023 Sep 20.

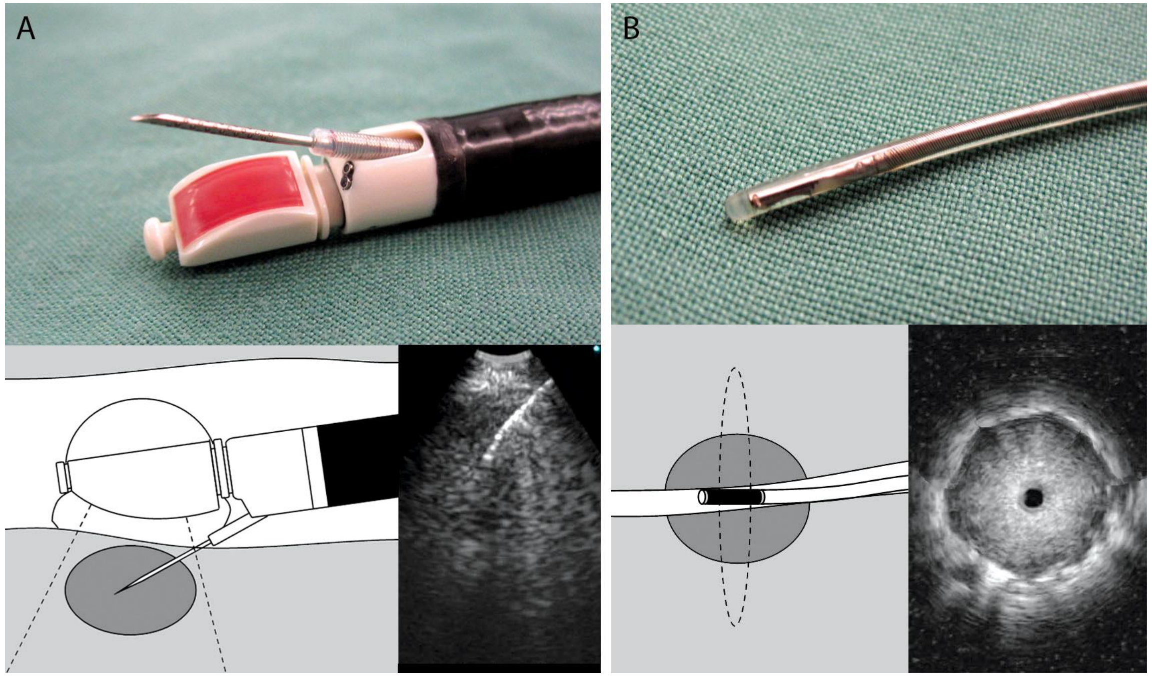
Autonomous medical needle steering in vivo

Alan Kuntz [1], Maxwell Emerson [2], Tayfun Efe Ertop [2], Inbar Fried [3], Mengyu Fu [3], Janine Hoelscher [3], Margaret Rox [2], Jason Akulian [4], Erin A Gillaspie [5], Yueh Z Lee [6], Fabien Maldonado [5], Robert J Webster 3rd [2], Ron Alterovitz [3]



If I had to choose just 1?

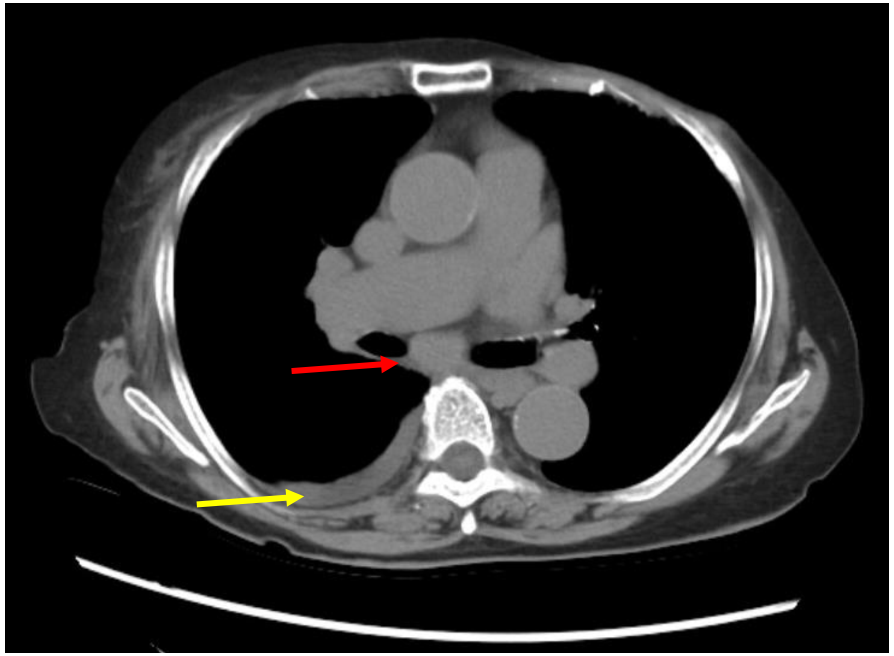
- Transthoracic needle aspiration
- Flexible bronchoscopy
- **EBUS (endobronchial ultrasound guided FNA)**
- Robotic bronchoscopy
- Surgery

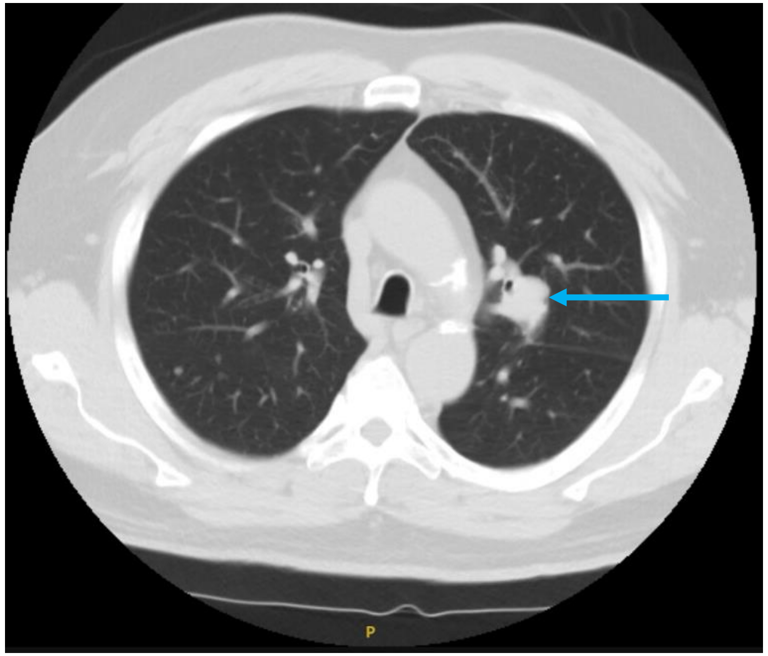


https://mforum.com.au/endobronchial-ultrasound/

Choosing the method of biopsy

- Ensure the diagnosis
- Ensure the highest stage
- Decision is either MDD or proceduralist – Pulmonary (IP/ADB) or Thoracic Surgery





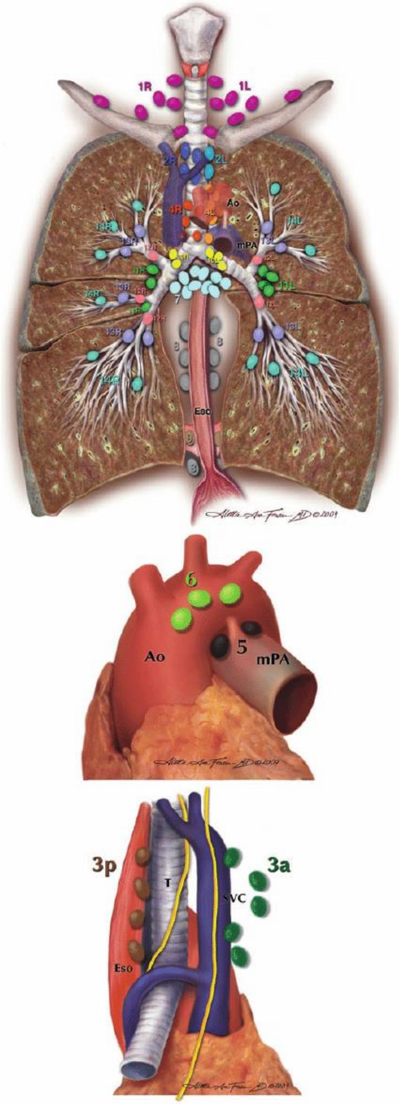
Lung cancer stages

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1 to 2*	IA2	IIB	IIIA	IIIB
	T1c *>2 to 3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3 to 4*	IB	IIB	IIIA	IIIB
	T2b *>4 to 5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5 to 7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Original figure modified for this publication. Detterbeck FC, Boffa DJ, Kim AW, et al. The eighth edition lung cancer stage classification. Chest 2017; 151:193. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 110964 Version 2.0

Lung cancer stages



Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

Superior mediastinal nodes

Upper zone

2R Upper paratracheal (right)
2L Upper paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower paratracheal (right)
4L Lower paratracheal (left)

