

COPD and ILD

Review for Primary Care

NW Primary Care CME

Dec 5th 2025

Objective

- Review COPD diagnosis, staging and treatment
- Review data for newer COPD treatment
- Present Interstitial lung abnormalities and what to do when they are identified on Lung Cancer Screening CT scan.

Outline

COPD

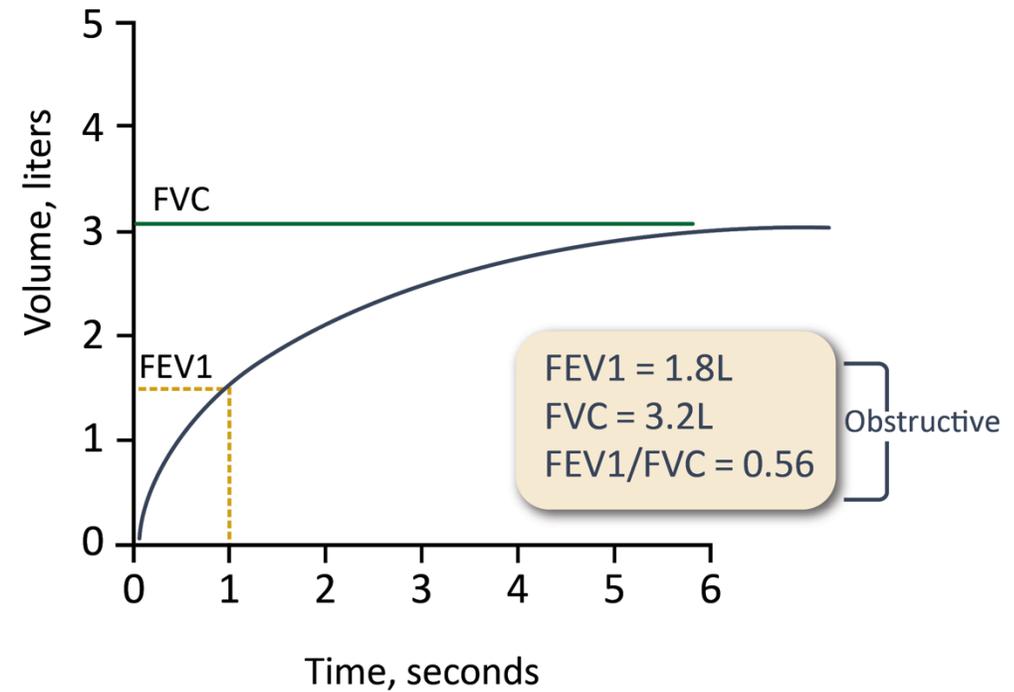
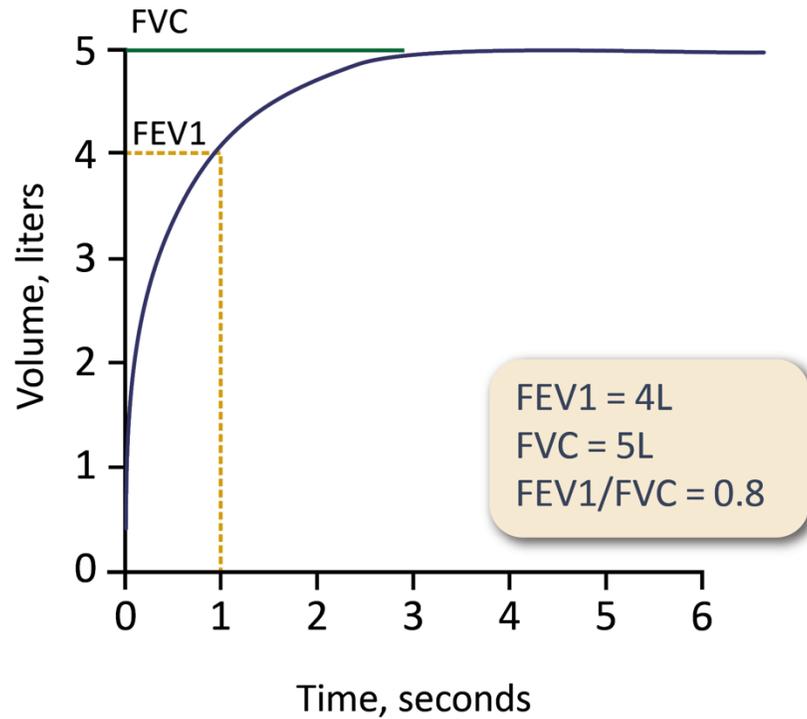
- Diagnosis
- Assessment of Severity (prognosis)
- Therapies → beyond inhalers
- Non-pharmacological interventions

Interstitial lung abnormalities

- Background
- When to refer

COPD diagnosis

- Spirometry



GOLD COPD diagnosis: $FEV_1/FVC < 70$

Severity (Score)

FEV₁ (% Predicted)

0 – Normal

$\geq 80\%$ AND $FEV_1/FVC \geq 0.70$

1 – Mild COPD

$\geq 80\%$ (with $FEV_1/FVC < 0.70$)

2 – Moderate COPD

50–79%

3 – Severe COPD

30–49%

4 – Very Severe COPD

$< 30\%$

ATS COPD diagnosis: LLN (z-score < -1.65)

Severity / Score

FEV₁ raw value

0 – Normal (no airflow obstruction)

Post-bronchodilator FEV₁/FVC ≥ LLN
z-score > -1.65) **AND** FEV₁ z-score > -1.65

1 – Mild airflow limitation

z-score between -1.65 and -2.5 (≈ mild reduction)

2 – Moderate airflow limitation

FEV₁ z-score between -2.51 and -4.0

3 – Severe airflow limitation

FEV₁ z-score < -4.0

4 – Very severe airflow limitation

FEV₁ z-score << -4.0

COPD diagnosis

Spirometry		Pre	Ref	Pre	LLN	Pre	ULN
		Meas		% Ref		Zscore	
FVC	Liters	5.10	4.79	106	3.67	0.44	5.92
FEV1	Liters	4.10	3.86	106	2.93	0.44	4.79
FEV1/FVC	%	80	80		69		91
FEV3	Liters	4.79	4.57	105	2.85	0.20	6.30
FEF25-75%	L/sec	4.11	3.64	113	2.03	0.41	5.24
IsoFEF25-75	L/sec	4.11					
FEF50%	L/sec	6.33	5.00	127	2.83	1.01	7.17
FEF75%	L/sec	1.59	1.36	117	0.65	0.38	2.06
PEF	L/sec	10.42	9.14	114	7.15	1.05	11.13

COPD diagnosis

----- SPIROMETR	Pre-BD					Post- BD			
	<u>Actual</u>	<u>Pred</u>	<u>%Pred</u>	<u>LLN</u>	<u>Z Score</u>	<u>Actual</u>	<u>%Pred</u>	<u>VolChng</u>	<u>%Chng</u>
FVC (L)	2.92	4.24	68	3.16	-2.01	3.21	75	0.29	+6
FEV1 (L)	0.65	3.20	20	2.34	-4.44	0.65	20	-0.00	+0
FEV1/FVC (%)	22	77	29	63	-4.30	20	26		-9
FEF 25-75% (L/s)	0.19	2.42	7	1.07	-3.51	0.23	9		+17
FEF Max (L/sec)	2.08	8.67	23	6.28	-4.55	1.44	16		-30
FIVC (L)	2.84					2.83		-0.02	+0
FIF Max (L/sec)	4.95					3.96			-20

COPD

- ATS now recommends use of LLN in place of 70%.
 - Better age appropriate cut offs
 - Risk of underdiagnosis if mild → clinical interpretation is still important.

