SATURDAY, MARCH 22, 2025

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

MARY RICE, MD, MPH

Harvard/Beth Israel Deaconess)

KEYNOTE ADDRESS – THE IMPACT OF AIR POLLUTION AND CLIMATE CHANGE ON LUNG DISEASE

Saturday, March 22, 2025 8:10 am - 8:55 am

Dr. Mary B. Rice MD MPH is the director of the Center for Climate, Health, and the Global Environment (Harvard Chan C-CHANGE) and the Mark and Catherine Winkler Associate Professor of Environmental Respiratory Health at Harvard T.H. Chan School of Public Health. She is a pulmonary critical care physician and the director of the Beth Israel Deaconess Medical Center (BIDMC) Institute for Lung Health, where she is an associate professor of medicine at Harvard Medical School and director of research for the division of pulmonary, critical care and sleep medicine. Rice's area of investigation focuses on the influence of environmental exposures, especially air pollution and climate change, on the respiratory health of children and adults and the development of interventions to mitigate these health effects. She is the principal investigator of a National Institutes of Health (NIH)-funded clinical trial of home air purification for patients with COPD, and she leads the environmental health research program of the American Lung Association Lung Health Cohort. She also co-leads the Center for Climate: Equitable and Accessible Research-based Testing for Health (C-EARTH), an NIH-funded P20 Center which aims to bring sustainable climate solutions to heat stressed, low-income communities around the globe.

JYOTHI TIRUMALASETTY, MD

Stanford

THE CHANGING PATTERNS OF ALLERGENS DUE TO CLIMATE CHANGE AND MITIGATION OF ENVIRONMENTAL EXPOSURES

Saturday, March 22, 2025 8:55 am - 9:20 am

Jyothi Tirumalasetty, MD, FAAAAI has over 18 years of experience in allergy and clinical immunology. She started her career in medicine in Chicago after completing internal medicine residency and allergy fellowship at Northwestern University's Feinberg School of Medicine. She served as the clinical director of the Center for Lung Health at University of Illinois at Chicago and as section chief of allergy at the Jesse Brown VA in Chicago. She was recruited to Stanford University School of Medicine in 2022 and currently splits her time between teaching, clinical research, and patient care as a Clinical Assistant Professor within the Division of Pulmonary, Allergy, and Critical Care Medicine. Her research has focused on reducing greenhouse gas emissions in the healthcare sector, assessing the carbon footprint of asthma inhalers in the US, and understanding the effects of climate change and pollution on asthma and allergic diseases. Her second area of research focuses on health disparities in asthma and allergic diseases. In her free time, Dr. Tirumalasetty enjoys gardening, running, and spending time with her mini-goldendoodle named Roscoe.

SHEIPHALI GANDHI, MD, MPH

UCSF/San Francisco VA)

OCCUPATIONAL LUNG DISEASE AND THE NEW EPIDEMIC OF SILICOSIS IN CALIFORNIA

Saturday, March 22, 2025 9:20 am - 9:45 am

Sheiphali Gandhi, MD, MPH, is an Assistant Professor at the University of California San Francisco in the Divisions of Occupational, Environmental, and Climate Medicine and Pulmonary, Critical Care, Sleep, and Allergy Medicine. She is a dual-boarded pulmonologist and occupational medicine physician specializing in occupational and environmental respiratory disease. She is the Director of the California Silicosis Support and Research Network based at UCSF. Additionally, she is the Associate Director of the San Francisco Veteran's Association Post-Deployment Cardiopulmonary Evaluation Network, assessing veterans with military exposures in Southwest Asia. Her research concentrates on the epidemiology of interstitial lung disease, including pneumoconiosis, and the occupational contributions to health disparities.

ASTHMA/ATOPIC AIRWAYS DISEASE

REIKA MIYOKAWA, MD

Santa Clara Valley MC

THE NEW GINA GUIDELINES, WHAT YOU NEED TO KNOW

Saturday, March 22, 2025 10:25 am - 10:50 am

Reika received her medical degree from the University of Hawaii, where she grew up. She then completed her internal medicine residency at UC Davis followed by Pulmonary and Critical Care fellowship Stanford University, with a focus on asthma and medical education. Currently, she serves as faculty at Santa Clara Valley Medical Center in San Jose, California.

PRAVEEN AKUTHOTA, MD

UCSD

THE ROLE OF TH2 INFLAMMATION IN AIRWAYS DISEASES

Saturday, March 22, 2025 10:50 AM - 11:15 am

Dr. Praveen Akuthota is a Professor of Medicine in the Division of Pulmonary, Critical Care, Sleep Medicine & Physiology at the University of California San Diego. He is an expert in the care of patients with asthma and eosinophilic respiratory diseases and has authored chapters in leading sources such *as Harrison's Textbook of Internal Medicine, Middleton's Allergy*, and *UpToDat*e. Dr. Akuthota's research efforts range from basic scientific investigations of human eosinophil biology and eosinophilic inflammation to clinical and translational efforts in asthma and eosinophilic pulmonary disease. He is the corresponding Principal Investigator for the UCSD Clinical Center in the National Heart, Lung, and Blood Institute's PrecISE Network that is studying precision interventions in severe asthma. He was a co-investigator on a study published in the *New England Journal of Medicine* showing the efficacy of anti-IL-5 therapy in the treatment of the eosinophilic disease EGPA (Churg Strauss syndrome). His research group is involved in other multicenter studies in eosinophilic disease and asthma. Basic science investigations from Dr. Akuthota focus on *ex vivo* studies of human eosinophils.

MONICA TANG, MD

UCSF

UPDATE ON THE ROLE OF BIOLOGICS IN ASTHMA AND ATOPIC DISEASE

Saturday, March 22, 2025 11:15 am - 11:40 am

Dr. Monica Tang received her medical degree from Northwestern University. She did her residency in internal medicine and pediatrics followed by her fellowship in allergy/immunology at Duke University. She is an Assistant Professor of Medicine at UCSF and serves as the physician lead for the severe asthma clinic.

SHAZIA LUTFEALI, MD

Cedars-Sinai

PRO: CLINICAL REMISSION IS POSSIBLE IN ASTHMA

Saturday, March 22, 2025 11:40 am - 11:55 am

Dr. Lutfeali is a Southern California native and grew up in a college town called Claremont. After completing medical school at Georgetown University and residency at Weill Cornell Medical Center, she pursued a fellowship in Allergy & Immunology at the University of Texas, Southwestern Medical Center in Dallas, where she had a special focus in drug allergy. She then returned to Southern California where she practiced at Kaiser Permanente and most recently has joined the Faculty at Cedars-Sinai Medical Center, where she serves as an Assistant Professor in the Departments of Medicine and Pediatrics. Here, she collaborates with her colleagues in pulmonology and has initiated an adult and pediatric Severe Asthma Clinic. Optional: In her spare time, she enjoys hiking, swimming, ping-pong, and trying new restaurants.

NICHOLAS KENYON, MD
UC Davis

CON: CLINICAL REMISSION IS NOT POSSIBLE IN ASTHMA

Saturday, March 22, 2025 11:55 am - 12:10 pm

Dr. Kenyon is Professor of Medicine in Div of Pulmonary, Critical Care and Sleep Medicine at UC Davis and a VA Mather Staff Physician. He is director of the UC Davis Asthma Network clinics. His translational research focus on arginine metabolism, nitric oxide biology, airway inflammation, and asthma. He is PI of the NH**LBI** T32 Training Program on Comparative Lung Biology and Medicine and NHLBI R38 Training Program in Veterinary and Human Health and MPI of the UC Davis Clinical and Translational Science Center.

HANDS ON SESSION

SHEIPHALI GANDHI, MD, MPH

UCSF/San Francisco VA

HANDS-ON SESSION: DIY AIR FILTERS

Saturday, March 22, 2025 1:20 pm – 2:20 pm

Sheiphali Gandhi, MD, MPH, is an Assistant Professor at the University of California San Francisco in the Divisions of Occupational, Environmental, and Climate Medicine and Pulmonary, Critical Care, Sleep, and Allergy Medicine. She is a dual-boarded pulmonologist and occupational medicine physician specializing in occupational and environmental respiratory disease. She is the Director of the California Silicosis Support and Research Network based at UCSF. Additionally, she is the Associate Director of the San Francisco Veteran's Association Post-Deployment Cardiopulmonary Evaluation Network, assessing veterans with military exposures in Southwest Asia. Her research concentrates on the epidemiology of interstitial lung disease, including pneumoconiosis, and the occupational contributions to health disparities.

JOON CHANG, MD

Stanford

HANDS-ON SESSION: CRYOBIOPSY

Saturday, March 22, 2025 1:20 pm - 2:20 pm

Dr. Joon Chang received his medical degree from UCLA David Geffen school of medicine. He did her post-graduate medicine residency at NYU and pulmonary and critical care fellowship at Stanford. He completed his interventional pulmonology fellowship at the Hospital of University of Pennsylvania in 2022. Currently, he serves as an Assistant Professor of Medicine and an associate program director for interventional pulmonology fellowship at Stanford.

EMILY CASABAR, NP

Stanford

HANDS-ON SESSION: RESPIRATORS/FACE MASKS

Saturday, March 22, 2025 1:20 pm - 2:20 pm

Emily Casabar, MSN, NP-C received her Bachelor of Science Degree in Nursing from California State University, Bakersfield in 2005 and her Master of Science Degree in Nursing, FNP, at Holy Names University in Oakland, CA in 2012. Emily is the Lead Advanced Practice Provider in the Pulmonary clinic at Stanford Health Care. Emily's area of clinical practice is general pulmonology specializing in COPD, Asthma, and other pulmonary diseases. Emily also works collaboratively in the Stanford Interstitial Lung Disease (ILD) clinic.

JULIEANNE GARCIA, RRT

Palo Alto VA

HANDS-ON SESSION: FENO/PORTABLE SPIROMETRY

Saturday, March 22, 2025 1:20 pm - 2:20 pm

Mrs. Garcia received her Associate of Science Degree in Respiratory Care in 2019. Currently, she is working in the Pulmonary section at the Veteran's Affairs Palo Alto Health Care System, and training in assisting interventional pulmonologists with special pulmonary diagnostic procedures. Her interests lean towards embracing new technologies and helping others to do the same, as the Respiratory Care profession advances. She is also member of the American Association of Respiratory Care (AARC) and the California Society of Respiratory Care (CSRC).

INSTERSTITIAL LING DISEASE

TOBY MAHER, MD MSC PHD

USC

FROM ILA TO PPF: UNDERSTANDING THE ALPHABET SOUP

Saturday, March 22, 2025 2:45 pm - 3:10 pm

Toby Maher is Professor of Medicine and Director of Interstitial Lung Disease at Keck School of Medicine, University of Southern California, Los Angeles.

Dr Maher has spent the last 20 years specializing in the management of all forms of pulmonary fibrosis and orphan interstitial lung diseases. He previously ran the ILD unit at Royal Brompton Hospital, London. Since June 2020 he has been Director of ILD at Keck Medicine of University of Southern California in Los Angeles. His research interests include: biomarker discovery, the lung microbiome and host immune response in the pathogenesis of IPF and clinical trials in interstitial lung disease. He has been involved in >100 trials in fibrotic lung disease from phase 1b through to phase 4 and including those assessing IPF, sarcoidosis, scleroderma, rheumatoid arthritis and inflammatory myositis. He is an associate editor for *American Journal of Respiratory and Critical Care Medicine* and is on the Editorial Board of *Lancet Respiratory Medicine*. He has authored over 400 papers and book chapters on pulmonary fibrosis.

LILA POURZAND, MD

UCLA

IMAGING PATTERNS IN INTERSTITIAL LUNG DISEASE

Saturday, March 22, 2025 3:10 pm - 3:35 pm

Dr. Lila Pourzand received her medical degree from Shahid Beheshti (Melli)University in Iran. She completed her Internal Medicine residency at LAC-USC. Subsequently, she pursued and completed her Radiology residency, Nuclear medicine fellowship and Thoracic Diagnostic and Interventional fellowship.

Dr. Pourzand serves as an Associate Professor of Radiology and Lead radiologist in CTD-ILD program at UCLA.

NIRANJAN JEGANATHAN, MD

Loma Linda

INVASIVE TESTING TO MAKE THE DIAGNOSIS IN ILD: FROM BAL TO OPEN LUNG BIOPSY

Saturday, March 22, 2025 3:35 pm - 4:00 pm

Dr. Jeganathan is an Associate Professor of Medicine at Loma Linda University Health. He completed his pulmonary and critical care fellowship training at Rush University, where he also earned a master's degree in clinical research.

Dr. Jeganathan established and leads the Interstitial Lung Disease program at Loma Linda University Health, which is recognized as a Pulmonary Fibrosis Foundation Center of Excellence. His research focuses on ILD epidemiology, and he has authored numerous original articles, reviews, and editorials. Additionally, he serves on the California Thoracic Society Conference Planning Committee.

GABRIELLE LIU, MD

UC Davis

WHEN TO USE IMMUNOSUPPRESSANTS AND ANTIFIBROTICS IN NON-IPF ILD

Saturday, March 22, 2025 4:00 pm - 4:25 pm

Gabrielle Y. Liu, MD, MS is an Assistant Professor of Medicine in the Division of Pulmonary, Critical Care, and Sleep Medicine and the Associate Director of the Interstitial Lung Disease Program at the University of California Davis. Her research explores the risk factors and biomarkers associated with impaired respiratory health and the transition to chronic lung disease. Her current work examines the association between wildfire smoke exposure and markers of impaired respiratory health.

STEPHANIE JI CHEN, MD
Stanford

MULTIDISCIPLINARY FELLOWS CASE CONFERENCE

Saturday, March 22, 2025 4:25 pm - 4:50 pm

Dr. Stephanie Chen received her medical degree from University of Michigan, then completed internal medicine residency at UCSF. She is currently a second year pulmonary and critical care fellow at Stanford University. She is interested in pursuing a career in ILD and critical care.

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH | C-CHANGE CENTER FOR CLIMATE, HEALTH, AND THE GLOBAL ENVIRONMENT

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

The impact of air pollution and climate on lung disease

Mary B. Rice, MD MPH
Director, BIDMC Institute for Lung Health
Associate Professor, Harvard Medical School

Director, Center for Climate, Health and the Global Environment

Mark and Catherine Winkler Associate Professor of Environmental Respiratory Health,
Harvard Chan School of Public Health

California Thoracic Society Meeting
March 22, 2025

Disclosures

- I have no relationships with ACCME defined ineligible companies

- I WILL NOT discuss off-label use and/or investigational use of any drugs or devices

Aims / Learning Objectives

1. Describe changes in air quality (smoke, smog and aeroallergens) attributable to climate change

2. Identify major respiratory effects these exposures among children and adults

3. Consider health implications of fuel combustion in policy and clinical care

How is climate change an air quality problem?

Ozone Smog

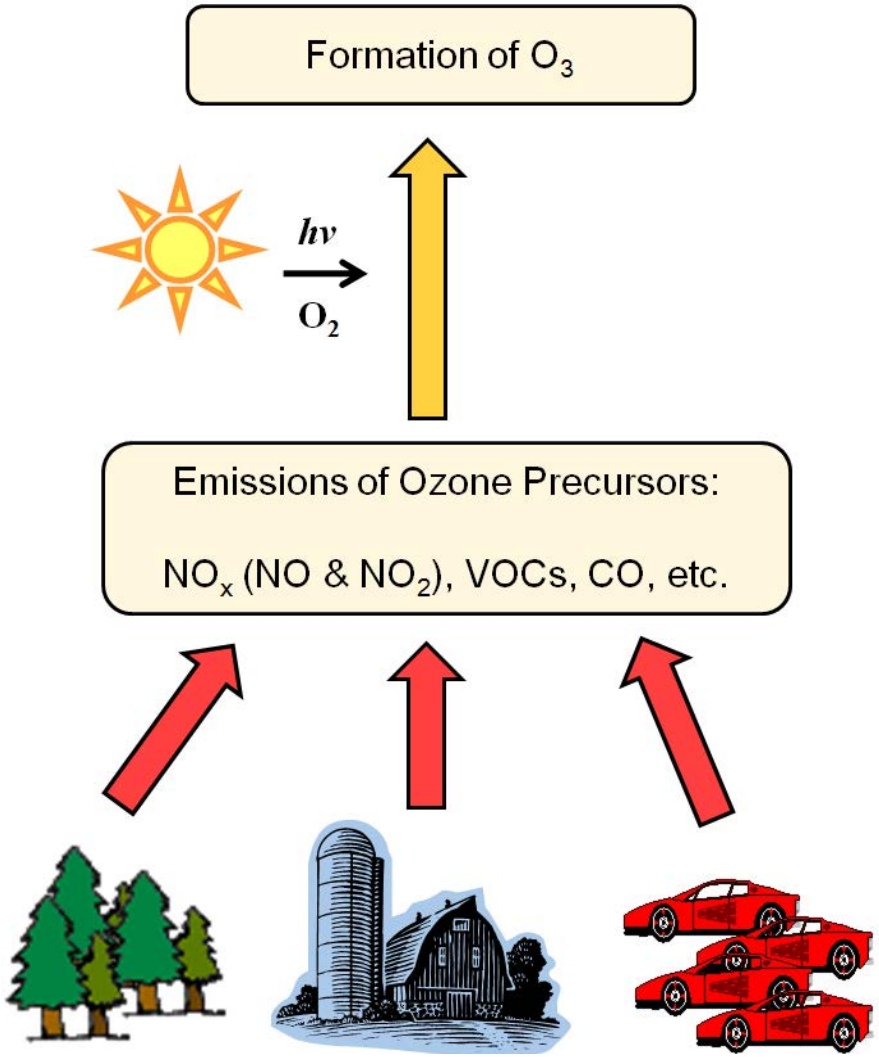
Pollen

Wildfires

Fuel Combustion Pollution

Higher temperatures increase ground-level ozone (O_3)

- Component of smog
- Formed by the reaction of NOx and VOCs in presence of UV radiation
- Very powerful oxidant
- Well-established respiratory irritant, trigger for respiratory hospitalization and all-cause mortality



Wiegman et al. *Clinical Science*. 2014

Repeated exposure to O_3 induces airway remodeling

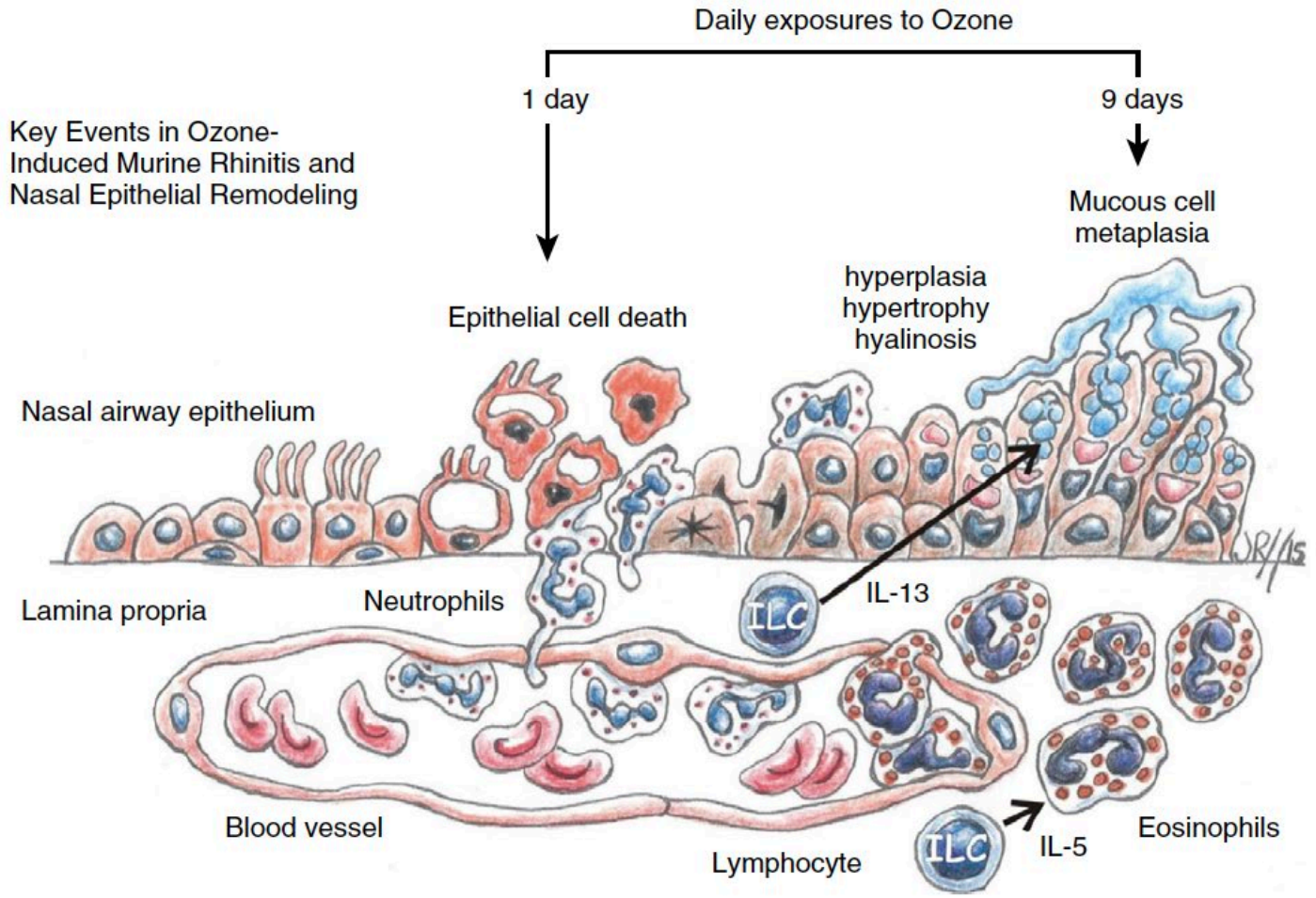
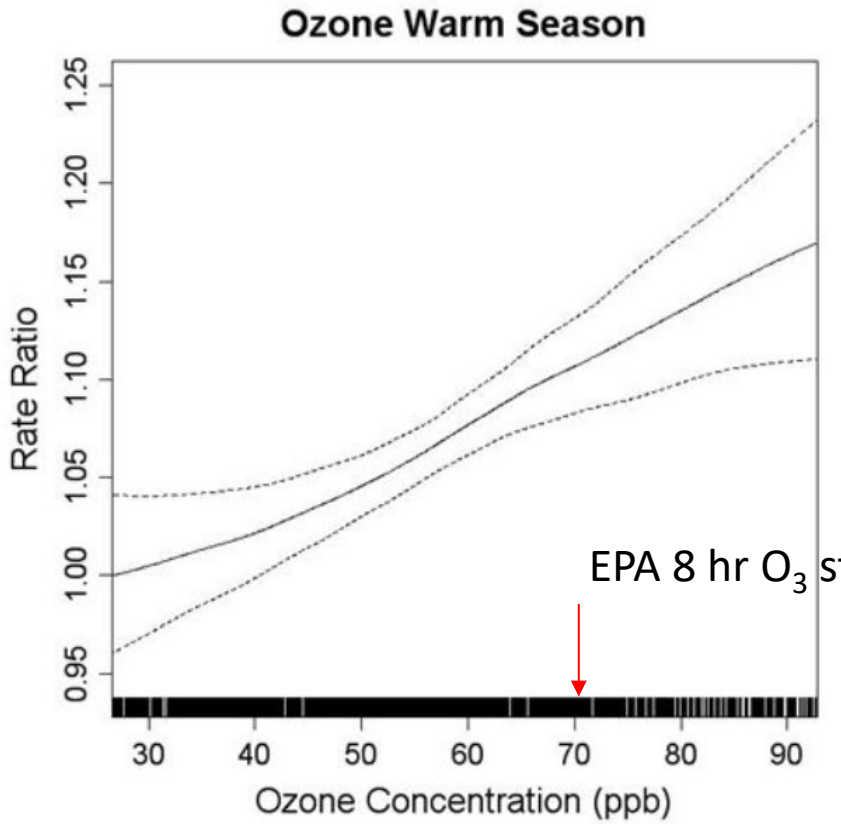


Image by Dr. Harkema in Thurston et al. *Annals ATS*. 2019.

Summer O_3 and child asthma hospitalizations



EPA 8 hr O_3 standard = 70 ppb

Atlanta on a smoggy day

Boston on a smoggy day

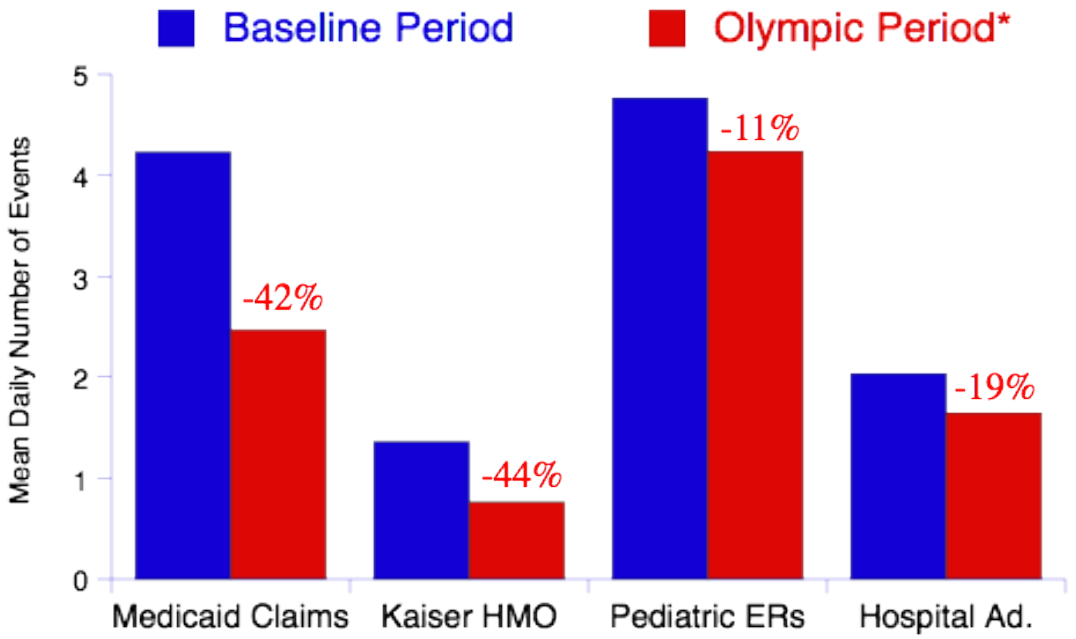
Strickland et al. *Am J Resp Crit Care Med.* 2010.