Aortic nodes

AP zone

5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

Inferior mediastinal nodes

Subcarinal zone

7 Subcarinal

Lower zone

8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 nodes

Hilar/interlobar zone

10 Hilar
11 Interlobar

Peripheral zone

12 Lobar
13 Segmental
14 Subsegmental

N0	N1	N2	N3
IA1	IIB	IIIA	IIIB
IA2	IIB	IIIA	IIIB
IA3	IIB	IIIA	IIIB
IB	IIB	IIIA	IIIB
IB	IIB	IIIA	IIIB
IIA	IIB	IIIA	IIIB
IIB	IIIA	IIIB	IIIC
IIB	IIIA	IIIB	IIIC
IIB	IIIA	IIIB	IIIC
IIIA	IIIA	IIIB	IIIC
IIIA	IIIA	IIIB	IIIC
IIIA	IIIA	IIIB	IIIC
IVA	IVA	IVA	IVA
IVA	IVA	IVA	IVA
IVA	IVA	IVA	IVA
IVB	IVB	IVB	IVB

he eighth edition lung cancer stage classification. Chest 2017; 151:193. Table used with the permission

Why do we stage lung cancer

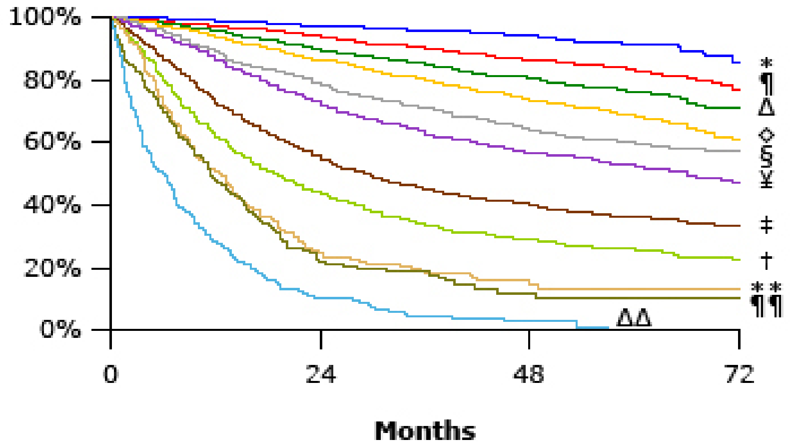
Stage shift

- Table shows differences in survival depending on stage of diagnosis

E.g.

- 97% patients alive at 2yr for stage IA1 (earliest)

- Only 10% patients alive at 2yr for stage IVB (last stage)



8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
¶¶ IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

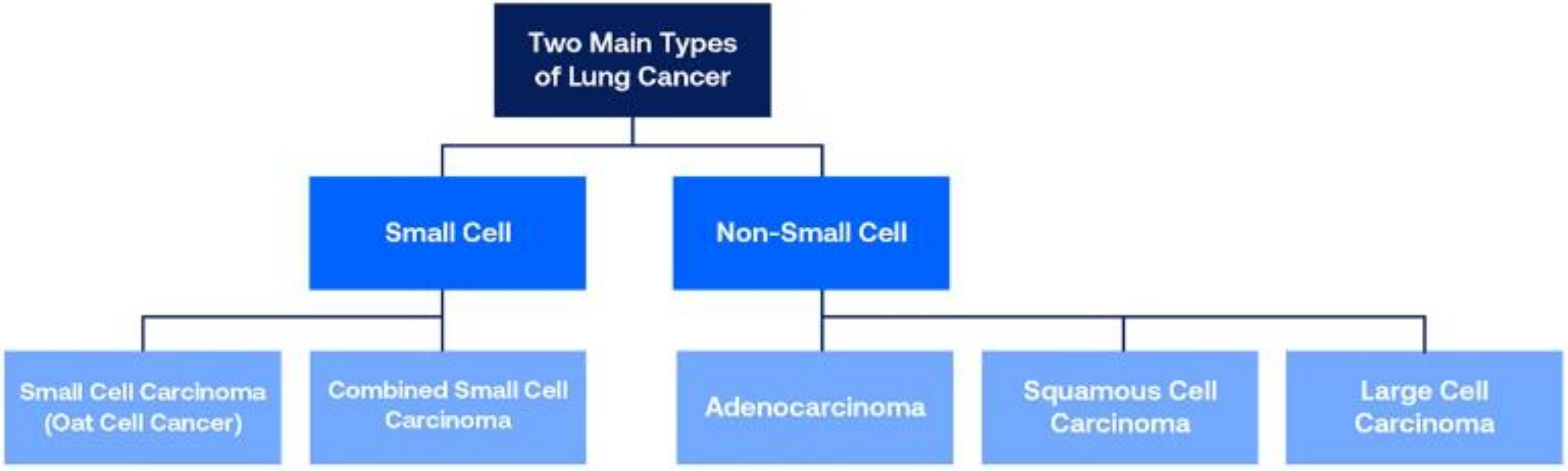
www.uptodate.com

Outline

- Nodule program structure
- Referral patterns & sources
- Biopsy or not
- Biopsy options
- **Treatment overview**
- BONUS - Role of AI

Treatment overview

- Types of lung cancer



www.lung.org

Lung Cancer Treatment

- Depends on type – Small cell lung cancer (SCLC) vs NSCLC (Non-small cell lung cancer)

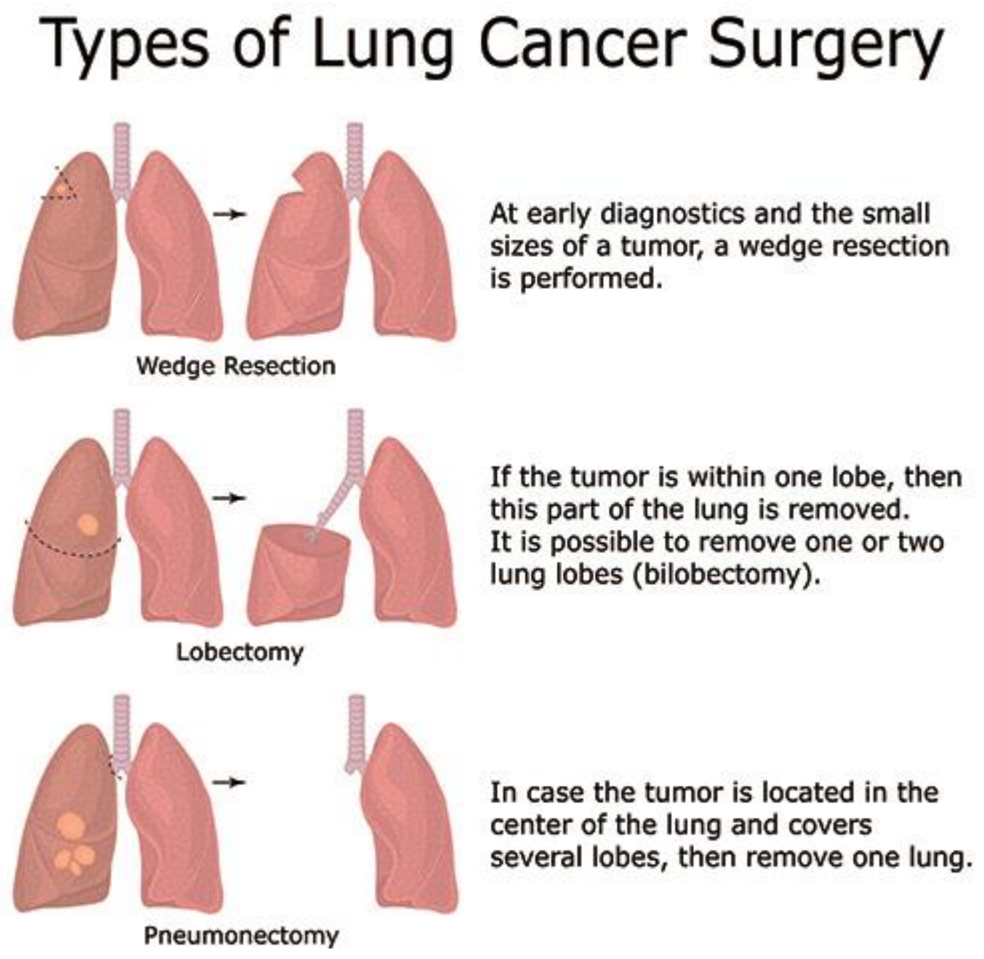
- Role of genetic analysis

- Surgery – open/VATS/RATS

- Non-surgical options
  - Chemotherapy
  - Immunotherapy
  - Radiation therapy

Lung cancer surgery

- Open
- Video-assisted thoracoscopic surgery (VATS)
- Robotic-assisted thoracoscopic surgery (RATS)



https://cancer.stonybrookmedicine.edu/LungCancer/Surgery

Chemotherapy & immunotherapy

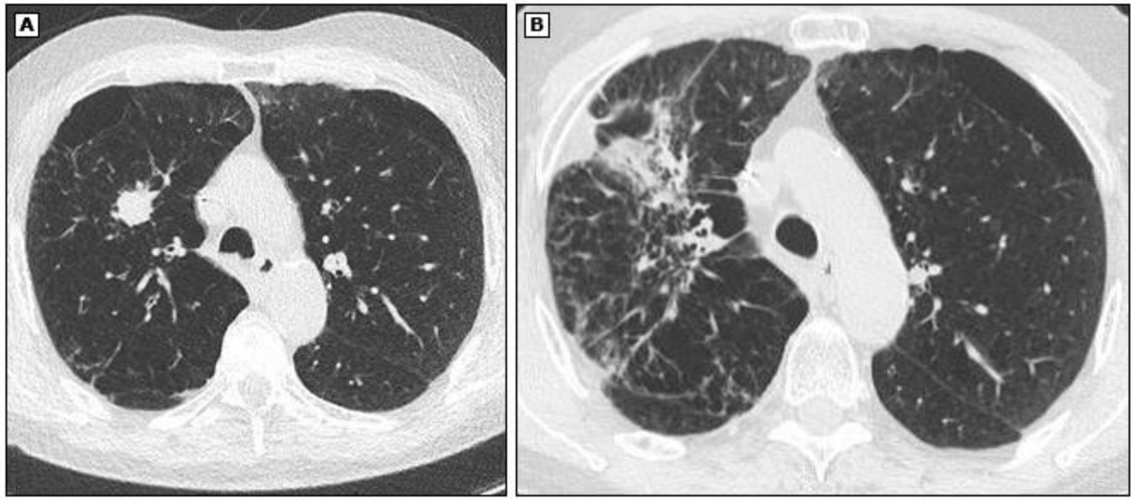
- Biomarker testing
  - Tissue
  - Liquid

markers with current FDA-approved treatments are:

- Epidermal Growth Factor Receptor (EGFR) mutation
- Anaplastic Lymphoma Kinase (ALK) gene rearrangement
- ROS1 rearrangement
- BRAF V600E mutation
- NTRK fusion
- MET amplification or MET exon 14 skipping
- RET rearrangements
- PD-L1 level (a protein that may help determine your tumor's likelihood of responding well to certain immunotherapy drugs.)

www.lung.org

Radiation therapy



(A) CT of a 76-year old male, former smoker with a 19 mm right upper-lobe non-small cell lung cancer. Due to an FEV1 of 0.65 L (23% predicted) and a DLCO of 5.6 (23% predicted), he was not offered surgery and underwent SBRT (5 fractions, 6000 cGy).

(B) CT one year post SBRT with postradiation changes but no evidence of recurrence.

CT: computed tomography; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lungs for carbon monoxide; SBRT: stereotactic body radiation therapy; cGy: centigray.

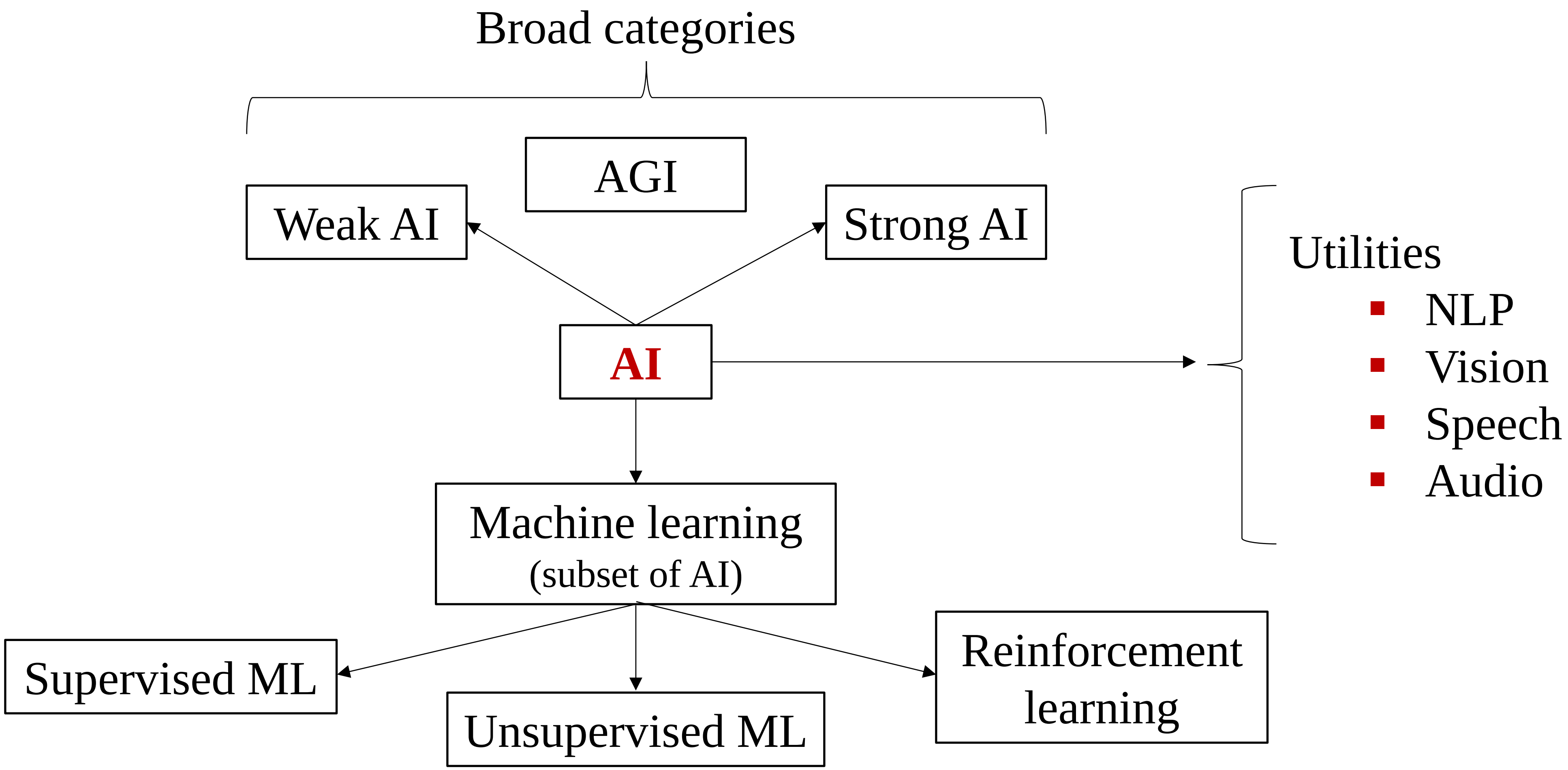
Courtesy of David E Midthun, MD.

Graphic 121114 Version 1.0

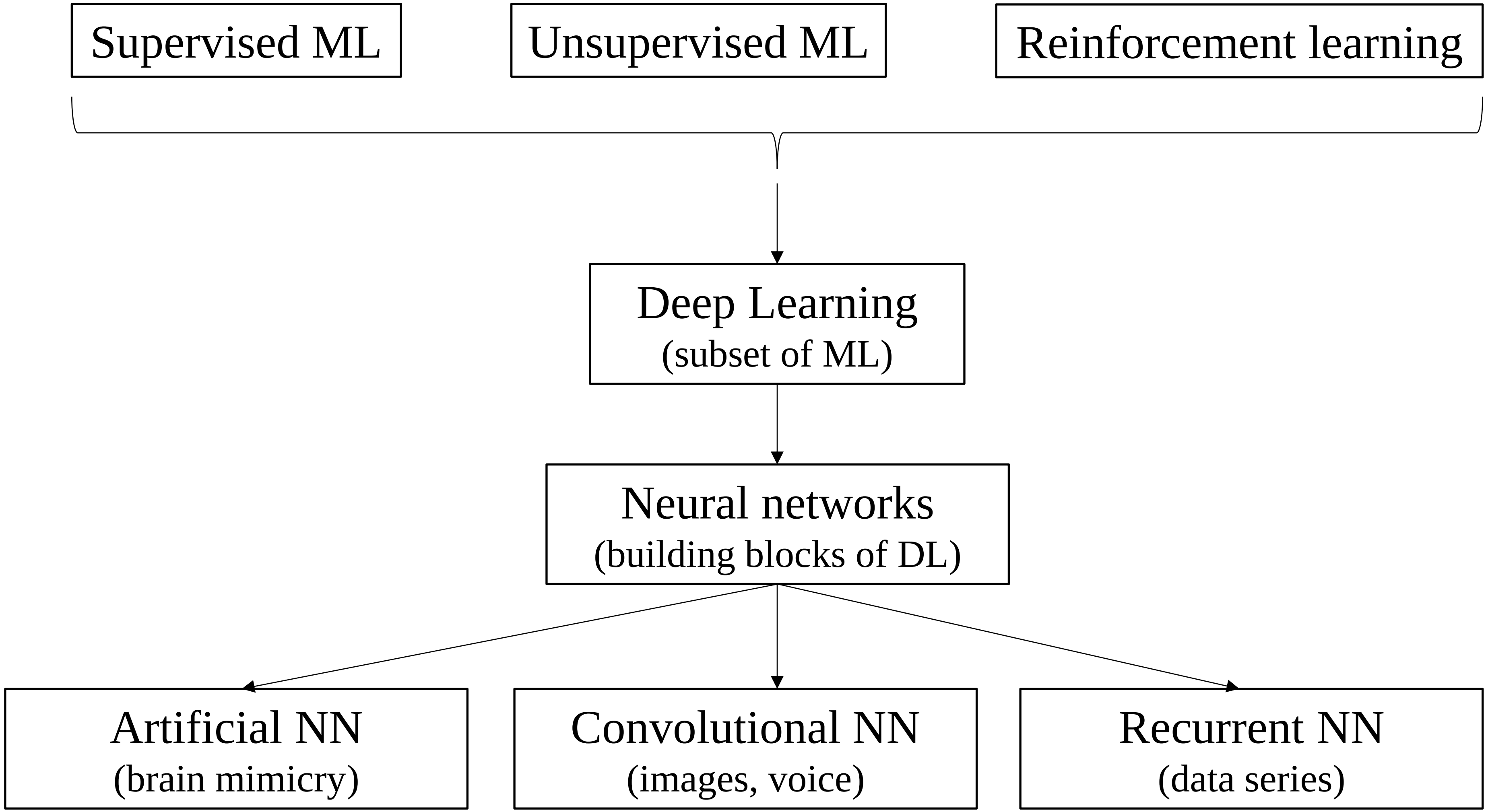
Outline

- Nodule program structure
- Referral patterns & sources
- Biopsy or not
- Biopsy options
- Treatment overview
- **BONUS - Role of AI**