COPD - diagnosis

In COPD patients (FEV1/FVC < 0.7): (ATS – now LLN)

GOLD 1:	Mild	FEV1 ≥ 80% predicted
GOLD 2:	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3:	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4:	Very Severe	FEV1 < 30% predicted

COPD - CAT

EXAMPLE: I am very happy	0 1 2 3 4 5	I am very sad	Score
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

COPD Group – MRC dyspnea scale

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

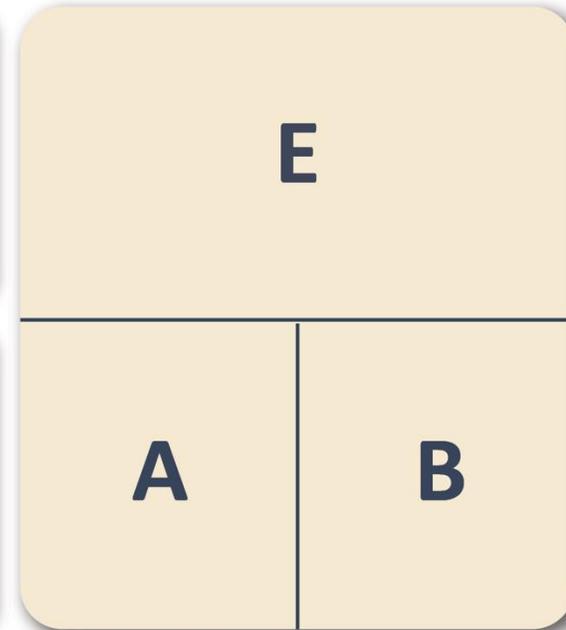
mMRC Grade 0	mMRC Grade 1	mMRC Grade 2	mMRC Grade 3	mMRC Grade 4
I only get breathless with strenuous exercise <input data-bbox="435 1172 504 1239" type="checkbox"/>	I get short of breath when hurrying on the level or walking up a slight hill <input data-bbox="828 1172 896 1239" type="checkbox"/>	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level <input data-bbox="1200 1172 1268 1239" type="checkbox"/>	I stop for breath after walking about 100 meters or after a few minutes on the level <input data-bbox="1612 1172 1681 1239" type="checkbox"/>	I am too breathless to leave the house or I am breathless when dressing or undressing <input data-bbox="2005 1172 2074 1239" type="checkbox"/>

GRADE	FEV1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

EXACERBATION HISTORY
(PER YEAR)

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

0 or 1 moderate exacerbations (not leading to hospitalization)



mMRC 0-1
CAT < 10

mMRC ≥ 2
CAT ≥ 10

SYMPTOMS

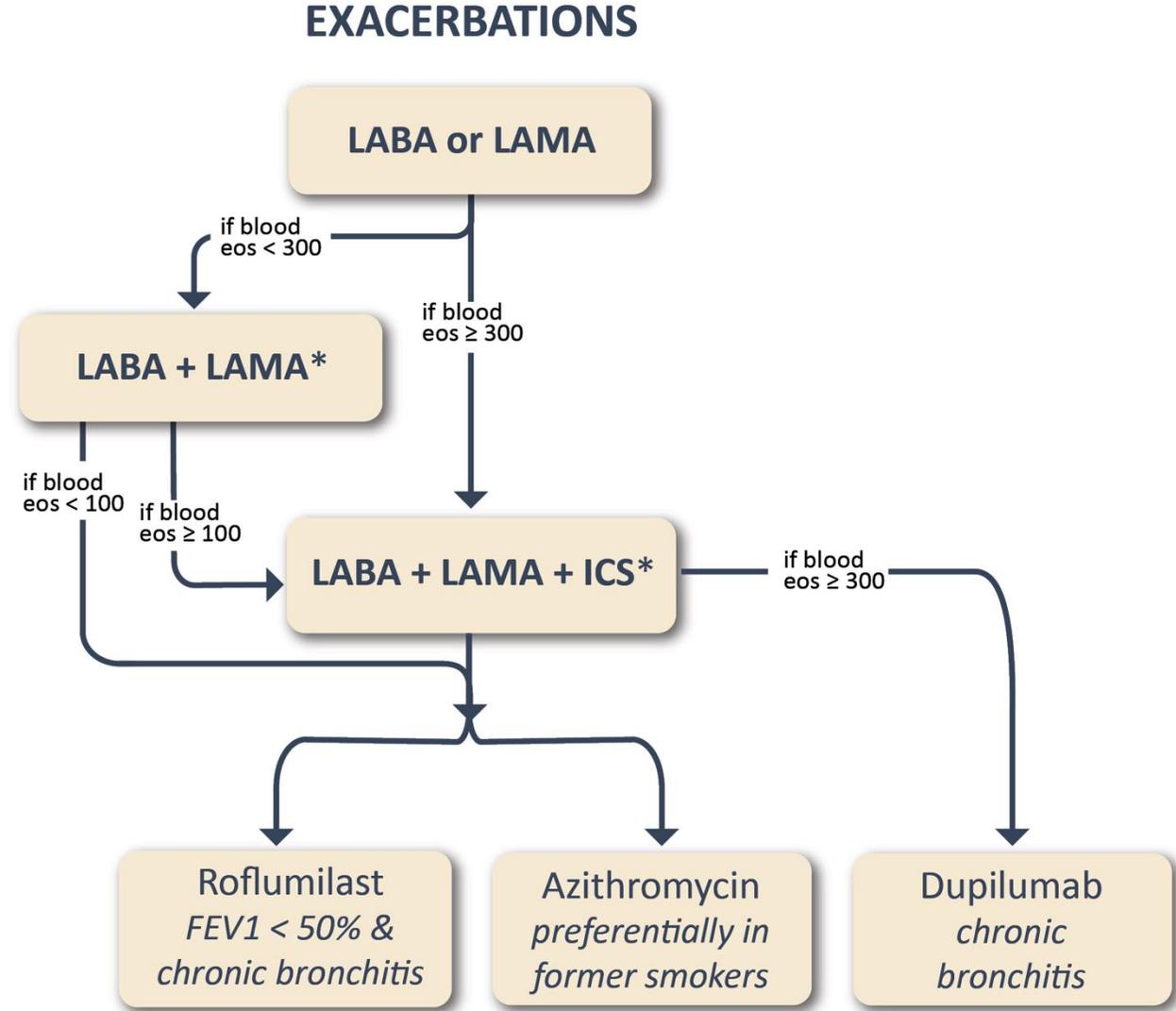
COPD Treatment



COPD Treatment

- LABA/ALMA
- LABA/LAMA → LABA/LAMA/ICS
 - Eos >100
 - Bronchodilator reactivity
 - Frequent exacerbation
- LABA/LAMA/ICS → Azithromycin/PDE/Biologics