Olympics traffic reduction program → fewer child asthma events

Traffic Counts **- 23%**

Ozone **-30%**

PM_{10} **-16%**

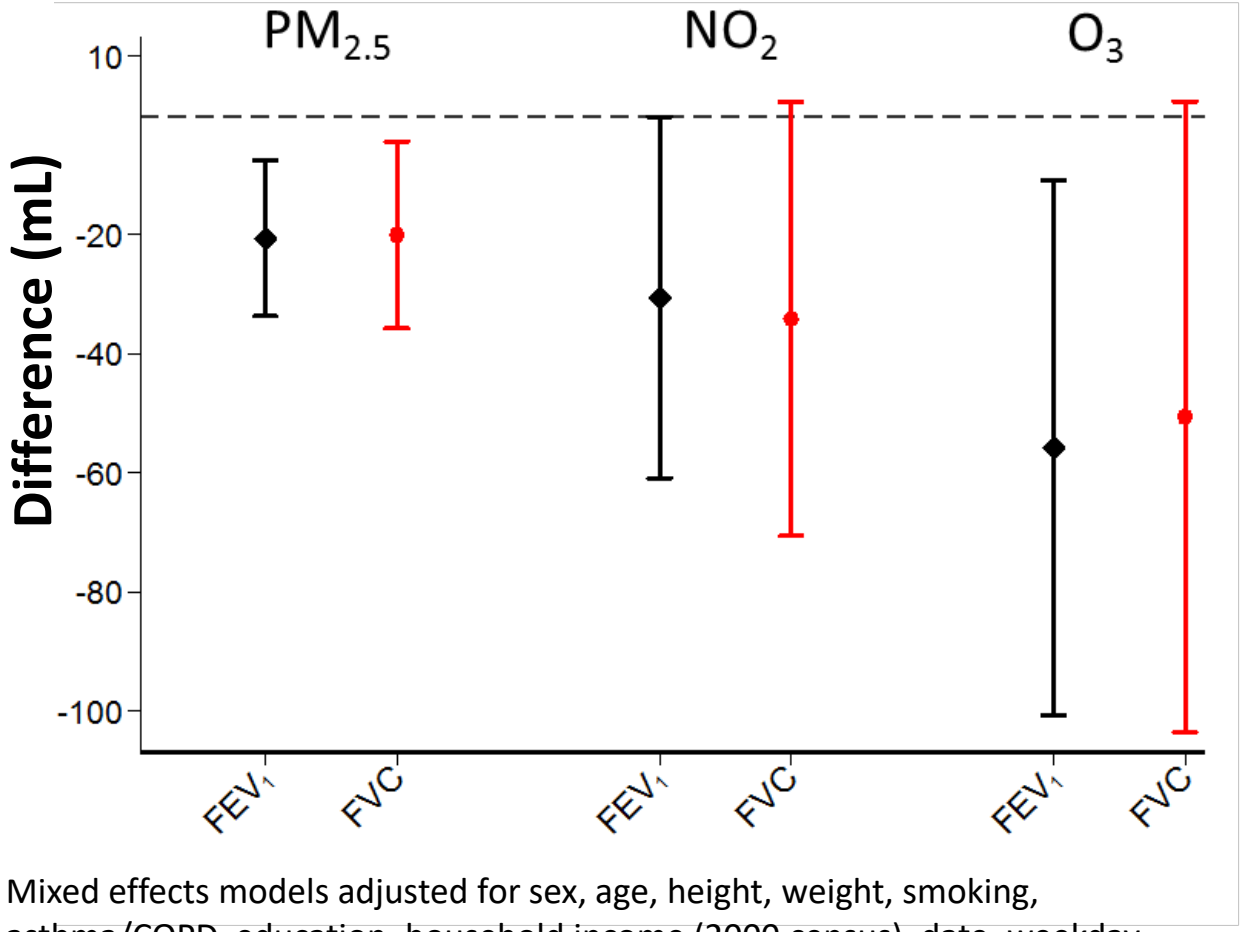


Non-asthma related acute care visits during same time period did not change

Friedman et al. *JAMA* 2001
Slide adapted from K Enfield

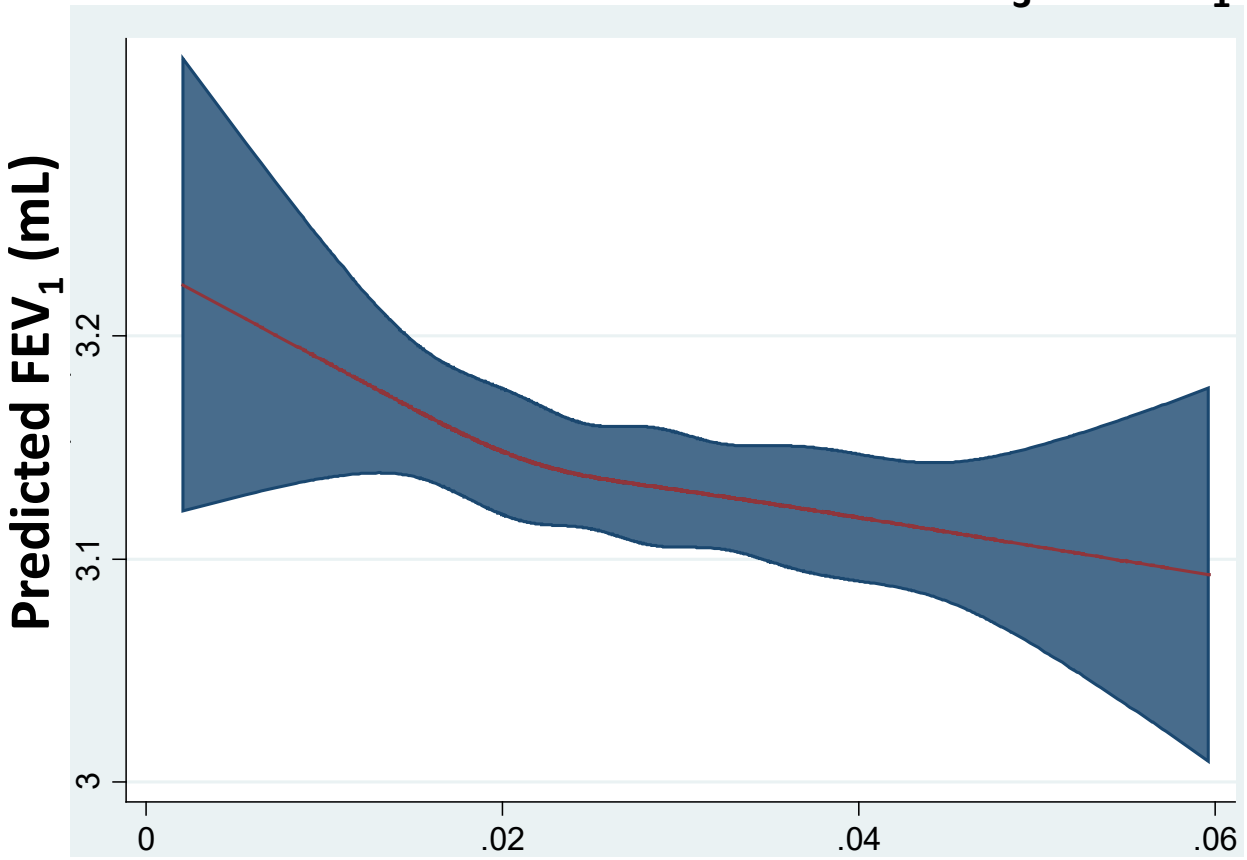
O_3 (within air quality standards) and lower adult lung function

Lung function after "moderate" vs "good" air quality



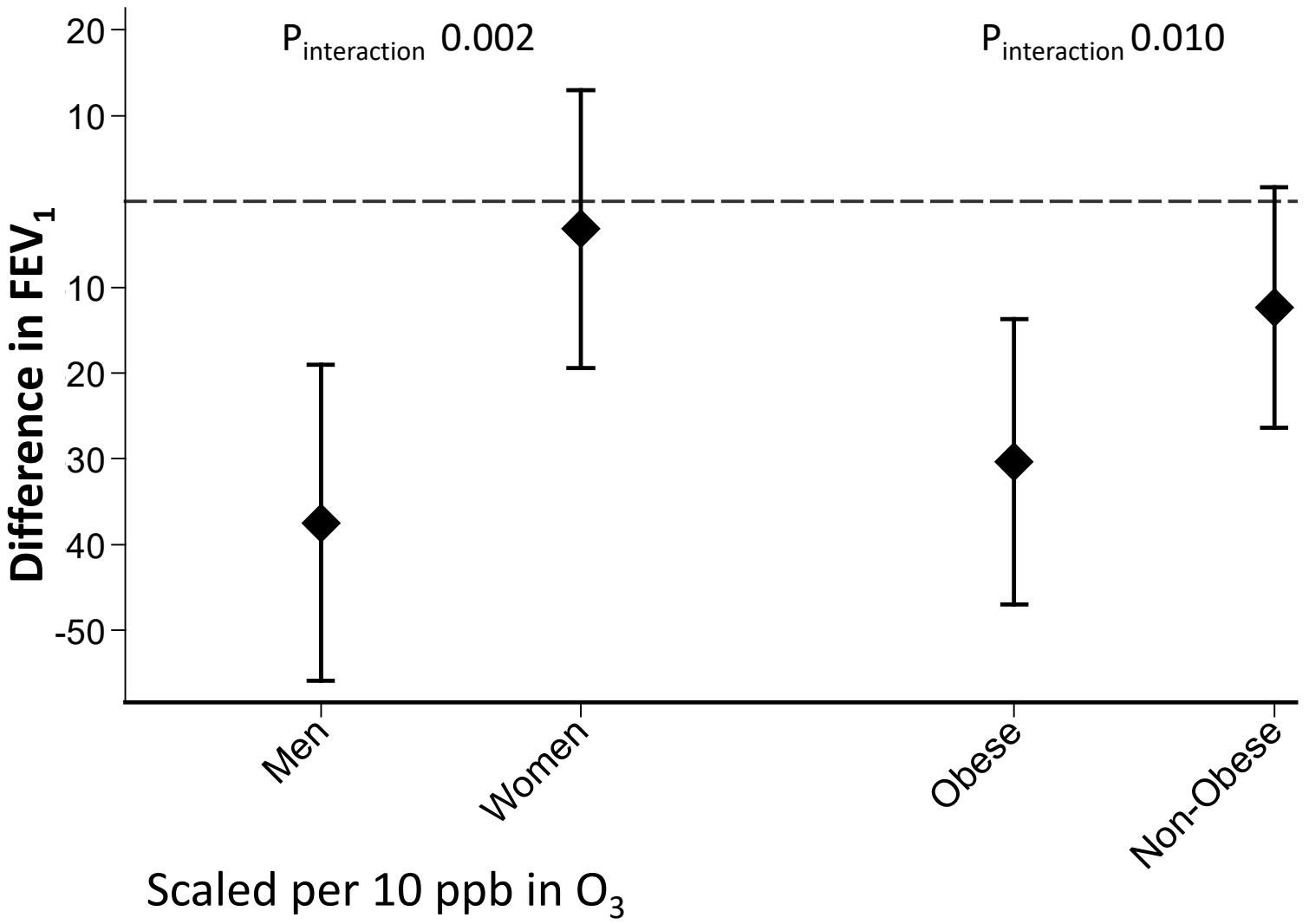
Mixed effects models adjusted for sex, age, height, weight, smoking, asthma/COPD, education, household income (2000 census), date, weekday, season, temperature, humidity and cohort

No evidence of a threshold effect of O_3 on FEV_1



Rice et al. *Am J Respir Crit Care Med.* 2013.

Men and obese adults may be more susceptible to O_3



Scaled per 10 ppb in O_3

Rice et al. *Am J Respir Crit Care Med.* 2013.

Consistent evidence obesity is a risk factor for O_3 susceptibility

J Appl Physiol 95: 938–945, 2003.
First published June 6, 2003; 10.1152/japplphysiol.00336.2003.

translational physiology

Responses to ozone are increased in obese mice

S. A. Shore, Y. M. Rivera-Sanchez, I. N. Schwartzman, and R. A. Johnston
Physiology Program, Harvard School of Public Health, Boston, Massachusetts 02115

Submitted 4 April 2003; accepted in final form 25 May 2003

Ozone Exposure and Lung Function*

Effect Modified by Obesity and Airways Hyperresponsiveness in the VA Normative Aging Study

Stacey E. Alexeeff, BSc; Augusto A. Litonjua, MD, MPH, FCCP; Helen Suh, ScD; David Sparrow, ScD; Pantel S. Vokonas, MD; and Joel Schwartz, PhD

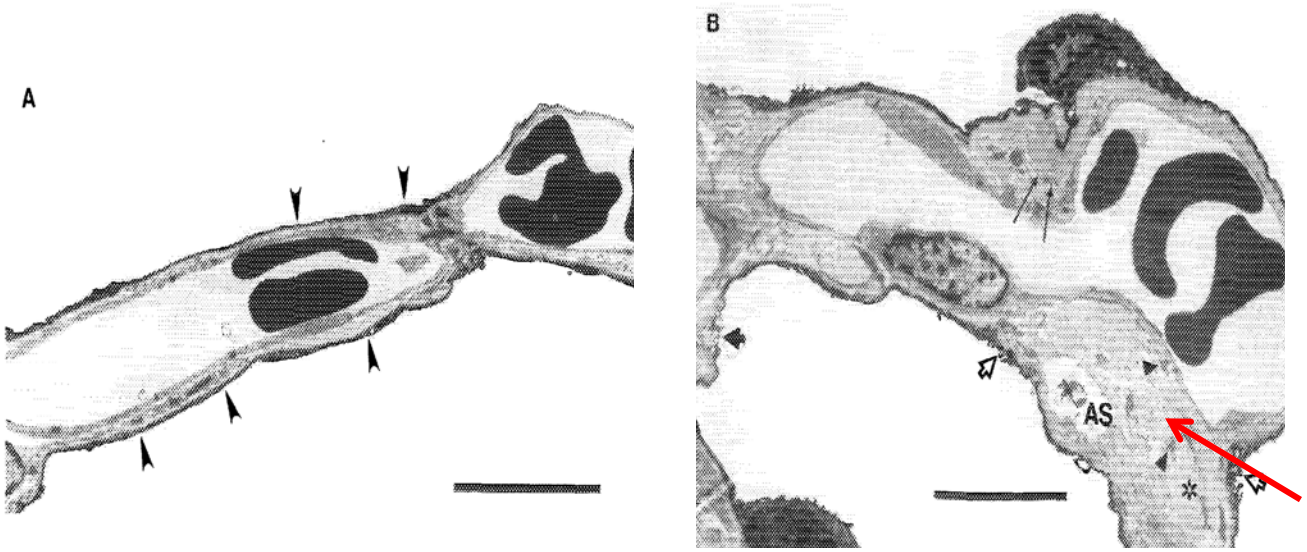
IL-33 Drives Augmented Responses to Ozone in Obese Mice

Joel A. Mathews,[1] Nandini Krishnamoorthy,[2] David Itiro Kasahara,[1] Youngji Cho,[1] Allison Patricia Wurmbrand,[1] Luiza Ribeiro,[1] Dirk Smith,[3] Dale Umetsu,[4] Bruce D. Levy,[2] and Stephanie Ann Shore[1]

Very high O_3 exposure causes pulmonary fibrosis

Alveolar septa from control lung

Alveolar septa from rat exposed to 1 ppm of O_3 for 20 months



↑ Collagen
↑ Elastin

Stockstill et al. *Toxicol Appl Pharmacol*. 1995

Cohort studies of O_3 exposure in adults have found*:

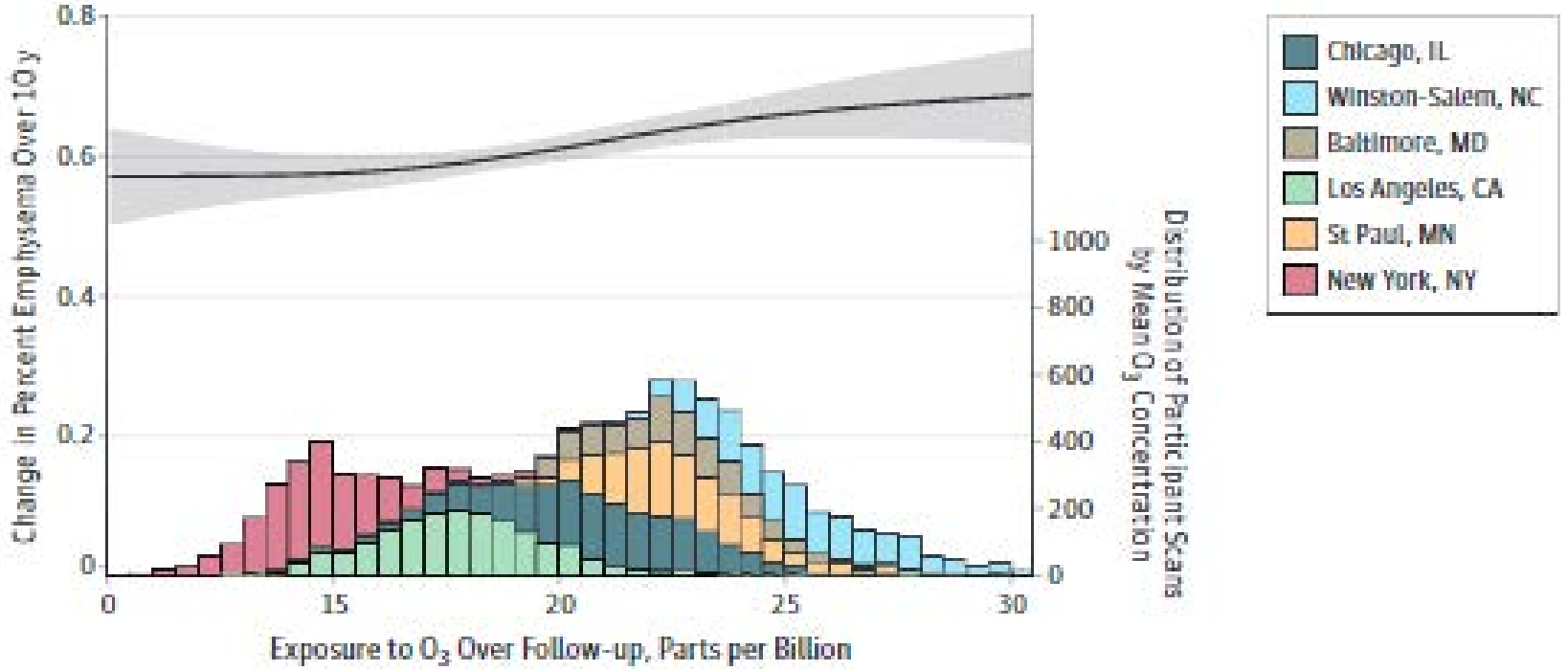
-Higher risk of **IPF exacerbation**

-No increased risk of interstitial changes with long-term O_3 (but increased risk with NO_2, traffic)

*Johannson et al. ERJ. 2014; Sack et al. ERJ 2017; Rice et al. Thorax 2019.

Long-term O_3 exposure associated with emphysema progression

Progression rate of % emphysema based on O_3 exposure



Every 3 ppb of O_3 associated with a 0.18 (95% CI 0.08 – 0.28) higher % emphysema over 10 years among 6,860 adults (Multi-Ethnic Study of Atherosclerosis)

Wang et al. *JAMA*. 2019.

Climate models predict higher O_3, delaying regulatory progress

Climate change could <u>overwhelm</u> ozone emission reduction efforts

2050 vs 2000

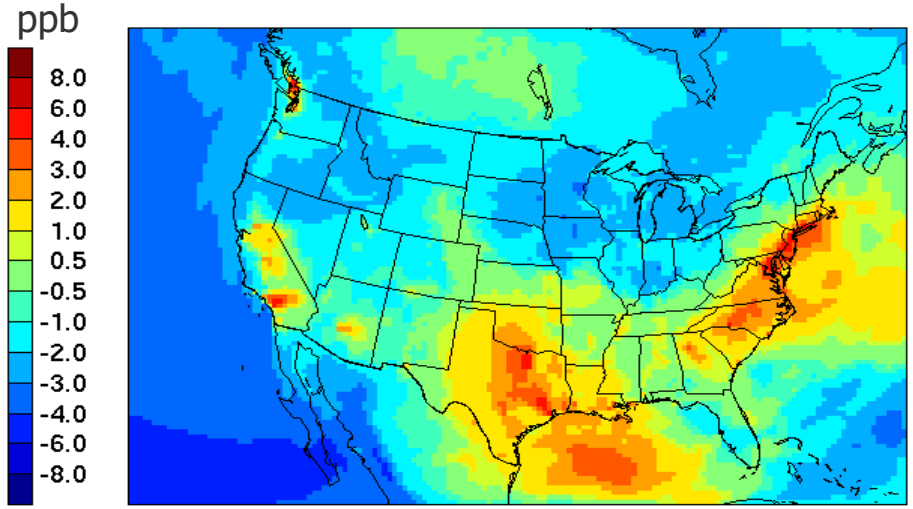
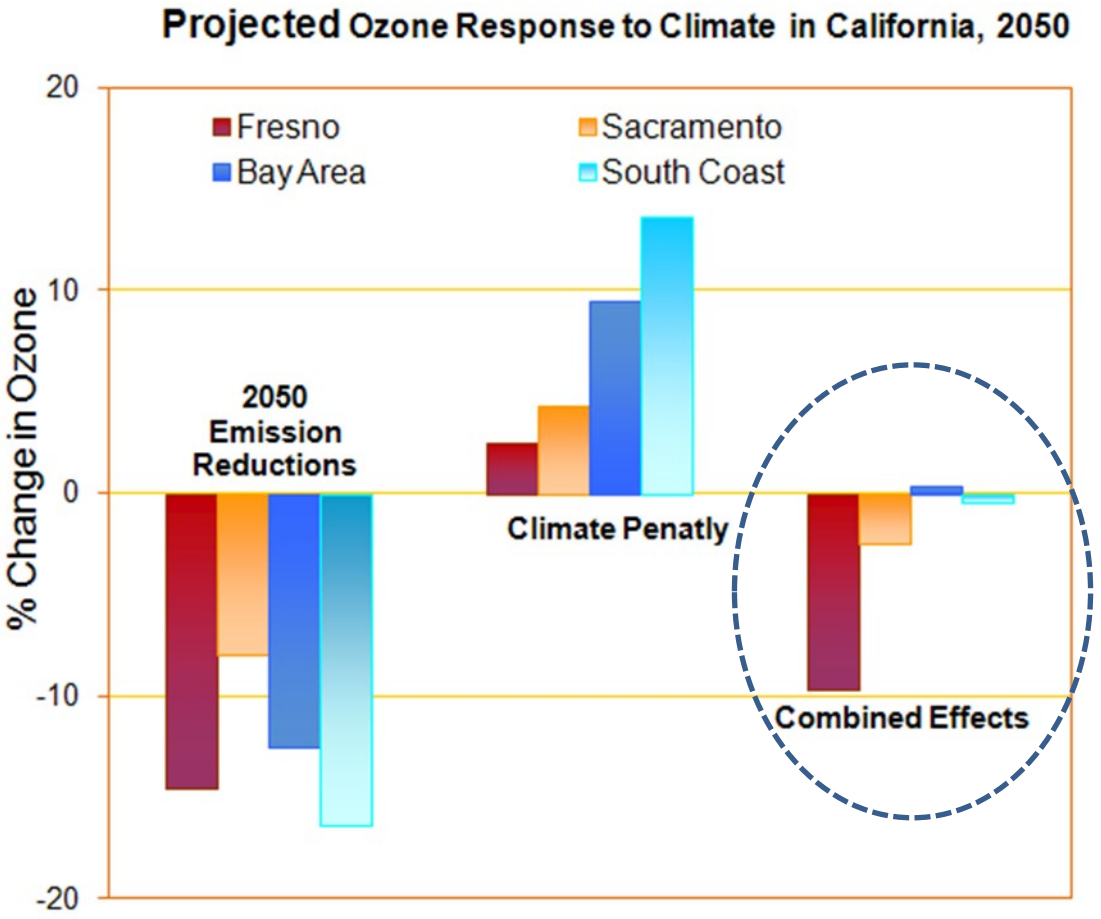


Image from Dan Costa, EPA



Steiner et al., *J. of Geophysical Research* 2006;
Millstein and Harley, JGR 2009.
(courtesy John Balmes)

Higher CO_2 and temperatures lengthen and amplify pollen season

- Longer pollen seasons (earlier blooming, later frost)
  - +20 days in past 20 years in N. America
- Faster plant growth and higher pollen quantity
  - +21% in past 20 years in N. America
- Higher pollen allergenicity
  - increase in allergenic protein / total pollen protein

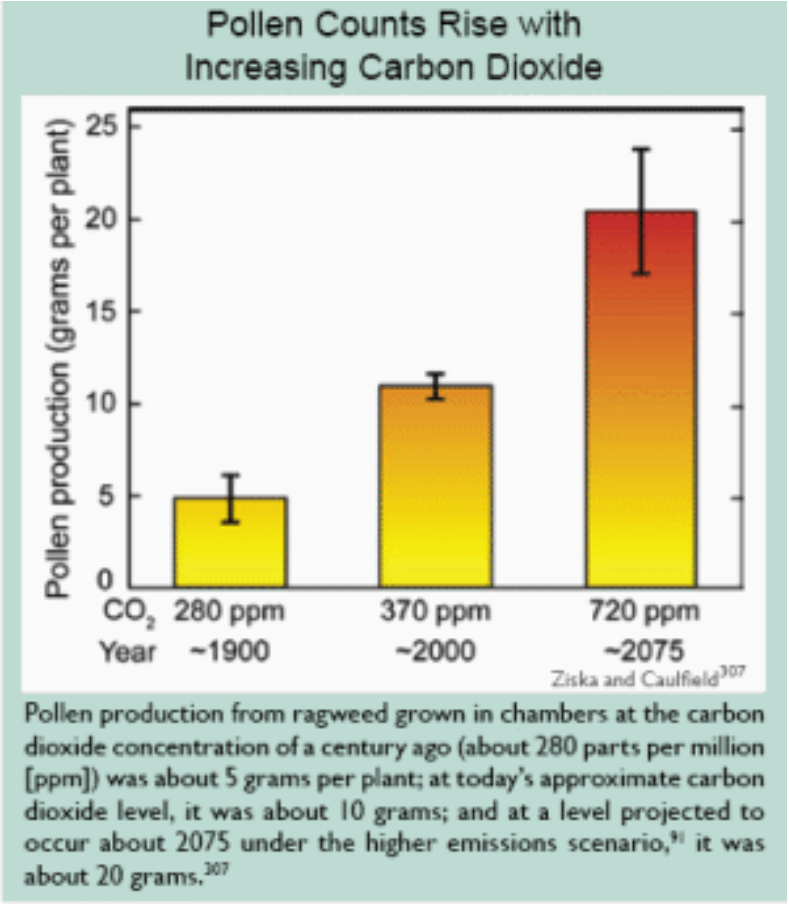


Figure: Ziska et al. *Aust J Plant Physiol.* 2000

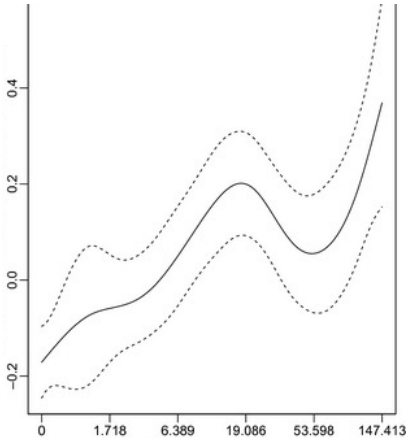
Anderegg et al. PNAS. 2022; D'Amato et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy*. 2020.