AI logic tree



AI logic tree



Lung nodules – ‘why’ AI

- Pattern recognition – a need for patients & a strength of AI
- Vast quantities of images and reports
- Does not fatigue
- Image analysis
- Current risk estimations
- Future risk predictions

Lung nodules – 'how' AI

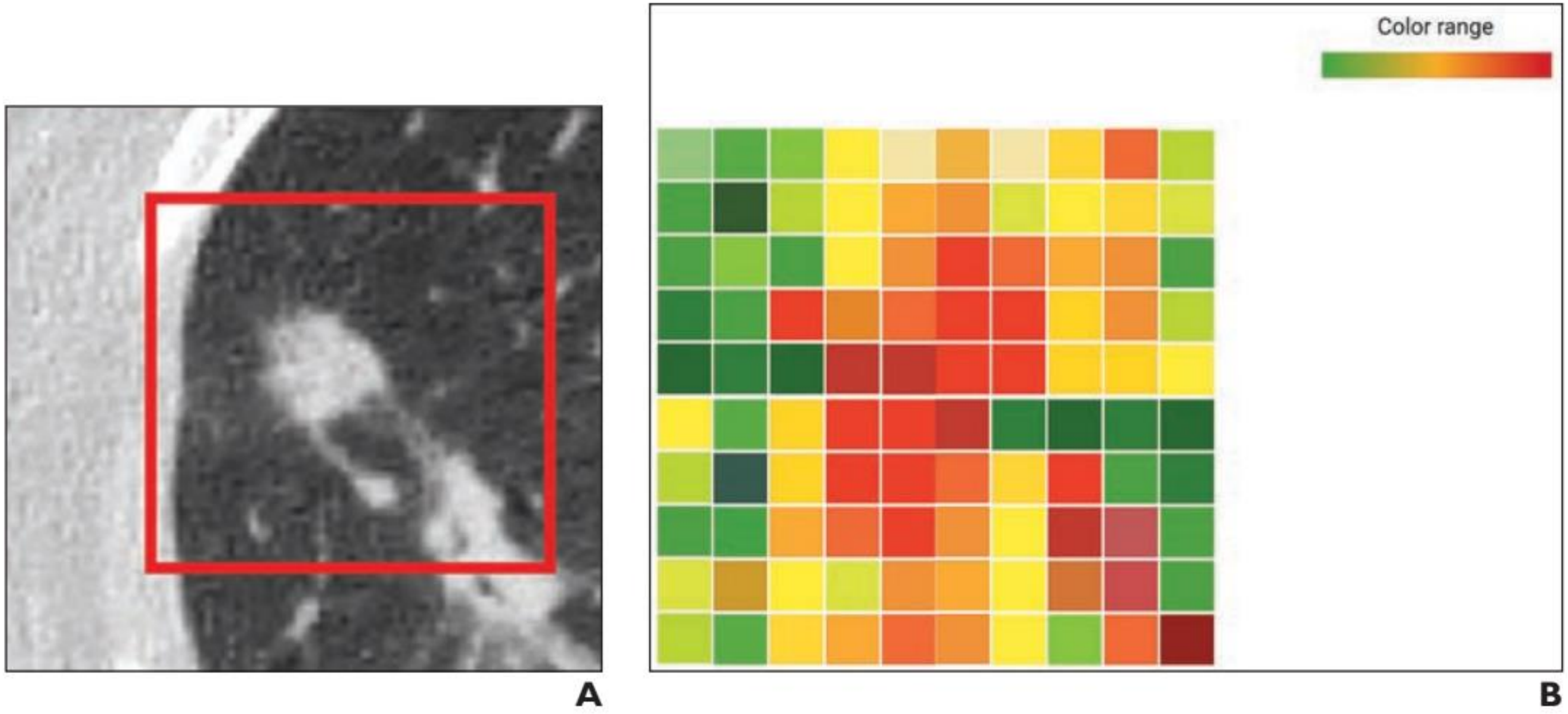
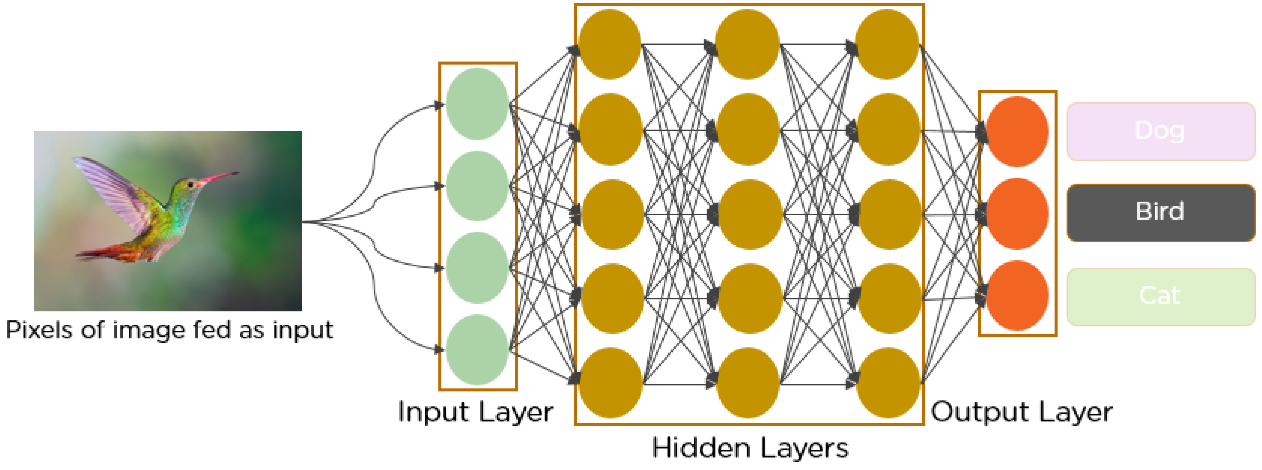


Fig. 7—Generation of heat map.
A, Axial chest CT image shows right lung nodule (*box*).
B, Heat map generated by artificial intelligence (AI) tool for demarcated region in **A** shows areas within nodule that AI algorithm considers concerning. Deeper shades of green indicate lesser degrees of concern; deeper shades of red indicate greater degrees of concern. (Created with BioRender.com. Used with permission of BioRender)

Liu JA, Yang IY, Tsai EB. Artificial Intelligence (AI) for Lung Nodules, From the AJR Special Series on AI Applications. AJR Am J Roentgenol. 2022 Nov;219(5):703-712. doi: 10.2214/AJR.22.27487. Epub 2022 May 11. PMID: 35544377.

Computer vision

- Form of deep learning
- Direct assessment of pixels
- Convolutional neural network
  - **Analogous to human brain**
  - Input layer → no. of hidden layers → output layer
  - Output compared to 'ground truth'



https://www.analyticsvidhya.com/blog/2021/05/convolutional-neural-networks-cnn/

Natural Language Processing

- Is distinct from computer vision
  - Images vs reports
- Began in 1950s as AI ←→Linguistics
- Must extract meaning from written text
- Use large volumes annotated text to train algorithms
- **Medical speak/grammar/jargon does not follow traditional rules & is challenging**

J Am Med Inform Assoc. 2011 Sep-Oct; 18(5): 544–551.
doi: 10.1136/amiajnl-2011-000464

Natural language processing: an introduction

Prakash M Nadkarni,[1] Lucila Ohno-Machado,[2] and Wendy W Chapman[2]