COPD Treatment



Azithromycin

- Macrolide
- 250mg daily
- RCT: reduced AECOPD (HR 0.73)
improved SGRQ
- Consider for “frequent exacerbators”

Azithromycin adverse effects:

- N/V/D/abd pain, vaginitis, dizziness, rash, anorexia, pruritis
- Hearing changes
- Prolonged QTC
- Med-med interactions
- Neuropathy
- Resistance (2.7 fold resistance risk)
- Worse for NTM infections

Roflumilast (Daliresp): PDE-I

- Initially studies at 500mcg daily.
 - (250mg daily x4 months → 500mg daily)
- Initial Phase III trial published in 2005
 - Modest improvement in FEV1, quality of life
 - Non-significant change in exacerbations
- Increased impact in subgroups:
 - Chronic bronchitis
 - Frequent exacerbators

Roflumilast (Daliresp): PDE-I

- AEs: N/V/D, weight loss, HA, back pain, insomnia, dizziness, anorexia
- Drug Drug interactions: Amiodarone, Diltiazem, Azoles, Cipro, antivirals (HIV meds), [DOAC (?)]
- Consider for patients:
 - Severe COPD
 - Chronic bronchitis
 - At HIGH risk for AECOPD

Ohtuvarye (Ensifentrine)

Mechanism: Dual PDE3 (bronchodilator) / PDE4 (anti-inflammatory) inhibitor (bronchodilator and antiinflammatory effects)

Formulation / Delivery: Nebulized, 3 mg BID

Indication: Maintenance treatment of COPD in adults

First-in-class therapy for COPD

ENHANCE-1 and ENHANCE-2

Population: COPD in adults (40-80) w/ h/o smoking, on or off standard maintenance therapy

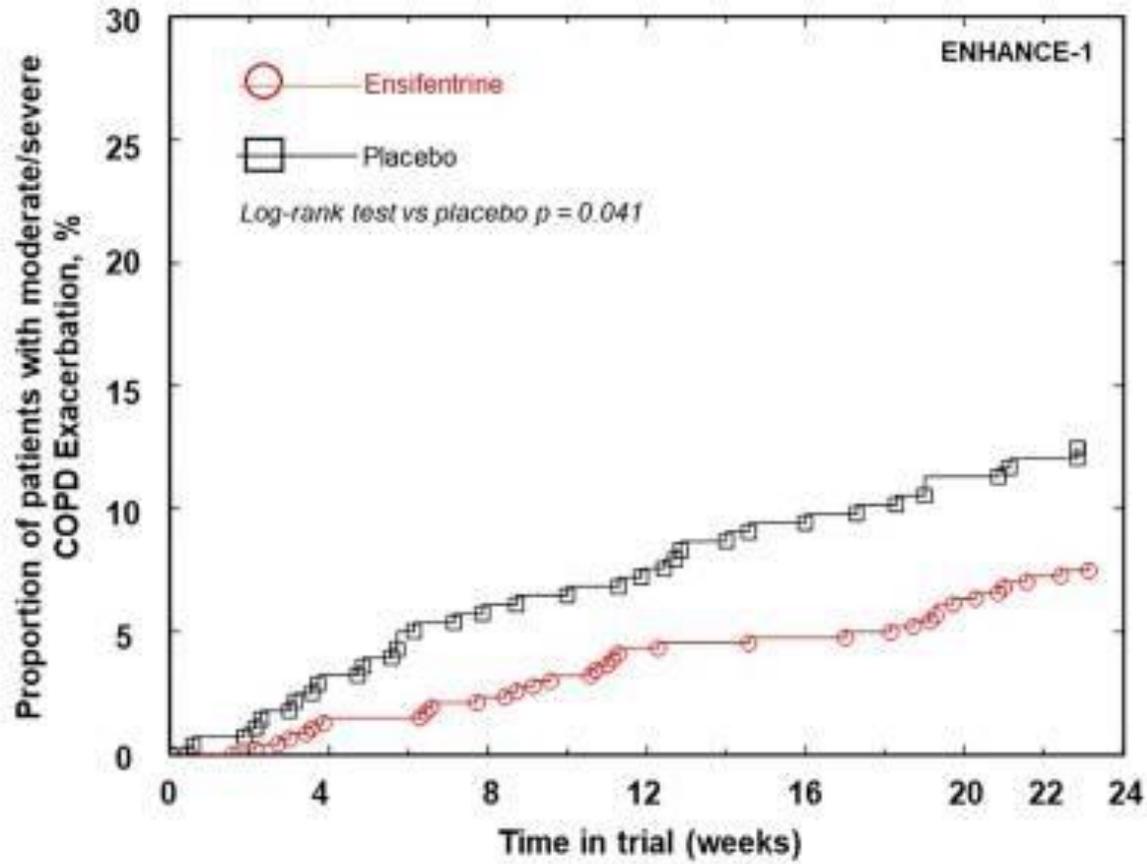
- (E-1) 760 randomized.
- (E-2) 763 randomized.

Treatment Duration: 24 weeks (primary endpoint), with 48-week safety cohort

Primary Endpoint: FEV_1 AUC_{0-12h} at Week 12

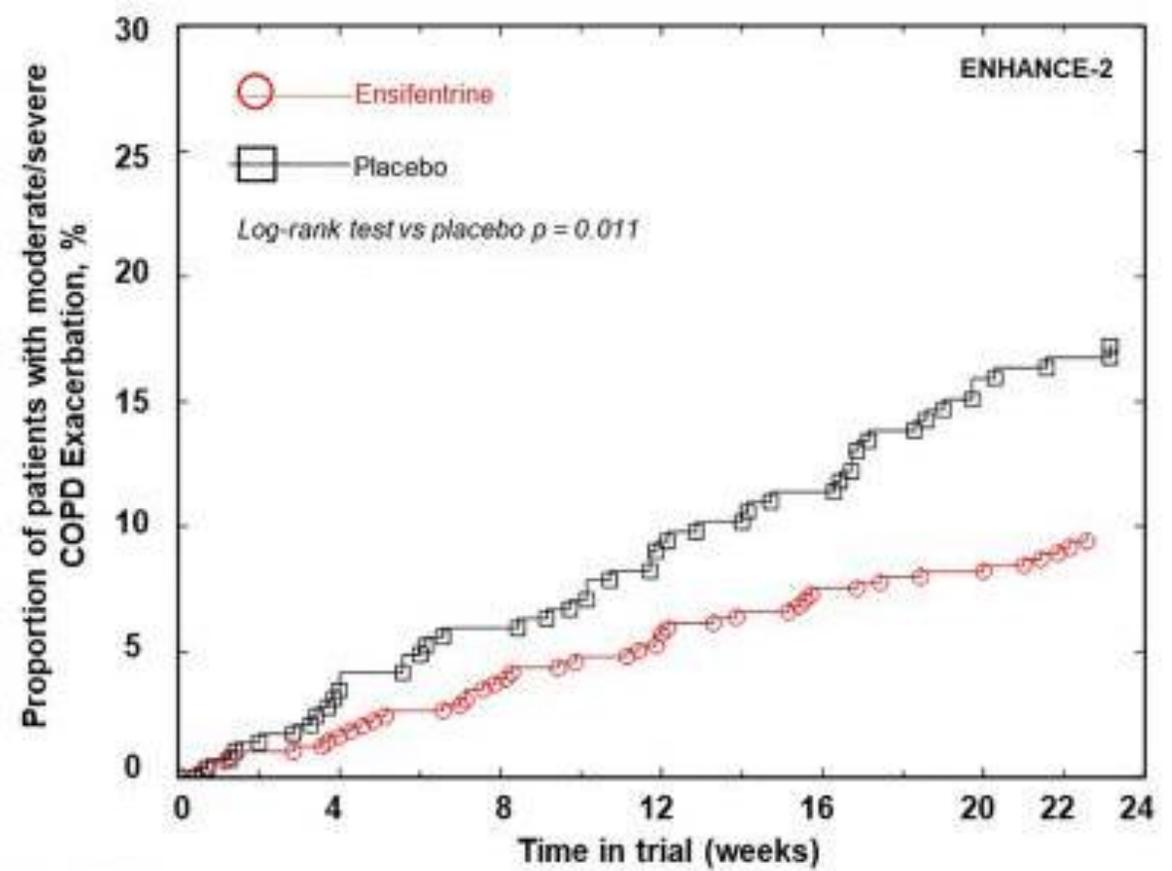
- Significant symptomatic improvement (SGRQ) in ENHACE-1
- Significant improvement in FEV_1
- Increased time to next exacerbation