Pollen provokes asthma and allergy, possibly respiratory mortality

- Allergy is **very** common
  - 10-30% of population has symptoms of allergic rhinitis
  - 10-35% of adults have IgE to grass pollen
  - ~70% of asthmatics are allergic

- Higher pollen levels associated with:
  - Allergy medication use and visits
  - Asthma admissions
  - **Mortality** due to COPD and pneumonia
    - 15% higher relative risk on high pollen days in Netherlands*

Grass pollen and child ER Visits for Asthma



Grass pollen (grains/m^3)

Erbas et al. *Clin & Exp Allergy*. 2012

*Brunekreef et al. Lancet 2000. Other sources: D'Amato et al. Allergenic pollen and pollen allergy in Europe. *Allergy*. 2007; D'Amato et al. *Allergy*. 2020.

Pollen and pollutants may interact to impair lung health

Association between lung function of school age children and short-term exposure to air pollution and pollen: the PARIS cohort

Amazouz H, *et al*. *Thorax* 2021

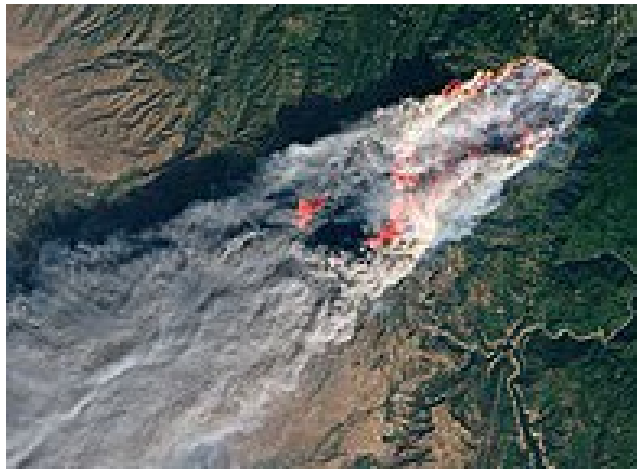
What is the bottom line?

- We found that children recently exposed to grass pollen had significantly lower FEV_1 and FVC levels, and children recently exposed to PM_{10} (particulate matter less than 10 µm) had higher FeNO levels, with a possible synergy between grass pollen and air pollution regarding lung function.

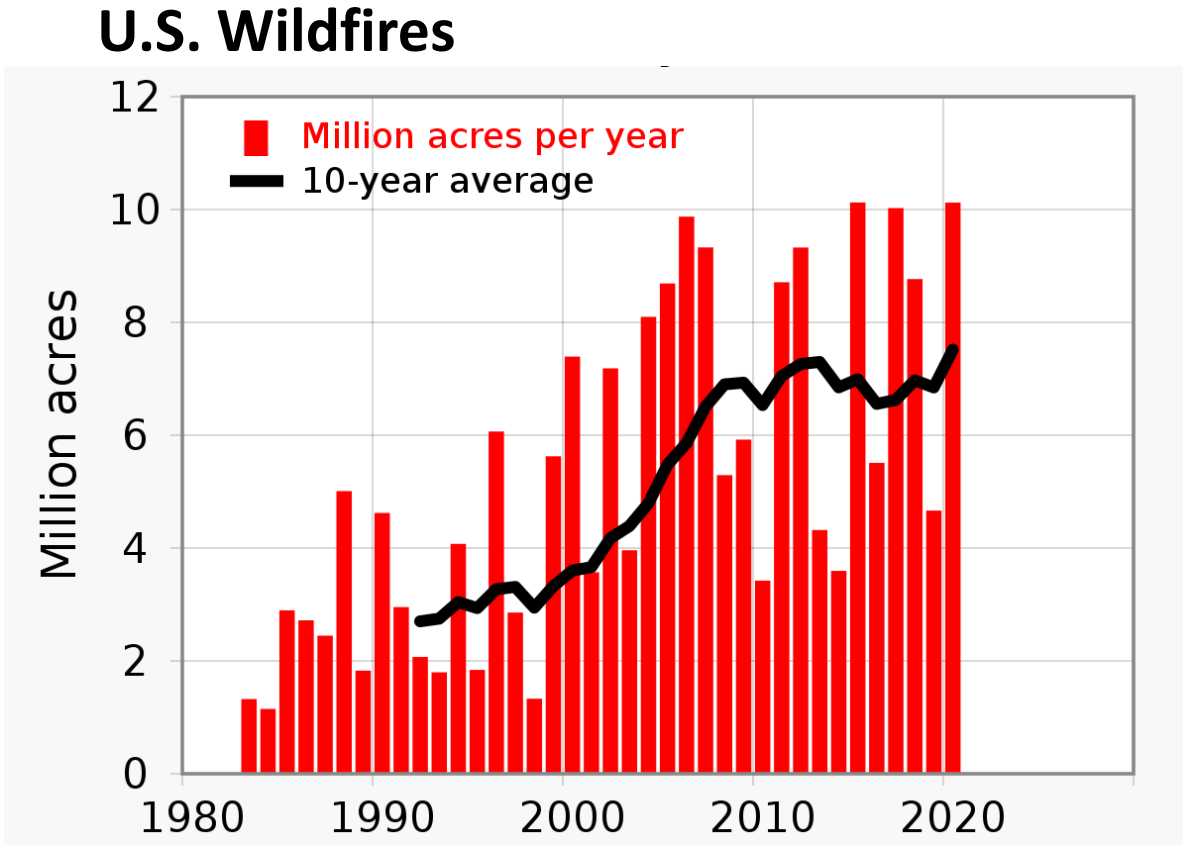
Slide courtesy of Chris Carlsten

Hot, dry conditions increase risk of large destructive wildfires

Australian Bush Fires 2020



Camp Fire, California 2018



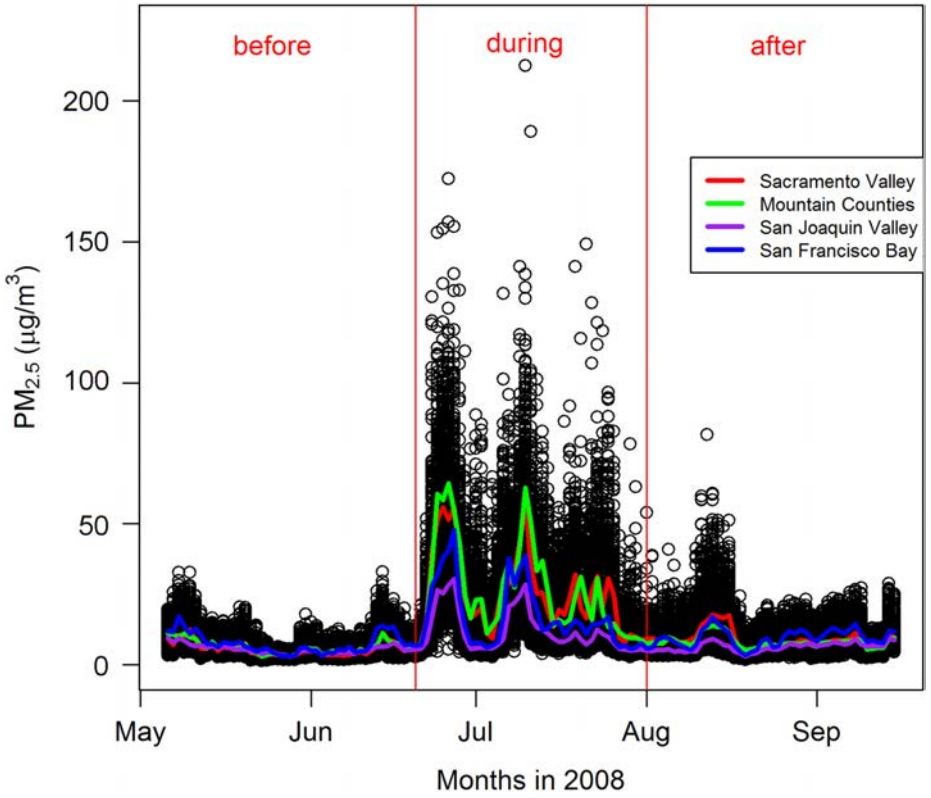
Wildfire $PM_{2.5}$ Really Exceeds Standards

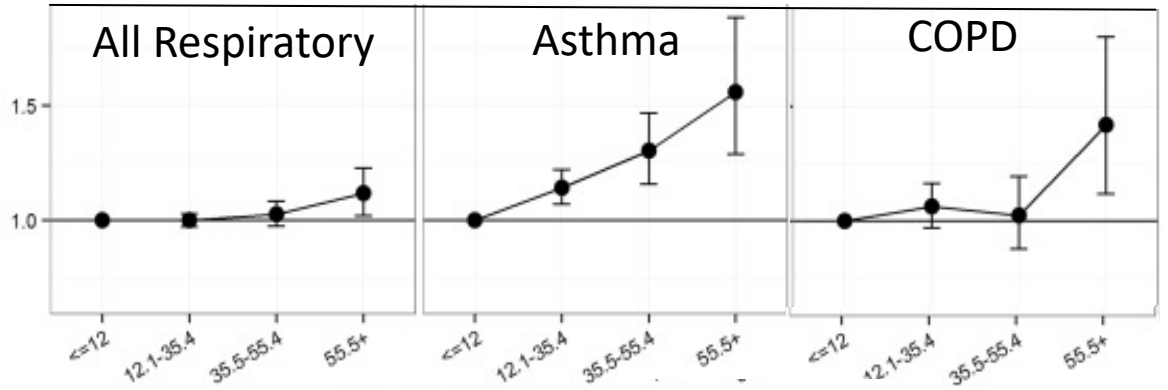
Air Quality Index (AQI) Values	Levels of Health Concern	Health Effects
0 to 50 < 12 µg/m³	Good	Little or no risk
51 to 100 12- 35 µg/m³	Moderate	Acceptable quality
101 to 150 35 – 55 µg/m³	Unhealthy for Sensitive Groups	General Public not likely affected
151 to 200 55 – 150 µg/m³	Unhealthy	All may experience some effects
201 to 300 150 – 250 µg/m³	Very Unhealthy	All may experience more serious effects
301 to 500 >250 µg/m³	Hazardous	Emergency conditions

July 2021, high $PM_{2.5}$ across East Coast due >80 wildfires burning in the West

Nov 2018 Camp Fire: $PM_{2.5}$ >200 µg/m³ in SF (typical level ~9)

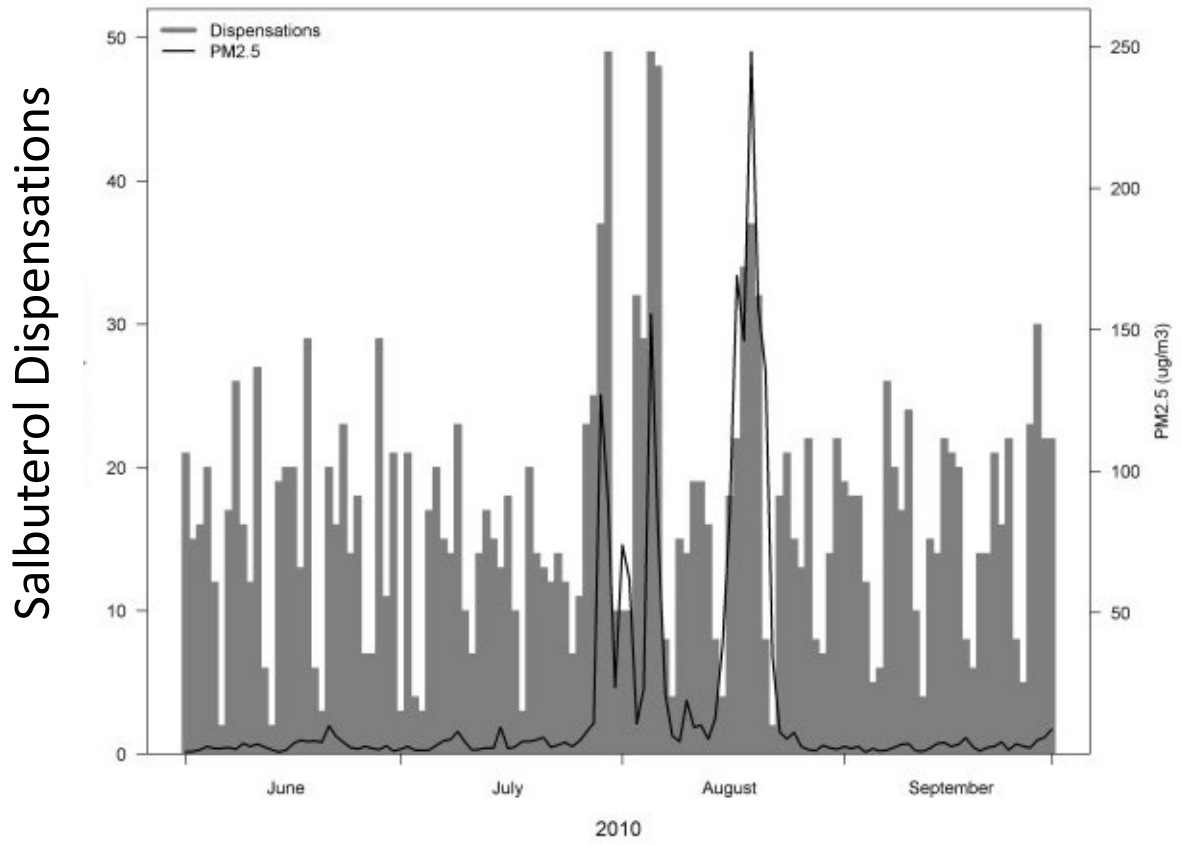
Wildfires increase respiratory admissions





Reid, Balmes et al. *Environ Res.* 2016

Wildfire-specific $PM_{2.5}$ Associated with Asthma Symptoms and Inhaler Use



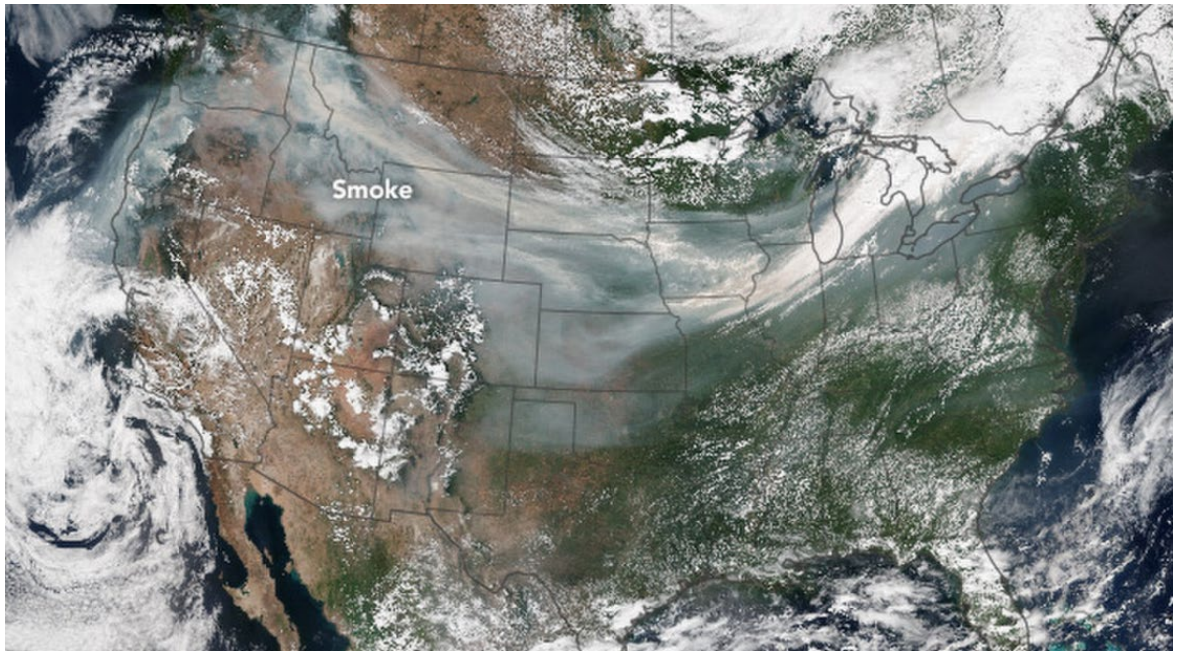
RR 1.06 (1.04-1.07) of inhaler dispensation per 10 µg/m^3 higher wildfire PM

Wildfire PM may be **more toxic for asthmatics** than PM from other sources:

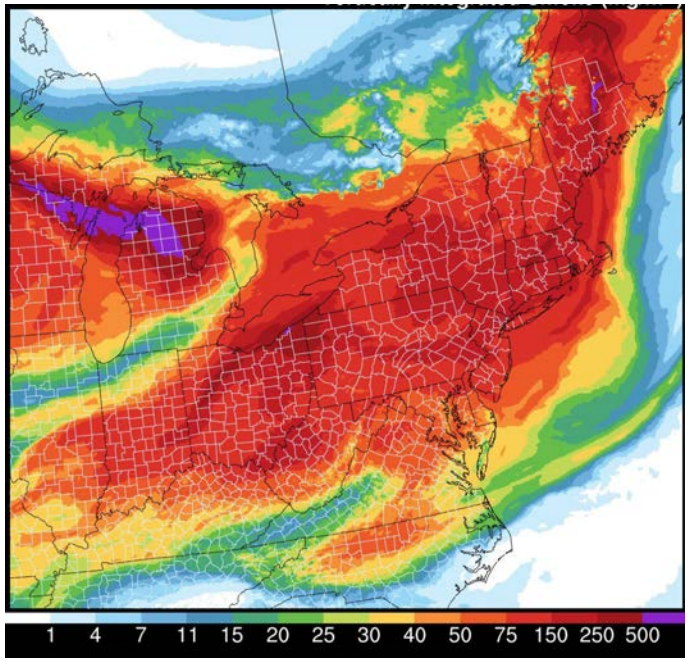
- 6.7% ↑ in asthma hospitalizations per 10 µg/m^3 of wildfire PM
- 1.3% ↑ per 10 µg/m^3 non-wildfire PM

Elliott et al. *Environ Health*. 2013
Johnston et al. *Int J Environ Health Res*. 2006
DeFlorio-Barker et al. *Environ Health Perspect*. 2019

Wildfires contribute more than a third of the total annual burden of $PM_{2.5}$



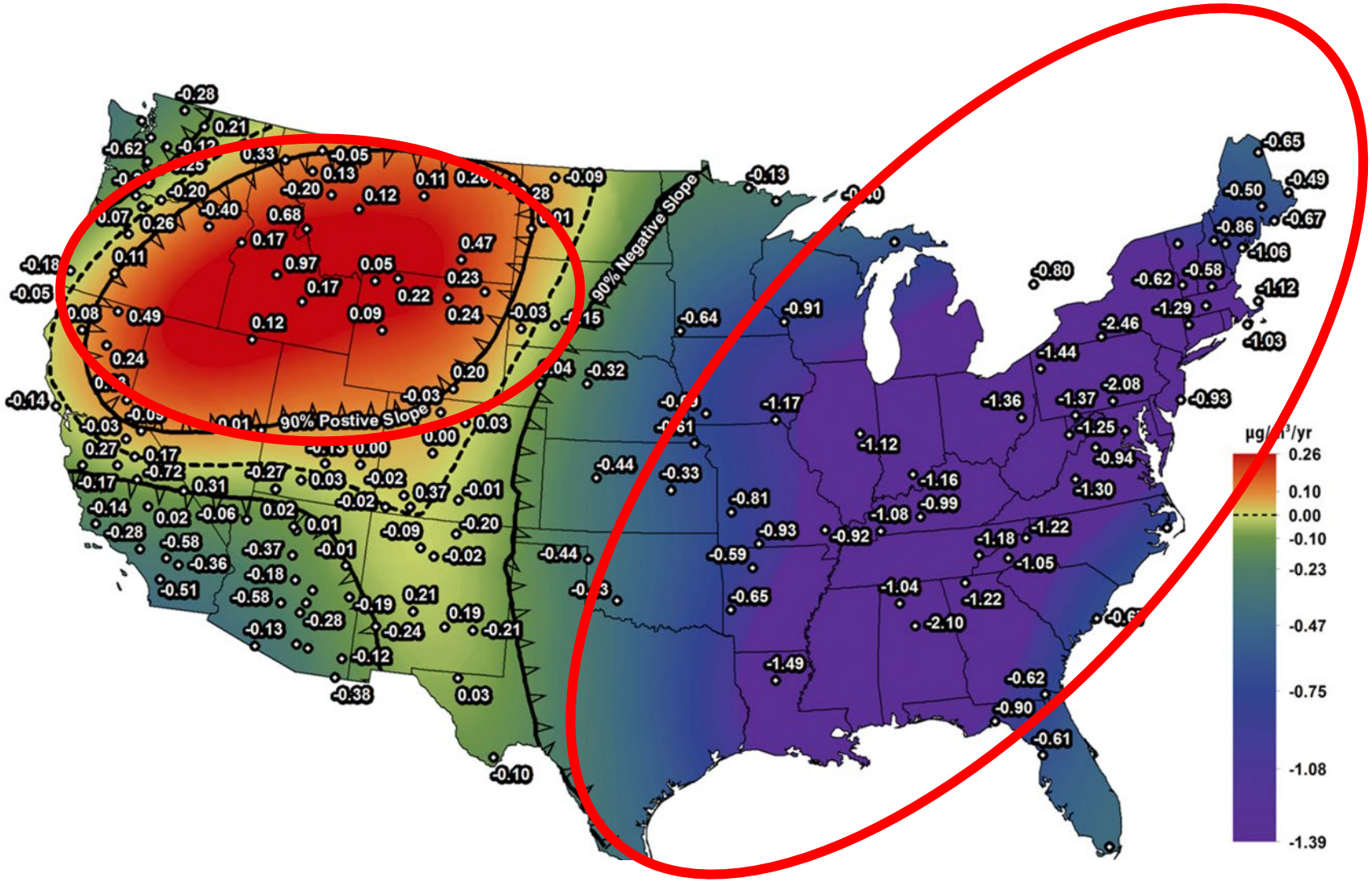
Oct 12 2017 NASA Satellite image



Smoke over East Coast July 19, 2021

*1/3 of $PM_{2.5}$ estimate from 2014 EPA Emissions Inventory

$PM_{2.5}$ air quality improved 1988-2016 except wildfire-prone areas



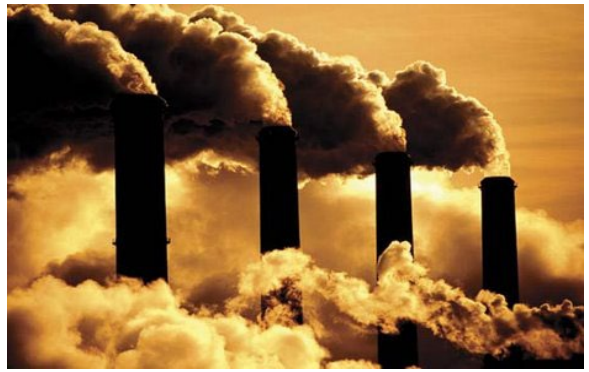
McClure CD and Jaffe DA. *PNAS*. 2018; * US EPA Emissions Inventory

Sources of Air Pollution = Sources of CO_2










Courtesy Dr. E. Mostofsky

Air pollution a cause in girl's death, coroner rules in landmark case

Coroner says failure to reduce pollution levels to legal limits was factor in death of Ella Kissi-Debrah, who had severe asthma

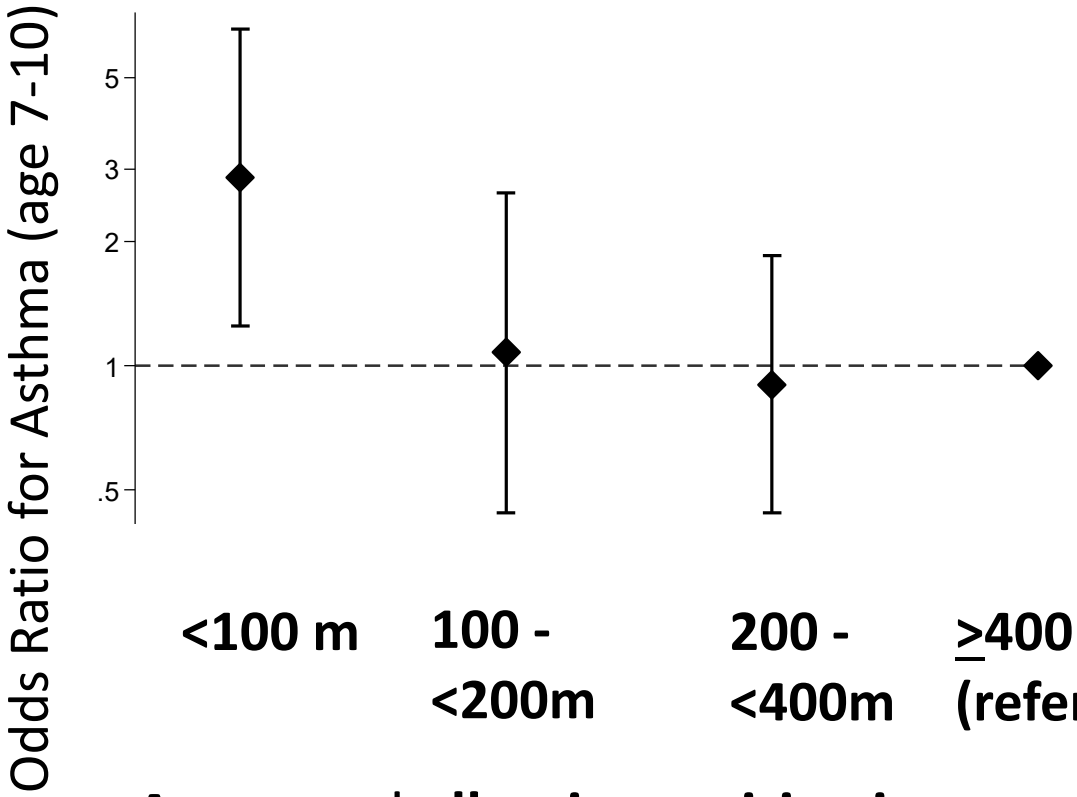
Ella Kissi-Debrah lived within 30 metres of London's South Circular road. Photograph: PA

The Guardian, Dec 16, 2020

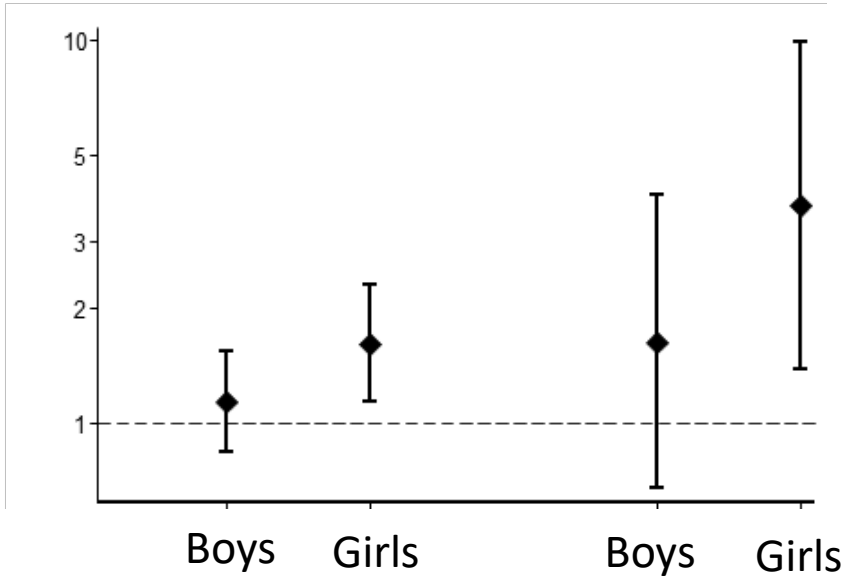
Traffic pollution associated with asthma and wheeze

PROJECT Viva
A Study of Health for the Next Generation

3 x Odds of Asthma if <100 m from Major Road



Greater Risk of Reactive Airways (Age 3-5) in Girls



Atopy and **allergic sensitization** may enhance respiratory effects of combustion pollution

Rice et al. *J Allergy Clin Immunol.* 2018.