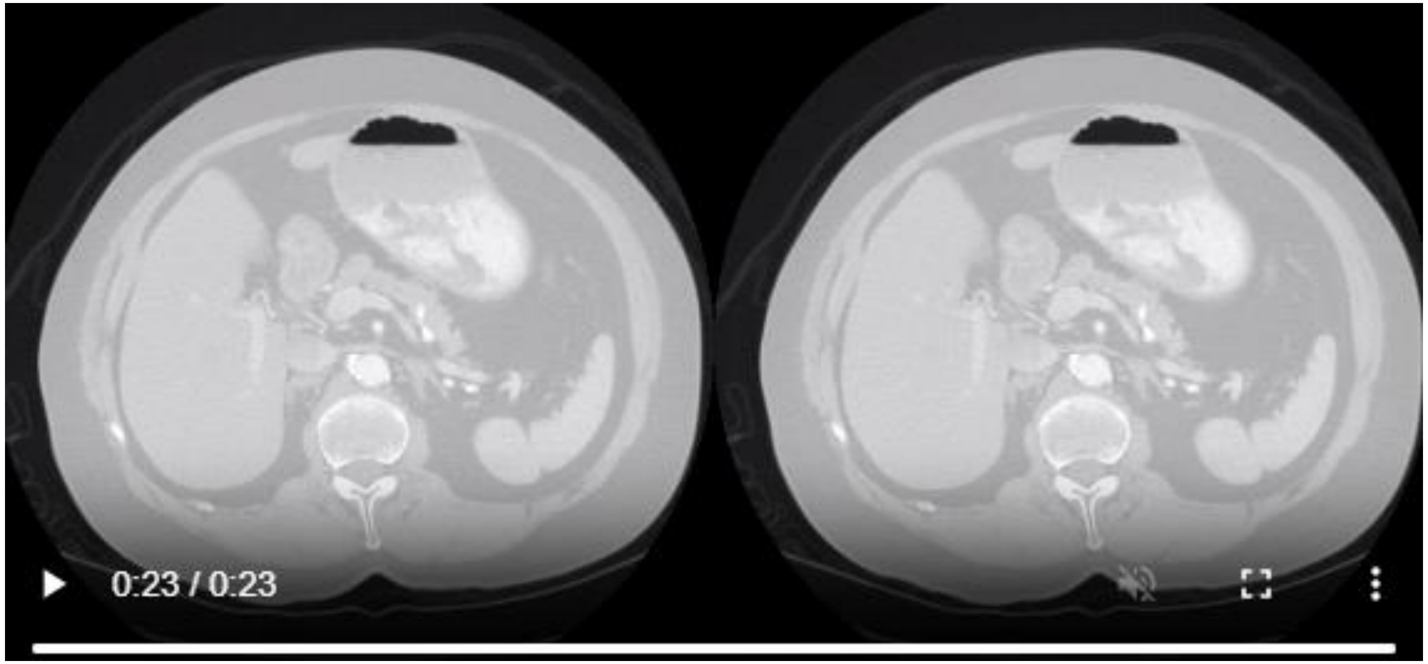
Riverain – ClearRead CT

Vessel suppression

Comparative Study > AJR Am J Roentgenol. 2018 Mar;210(3):480-488.
doi: 10.2214/AJR.17.18718. Epub 2018 Jan 16.

JOURNAL CLUB: Computer-Aided Detection of Lung Nodules on CT With a Computerized Pulmonary Vessel Suppressed Function

ShihChung B Lo [1] [2], Matthew T Freedman [1] [2], Laura B Gillis [3], Charles S White [4], Seong K Mun [1]



Optellum – Virtual Nodule Clinic

LCP-CNN

- Trained on NLST data
- LCP likelihood score – 0 to 100%
- Externally validated at 2 institutions
  (VUMC – Vanderbilt – US, OUH – Oxford – UK)
- VUMC – prospective, OUH – retrospective
- Computer Vision – Dense Convolutional Network (type of CNN)
- **Clinical variables found to not contribute to the score**, and were excluded
  (strength or weakness?)

› Am J Respir Crit Care Med. 2020 Jul 15;202(2):241-249. doi: 10.1164/rccm.201903-0505OC.

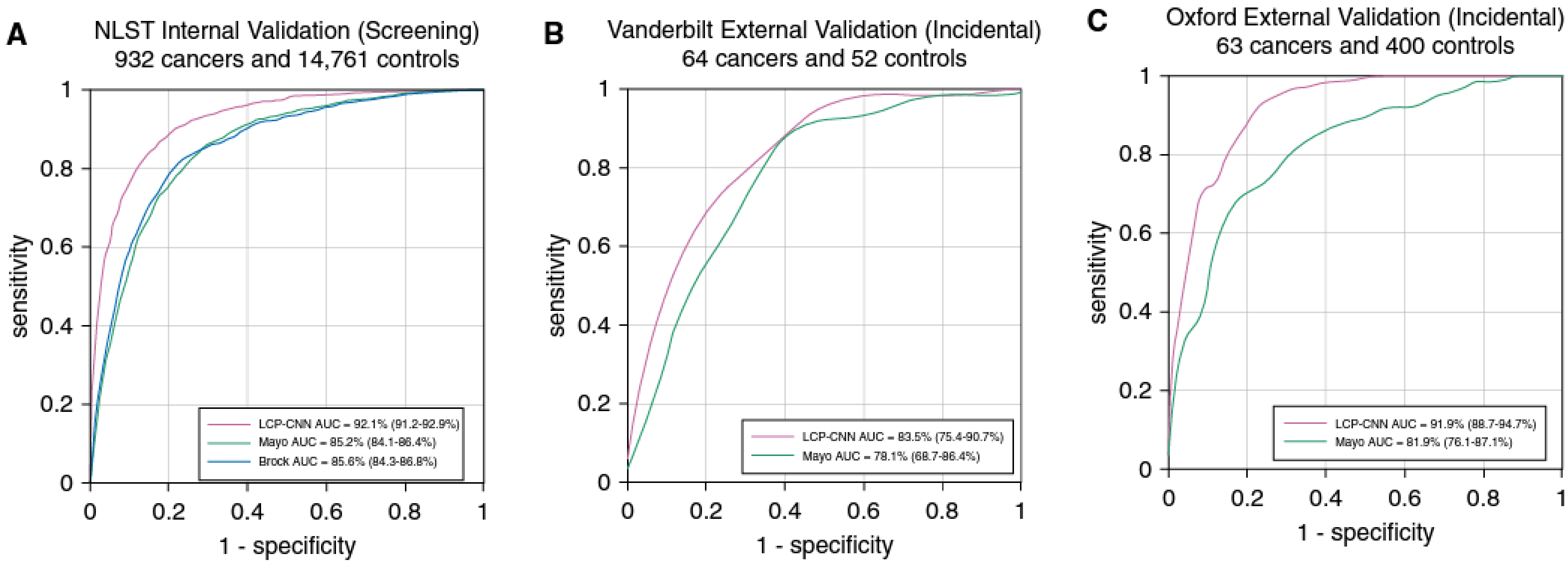
Assessing the Accuracy of a Deep Learning Method to Risk Stratify Indeterminate Pulmonary Nodules

Pierre P Massion [1] [2], Sanja Antic [1], Sarim Ather [3], Carlos Arteta [4], Jan Brabec [5], Heidi Chen [6], Jerome Declerck [4], David Dufek [5], William Hickes [3], Timor Kadir [4], Jonas Kunst [5], Bennett A Landman [7], Reginald F Munden [8], Petr Novotny [4], Heiko Peschl [3], Lyndsey C Pickup [4], Catarina Santos [4], Gary T Smith [9] [10], Ambika Talwar [3], Fergus Gleeson [3]

Massion PP, Antic S, Ather S, Arteta C, Brabec J, Chen H, Declerck J, Dufek D, Hickes W, Kadir T, Kunst J, Landman BA, Munden RF, Novotny P, Peschl H, Pickup LC, Santos C, Smith GT, Talwar A, Gleeson F. Assessing the Accuracy of a Deep Learning Method to Risk Stratify Indeterminate Pulmonary Nodules. Am J Respir Crit Care Med. 2020 Jul 15;202(2):241-249. doi: 10.1164/rccm.201903-0505OC. PMID: 32326730; PMCID: PMC7365375.

Optellum – Virtual Nodule Clinic

LCP-CNN – superior AUC to Mayo and Brock



Massion PP, Antic S, Ather S, Arteta C, Brabec J, Chen H, Declerck J, Dufek D, Hickes W, Kadir T, Kunst J, Landman BA, Munden RF, Novotny P, Peschl H, Pickup LC, Santos C, Smith GT, Talwar A, Gleeson F. Assessing the Accuracy of a Deep Learning Method to Risk Stratify Indeterminate Pulmonary Nodules. Am J Respir Crit Care Med. 2020 Jul 15;202(2):241-249. doi: 10.1164/rccm.201903-0505OC. PMID: 32326730; PMCID: PMC7365375.

Optellum – Virtual Nodule Clinic

LCP-CNN vs Brock (UK study)

- Incidental nodules 5-15mm
- 3 UK hospitals
- All cancer dx had histological ground truth
- LCP-CNN – 1 false negative, Brock – 6 FN
- Similar specificity

Multicenter Study > Thorax. 2020 Apr;75(4):306-312. doi: 10.1136/thoraxjnl-2019-214104. Epub 2020 Mar 5.