8



Number at Risk

Ensilfentrine	477	466	453	431	422	412	404	279
Placebo	283	270	258	250	243	235	232	155



Number at Risk

Ensilfentrine	498	481	443	422	399	390	380	278
Placebo	291	275	257	232	218	201	198	151

Outcomes

- **Moderate-to-severe exacerbations:** 42% reduction vs placebo
- **Time-to-first exacerbation:** 42% reduced risk
- **Clinical significance:** Reduces hospitalizations and morbidity in COPD

Ohtuvayre

Who may benefit:

- Adults ≥ 18 with **moderate–severe COPD**
- Persistent symptoms despite **LAMA/LABA/ICS**
- History of **≥ 1 moderate/severe exacerbation/year**

Not suitable for:

- Acute exacerbation or bronchospasm
- Severe uncontrolled **heart disease**
- Hypersensitivity to drug

Practical:

- Must be able to **use nebulizer BID**
- Monitor for **cough, headache, mild bronchitis**

Potential cardiac risks

<u>Issue</u>	<u>Mechanism / Notes</u>	<u>Clinical Relevance</u>
Tachycardia	PDE3 increases cAMP → higher heart rate	Usually mild in trials, but may exacerbate pre-existing tachyarrhythmias
Arrhythmias	Increased myocardial excitability	Caution in patients with atrial fibrillation, flutter, or ventricular arrhythmias
Palpitations	Direct effect on cardiac conduction	Often transient, usually mild
Heart failure exacerbation	Positive inotrope effect can increase myocardial oxygen demand	Rare in trials; caution in unstable or severe heart failure
Hypotension	PDE3 vasodilatory effect (mild)	Monitor in patients with borderline blood pressure

PDE inhibitors

Feature

Ohtuvayre (Ensifentrine)

Roflumilast

Drug Class

Dual PDE3 / PDE4 inhibitor

Selective PDE4 inhibitor

Primary Mechanisms

- **PDE3 inhibition** → bronchodilation
- **PDE4 inhibition** → anti-inflammatory effects

- **PDE4 inhibition only** → anti-inflammatory (reduces neutrophil-mediated inflammation)

Overlap

Both inhibit **PDE4**, which reduces airway inflammation

Shares only the anti-inflammatory PDE4 effect

Additional Actions

PDE3 inhibition gives **direct bronchodilator effect**

No direct bronchodilation

Biologics in COPD

- **2003** — **Omalizumab** becomes the **first FDA-approved biologic for asthma**, launching modern biologic therapy.
- **2015–2018** — Additional biologics approved for eosinophilic and type-2 asthma (IL-5 and IL-4/13 pathways).
- **2020s** — Expansion of biologics across broader severe asthma phenotypes.
- **2024** – **Dupixent** approved for COPD
- **2025** – **Mepolizumab** approved for COPD

Biologics in COPD

BOREAS Trial: Randomized, double-blind, placebo-controlled

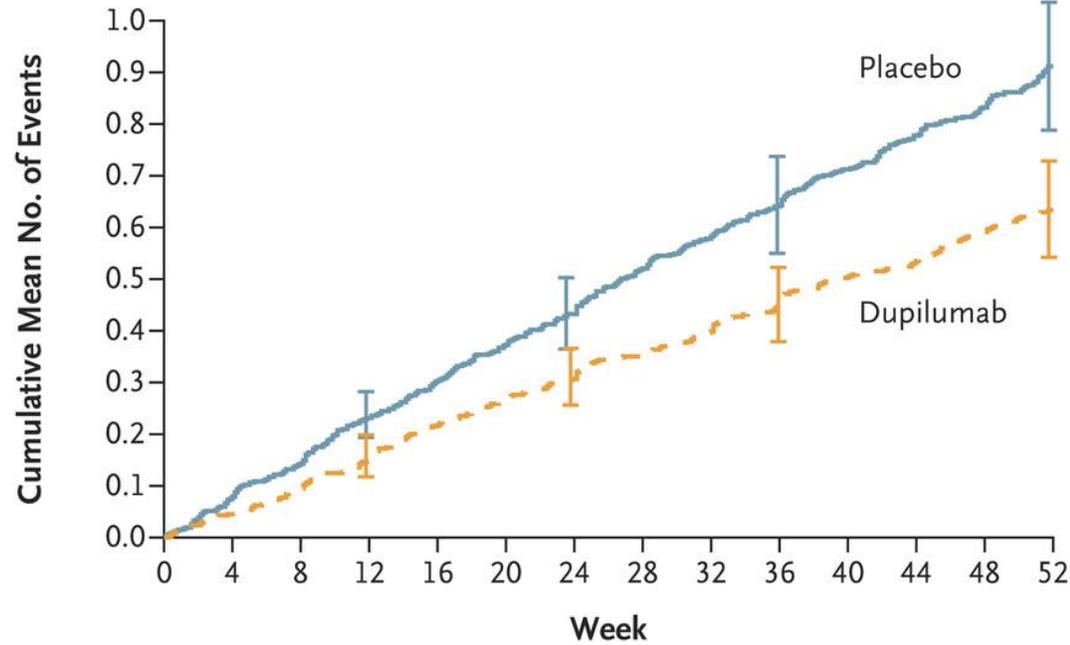
Population: 939 ppl, COPD, Triple therapy, increased exacerbations,
Eos > 300

Intervention: Dupilumab 300 mg v. placebo every 2 weeks for 52 weeks.

Primary outcome: Rate of moderate or severe exacerbations.