Bougas et al. Traffic-related Air Pollution, Lung Function, and Host Vulnerability PARIS Birth Cohort. *Annals ATS*. 2018

Traffic pollution causes childhood asthma

AMERICAN THORACIC SOCIETY DOCUMENTS

Outdoor Air Pollution and New-Onset Airway Disease

An Official American Thoracic Society Workshop Report

George D. Thurston, John R. Balmes, Erika Garcia, Frank D. Gilliland, Mary B. Rice, Tamara Schikowski, Laura S. Van Winkle, Isabella Annesi-Maesano, Esteban G. Burchard, Christopher Carlsten, Jack R. Harkema, Haneen Khreis, Steven R. Kleeberger, Urmila P. Kodavanti, Stephanie J. London, Rob McConnell, Dave B. Peden, Kent E. Pinkerton, Joan Reibman, and Carl W. White; on behalf of the American Thoracic Society Assembly on Environmental, Occupational and Population Health

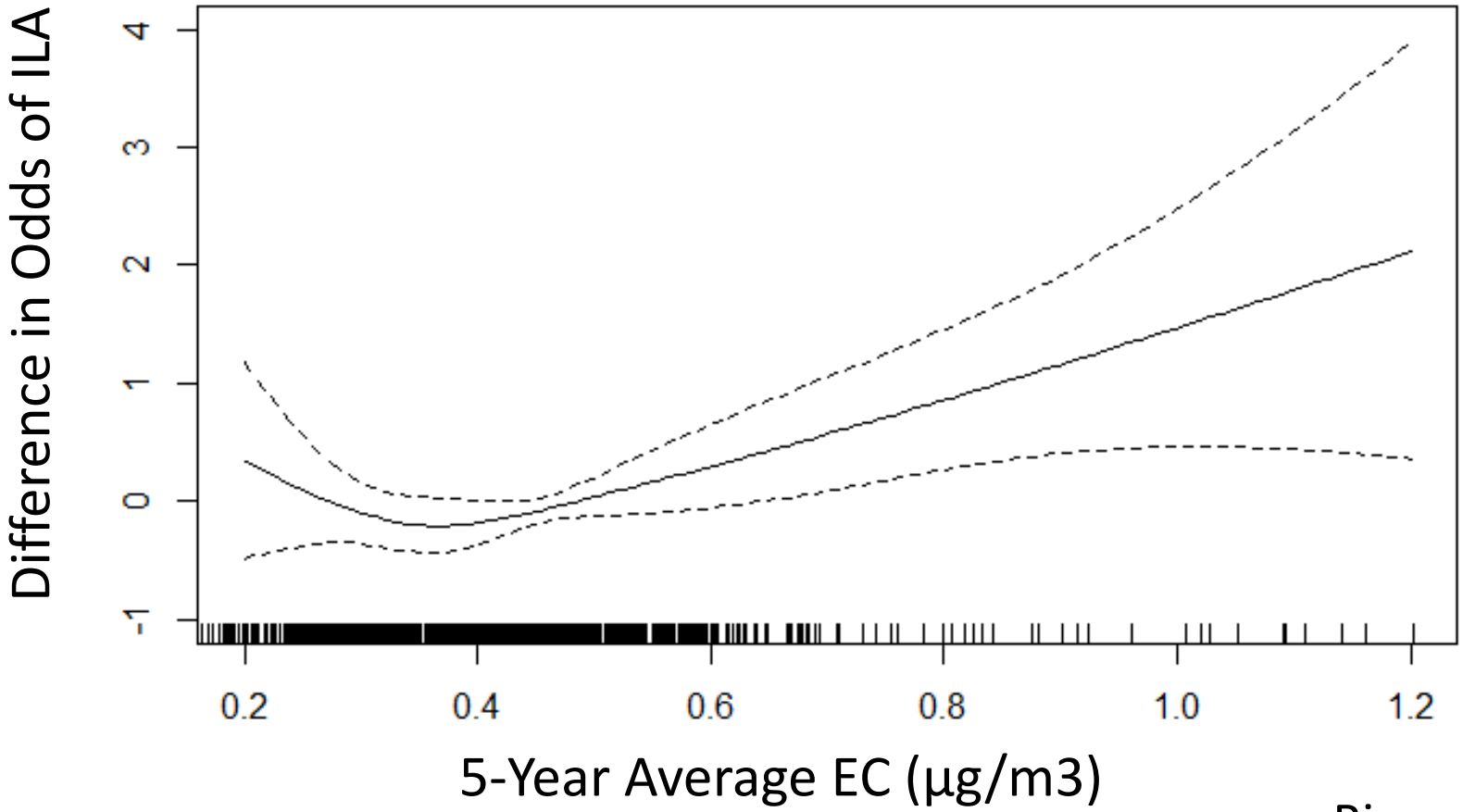
THIS OFFICIAL WORKSHOP REPORT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED DECEMBER 2019

Workshop Conclusions

- Epidemiologic and toxicological evidence convincingly indicate a causal induction of new childhood asthma by long-term outdoor air pollution exposure
- Although combined evidence supports the hypothesis that air pollution is related to adult onset asthma and COPD, additional evidence is needed to definitively conclude a causal connection

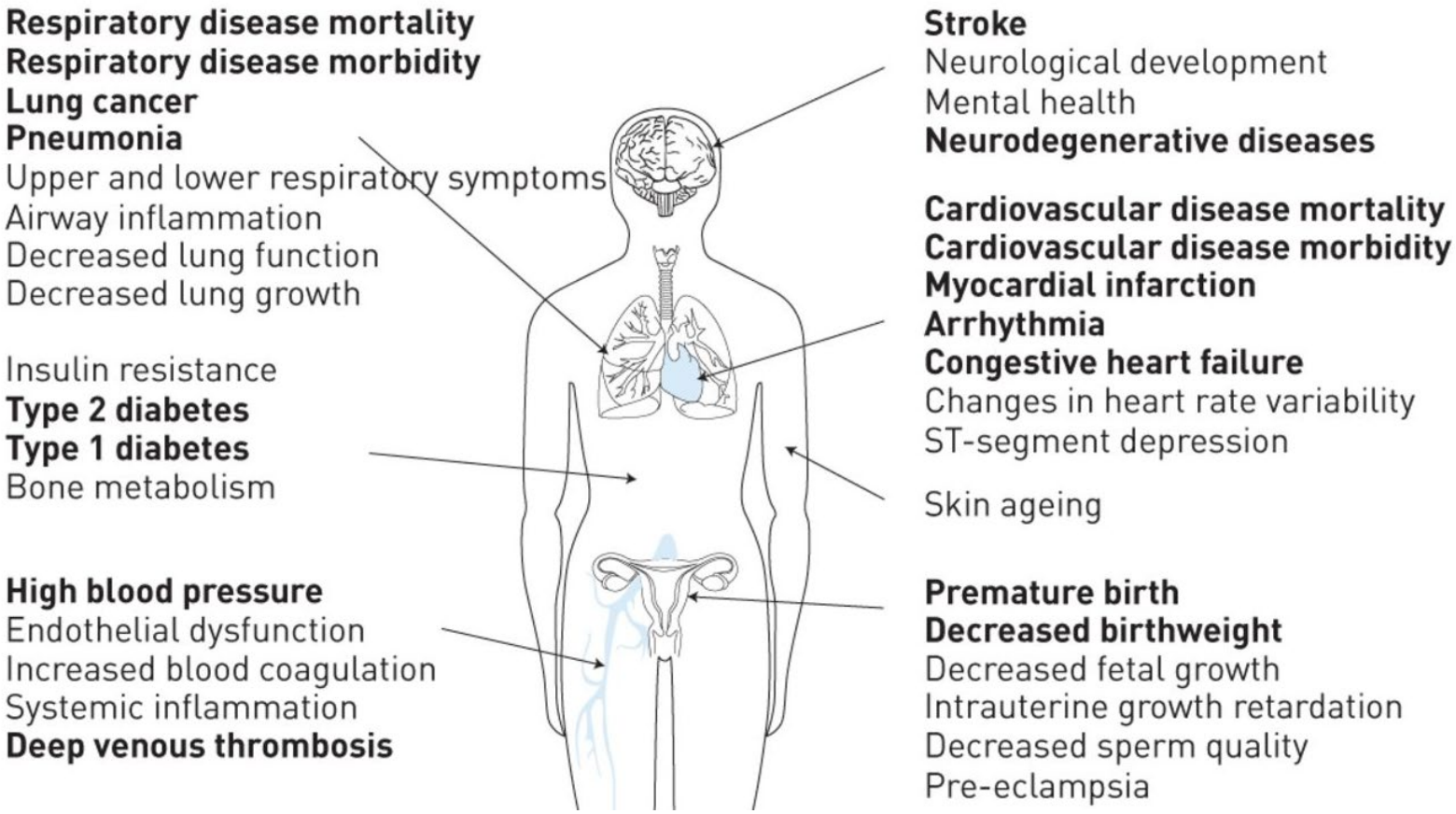
Thurston et al. *Annals ATS*. 2019.

Traffic pollution associated interstitial lung abnormalities



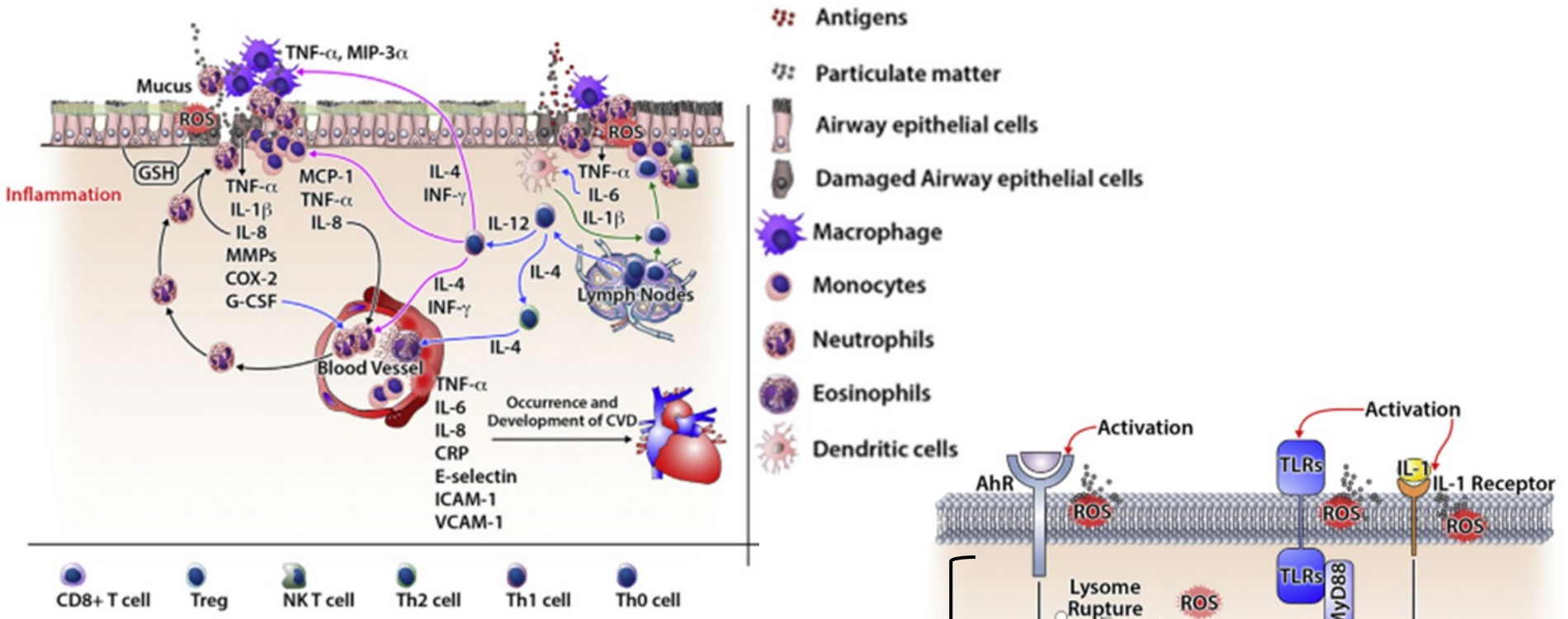
Rice et al. Thorax. 2019
Also: Sack et al. ERJ. 2017;
Goobie et al. AJRCCM. 2020

Air pollution impairs many organ systems

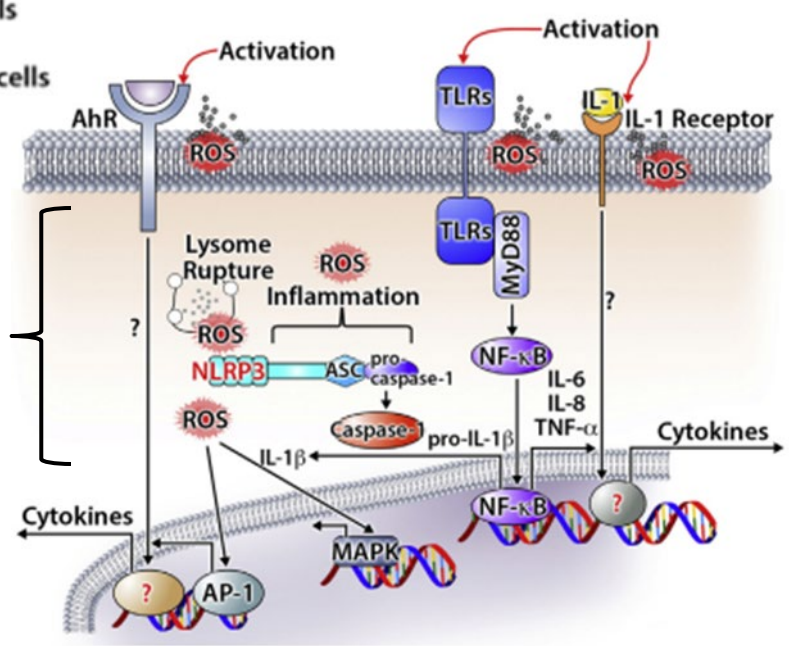


Thurston et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? *Eur Respir J* 2017

Cellular pathways of inflammation triggered by combustion-derived PM



Endogenous ROS cause cytokine release

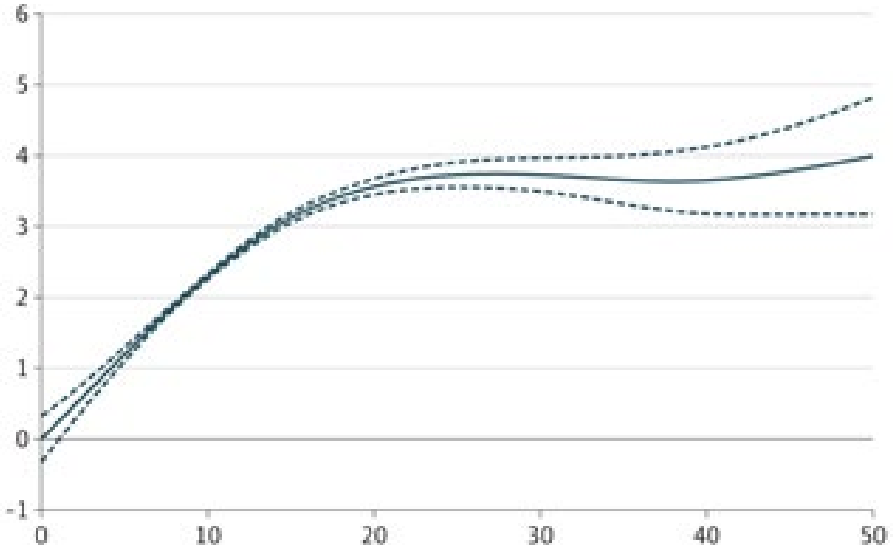


Wu, Jin and Carlsten. *J Allergy Clin Immunol.* 2018

Even low $PM_{2.5}$ pollution associated with death

Entire U.S. Elderly (age > 65) Population

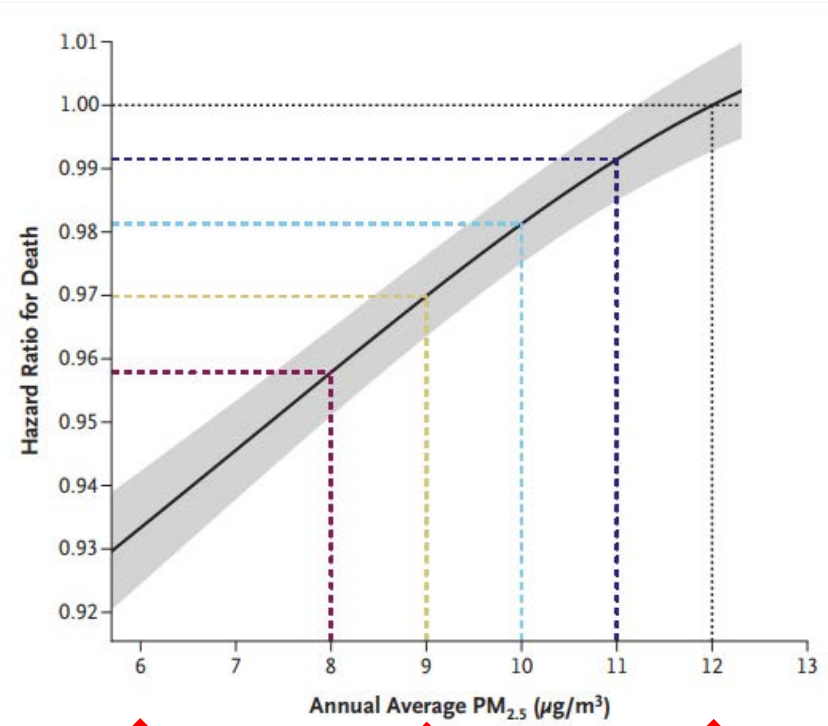
% Increase in Risk of Death



Daily $PM_{2.5}$ (µg/m³)

Di Q et al. *JAMA* 2017

HR for death



2021 WHO Air Quality Guideline for $PM_{2.5}$

New EPA Standard

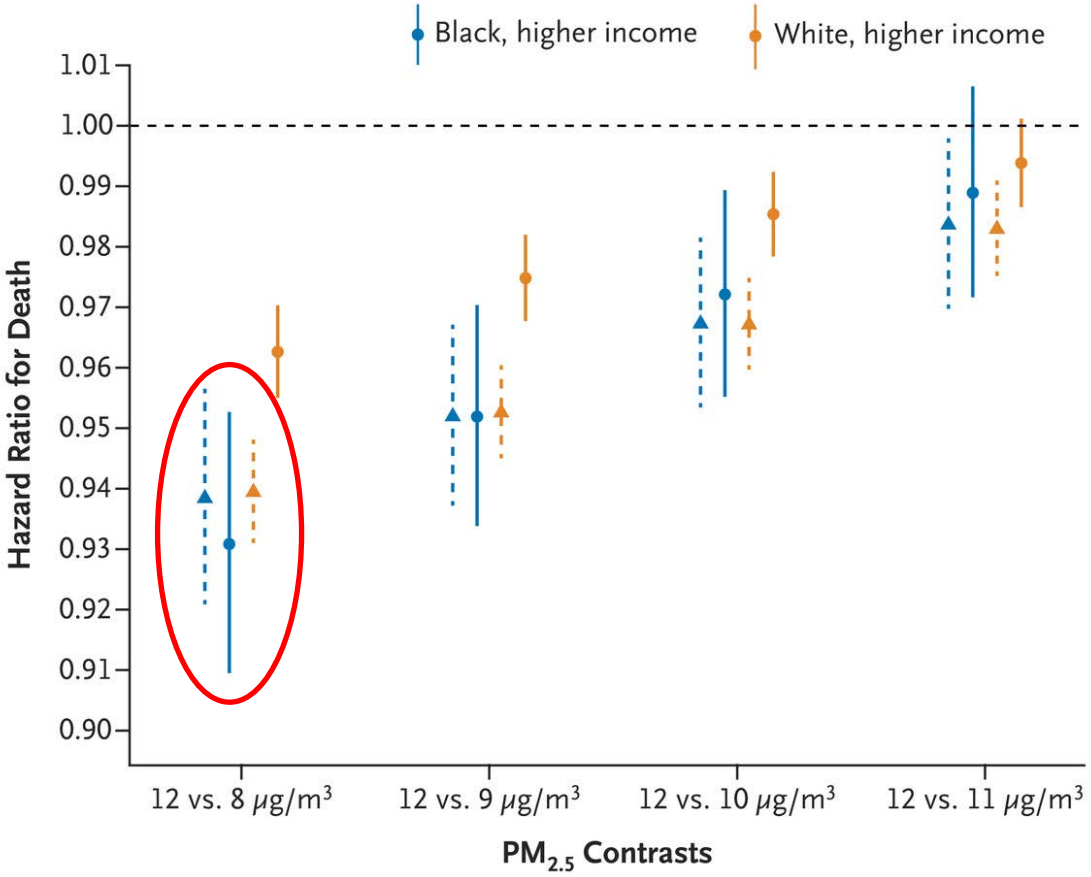
Current EPA Standard

Josey et al. *NEJM. 2023*

SPECIAL ARTICLE

Air Pollution and Mortality at the Intersection of Race and Social Class

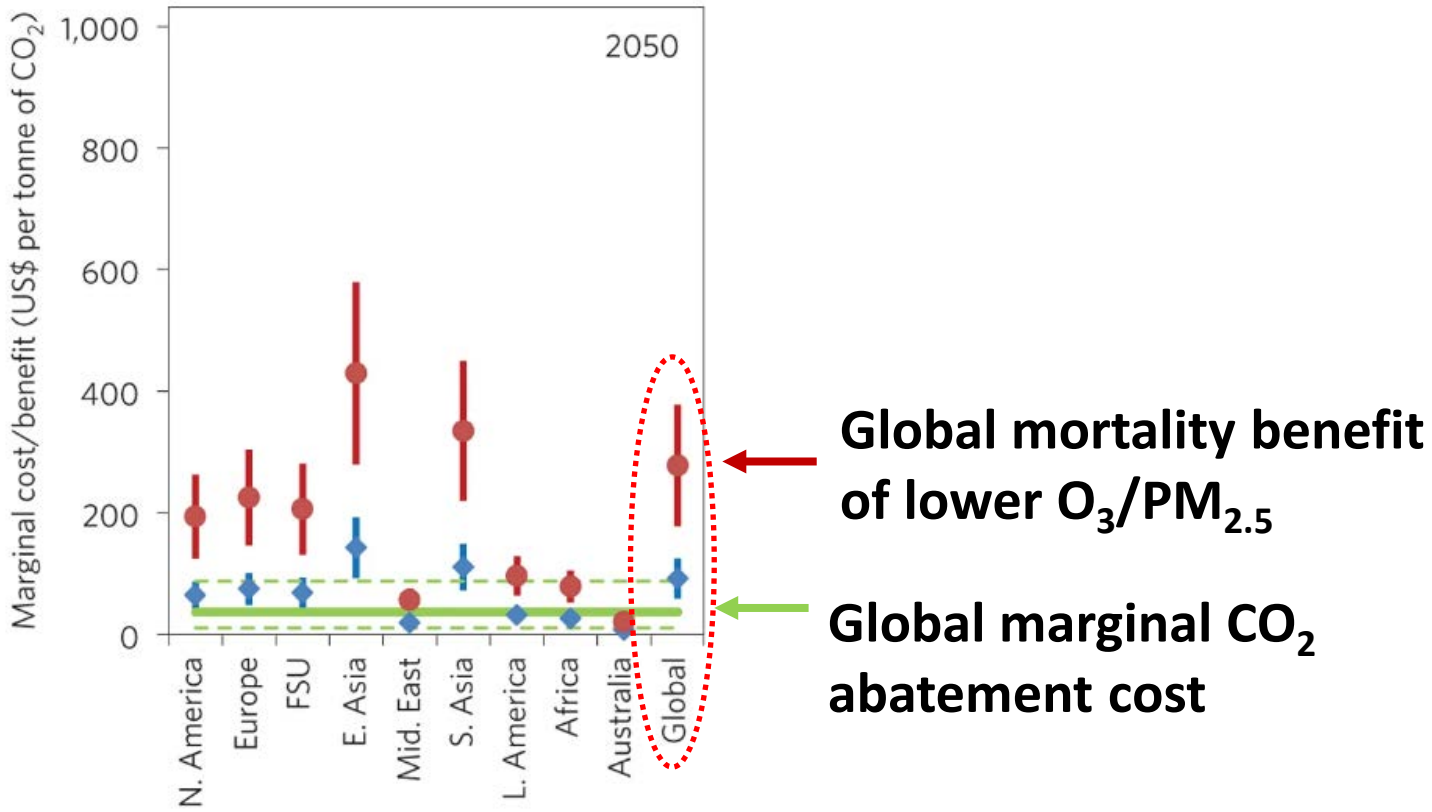
Kevin P. Josey, Ph.D., Scott W. Delaney, Sc.D., J.D., Xiao Wu, Ph.D., Rachel C. Nethery, Ph.D., Priyanka DeSouza, Ph.D., Danielle Braun, Ph.D., and Francesca Dominici, Ph.D.



- **Low income** older adults (regardless of race) *benefit more* from $PM_{2.5}$ reductions than higher income adults
- **Black subpopulations** (high and low income) *benefit more* from $PM_{2.5}$ reduction than high income whites

Josey et al. *NEJM*. 2023

Health benefits of cleaner air >> costs of fossil fuel phase out



- Health benefits include:
  - ↓Mortality (pulmonary, CV, cancer)
  - ↓ Respiratory events
  - ↓ Cardiovascular events

Mortality benefits due to lower O_3 and $PM_{2.5}$ under CO_2 emissions reduction scenario (RCP4.5). Red /blue = high / low value of statistical life.