External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules

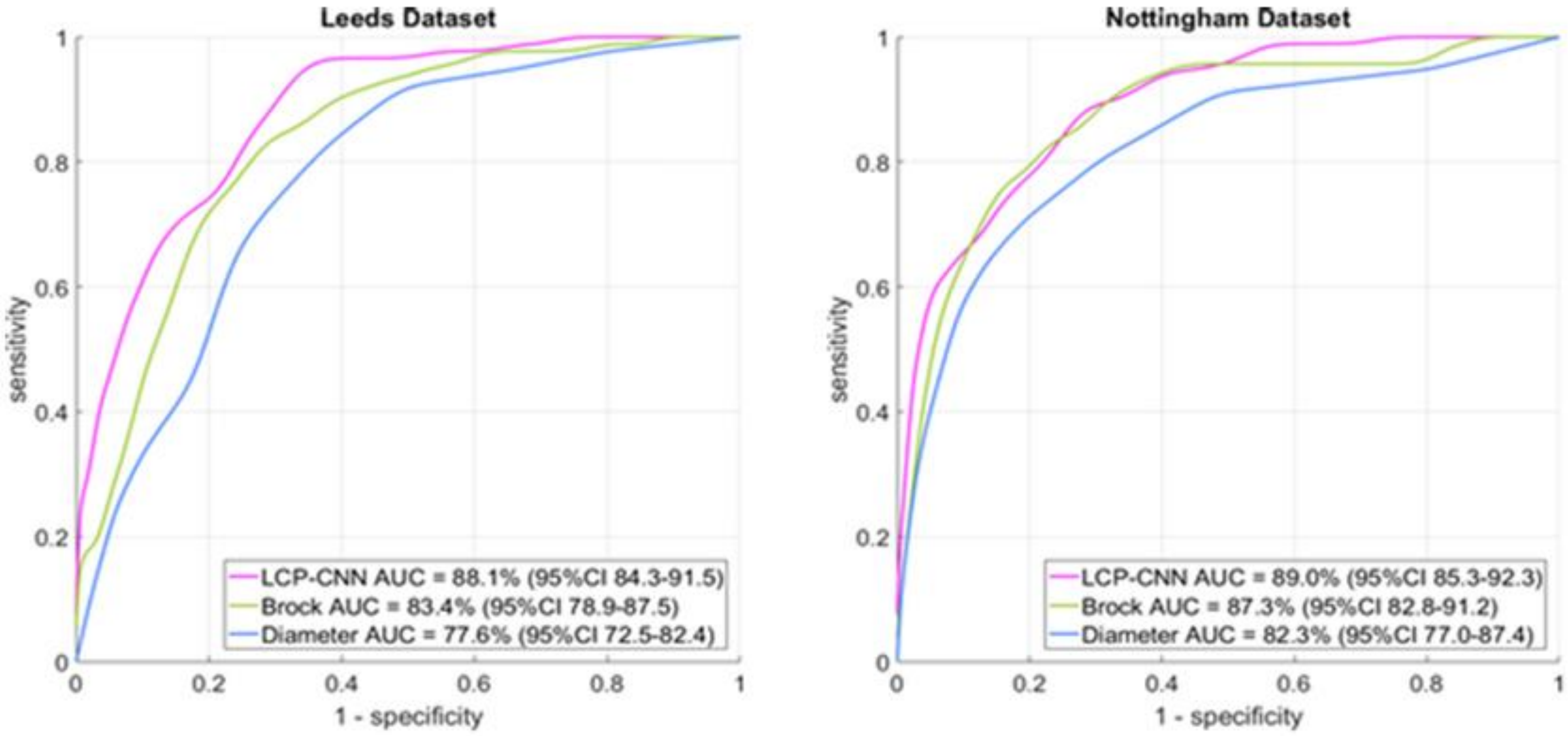
David R Baldwin [1], Jennifer Gustafson [2], Lyndsey Pickup [3], Carlos Arteta [3], Petr Novotny [4], Jerome Declerck [3], Timor Kadir [3], Catarina Figueiras [2], Albert Sterba [5], Alan Exell [6], Vaclav Potesil [3], Paul Holland [7], Hazel Spence [7], Alison Clubley [7], Emma O'Dowd [8], Matthew Clark [9], Victoria Ashford-Turner [10], Matthew Ej Callister [10], Fergus V Gleeson [2]

"LCP-CNN score has better discrimination and allows a larger proportion of benign nodules to be identified without missing cancers than the Brock model."

Baldwin DR, Gustafson J, Pickup L, Arteta C, Novotny P, Declerck J, Kadir T, Figueiras C, Sterba A, Exell A, Potesil V, Holland P, Spence H, Clubley A, O'Dowd E, Clark M, Ashford-Turner V, Callister ME, Gleeson FV. External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules. Thorax. 2020 Apr;75(4):306-312. doi: 10.1136/thoraxjnl-2019-214104. Epub 2020 Mar 5. PMID: 32139611; PMCID: PMC7231457.

Optellum – Virtual Nodule Clinic

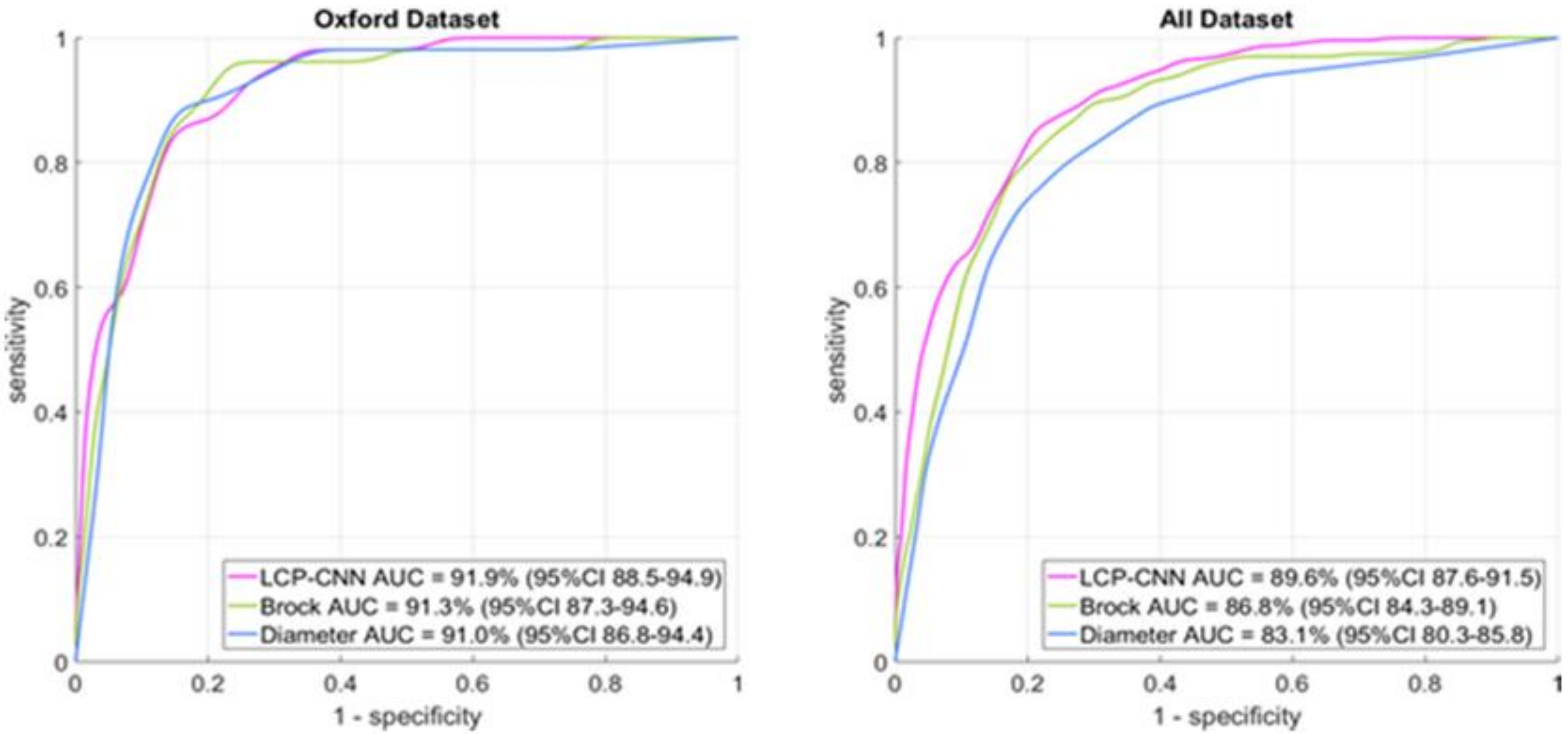
LCP-CNN vs Brock (UK study)



Baldwin DR, Gustafson J, Pickup L, Arteta C, Novotny P, Declerck J, Kadir T, Figueiras C, Sterba A, Exell A, Potesil V, Holland P, Spence H, Clubley A, O'Dowd E, Clark M, Ashford-Turner V, Callister ME, Gleeson FV. External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules. Thorax. 2020 Apr;75(4):306-312. doi: 10.1136/thoraxjnl-2019-214104. Epub 2020 Mar 5. PMID: 32139611; PMCID: PMC7231457.

Optellum – Virtual Nodule Clinic

LCP-CNN vs Brock (UK study)



Baldwin DR, Gustafson J, Pickup L, Arteta C, Novotny P, Declerck J, Kadir T, Figueiras C, Sterba A, Exell A, Potesil V, Holland P, Spence H, Clubley A, O'Dowd E, Clark M, Ashford-Turner V, Callister ME, Gleeson FV. External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules. Thorax. 2020 Apr;75(4):306-312. doi: 10.1136/thoraxjnl-2019-214104. Epub 2020 Mar 5. PMID: 32139611; PMCID: PMC7231457.

Open-source *threat (?)* – Sybil – publicly available model & annotations

- **Hypothesis:** DL model assessing entire volumetric data can predict cancer risk without demographic or clinical data
- **Hypothesis:** future cancer risk can be predicted without current nodule
- Development
  - 3 sets – NLST, MGH, CGMH (Taiwan)
  - CGMH – even never-smokers can screen

› J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12.