Biologics in COPD

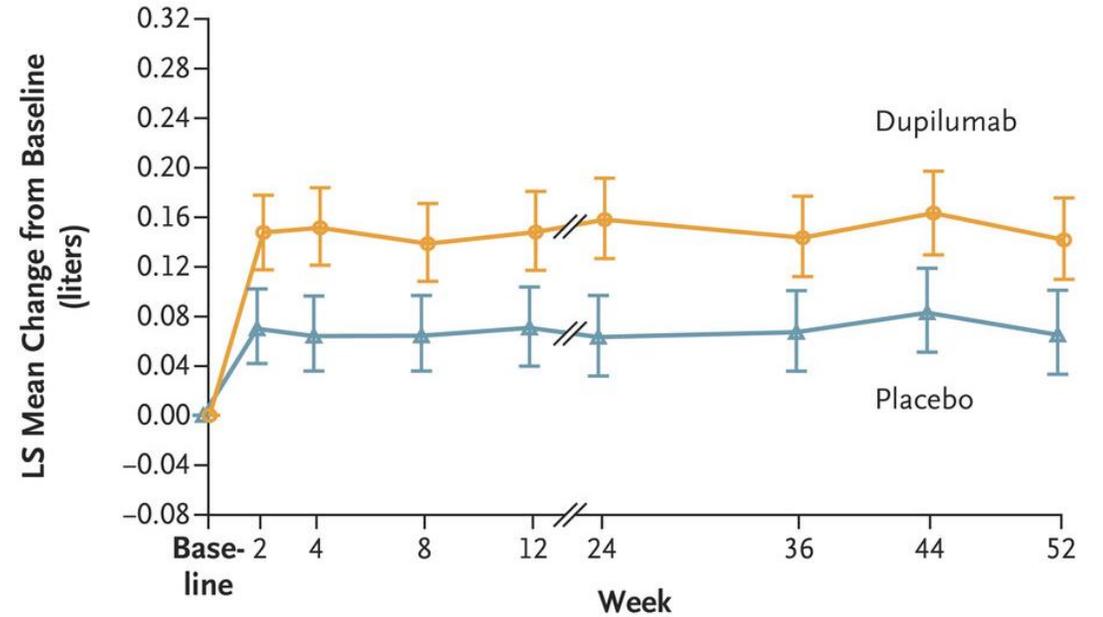
A Cumulative Moderate or Severe COPD Exacerbations



No. at Risk

Placebo	471	470	466	461	457	457	456	451	451	449	445	442	441	437
Dupilumab	468	467	465	464	462	460	458	457	456	454	451	450	448	437

B Prebronchodilator FEV₁



No. of Patients with Data

Placebo	471	455	459	439	439	435	415	404	420
Dupilumab	467	457	454	446	449	443	415	410	426

Biologics in COPD

- Significant reduction in exacerbations
- Improved lung function (FEV₁)
- Better symptom control/quality-of-life measures

Results:

- **Reduction in exacerbations:** ~30% fewer in dupilumab vs placebo over 52 weeks.
- **Lung function:** Significant improvement in pre-bronchodilator FEV₁ — 160 mL at 12 weeks (dupilumab) vs 77 mL (placebo). Benefit maintained through 52 weeks. **Quality of life / symptoms:** Improvements in SGRQ (St. George's Respiratory Questionnaire) and respiratory symptom scores (E-RS COPD).

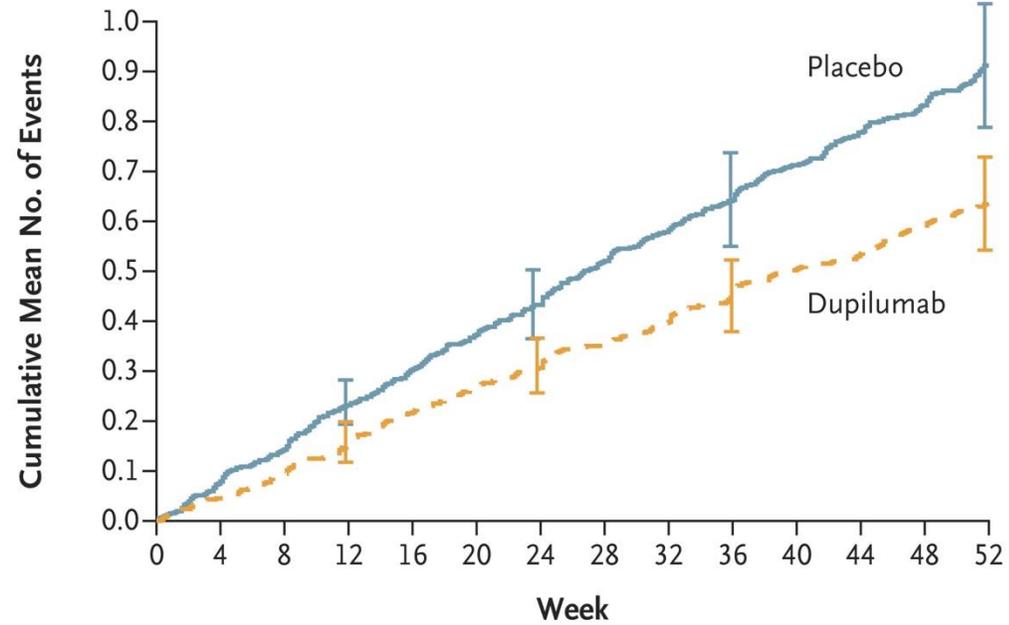
Subgroup / secondary analysis:

- In *emphysema vs non-emphysema* groups, dupilumab reduced exacerbations and improved lung function in both. [PubMed](#)
- By **BODE index** (which combines BMI, airflow obstruction, dyspnea, exercise capacity): dupilumab's benefit was consistent across low (≤ 4) and high (> 4) BODE index groups. [PubMed](#)

Safety:

- Adverse events were similar between dupilumab and placebo arms; consistent with known dupilumab safety profile.

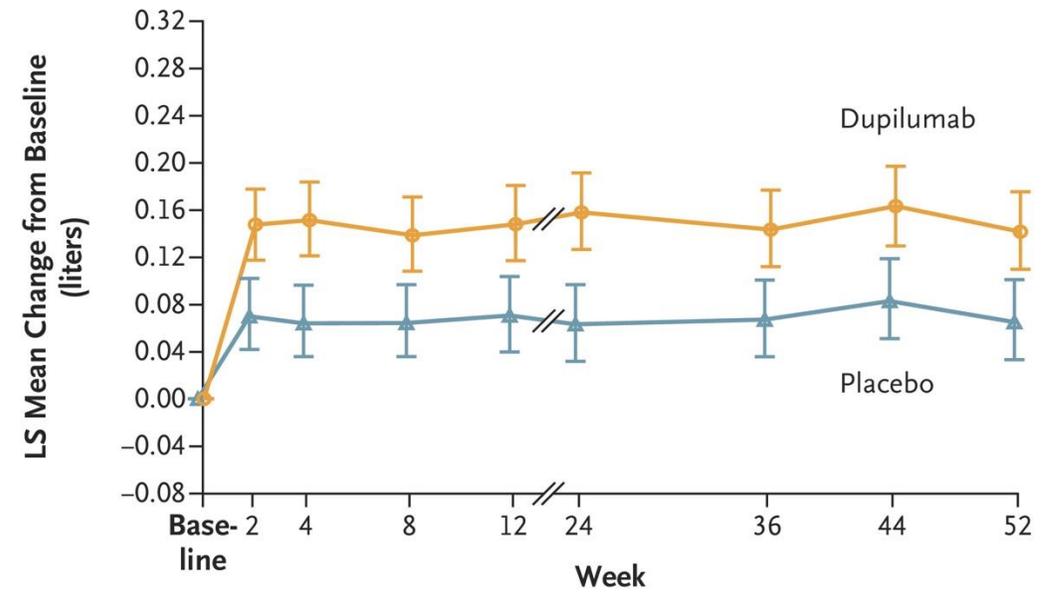
A Cumulative Moderate or Severe COPD Exacerbations