West et al. Nature Climate Change. 2013
Hoffman et al. WHO Air Quality Guidelines Joint Statement. *Int J Public Health.* 2021;
Buonocore et al. *PLOS One*. 2016;

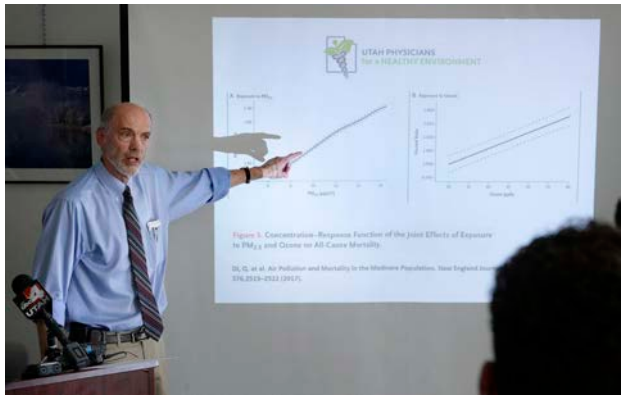

TACKLING CLIMATE CHANGE COULD BE THE GREATEST GLOBAL HEALTH OPPORTUNITY OF THE 21ST CENTURY
The Lancet, June 2015

Add the Physician's Voice to Energy & Transportation Policy Discussions

Hearing on Bill to Transition MA to renewable energy

Dr. Alex Rabin MD
Sept, 19 2017
Image © Bill Ravanesi

Utah State Air Quality Board



Dr. Robert Paine III MD
Chief, Pulmonary Medicine, U Utah

Senate EPW Committee hearing on carbon regulation

ATS Testimony, 2016

Engage with hospital leadership on energy and transportation

- Hospitals are especially energy-intensive buildings
- Healthcare is responsible for ~10% of U.S. greenhouse gas emissions[1]
- Healthcare employs largest commuting workforce of the U.S. (>10% of working population)[2]

1. Eckelman et al. *PLOS One.* 2016.
2. Kaiser Family Foundation. 2019.

Talk to patients about climate change

On this day, patient Mary Heafy has come to discuss with Dr. Rice whether she's on the right medications, but also why her eyes and nose are running and her chest is tight for longer periods every year. (Jesse Costa/WBUR)

NPR story by Martha Bebinger. “Some Boston Doctors Bring Climate Change Into The Exam Room.” May 1, 2019.

Different addiction, Same outcomes

Health effects

Tobacco Use

Fossil Fuel Use

- Death
- Lung cancer
- Asthma & COPD exacerbation
- Impaired fetal growth & premature birth

Children are especially vulnerable

Powerful economic interests

Rationalization for not quitting

Different addiction, Same outcomes

Health effects	**Tobacco Use**	**Fossil Fuel Use**
Death	✓	✓
Lung cancer		
Asthma & COPD exacerbation		
Impaired fetal growth & premature birth		

Children are especially vulnerable

Powerful economic interests

Rationalization for not quitting

Different addiction, Same outcomes

Health effects	**Tobacco Use**	**Fossil Fuel Use**
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Rationalization for not quitting		

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Impaired fetal growth & premature birth	✓	✓
Children are especially vulnerable	✓	✓
Powerful economic interests	✓	✓
Rationalization for not quitting	✓	✓

Thank you

mrice1@bidmc.harvard.edu

***Support*, by Lorenzo Quinn. Venice, Italy.**

Climate Change, Allergies, and Asthma: Adaptation and Mitigation

Jyothi Tirumalasetty, MD

Clinical Assistant Professor

Division of Pulmonary, Allergy, and Critical Care Medicine

Stanford University School of Medicine

Saturday, March 22, 2025

Disclosures

- I have the following relationships with ACCME defined ineligible companies: **None**
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Objectives

- Understand The Effects of Climate Change on Environmental Allergens and Strategies for Adaptation.
- Climate Change Mitigation: Understand Why Healthcare Systems Should Reduce Their Carbon Emissions.
- Understand the Carbon Emissions Associated with Inhalers.

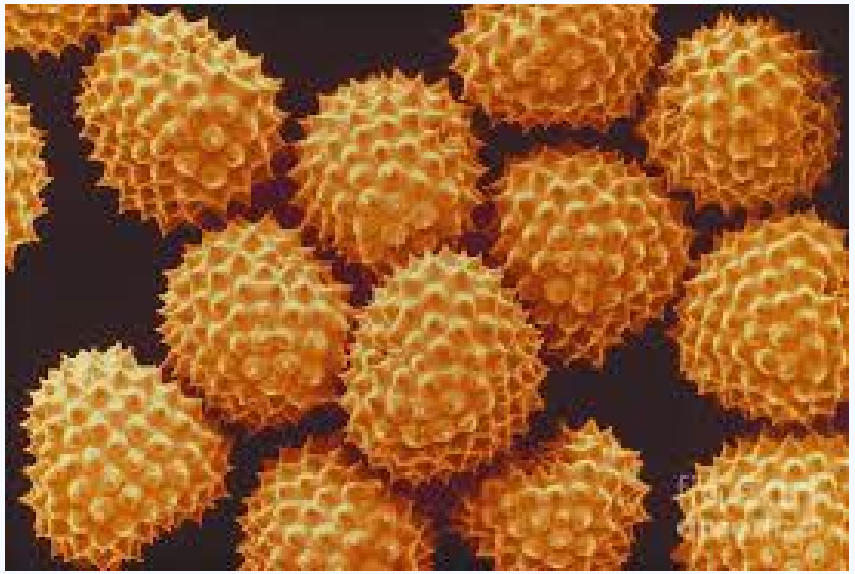
Sabai Tsho Lake, formed by the melting of Sabai Glacier in Nepal.

AFRIPICS / ALAMY STOCK PHOTO

California Thoracic Society
ATS Chapter Serving California and Arizona

Climate Change and Environmental Allergens

- Several studies have shown higher temperatures and CO_2 levels promote plant growth and increase pollen concentrations.
- Flooding can lead to higher mold concentrations outdoors and indoors.
- Overall, pollen concentrations and pollen season duration are increasing in the US (varies by species).
- Modeling has predicted up to 40% increase in pollen in the US by 2081.
- New pollen species and molds becoming more prevalent while detection and allergy testing has not kept up.



Ragweed pollen

Beggs PJ. Thunderstorm Asthma and Climate Change. JAMA. 2024 Mar 12;331(10):878-879.

Ziska et al. Lancet Planet Health. 2019 Mar;3(3):e124-e131.

Climate Change and Environmental Allergens

- Over the past several decades, spring pollen season (trees) has started earlier (3-27 days).
- Summer and fall pollen seasons (grass/ragweed) have ended later (27 days).
- Heavy short-term precipitation reduces pollen concentrations by about 30-40% (with the exception of thunderstorms/high winds).
- Local data not always consistent with national trends.

Paudel B. et al. Sci Rep. 2021 Jun 17;11(1):12816..

Ziska et al. Lancet Planet Health. 2019 Mar;3(3):e124-e131

Climate Change Worsens Allergic Diseases

- Higher pollen and mold counts associated with seasonal asthma exacerbations in children and adults.
- Exposure to air pollution and environmental allergens can increase the risk of allergic sensitization.
- Particulate matter found in air pollution can interact with environmental allergens to create highly allergenic particles.
- Thunderstorm asthma events can occur when environmental allergens such as pollen become supercharged by high winds and thunderstorms.

- Pacheco SE et al. J Allergy Clin Immunol. 2021 Dec;148(6):1366-1377.

Thunderstorm Asthma Events

Reported in the Australia, US, UK, and Canada.

Three factors present during each event:

- High aeroallergen concentrations
- Thunderstorms with high winds (>40 mph)
- Local population with allergic rhinitis and sensitized to grass pollen allergen

Specific **environmental conditions exposed the population to large amounts of 'supercharged' allergens.**

Largest event in Melbourne in 2016 led to 3365 ED visits for acute respiratory symptoms which overwhelmed area hospitals.

Beggs PJ. Thunderstorm Asthma and Climate Change. JAMA. 2024 Mar 12;331(10):878-879.

What Can We Do To Prevent/Prepare?

Mitigation

Reduce carbon emissions

Adaptation

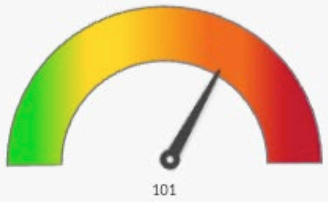
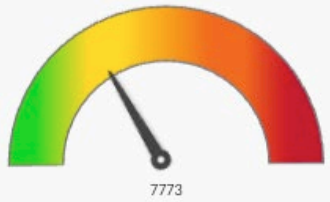
- Pollen/Mold count alerts
- Prepare our patients for longer/more intense allergy seasons

Beggs PJ. Thunderstorm Asthma and Climate Change. JAMA. 2024 Mar 12;331(10):878-879.

Pollen/Mold Count Alerts

National Allergy Bureau

https://bit.ly/40EKkXu

Trees High	Weeds Not Present	Grass Not Present	Mold Moderate
			
Top 3 species: **Juniper family, Cedar** *juniper family, cedar Cupressaceae* **Ash** *Oleaceae (olive family) Fraxinus* **Pine Family with air bladders** *Pinaceae (pine family) Pinaceae*	No weeds present.	No grass present.	Top 3 species: **Ascospores: includes Leptosphaeria, Venturia, Ascobolus, Diatrypaceae, Pleospora, Xylaria, Chaetomium, Sporomiella, Claviceps, Ascomycete, et al.** *Ascospores (Undifferentiated)* **Basidiospores: includes Coprinus, Agrocybe, Agaricus, Inocybe, Laccaria, Ganoderma, et al.** *Basidiospores (Undifferentiated)* **Cladosporium** *Cladosporium*
			
High Concentration	Not Present	Not Present	Moderate Concentration

Concentrations are measured as pollen or spores per cubic meter.

Management of Allergic Component

- **Allergen avoidance**: Reduce indoor and outdoor exposure.
- **Medical Management**:
  - Intranasal steroids/antihistamines, MART, etc.
  - Biologics for allergic asthma
- **Immunotherapy**:
  - Subcutaneous
  - Sublingual (tablets FDA approved)
- No biologics available for allergic rhinitis alone.

Impact of Climate Change on Health

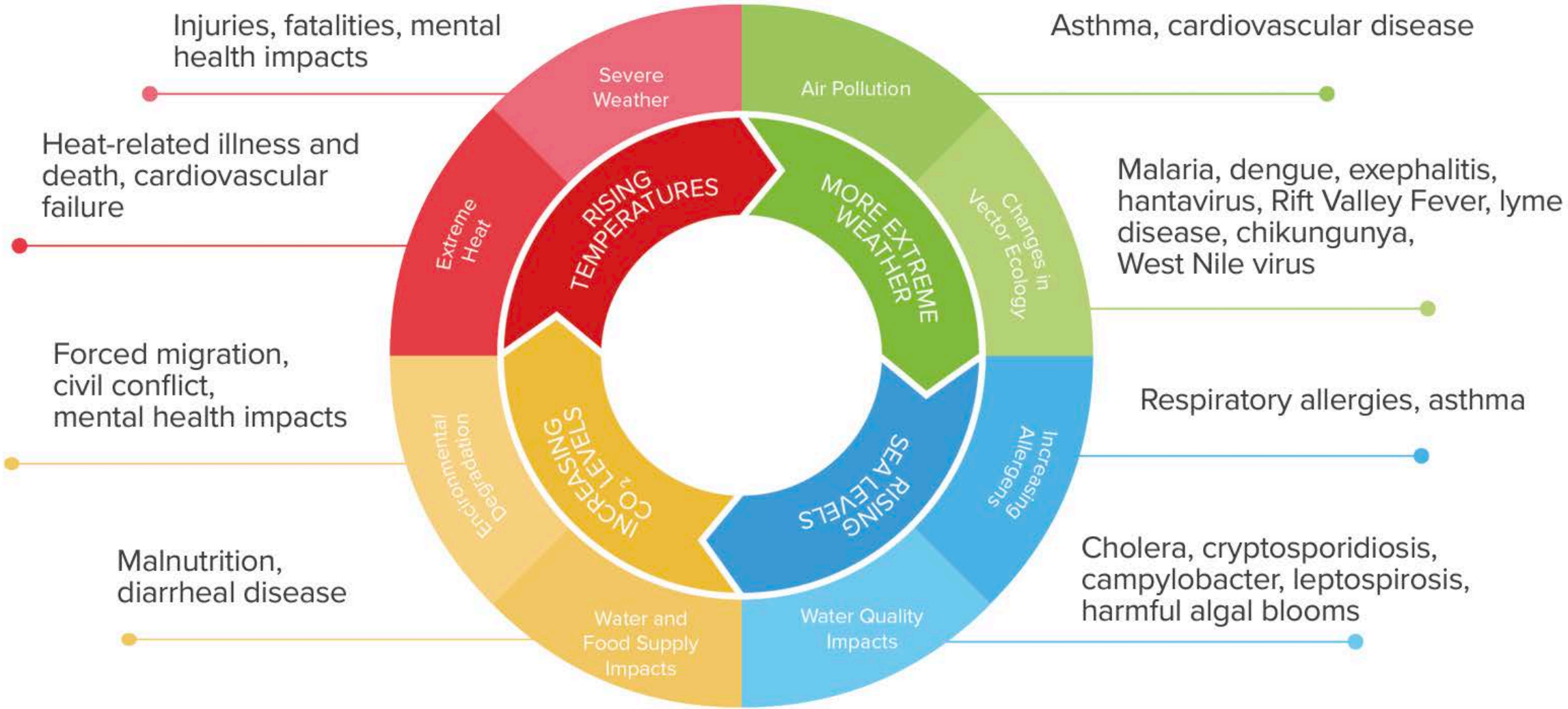


Figure 1: Impact of climate change on human health (Source: U.S. Centers for Disease Control and Prevention)

200 major medical journals, including the New England Journal of Medicine, BMJ, and the Lancet, published the same editorial on the same day calling climate change **"the greatest threat to public health in the 21st century."**

Call for Emergency Action to Limit Global Temperature Increases, Restore Biodiversity, and Protect Health

The science is unequivocal: a global increase of 1.5° C above the pre-industrial average and the continued loss of biodiversity risk catastrophic harm to health that will be impossible to reverse.

N Engl J Med. 2021 Sep 16;385(12):1134-1137.

Healthcare and Climate Change

- "*The health sector, whose mission is protecting and promoting health, makes a major contribution to the climate crisis — the greatest health threat of the 21st century — and therefore has an important role to play in resolving it.*"

- The healthcare sector now faces an urgent call to action to reduce its carbon emissions and protect communities from climate threats.

Sampath et al. Reducing Healthcare Carbon Emissions: A Primer on Measures and Actions for Healthcare Organizations to Mitigate Climate Change. AHRQ Publication No. 22-M011.

Health Care Without Harm Climate-smart health care series Green Paper Number One Produced in collaboration with Arup September 2019

Why Should US Health Systems Decarbonize?

US healthcare emissions were estimated at 550 MMT CO_2e in 2018. (Equivalent to powering all of the homes in the US for one year)

This is 8.5 percent of domestic US greenhouse gas (GHG) emissions.

US healthcare system is responsible for ~25% of global healthcare GHG emissions.

1,693 kg CO_2e per capita for US healthcare is still the highest value for any country.

Health Aff (Millwood). 2020 Dec;39(12):2071-2079.
Eckelman MJ, et al. Health Care Pollution And Public Health Damage In The United States: An Update. Health Aff Proj Hope. 2020;39(12):2071-2079
https://www.epa.gov/energy/greenhouse-gas-equivalencies-calculator

Figure 1. Summary of Key Measures and Strategies for Healthcare Decarbonization

Reducing Healthcare Carbon Emissions

A Primer on Measures and Actions for Healthcare Organizations to Mitigate Climate Change

AHRQ Agency for Healthcare Research and Quality

HIGH-LEVEL AIM

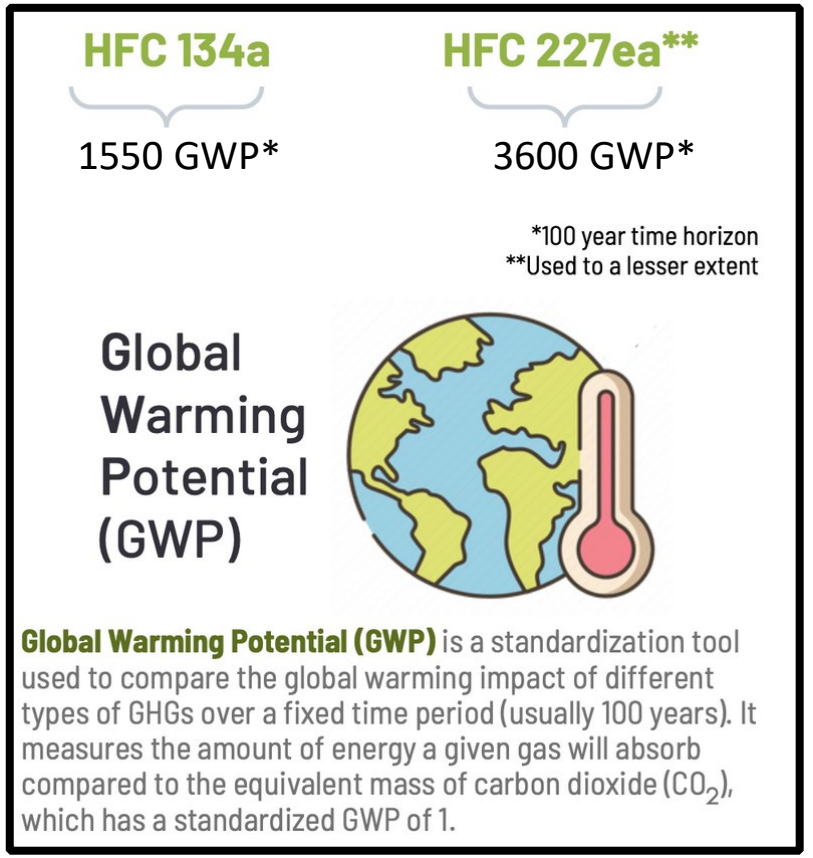
Reduce organizational emissions by 50% by 2030 and to net zero by 2050

	High-Priority Measures		Key Strategies	
	Core Measures	Elective Measures	Reduce Waste	Reduce Emissions Intensity
Energy	• Total GHG emissions from energy use	• Energy use intensity of health care facilities • ENERGY STAR® score of health care facilities	• Conserve and optimize energy efficiency	• Transition to zero-carbon fuel sources • Meet and exceed the current green building/retrofitting standards
Transportation	• Total GHG emissions of owned and leased vehicles	• Total GHG emissions from staff and patient travel	• Centralize oversight to actively manage transportation reduction	• Transition to sustainable transportation systems
Anesthetic Gas	• Total GHG emissions from inhaled anesthetics	• Mean fresh gas flow rates	• Minimize fresh gas flow rates • Decommission or avoid construction of central nitrous oxide piping	• Manage anesthetic choices
Pharmaceuticals & Chemicals	Overarching Scope 3 Measure: • Total GHG emissions from (or total spend on) goods and services	• Metered-dose inhaler outpatient prescriptions as a percentage of all inhaler prescriptions	• Prevent disease exacerbation • Launch appropriate use campaigns	• Maximize lower carbon alternatives for inhalers
Medical Devices & Supplies		• Percent purchased goods and services supplied by companies performing carbon disclosures with a science-based target for emissions reduction	• Ensure resource stewardship	• Adopt and expand circular economy policies and practices related to reuse, reprocessing, repair, repurposing, and recycling • Adopt preferential purchasing with suppliers or service providers that perform carbon disclosures and have set a science-based target for decarbonization
Food		• Total GHG emissions from food procurement	• Adopt food waste prevention and diversion programs	• Design plant-forward menus and retail options

Sampath B, Jensen M, Lenoci-Edwards J, Little K, Singh H, Sherman JD. Reducing Healthcare Carbon Emissions: A Primer on Measures and Actions for Healthcare Organizations to Mitigate Climate Change. (Prepared by Institute for Healthcare Improvement under Contract No. 75Q80122P00007.) AHRQ Publication No. 22-M011.

HFC Propellants in Inhalers Worsen Global Warming

Metered-dose inhalers contain hydrofluorocarbon propellants – *potent greenhouse gases that trap heat in the atmosphere thousands of times more powerfully than carbon dioxide.*



Tirumalsetty et al. *JAMA.* 2024;332(12):1017–1019.

CASCADES Canada

The Environmental Impact of MDIs in the US

US healthcare system produced 550 MMT of CO_2e emissions annually vs 30.4 MMT of CO_2e for NHS England in 2020.

Efforts to reduce inhaler-related emissions in the US have been hindered by a lack of data on carbon emissions associated with inhalers available in our country.

We assessed mean emissions and costs and estimated total yearly emissions and costs for US brand-name inhalers prescribed to Medicare Part D and Medicaid beneficiaries.

Medicare Part D and Medicaid account for approximately 40% of US retail prescription drug spending.

Eckelman MJ, et al. Health Care Pollution And Public Health Damage In The United States: An Update. Health Aff Proj Hope. 2020;39(12):2071-2079

The Environmental Impact of MDIs

RESEARCH LETTER

CLIMATE CHANGE AND HEALTH

Greenhouse Gas Emissions and Costs of Inhaler Devices in the US

JAMA Published online August 29, 2024

- MDIs alone accounted for 1.13 MMT CO_2e emissions and 70.2% of inhaler claims.
- This is equivalent to 223,012 US homes' electricity use for one year (city the size of Milwaukee).
- Nearly all inhaler-related emissions (98.3%) were ascribed to metered-dose inhalers.

Stanford MEDICINE | School of Medicine

Tirumalasetty et al. *JAMA.* 2024;332(12):1017–1019.

RESEARCH LETTER

CLIMATE CHANGE AND HEALTH

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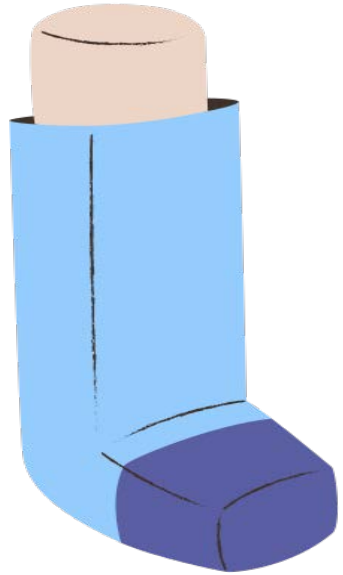
Inhalers Prescriptions and Emissions in the US

- The largest contribution of emissions arose from short-acting beta agonists.
- Albuterol alone made up 72% of MDI claims.
- Dry-powder inhalers accounted 24.5% of total inhaler claims.
- Soft-mist inhalers were prescribed the least (5.2% of total claims).



Tirumalasetty et al *JAMA*. 2024;332(12):1017–1019.

US Metered Dose Inhaler Individual Emissions

RESEARCH LETTER

CLIMATE CHANGE AND HEALTH

Greenhouse Gas Emissions and Costs of Inhaler Devices in the US

JAMA Published online August 29, 2024

Table. Estimated Greenhouse Gas Emissions, Costs, and Number of Claims of US Inhalers by Device Class Among Medicare Part D and Medicaid Beneficiaries in 2022

Inhaler brand name (generic name), No. of inhalations, medication category	Estimated CO_2e per inhalation, g	Estimated CO_2e per inhaler, kg[a]	Mean Medicare Part D cost per claim, $[b]	No. of Medicare Part D claims[c]	Mean Medicaid cost per claim, $[b]	No. of Medicaid claims[c]
Metered-dose inhaler (n = 14)						
Advair HFA (fluticasone/salmeterol), 120, ICS/LABA	170.8	20.5	608.71	632 024	447.40	451 414
Alvesco (ciclesonide), 60, ICS	180.0	10.8	154.43	215 905	416.20	72 286
Asmanex HFA (mometasone), 120, ICS	400.0	48.0	287.79	26 421	199.58	78 250
Atrovent HFA (ipratropium), 200, SAMA	100.0	20.0	571.74	235 718	464.75	159 409
Bevespi Aerosphere (glycopyrrolate/formoterol), 120, LAMA/LABA	148.3	17.8	544.85	127 443	419.57	33 802
Breztri Aerosphere (budesonide/glycopyrrolate/formoterol), 120, ICS/LAMA/LABA	148.3	17.8	792.09	579 924	612.77	57 737
Dulera (mometasone/formoterol), 120, ICS/LABA	400.8	48.1	444.37	231 005	331.80	462 616
Flovent HFA (fluticasone), 120, ICS	170.8	20.5	374.31	1 126 151	263.46	2 869 186
ProAir HFA (albuterol sulfate), 200, SABA	63.5	12.7	97.91	7 532 750	84.15	8 791 641
Proventil HFA (albuterol sulfate), 200, SABA	49.5	9.9	125.13	3 651 614	91.32	2 524 937
Symbicort (budesonide/formoterol), 120, ICS/LABA	318.3	38.2	526.80	3 729 724	385.69	1 819 765
QVAR Redihaler (beclomethasone), 120, ICS	138.3	16.6	321.46	150 586	246.37	356 947
Ventolin HFA (albuterol sulfate), 200, SABA	143.5	28.7	74.12	6 535 681	62.48	6 234 078
Xopenex HFA (levalbuterol), 200, SABA	114.0	22.8	103.57	217 873	78.09	102 550

Emissions from one Dulera inhaler equivalent to driving 122 miles in a gasoline powered passenger vehicle.

https://www.epa.gov/energy/greenhouse-gas-equivalencies-calculator

RESEARCH LETTER

CLIMATE CHANGE AND HEALTH

US Dry Powder Inhaler Individual Emissions

Greenhouse Gas Emissions and Costs of Inhaler Devices in the US

JAMA Published online August 29, 2024

Inhaler brand name (generic name), No. of inhalations, medication category	Estimated CO_2e per inhalation, g	Estimated CO_2e per inhaler, kg[a]	Mean Medicare Part D cost per claim, $[b]	No. of Medicare Part D claims[c]	Mean Medicaid cost per claim, $[b]	No. of Medicaid claims[c]
Dry-powder inhaler (n = 19)						
Advair Diskus (fluticasone/salmeterol), 60, ICS/LABA	15.0	0.898	581.60	1 629 000	443.31	842 908
AirDuo Digihaler (fluticasone/salmeterol), 60, ICS/LABA	13.2	0.790	546.07	1012	474.12	2046
AirDuo RespiClick (fluticasone/salmeterol), 60, ICS/LABA	13.2	0.790	409.77	665	414.80	2281
Anoro Ellipta (umeclidinium/vilanterol), 30, LAMA/LABA	26.1	0.784	601.99	1 439 975	463.28	283 984
ArmonAir Digihaler (fluticasone), 60, ICS	13.2	0.790	313.36	244	261.27	198
Arnuity Ellipta (fluticasone), 30, ICS	25.7	0.771	310.67	285 882	224.84	133 874
Asmanex Twisthaler (mometasone), 120, ICS	6.6	0.790	375.14	42 555	243.76	51 726
Breo Ellipta (fluticasone/vilanterol), 30, ICS/LABA	25.9	0.776	527.66	2 705 981	413.19	191 333
Duaklir Pressair (aclidinium/formoterol), 60, LAMA/LABA	13.2	0.790	1136.30	62	924.82	38
Flovent Diskus (fluticasone), 60, ICS	13.9	0.833	333.79	144 378	240.37	79 390
Incruse Ellipta (umeclidinium), 30, LAMA	24.6	0.739	474.33	1 051 785	371.25	222 231
ProAir Digihaler (albuterol sulfate), 200, SABA	4.0	0.790	175.35	2970	166.17	4931
ProAir RespiClick (albuterol sulfate), 200, SABA	4.0	0.790	90.78	87 492	74.05	52 589
Pulmicort Flexhaler (budesonide), 120, ICS	6.5	0.790	336.81	139 283	240.27	84 390
Serevent Diskus (salmeterol), 60, LABA	12.2	0.732	631.52	75 323	447.06	33 462
Spiriva HandiHaler (tiotropium), 30, LAMA	26.3	0.790	791.99	1 181 232	552.61	586 303
Trelegy Ellipta (fluticasone/umeclidinium/vilanterol), 30, ICS/LAMA/LABA	26.3	0.790	850.64	3 926 585	637.96	400 362
Tudorza Pressair (aclidinium), 60, LAMA	13.2	0.790	883.29	16 444	586.58	10 327
Wixela Inhub (fluticasone/salmeterol), 60, ICS/LABA	15.0	0.898	298.63	1 094 388	172.58	324 920

Tirumalasetty et al. *JAMA.* 2024;332(12):1017–1019.