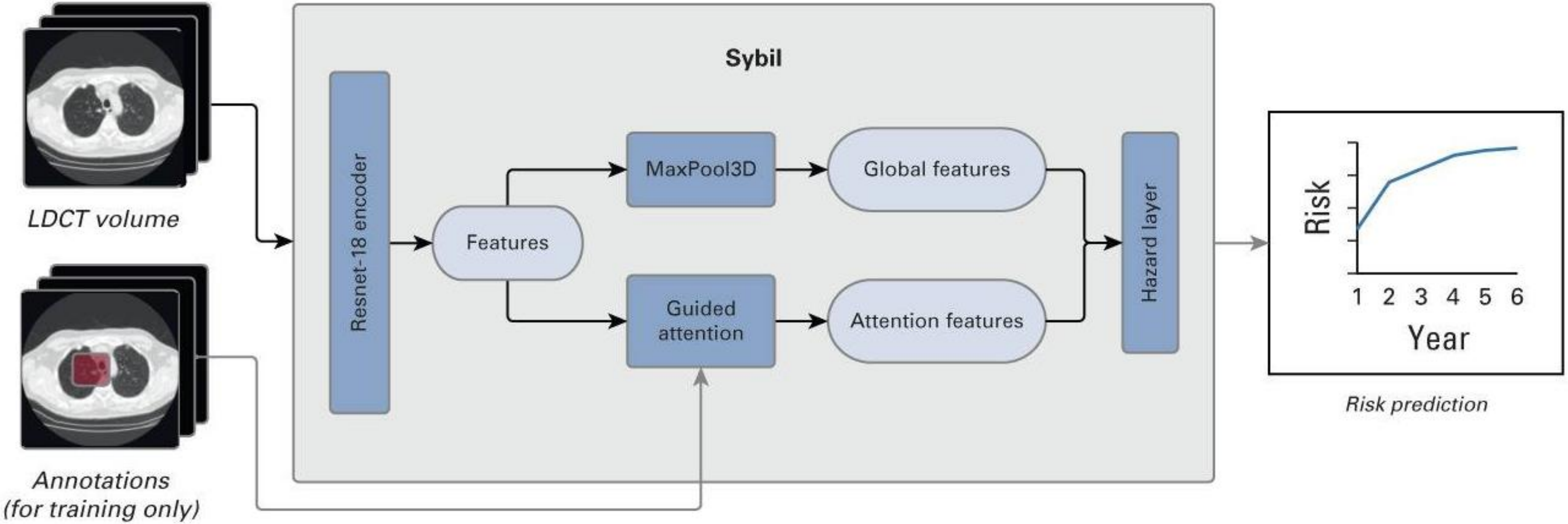
Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography

Peter G Mikhael [1 2], Jeremy Wohlwend [1 2], Adam Yala [1 2], Ludvig Karstens [1 2], Justin Xiang [1 2], Angelo K Takigami [3 4], Patrick P Bourgouin [3 4], PuiYee Chan [5], Sofiane Mrah [4], Wael Amayri [4], Yu-Hsiang Juan [6 7], Cheng-Ta Yang [6 8], Yung-Liang Wan [6 7], Gigin Lin [6 7], Lecia V Sequist [3 5], Florian J Fintelmann [3 4], Regina Barzilay [1 2]

Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMID: 36634294; PMCID: PMC10419602.

Open-source *threat (?)* – Sybil – publicly available model & annotations

- Vectors passed through hazard layer → cumulative lung cancer risk over 6 years
- Sybil – ensemble of 5 algorithms trained as below (annotations guide attention)



Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMID: 36634294; PMCID: PMC10419602.

Open-source *threat (?)* – Sybil – publicly available model & annotations

- Examining Sybil's accuracy in predicting future lung cancer – **NLST test set**
  - **1-year AUC of 0.92** (95% CI, 0.88 to 0.95)
  - **2-year AUC of 0.86** (95% CI, 0.82 to 0.90)
  - **C-index over the 6 years of prediction** of 0.75 (95% CI, 0.72 to 0.78).

- Sybil maintained performance across sex, age, and smoking history subgroups

- Test sets – MGH and CGMH – comparable C-indices to NLST
  - MGH – 0.81 (95% CI, 0.77 to 0.85)
  - CGMH – 0.80 (95% CI, 0.75 to 0.86)

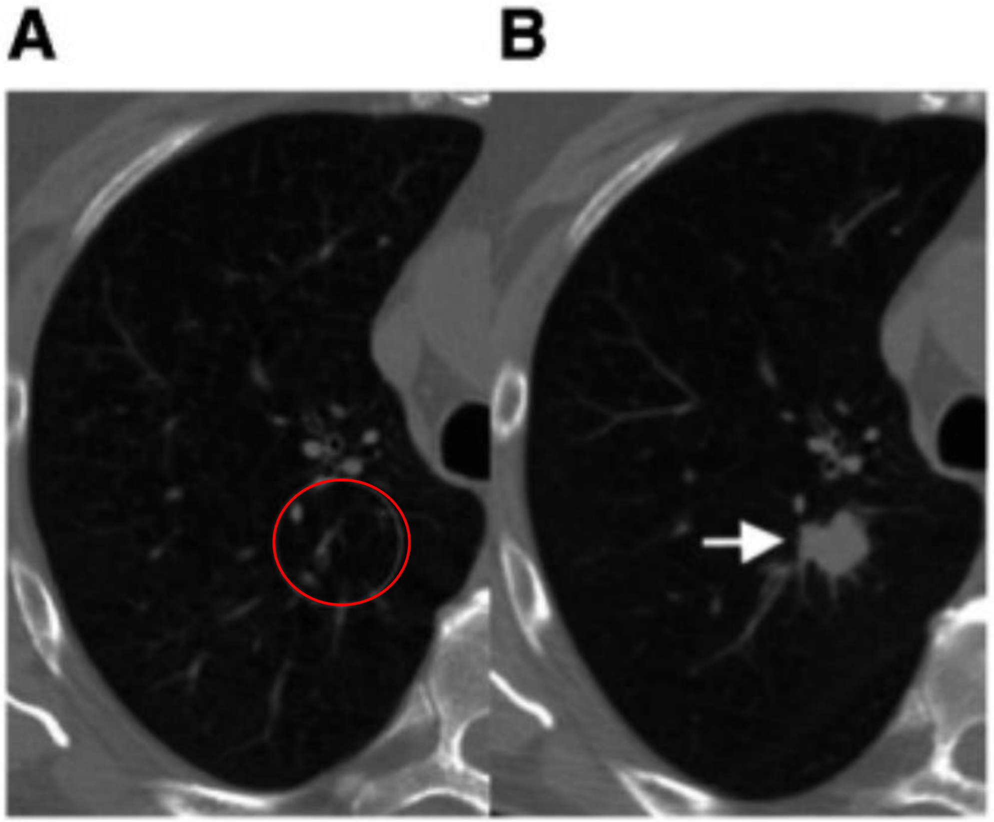
Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMID: 36634294; PMCID: PMC10419602.

Open-source *threat (?)* – Sybil – publicly available model & annotations

Sybil vs L-RADS – low L-RADS (1, 2) and high Sybil risk scores

- 69M, 99 PYH, no visible nodule
- L-RADS 2, Sybil risk 75th percentile
- New spiculated nodule 2 yr later → NSCLC

(red circle, emphasis mine)



Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Se
From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMI

Open-source *threat (?)* – Sybil – publicly available model & annotations

Sybil

- DL algorithm predicts future cancer risk up to 6yr out
- Runs in background, no radiologist input
- No clinical context required

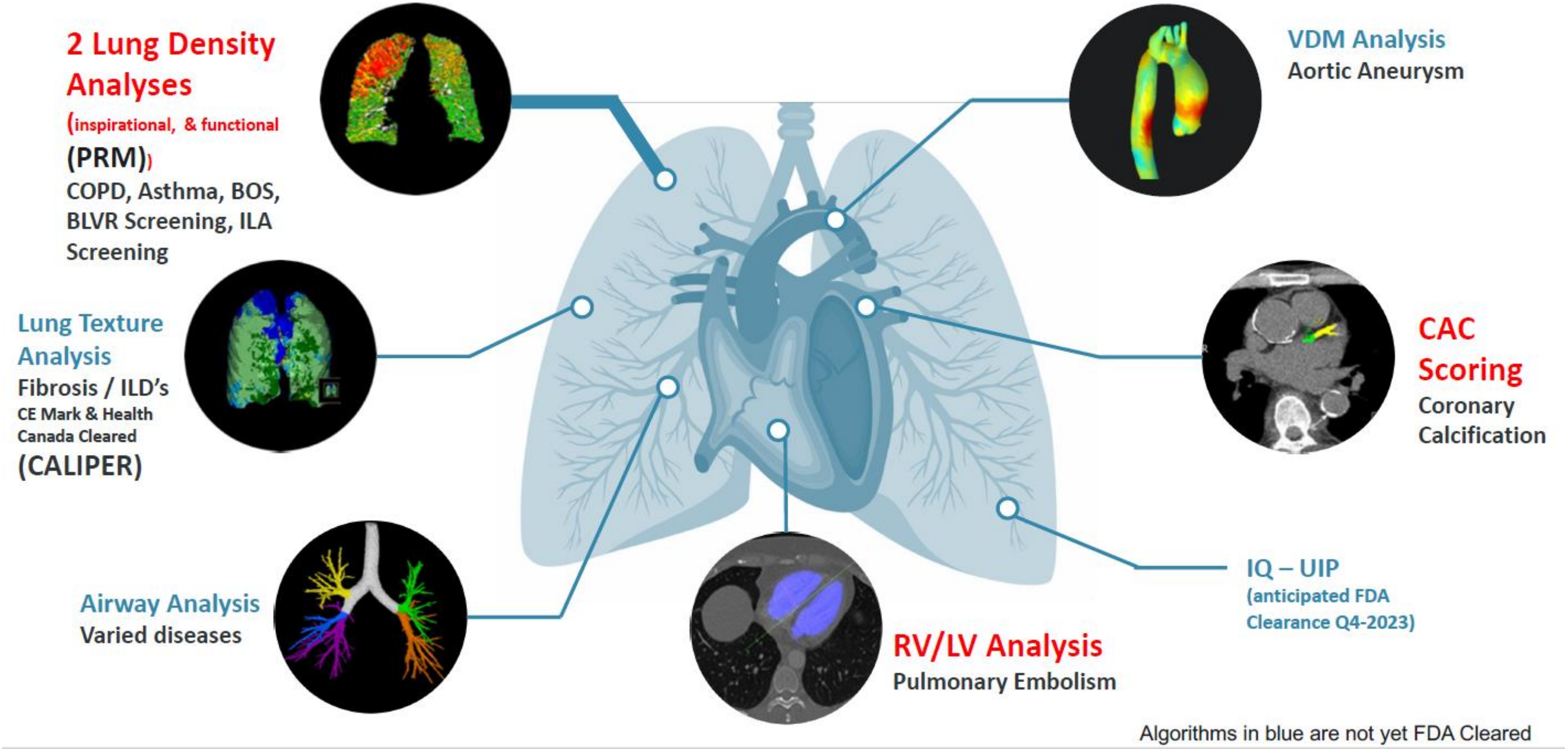
Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMID: 36634294; PMCID: PMC10419602.