No. at Risk

Placebo	471	470	466	461	457	457	456	451	451	449	445	442	441	437
Dupilumab	468	467	465	464	462	460	458	457	456	454	451	450	448	437

B Prebronchodilator FEV₁



No. of Patients with Data

Placebo	471	455	459	439	439	435	415	404	420
Dupilumab	467	457	454	446	449	443	415	410	426

Mepolizumab

MATINEE Trial: Phase III, randomized, double-blind, placebo-controlled.

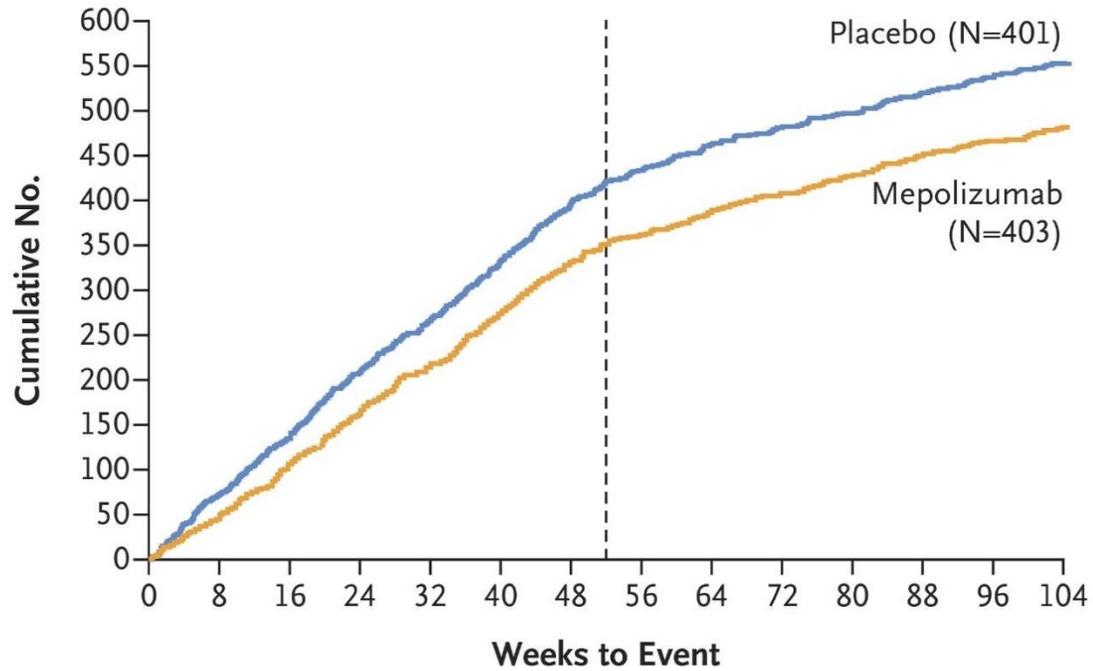
Populations: 804 ppl, COPD, + exacerbations, on triple inhaled therapy, Eos > 300.

Intervention: Monthly subcutaneous mepolizumab (100 mg) v placebo for 52–104 weeks.

Primary outcomes: Rate of moderate or severe exacerbations.

Mepolizumab

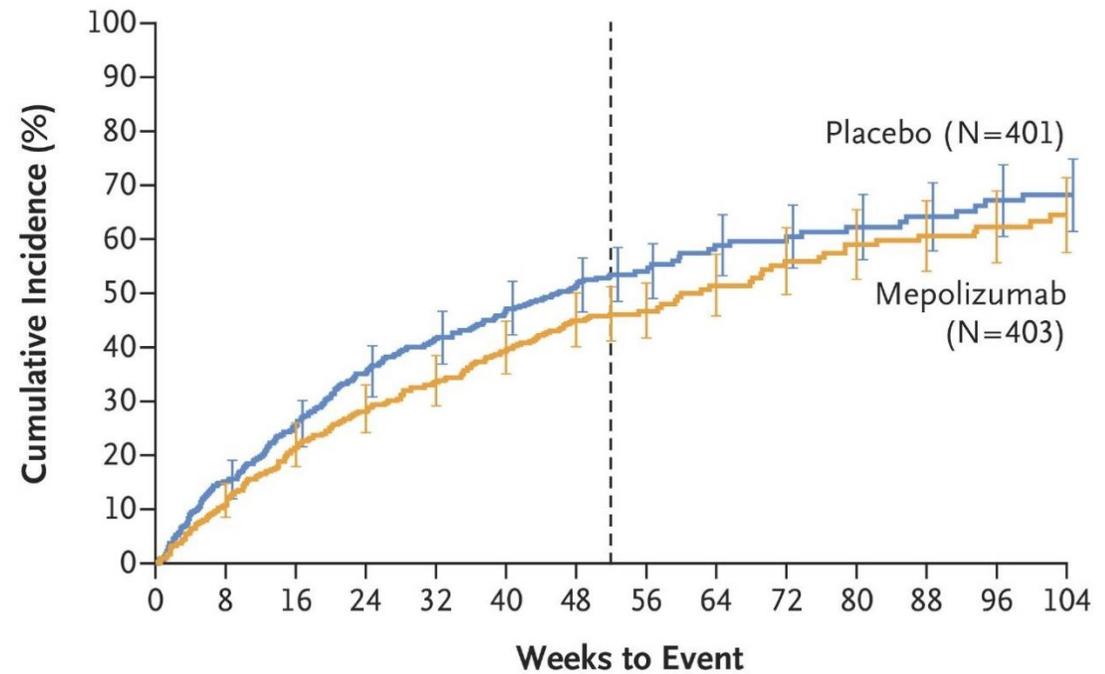
A Moderate or Severe Exacerbations



No. at Risk

Placebo	401	333	292	250	223	203	180	71	56	46	41	37	32	22
Mepolizumab	403	355	309	277	251	222	202	82	69	58	52	48	41	24

B First Moderate or Severe Exacerbation



No. at Risk

Placebo	401	333	292	250	223	203	180	71	56	46	41	37	32	22
Mepolizumab	403	355	309	277	251	222	202	82	69	58	52	48	41	24

Mepolizumab

Results:

- Exacerbations: 0.80/year in mepolizumab group vs 1.01/year in placebo → **21% relative reduction** (rate ratio 0.79, 95% CI 0.66–0.94, P = 0.01).
- Time to first exacerbation: median 419 days (mepolizumab) vs 321 days (placebo) → HR = 0.77.
- Quality-of-life / symptom measures (e.g., SGRQ, CAT, E-RS): **no statistically significant improvement**.
- Over 2-year period, maintained benefit; favorable safety profile.