Putting It All Together

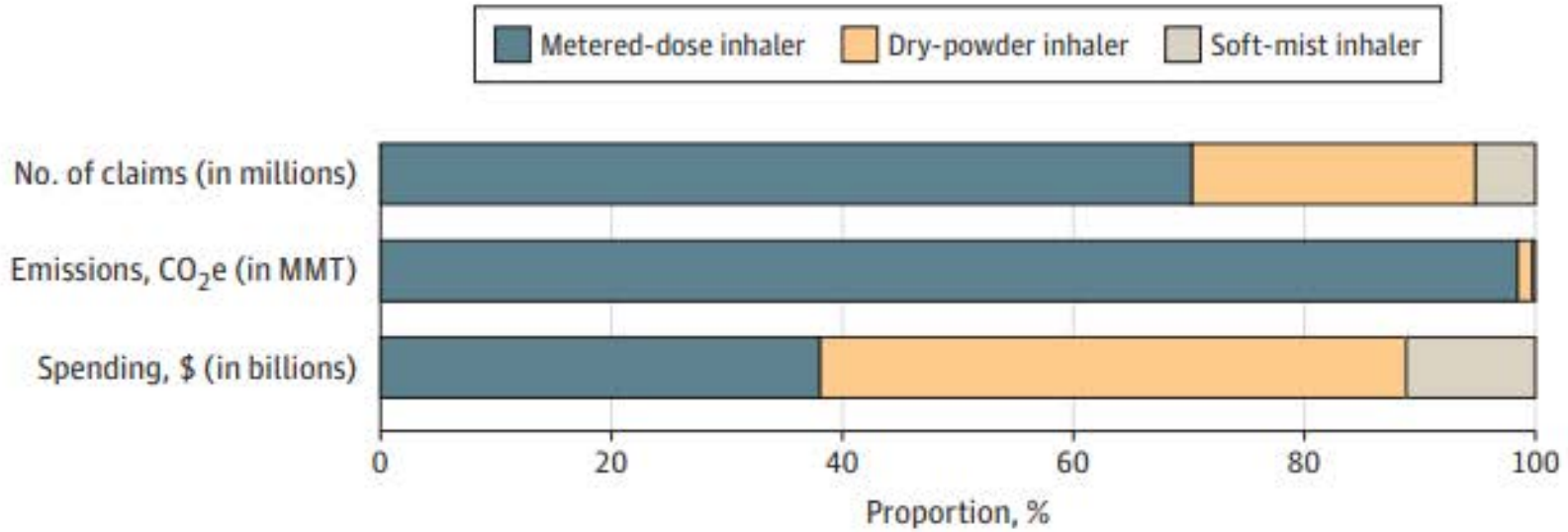
RESEARCH LETTER

CLIMATE CHANGE AND HEALTH

Greenhouse Gas Emissions and Costs of Inhaler Devices in the US

JAMA Published online August 29, 2024

Figure. Claims, Estimated Greenhouse Gas Emissions, and Spending for All Inhalers Filled by Medicare Part D and Medicaid Beneficiaries in 2022 by Device Class



Number of claims, estimated greenhouse gas emissions, and spending for inhalers by device class are shown for Medicare Part D and Medicaid beneficiaries from January 2022 through December 2022. CO_2e indicates carbon dioxide equivalent; MMT, million metric tons.

MDIs=70% of claims and 38% of spending
$7.5 billion

DPIs= 25% of claims and 51% of spending
$10 billion

Tirumalasetty et al. *JAMA.* 2024;332(12):1017–1019.

Lowering Inhaler-Related Emissions in the US

- Other countries have moved to DPIs and SMIs – in Sweden, only 13% of inhalers sold are MDIs.
- Dry powder Symbicort available in Europe/Canada but not in US, making it difficult to implement inhaler decarbonization in the US while following GINA guidelines.
- DPIs in US more expensive and often not preferred under many insurance plans – exception is generic fluticasone-salmeterol (Wixela Inhub).

- Janson et al. Thorax. 2019 Nov 7;75(1):82–84.

California Thoracic Society
ATS Chapter Serving California and Arizona

Lowering Inhaler-Related Emissions in the US

- In those who cannot be on GINA track 1 preferred treatment – consider DPIs, lower emissions MDIs, and SMIs if out-of-pocket cost acceptable.
- Consider DPI albuterol – ProAir Respiclick or lower emissions albuterol HFA.
- Brand/generic Ventolin HFA has approximately 3 times the emissions of brand/generic Proventil HFA.

The Future of Inhaler Propellants

Next generation propellants with low or “zero” emissions propellants coming.

HFA 152a a new, low global warming potential (LGWP) medical propellant, developed for Ventolin.

Lower emissions Ventolin (GSK) in phase III trials in the US currently.

Aztra Zeneca has completed phase III trials for LGWP propellant for Breztri in Europe.

Honeywell’s Solstice Air (HFO-1234ze) has 99.9% less GWP than propellants currently used in inhaled respiratory medicines.

These inhalers will come with new patents on old medications and higher prices!

Initiating Decarbonization Efforts

- Climate health and healthcare sustainability organizations (**Practice GreenHealth, Healthcare Without Harm, Medical Society Consortium on Climate and Health**).
- Networking and outreach within local/state medical societies.
- Pilot initiatives within your institution – do you have a sustainability program office?
- Grant funding for sustainability research (AHRQ).
- Partner with experts in other divisions within your institution (carbon life cycle engineers).
- For those interested in inhaler decarbonization: **email me to join Clin-AIR (Clinician Action for Inhaler Emissions Reduction, jtsetty@stanford.edu).**

Practice GreenHealth

bit.ly/3EFIJta

Medical Society Consortium on Climate and Health

bit.ly/4hZoCUP

California Thoracic Society
ATS Chapter Serving California and Arizona

Climate ~~Crisis~~ Opportunity

- Reduce the healthcare sector's greenhouse gas emissions.
- Create resilient healthcare systems and communities that can plan, prepare, respond, and adapt to climate-related threats.
- Address the inequitable impacts of climate change.
- Incorporate climate change education into medical school and GME curricula.
- Educate and prepare your patients on the effects of climate change on allergies and asthma.

California Wildflower Bloom

Photo credit: LeWildExplorer.com

Thanks to everyone who supported and contributed to this work!

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Silicosis Among Immigrant Engineered Stone Countertop Fabrication Workers in California

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Assistant Professor of Medicine
Divisions of OECM and PCCAS
Director of the California Silicosis Support and Research Program

November 5, 2024

OCCUPATIONAL LUNG DISEASE AND THE NEW EPIDEMIC OF SILICOSIS IN CALIFORNIA

Sheiphali Gandhi, MD, MPH
Assistant Professor of Medicine
Divisions of OECM and PCCAS
Director of the California Silicosis Support
and Research Program

California Thoracic Society

RELEVANT FINANCIAL DISCLOSURES

- I have the following relationships with ACCME defined ineligible companies:

- None

- I WILL NOT discuss off-label use and/or investigational use of any drugs or devices.

California Thoracic Society

Financial disclosures

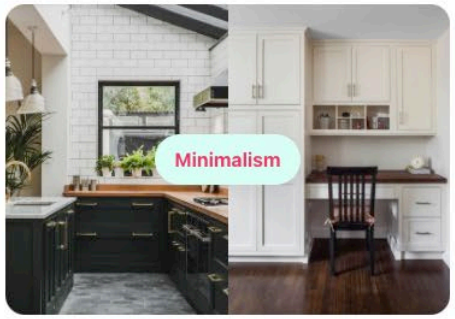
- none

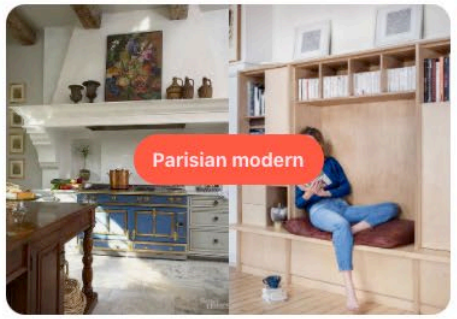
Outline

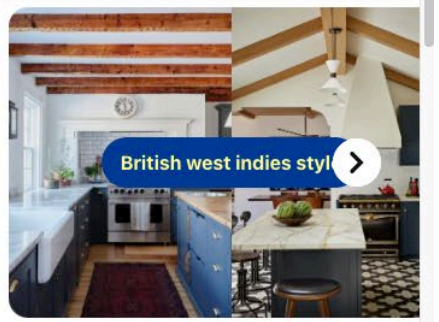
- What is engineered stone?
- Sentinel case identification
- California epidemiology
- Medical screening
- Updates on the California Outbreak

Home Today kitchen remodel All Pins 99+

Explore Shop Profiles







Create the most functional kitchen island

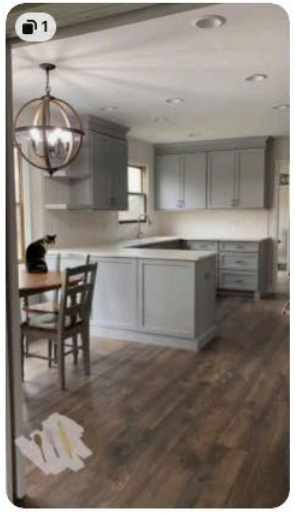
8.1k

Large island kitchen with coffee wine bar addition

7.5k

Termo electrico TESY Bilight h 80l - Leroy Merlin

Promoted by Leroy Merlin España



Kitchen design

5.3k

Kitchen Makeover! Find the whole thing on my Youtube...

2.9k

Kitchen organisation ideas| Kitchen storage cabinets |...

3.5k

small white kitchen | small white bathroom | timeless modern...

8.4k

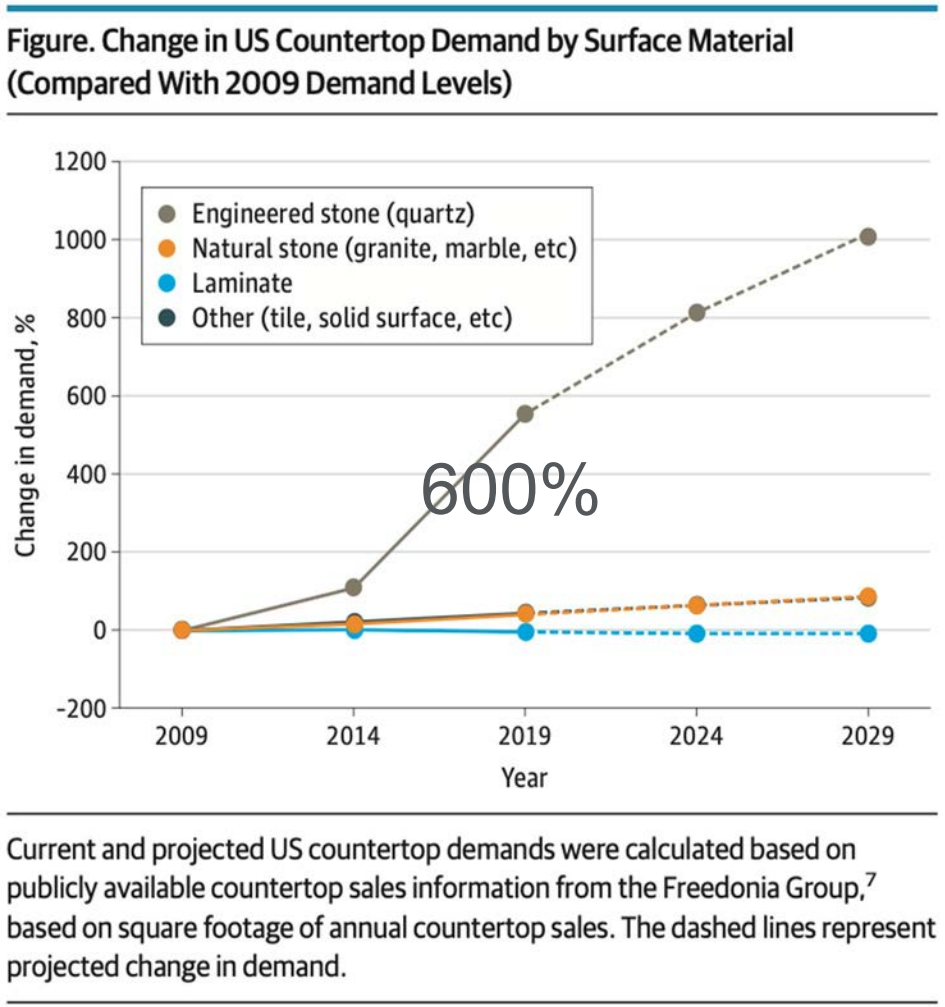

What is silestone?
Quartz?

What is engineered (artificial) stone?

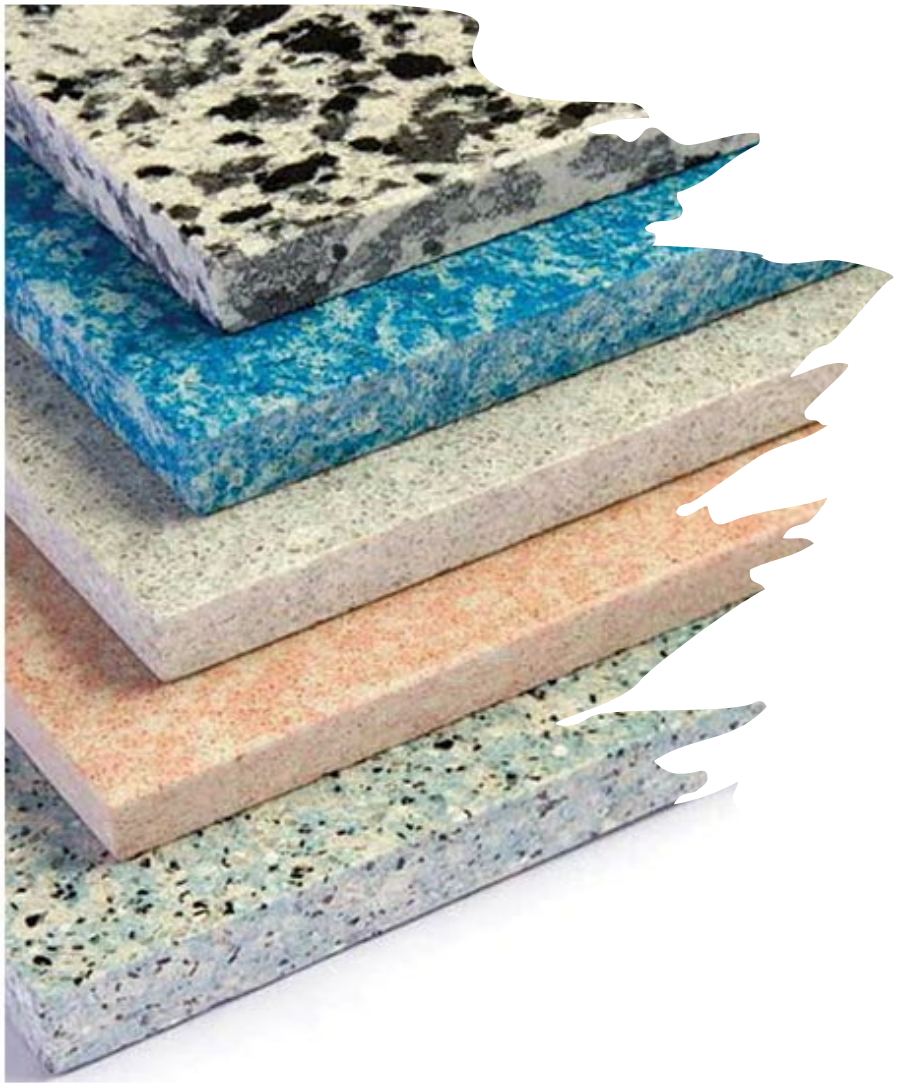
Increased distribution of engineered stone

Since 2000 the countertop industry has moved towards using engineered quartz —resin conglomerate stone

- Cheaper production
- Easier installation/maintenance
- **90% silica content** (granite 30%, marble 3%)
- Smaller particulates (<1 micron in dry cutting)



Data source: U.S. International Trade Commission.



Artificial stone

- Composite material: crushed quartz (SiO_4) bound together with polymer resins, pigment, glass, and other additives
- AKA: engineered, agglomerate, quartzite
- Brand names: Silestone, Caesarstone, Cambria, Consentino

Stone	Average % Silica
Engineered stone	≥93
Quartzite	95
Quartzitic sandstone	90
Sandstone	60
Granite	10 - 45
Slate	Varies
Soapstone	Varies

Sources: Silica Hazards from Engineered Stone Countertops, NIOSH Science Blog, March 2014; ASTM C616, *Standard Specification for Quartz-Based Dimension Stone;* American Geological Institute, *Dictionary of Geological Terms*

Processing Stone

- Highest exposure in workers operating powered hand tools
  - Saws, grinders, polishers
- Occurs in shop environments or where finishing work is completed
- Less exposure where stone is manufactured but risk still present
- Wet cutting, localized vacuum, and half-face respirators decrease risk

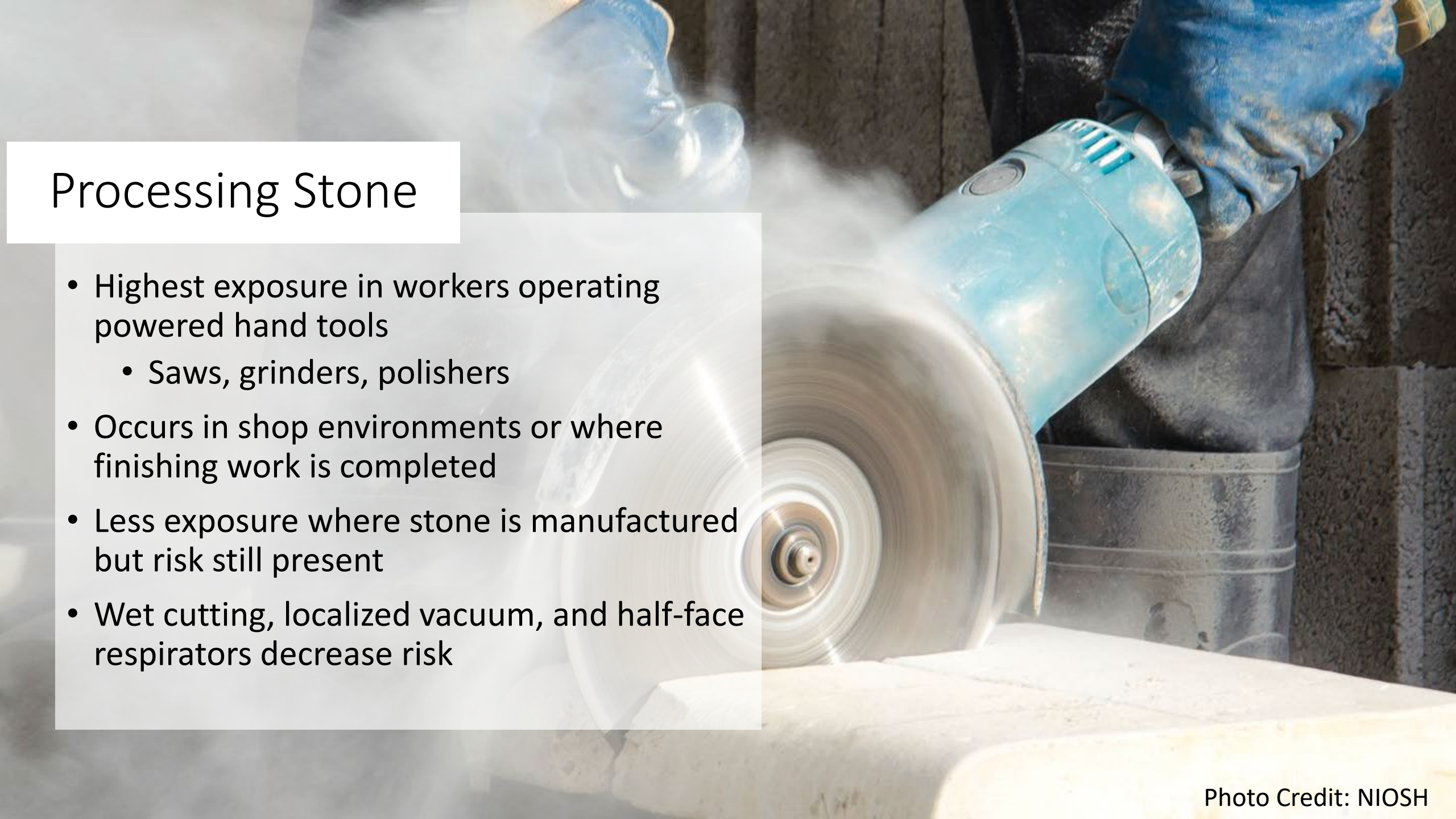
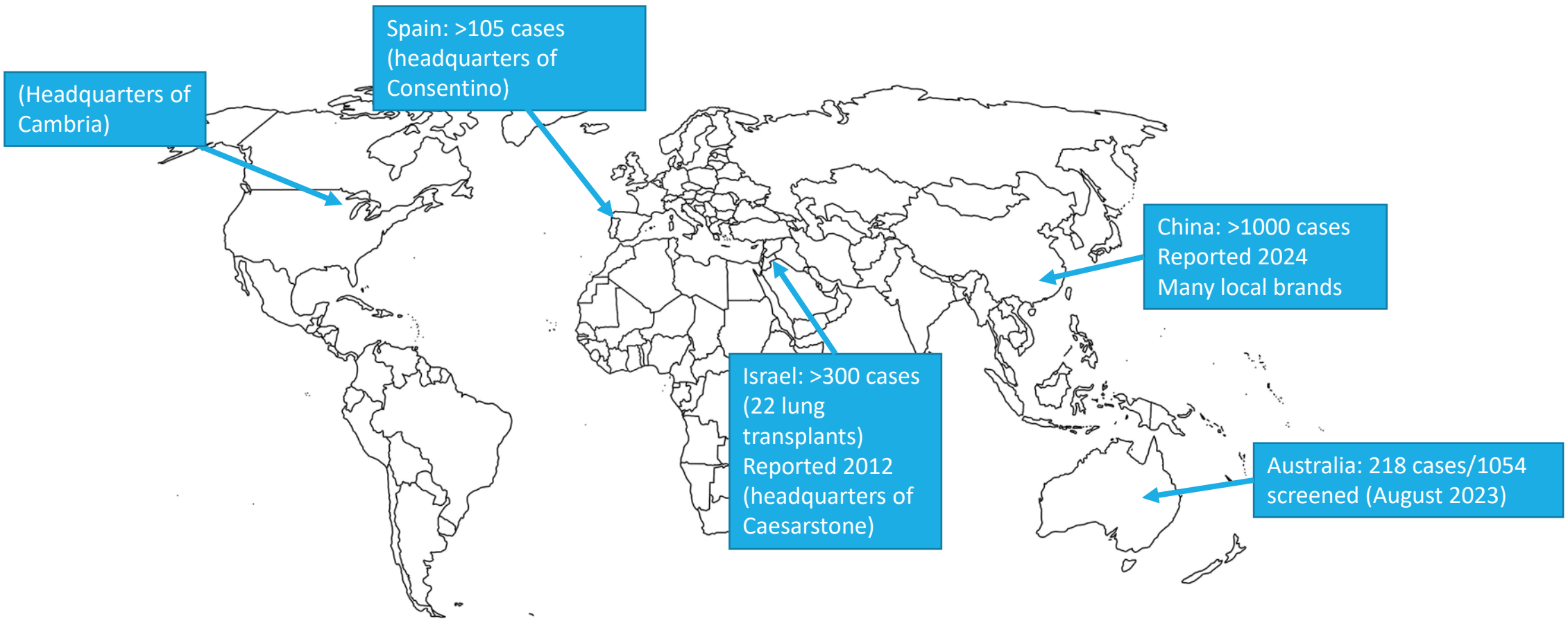


Photo Credit: NIOSH

Sentinel Case Identification

Global Emergence of Engineered Stone associated Silicosis



Sentinel California Case Identification Timeline

CDPH identifies case

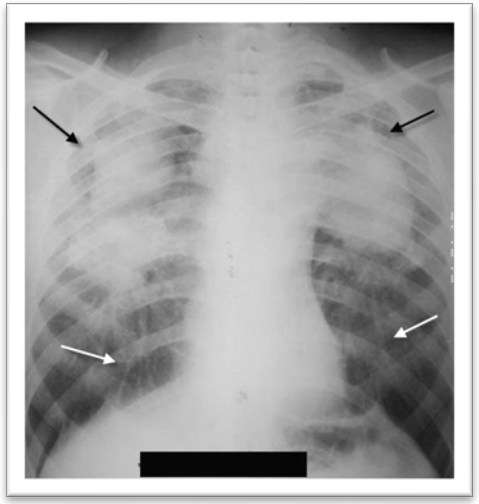
2004 — 2013 — 2014 — 2017 — 2018 — January 2019

Employed at stone countertop fabrication shop

Diagnosed with silicosis

Worsening symptoms and lung function

- January: Ineligible for lung transplant
- September: Dies of accelerated silicosis



Slide Credit: Amy Heinzerling MD

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Search

Morbidity and Mortality Weekly Report (*MMWR*)

Severe Silicosis in Engineered Stone Fabrication Workers — California, Colorado, Texas, and Washington, 2017–2019