Open-source *threat (?)* – Sybil – publicly available model & annotations

- Sybil use-cases
  - Decrease follow up scans for low-risk nodules
  - Prioritize scans for high-risk patients (?even in absence of nodules)
- Strengths
  - Sybil generalized well in the validation cohorts (for ref., NLST cohort was 92% Caucasian)
  - CGMH cohort included never smokers

Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. Epub 2023 Jan 12. PMID: 36634294; PMCID: PMC10419602.

Pulmonary AI orchestrator – Imbio



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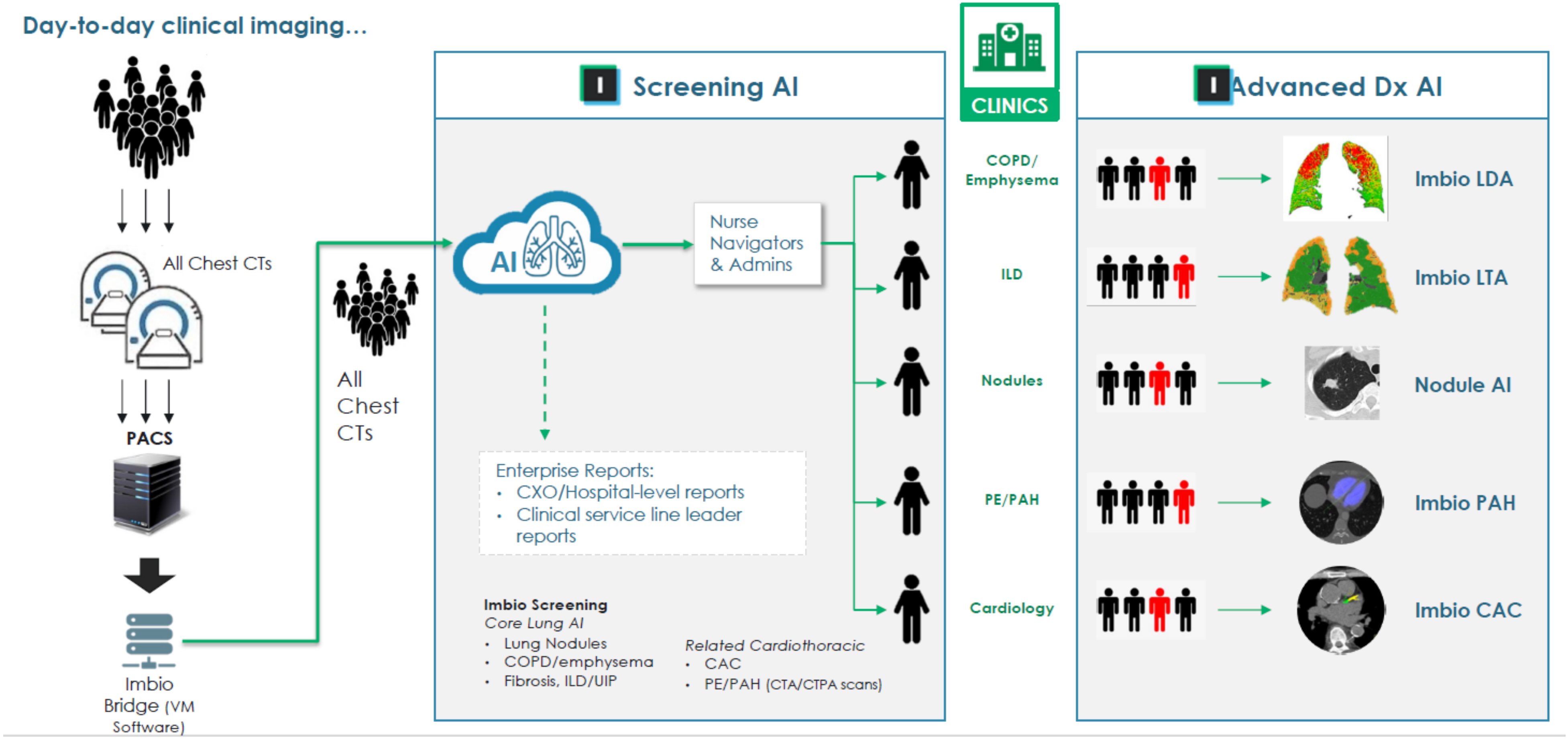
Pulmonary AI orchestrator – Imbio



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Limitations & concerns

- Black box
- Efficacy
- Data security
- Reproducibility & generalizability
- Bias
- Threats of job loss?

Job loss?

- Nobody knows
- Support/supplement radiologists? Displacement?
- Liability for AI errors? Humans or device (manufacturer)?

How do I pay for AI?

- Defensive deployment

- “Offensive” deployment

Are we being hasty?

Let's not forget …

	(your pulmonologist here)	AI
Speaks about screening	X	
Source patients to screen	X	
Scans reviewed	X	X
Score risk of nodule	X	X
Scopes	X	
Sends (to Sx, Onc etc)	X	
Survivorship	X	

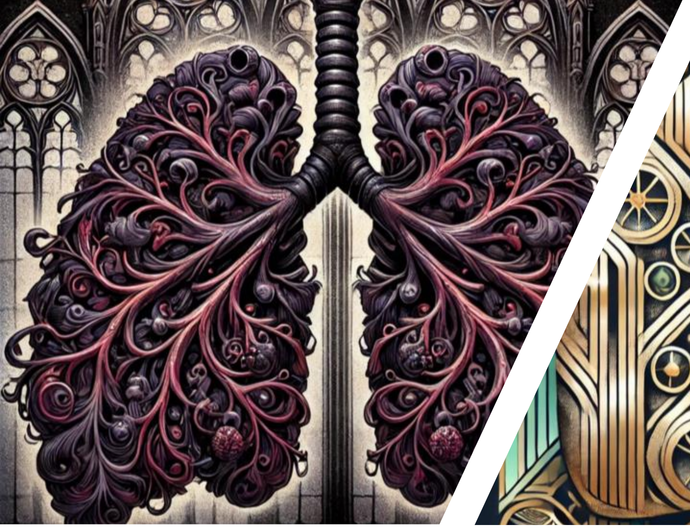
Take home message

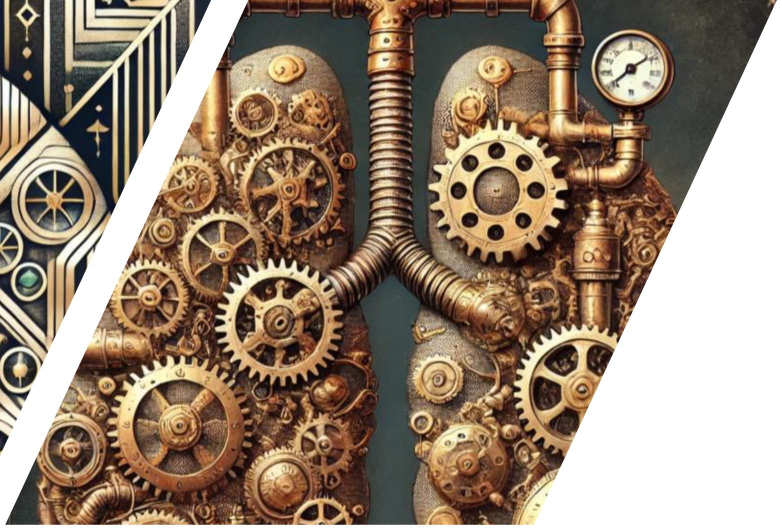
- Lung cancer screening saves lives

- Lung nodule management is complex, changing rapidly, and should involve specialist decisions (‘abdomen guy’)

- AI will play *some* role

- Joint decision making with the patient





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