Safety:

- Adverse events incidence similar between mepolizumab and placebo.

Subgroup / post-hoc findings:

- In chronic bronchitis subgroup: ~31% reduction in exacerbations in post-hoc analysis.
- Reduction in exacerbations leading to ED visits / hospitalization (secondary endpoint): ~35%.

Pulmonary rehab

Improved functional exercise capacity: Significant increase in walking distance (e.g. 6-minute walk test) compared to usual care.

Better quality of life & reduced symptoms (dyspnea, general well-being): Leads to clinically meaningful improvements in health-related quality of life (HRQoL) and decreases breathlessness.

Less readmissions and exacerbations when started after an acute COPD exacerbation: When started shortly after a hospitalization for exacerbation, it significantly reduces rehospitalization risk and improves recovery.

Zhang, H. *et. al.* Ann Med. 2022

COPD working group. Ont Health Technol Assess Ser. 2012

Bronchoscopic-Lung Volume Reduction: B-LVR

- Lung Volume reduction achieved through placement of one-way valves in the small airways allowing air to leave a lobe but not re-enter.
- This atelectasis reduces the volume in the chest and has on multiple studies shown improvements in exercise capacity and quality of life (nobody has done studies to look at mortality, too expensive to run)
- Highly selective process to ensure maximum safety

Lung Volume Reduction



© 2010 Medtronic AVE



Who should be considered/referred for B-LVR

- Severe COPD (FEV1 <50%)
- Emphysema on either CT scan or chest X-ray
- Quit smoking or willing to quit smoking
- Completed or willing to complete a pulmonary rehab program (even structured home based)

COPD subtypes

- G: Genetic (Alpha-1-antitrypsin deficiency)
- D: Developmental abnormalities (Childhood disease)
- C: Environmental (in utero exposure, smoking)
- P: Pollution (biomass, pollution, occupational)
- I: Infection (TB, HIV, childhood pneumonia)
- A: Asthma/COPD overlap (childhood asthma)
- Combined emphysema and pulmonary fibrosis (CEPF)

COPD and ILD prevalence

<u>Condition</u>	<u>U.S. Prevalence</u>	<u>Approx. Number of People Affected</u>
COPD	~3.8% of U.S. adults (≥18 years)	~11–16 million adults diagnosed
All ILD (broad category)	~0.2% (≈ 200 per 100,000)	~250,000 to 650,000 Americans (range varies by definition)
Fibrosing ILD (all forms)	~118 per 100,000	≈ 300,000+
Progressive Fibrosing ILD (PF-ILD)	~70 per 100,000	≈ 180,000+
Idiopathic Pulmonary Fibrosis (IPF)	14–43 per 100,000	~50,000–100,000

Lung Cancer Screening

- According to the 2025 American Lung Association (ALA) “State of Lung Cancer” report:
~ **15.8%** of Washington’s “high-risk” individuals got screened annually
- In that same report, Washington ranks 37th in the U.S. for lung cancer screening uptake among high-risk people.
- By comparison, the national screening rate (among high-risk individuals) was ~18.2%.

Incidental lung abnormalities (ILAs)

- **Non-dependent, incidental CT findings involving $\geq 5\%$ of a lung zone** that suggest abnormal interstitial changes, such as fibrosis or inflammation.

Non-fibrotic Buzwords:

- Ground-glass opacities
- Reticulation
- Mild centrilobular nodularity
- Mild intersitial thickening

Fibrotic ILAs (higher-risk):

- Traction bronchiectasis
- Architectural distortion
- Subpleural fibrosis
- Early or focal honeycombing

What ILAs Are NOT

- They are not a diagnosis of ILD
- They are not necessarily progressive
- They do not automatically require treatment
- They do not always correlate with symptoms

Lung Cancer Screening and Interstitial Lung Abnormalities (ILA)

Study / Review / Cohort

National Lung Screening Trial (NLST — 25,041 participants)

Single-site NLST screening sub-cohort (884 smokers)

Summary estimates (from position-paper / review across screening and general cohorts)

Prevalence of ILA on baseline CT

≈ **20.2%** had ILA on low-dose CT.

~ **9.7%** had ILA; additional ~11.5% had equivocal findings.

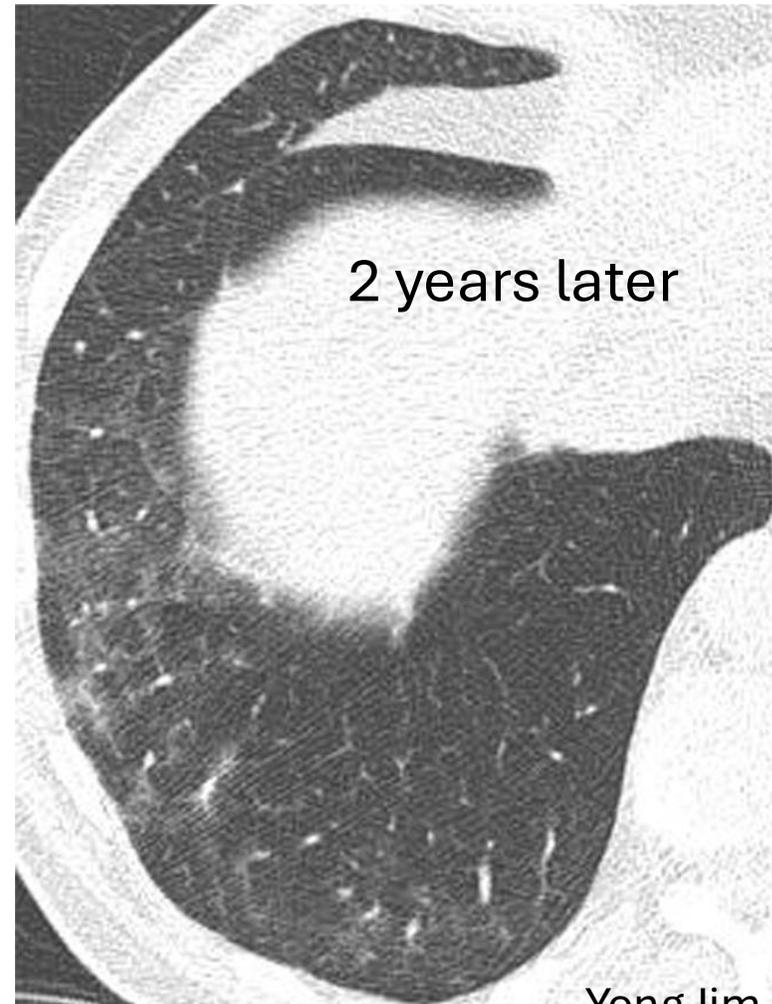
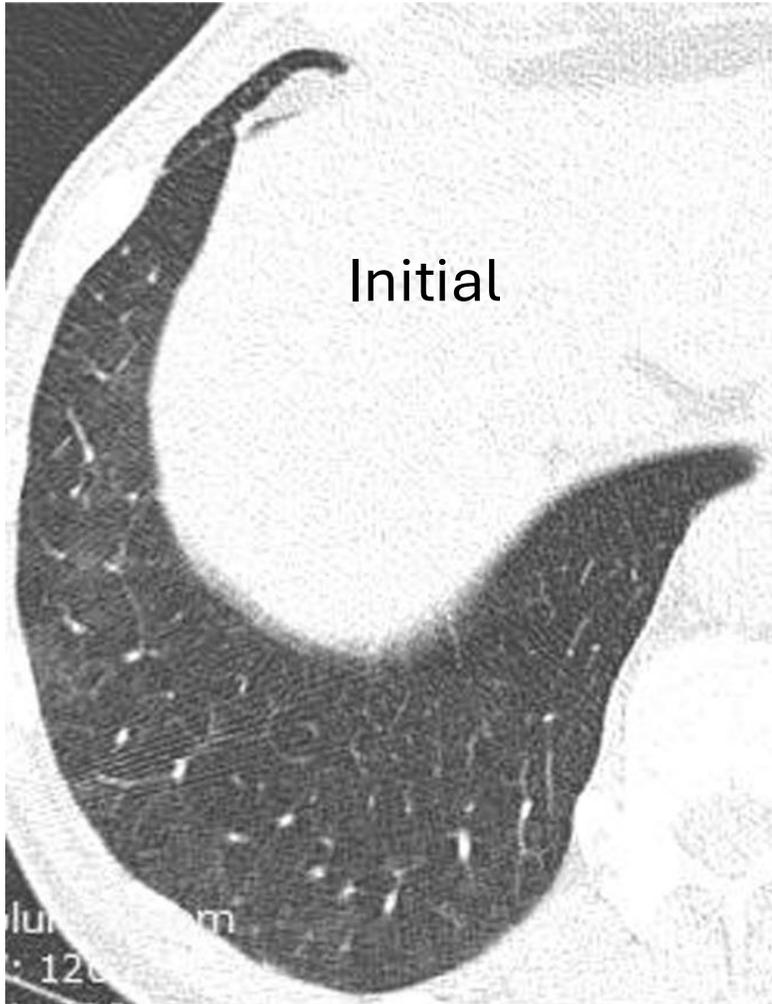
Among smokers: ~4–9%; among nonsmokers: ~2–7% (varies by age, risk).