Weekly / September 27, 2019 / 68(38);813–818

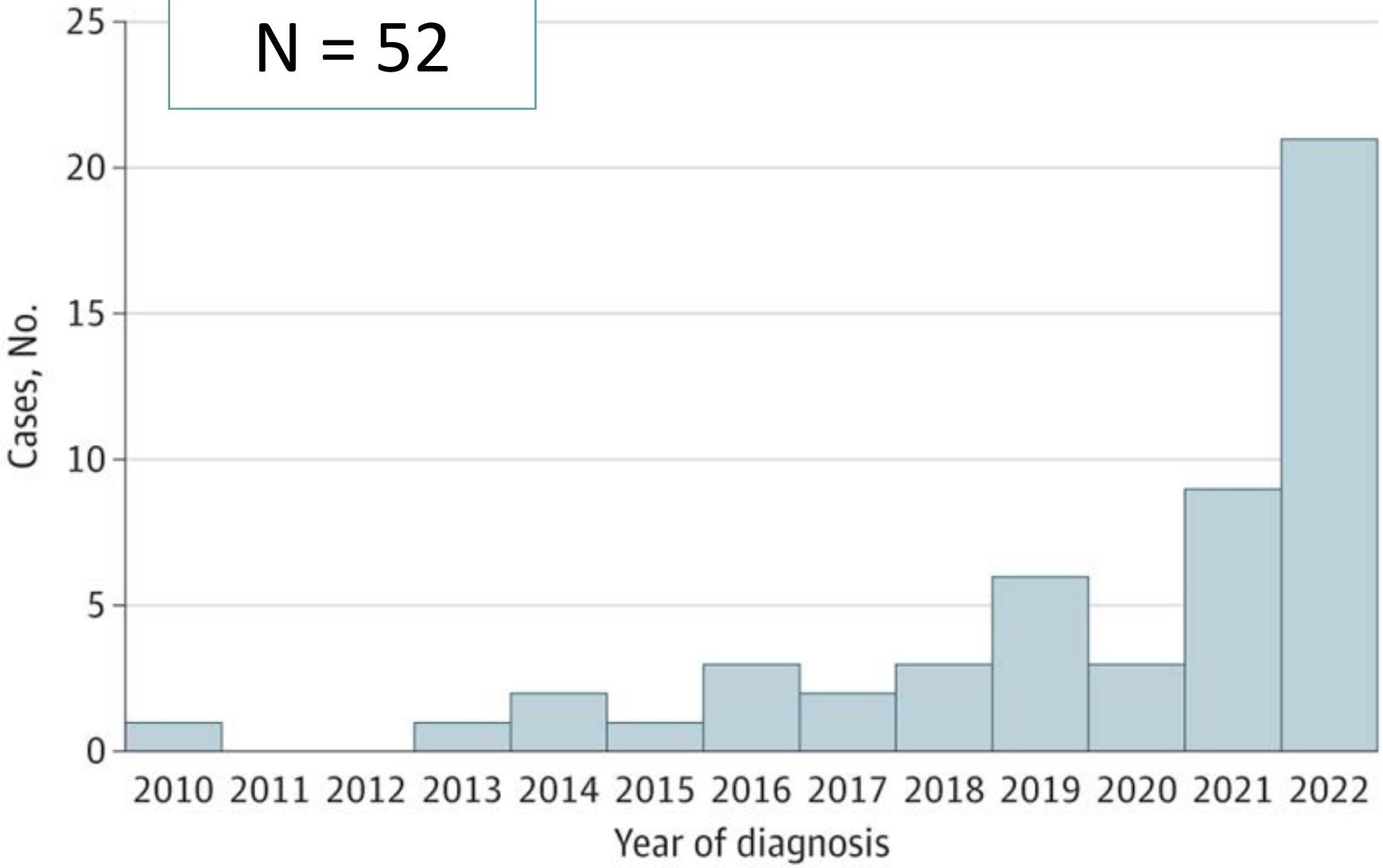
Cecile Rose, MD[1,2]*; Amy Heinzerling, MD[3,4]*; Ketki Patel, MD, PhD[5]; Coralynn Sack, MD[6,7]; Jenna Wolff[1]; Lauren Zell-Baran, MPH[1,8]; David Weissman, MD[9]; Emily Hall, MPH[5]; Robbie Sooriash, MD[5]; Ronda B. McCarthy, MD[10]; Heidi Bojes, PhD[5]; Brian Korotzer, MD[11]; Jennifer Flattery, MPH[3]; Justine Lew Weinberg, MSEHS[3,12]; Joshua Potocko, MD[13]; Kirk D. Jones, MD[14]; Carolyn K. Reeb-Whitaker, MS[15]; Nicholas K. Reul, MD[6,7,16]; Claire R. LaSee, MPH, MSW[15]; Barbara L. Materna, PhD[3]; Ganesh Raghu, MD[6]; Robert Harrison, MD[3] (VIEW AUTHOR AFFILIATIONS)

California Epidemiology

Methods

- Cases identified 2019– 2022
  - Statewide hospital-based patient discharge data, report to CDPH, cases identified following OSHA investigation
- Data collection
  - Interviews of patients and/or next-of-kin AND medical record review
  - Data:
    - Demographics/occupational history
    - Clinical findings and comorbidities
    - Healthcare utilization
    - Clinical Outcomes

N = 52


25
20
15
10
5
0
Cases, No.
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
Year of diagnosis

Undocumented
Uninsured
Unprotected

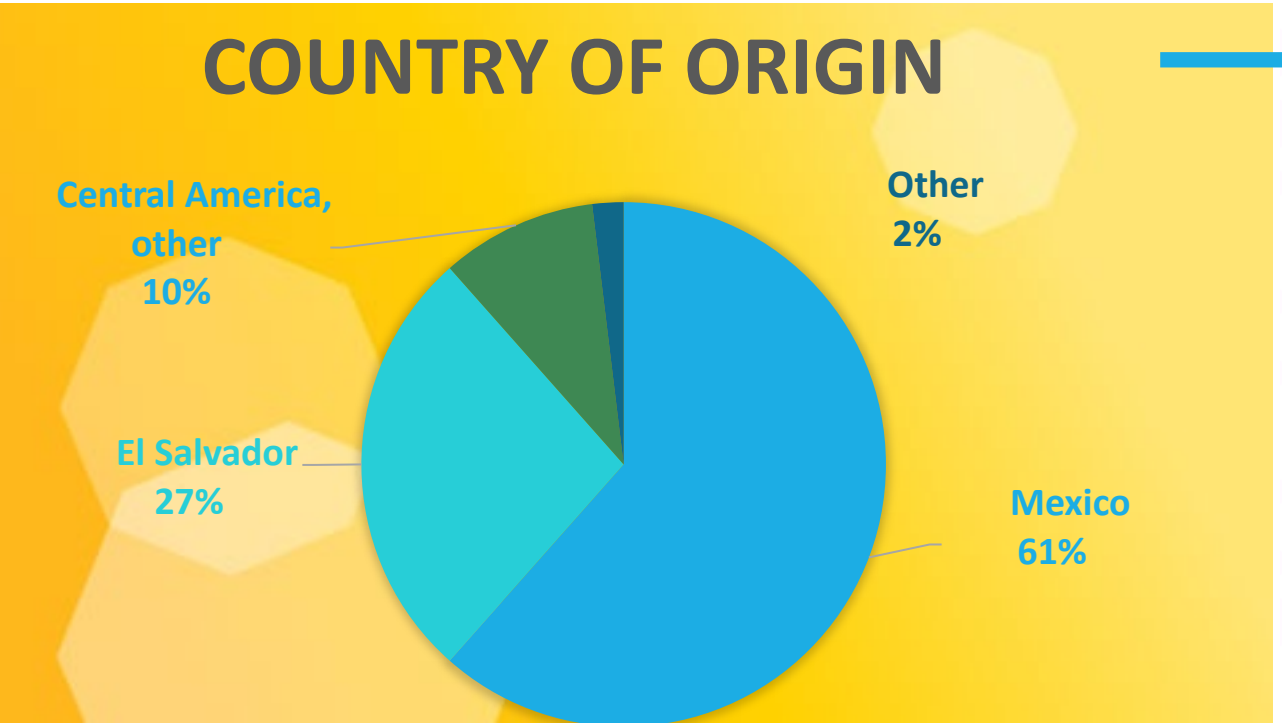


Table 3. Health Care Utilization of Patients With Engineered Stone–Associated Silicosis

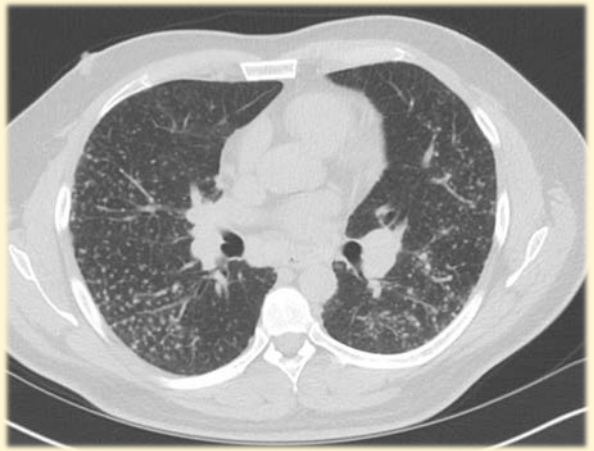
Health care utilization characteristic (No. with data available)	Overall (n = 52), No. (%)
Health insurance (52)	
Uninsured or self-pay	10 (19)
Restricted-scope Medi-Cal	20 (38)
Full-scope Medi-Cal	7 (13)
Private insurance	8 (15)
Medicare	0 (0)
Workers' compensation	7 (13)
Location of initial presentation (52)	
Emergency department	25 (48)
Outpatient clinic	19 (37)
Medical surveillance	8 (15)
Emergency department (52)	
Ever visited emergency department (52)	42 (82)
No. of emergency department visits (42), median (IQR)	2.50 (1.00-4)
Hospitalization (51)	
Ever hospitalized for breathing	31 (61)
No. of times hospitalized (31), median (IQR)	2.0 (1-3.5)
Cumulative hospital length of stay per patient (30), median (IQR), d	9.5 (4.3-19.8)

Significant symptoms at presentation

Presenting symptoms (52)	
Asymptomatic	7 (13)
Shortness of breath	45 (87)
Cough	38 (73)
Chest/back pain	25 (48)
Weight loss	18 (35)
Fevers	10 (19)
Wheezing	8 (15)
Pneumothorax	5 (10)

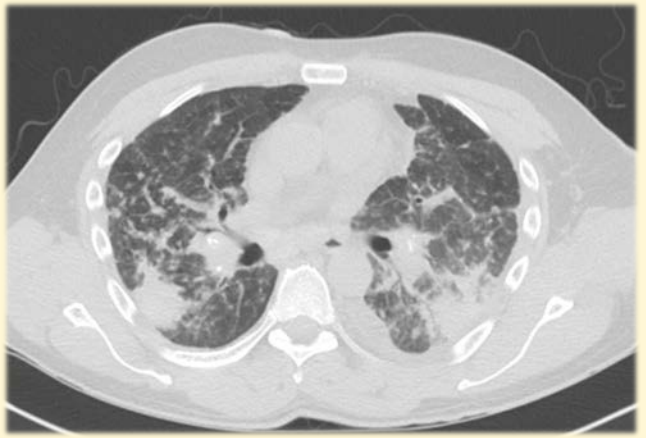
Present with advanced disease

Simple



62%

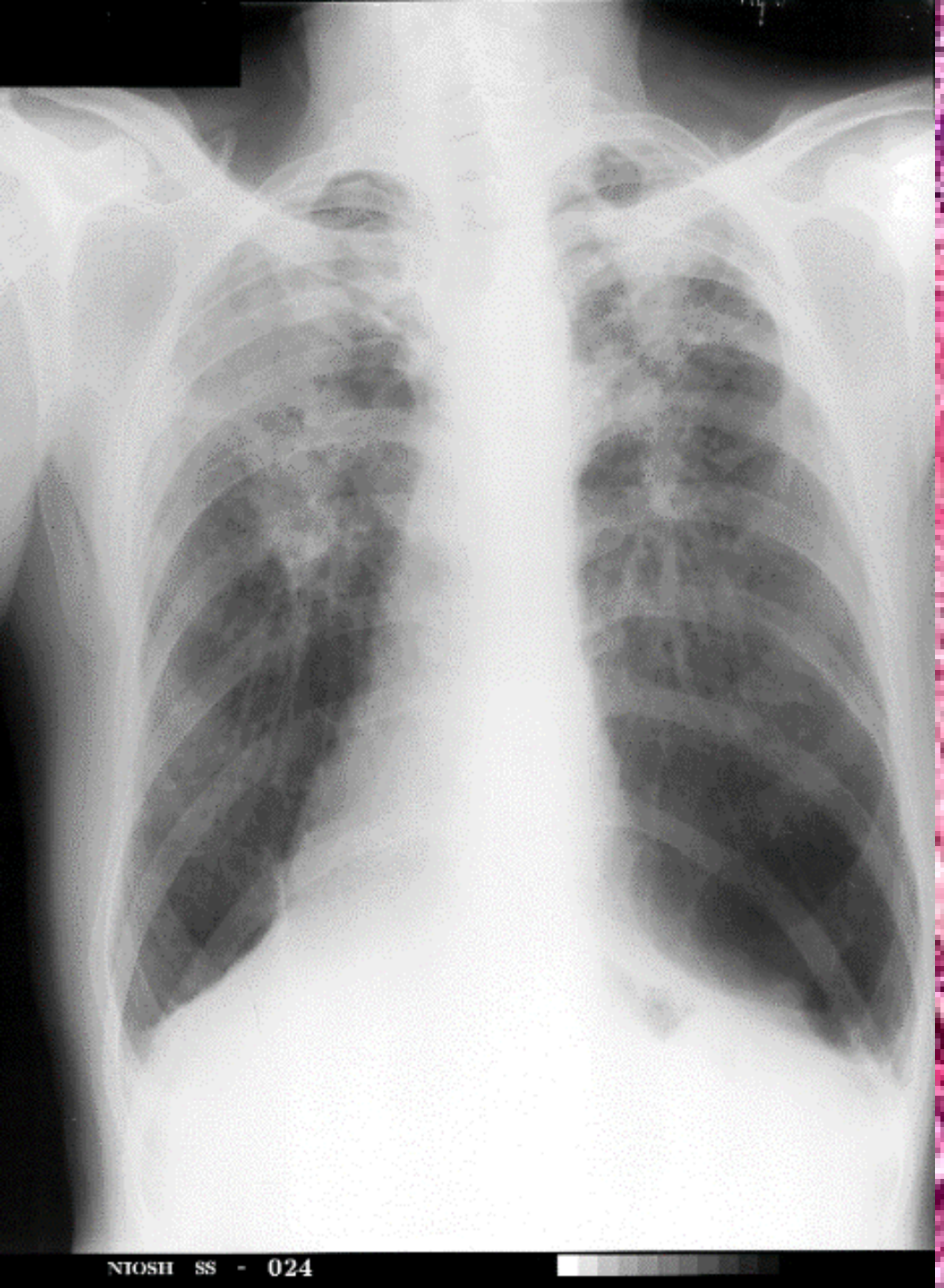
Complicated



38%

15% fatal and counting….

Source: Fazio JC et al. Epidemic of silicosis among immigrant engineered stone (quartz) countertop fabrication workers in California. JAMA IM, July 24, 2023



Health Effects of Silica

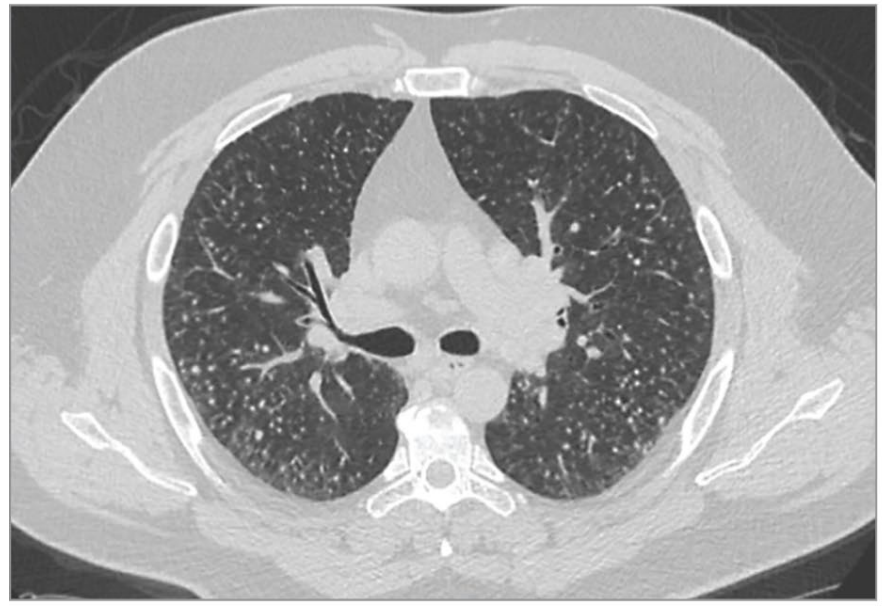
- Chronic = after 10+ years, lower concentrations
- Accelerated = after 5-10 years, higher concentrations
- Acute = after weeks to years, highest concentrations

Silicosis

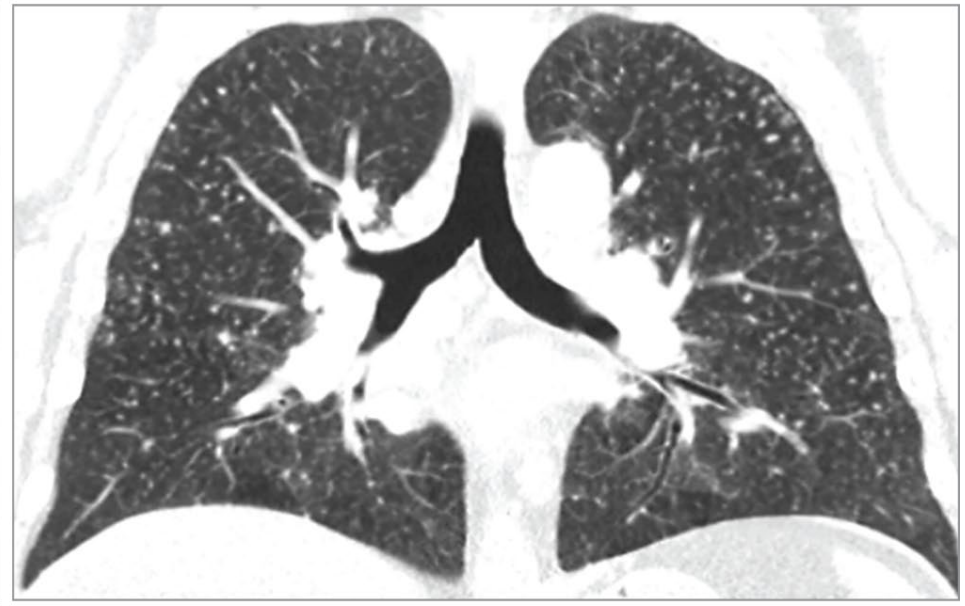
Fibrotic interstitial lung disease resulting from occupational inhalation of respirable crystalline silica

Chronic	Accelerated	Acute
Moderate-low exposure	High exposure	High exposure
15-20 years after first exposure	5-10 years after exposure	Weeks to years
Asymptomatic Cough and sputum production	Asymptomatic Cough, dyspnea on exertion	Rapid onset dyspnea, cough, weight loss, fatigue, fever
Innumerable centrilobular nodules, predominantly in upper lungs, emphysematous changes, calcified lymph nodes	Same as chronic silicosis	Bilateral ggos, centrilobular nodular opacities, calcifications, lymphadenopathy
Can develop progressive massive fibrosis		Poor prognosis, <4 years

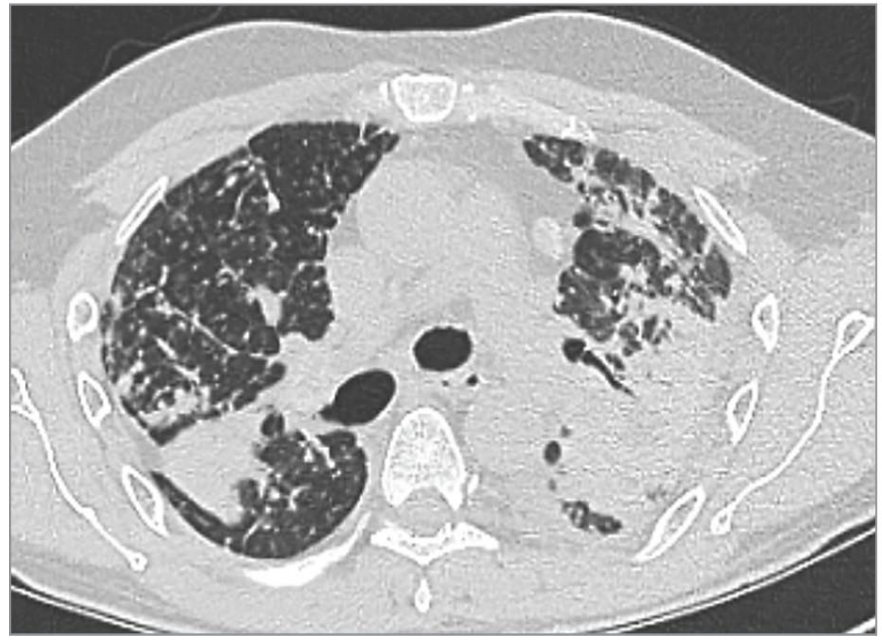
A Axial view of early simple silicosis



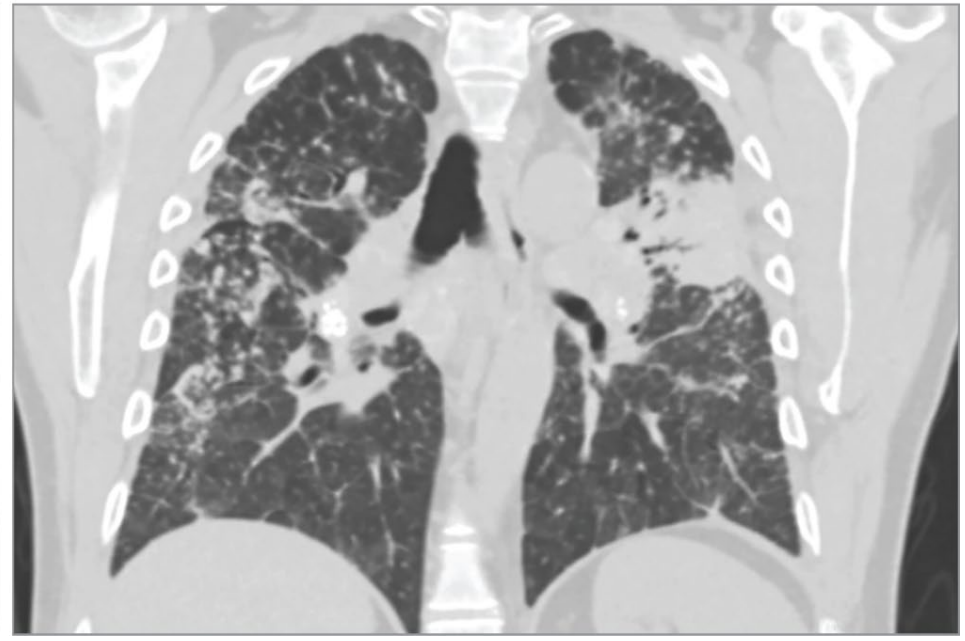
B Coronal view of early simple silicosis