Yong Jim, G *et. al.* Radiology 2013
Whittaker Brown, S *et. al.* CHEST 2019
Hatabu *et al.* Lancet 2021

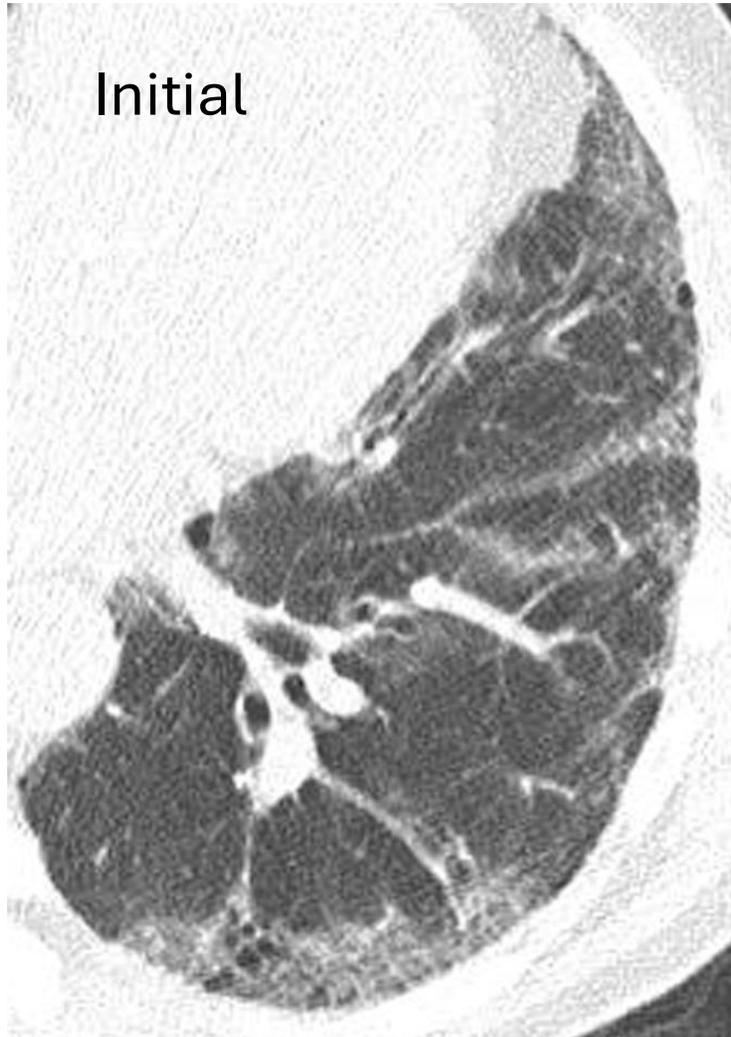
Incidental lung abnormalities (ILAs)

- Of 25,041 study participants in NY – 20.2% had interstitial lung abnormalities.
 - Associated with a higher incidence of lung cancer (incidence rate ratio, 1.61; 95% CI, 1.30-1.99).
- Nonfibrotic ILA improved in about 50% of cases, and fibrotic ILA progressed in about 37%.

69-year-old male current smoker with 60 pack-years of cigarette consumption



68-year-old male former smoker with 61.5 pack-years of cigarette consumption.



ILAs

- Are their dyspnea symptoms → Further ILD work up
 - Dyspnea
 - Exercise intolerance
 - Chronic cough
 - Abnormal exam: wheezing or crackles?
 - Abnormal PFTs: decreased DLCO or lung volumes
- If unclear order High Resolution CT Chest
- Evaluate for the speed of change

ILA Management (asymptomatic)

Management notes for primary care.

- Continue **smoking cessation counseling**—the strongest modifiable intervention.
- Review **medications** (e.g., amiodarone, methotrexate) that may worsen ILD risk.
- Ask about occupational exposures (e.g., silica, asbestos, metal dusts).
- Encourage pulmonary rehab or exercise for patients with early symptoms.

Follow-up

- Repeat CT 12 – 24 months. LCS or HRCS
- Sooner follow up if symptomatic
- Pulmonary function test. *spirometry, lung Volumes, and diffusion capacity.

ILA with risk features

Risk features:

- Fibrotic feathers – traction bronchiectasis, honeycombing
- Older age
- Smoking history
- Family history of ILD
- History of autoimmune or connective tissue disease

These individuals have a higher likelihood of progression and should undergo:

- Pulmonary referral
- Baseline PFTs (spirometry, lung volumes, DLCO)
- Repeat high-resolution CT in 6–12 months
This helps catch early ILD before respiratory impairment becomes irreversible.

Questions

- Catherine.miele@commonspirit.org