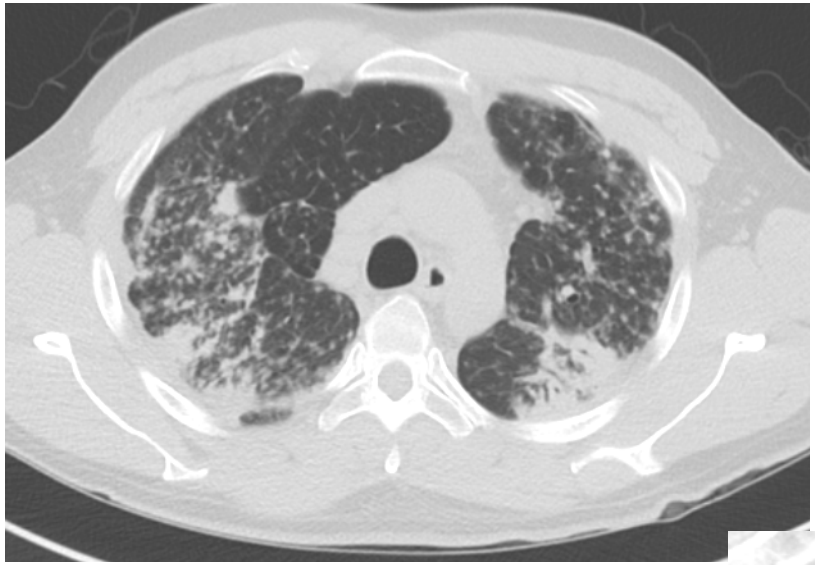
C Axial view of complicated silicosis

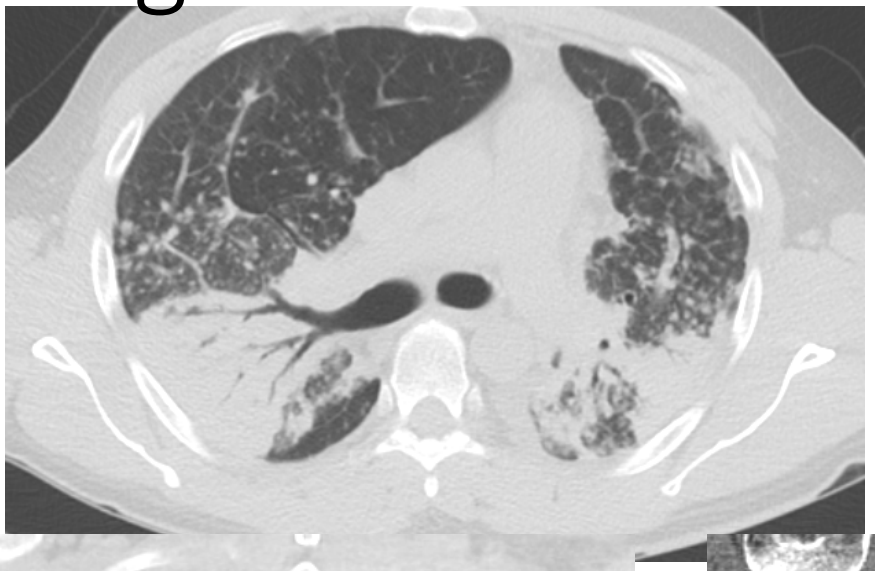


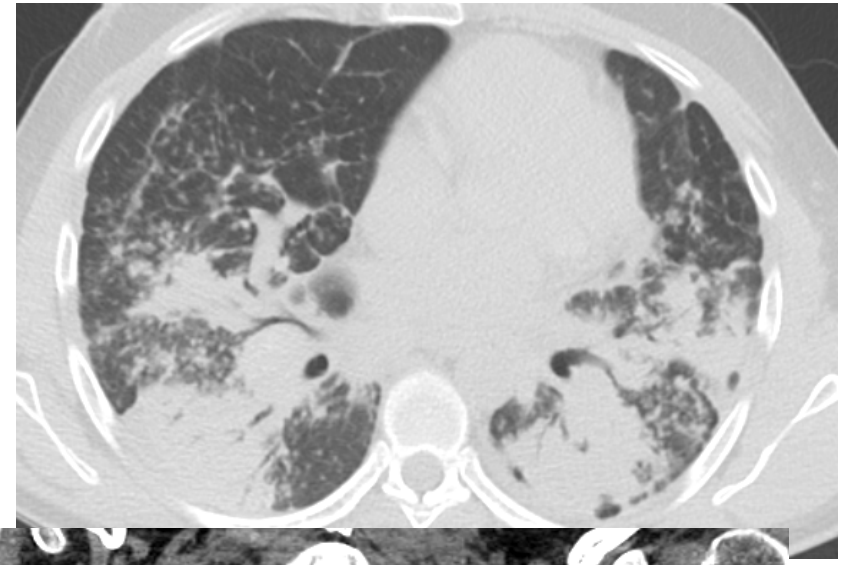
D Coronal view of complicated silicosis

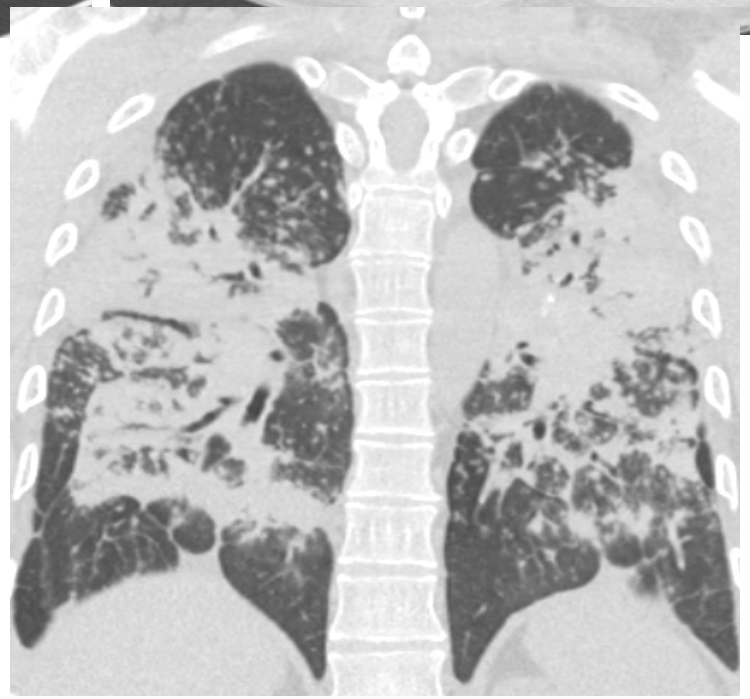


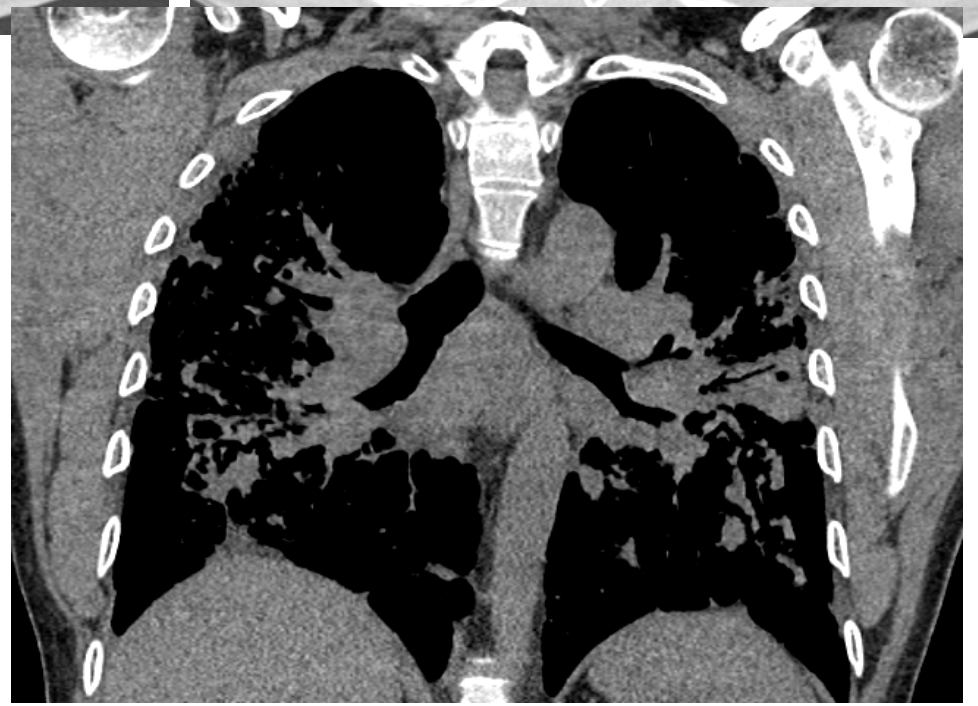
CT with Progressive Massive Fibrosis











Micronodular pattern, upper lobe predominant, with areas of consolidation with calcification, and mediastinal and hilar lymphadenopathy.

Misdiagnosis and Lack of Occupational History Taking

Delayed diagnosis (52)	
Initial delay in diagnosis	30 (58)
Time to correct diagnosis, median (IQR), mo	3 (0-8)
Alternative initial diagnosis (30)	
Pulmonary tuberculosis	8 (27)
Nontuberculous mycobacterial infection	3 (10)
Sarcoidosis	2 (7)
Asthma	2 (7)
Bacterial pneumonia	9 (30)
Other	6 (20)

Cross-section of notes from 2002

- Occupational history only taken 27.8% admissions

Comorbid conditions

Comorbidities (52)	
Autoimmune disease	6 (12)
Myositis	1 (2)
Rheumatoid arthritis	4 (8)
Systemic sclerosis or CREST syndrome	1 (2)
Nontuberculous mycobacterial infection	5 (10)
History of active pulmonary TB	1 (2)
Other lung disease (COPD/asthma)	2 (4)

Comorbid conditions

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- Autoimmunity
  - Rheumatoid arthritis (OR = 1.94, PMID: 33651342)
  - Systemic sclerosis
    - 37.5-86% of males with systemic sclerosis report silica exposure (PMID: 26186806)
  - Vasculitis (ANCA OR 2.5, PMID: 23820041)
- Can occur WITHOUT silicosis
- Silica is an adjuvant on antibody production and potentiates and immune response to an antigen.

Comorbid conditions

Comorbidities (52)	
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- Tuberculosis (PMID 34016067)
  - With Silicosis: RR 4.01
  - Without silicosis: RR 1.92
- Non-tuberculous mycobacteria (NTM)
  - Increasing odds with more severe radiographic disease
  - OR 1.82 ---> 7.58 (PMID: 31163598)

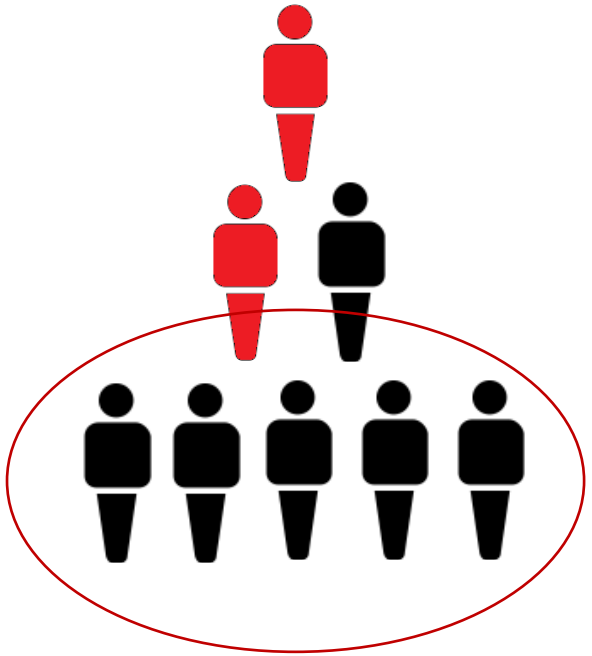
Undocumented
Uninsured
Unprotected

Occupational history	
Years of work in engineered stone industry (51), median (IQR)	15 (10-20)
Continued working after diagnosis (52)	
Still working	25 (48)
Not working	18 (35)
Unknown	9 (18)
Engineering controls: water suppression methods (51)	23 (45)
Respirator use (47)	
Sometimes	35 (74)
Always	12 (26)
Type of respirator (37)	
N-95	33 (89)
Half-face respirator	17 (46)
Full-face respirator	2 (5)
No. of employees in workshop (35)	
<10	17 (49)
10-50	17 (49)
>50	1 (2)

Source: Fazio JC et al. Epidemic of silicosis among immigrant engineered stone (quartz) countertop fabrication workers in California. JAMA IM, July 24, 2023

Public health follow up

Employer screening of 43 employees in California screened with Chest X-ray and PFT

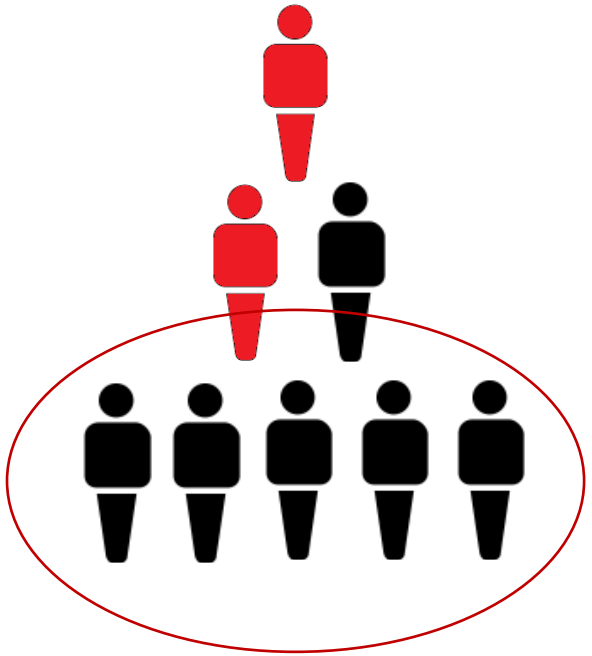


12%

Heinzerling, et al. *AJRCCM.* 2021;203(6):764-6.

Public health follow up

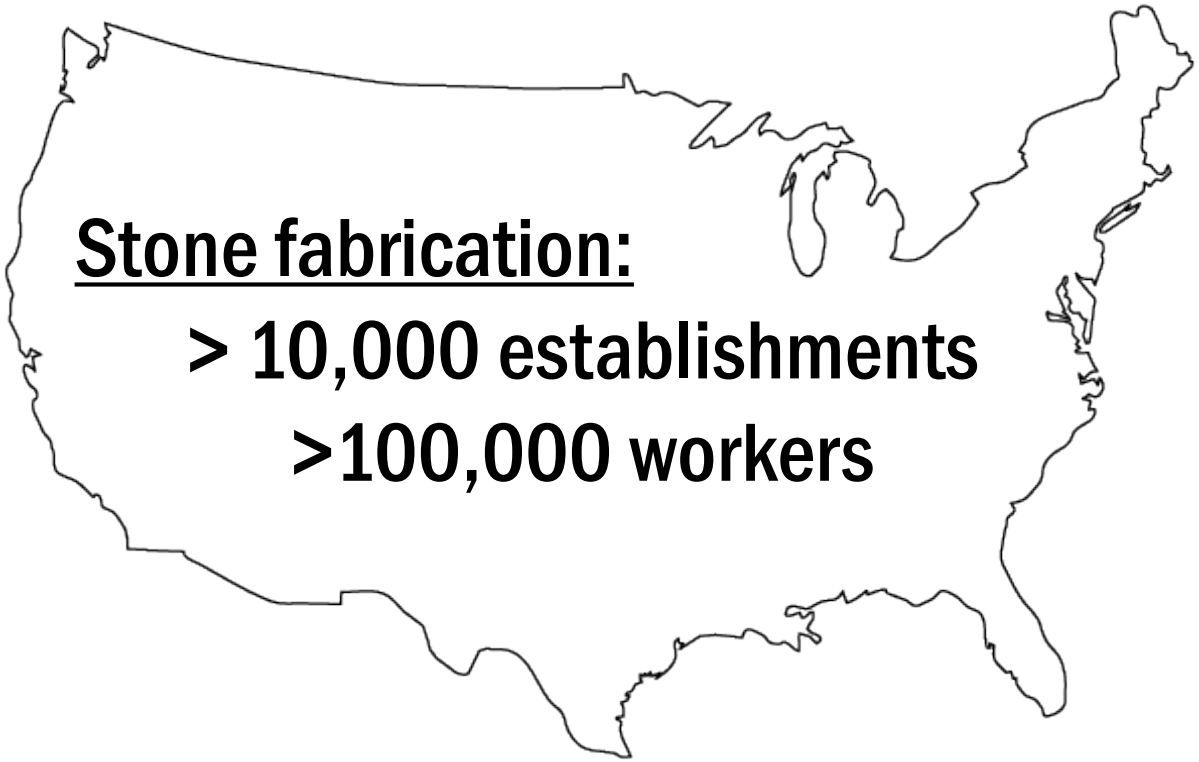
Screening of 544 employees in Australia screened with CT Chest



22%

Hoy RF, et al. Occup Environ Med 2023;0:1–8.

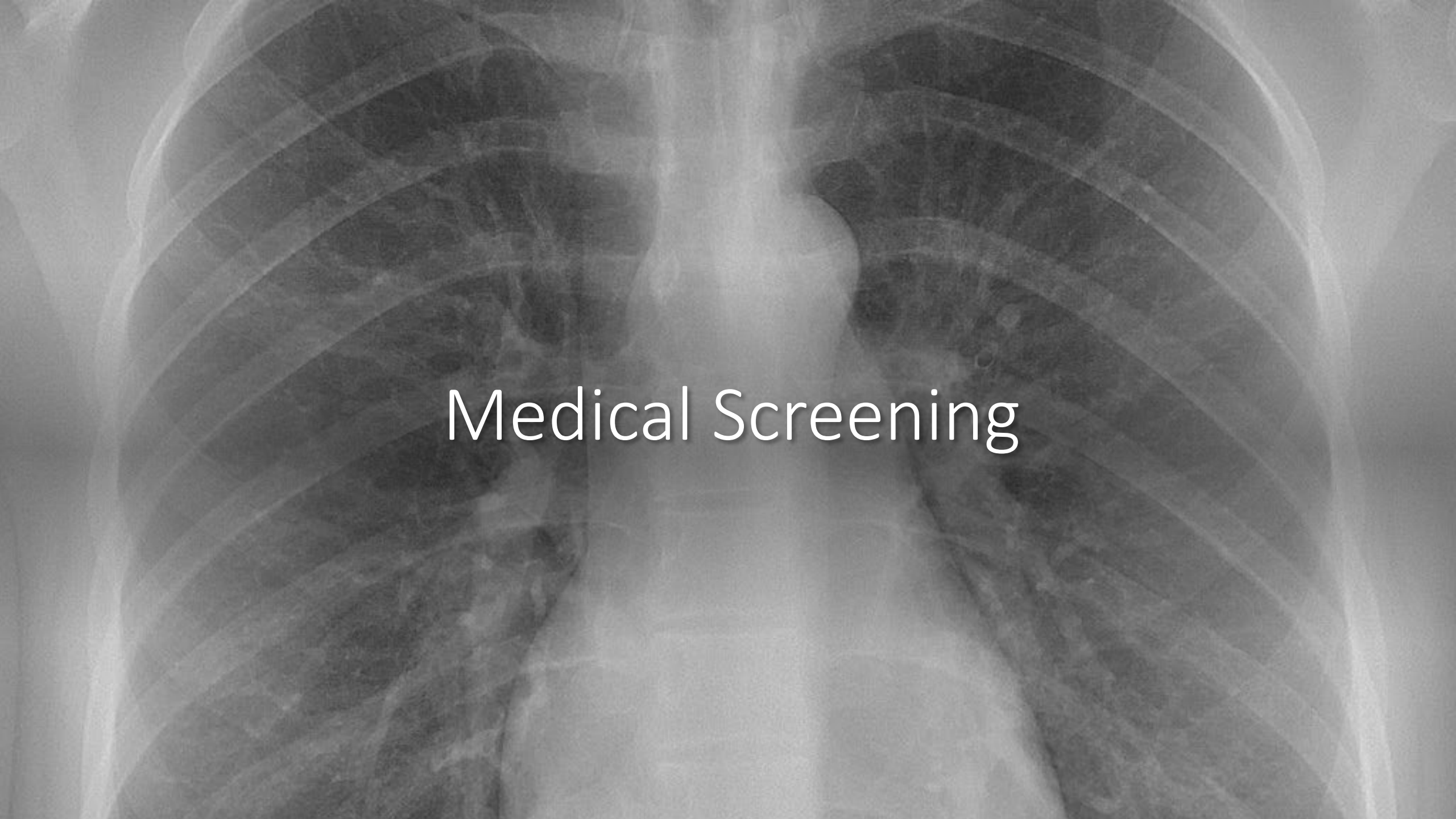
How many cases are there?



Stone fabrication:

> 10,000 establishments

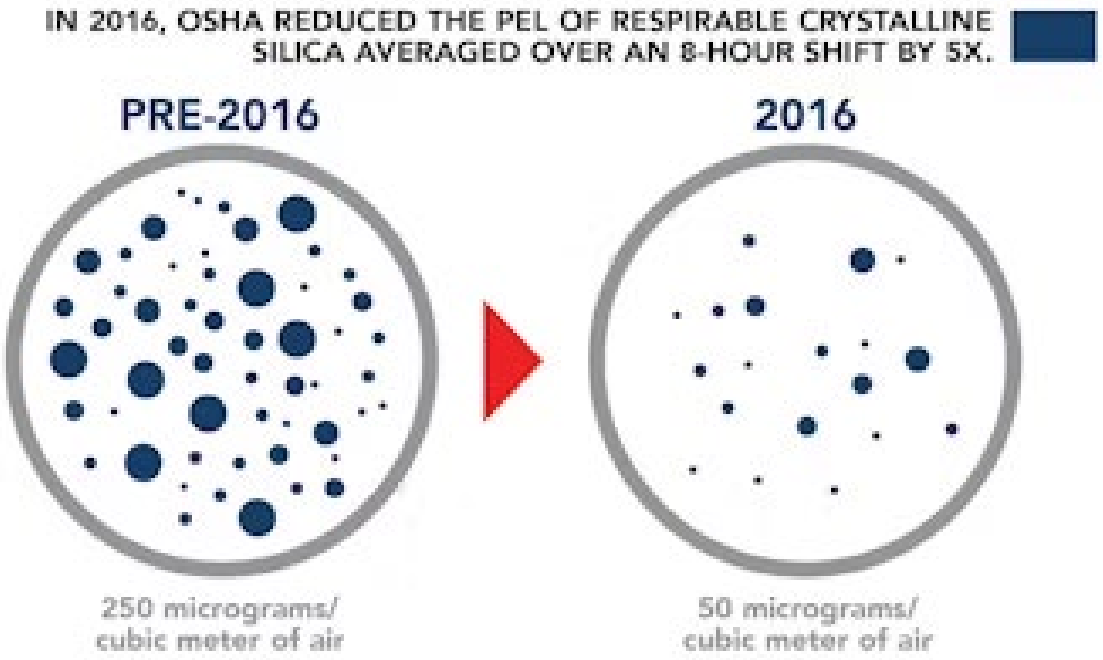
>100,000 workers



Medical Screening

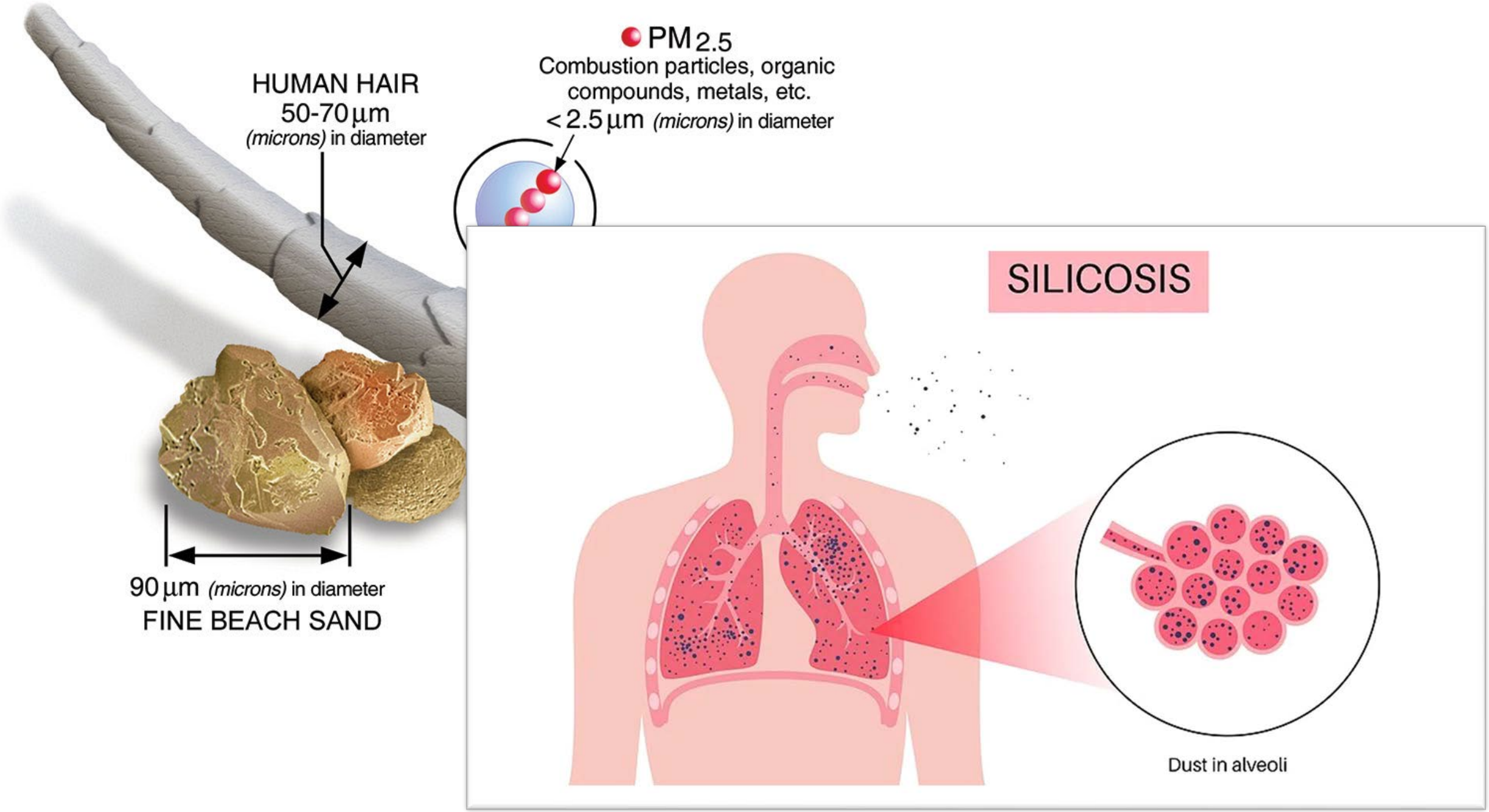
2016 Silica Rule

- Lower exposure limit for respirable crystalline silica
  - AL = 25 µg/m^3 and PEL = 50 µg/m^3
- Exposure monitoring
- Specified exposure controls, including respirators
- Medical surveillance



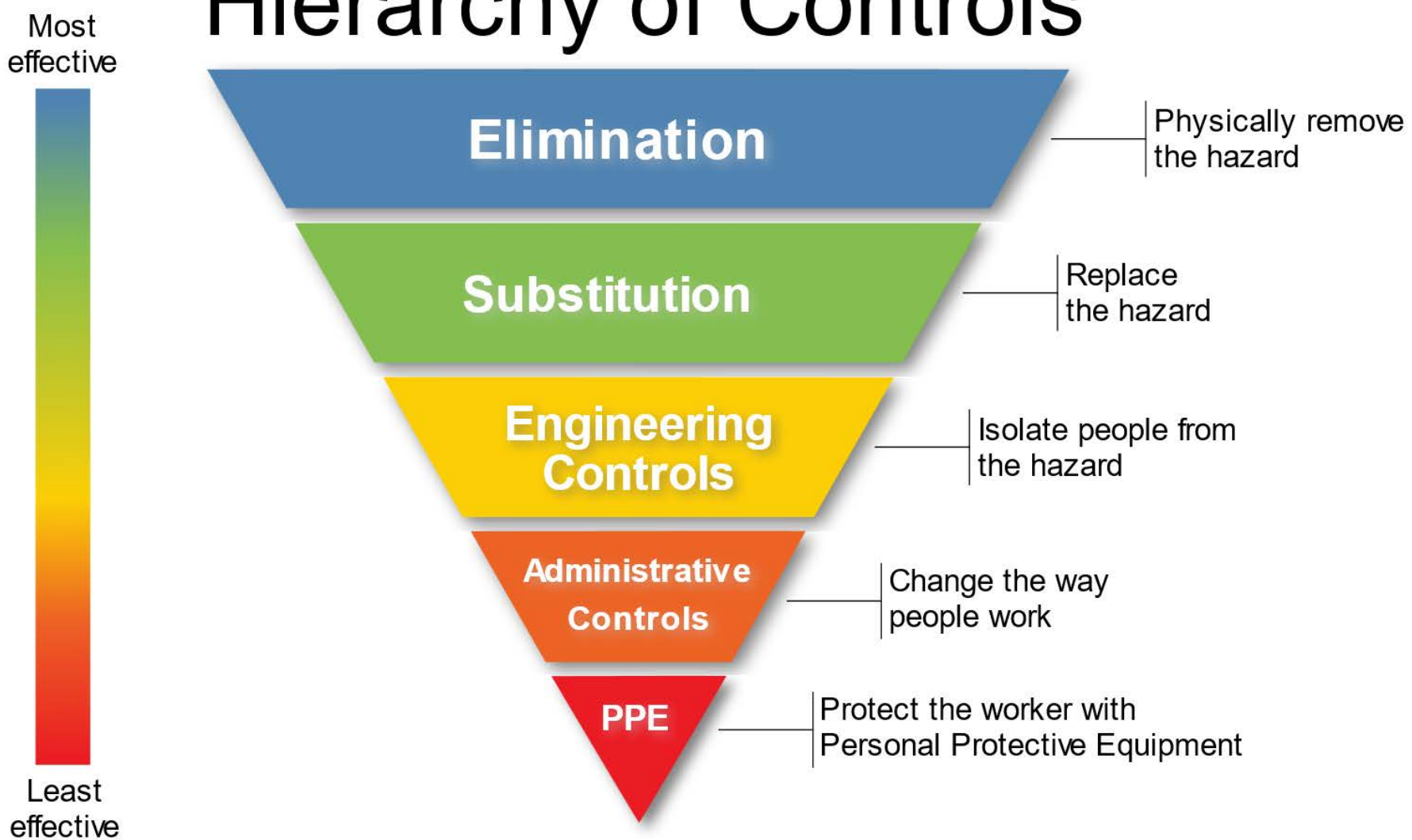
Medical Surveillance

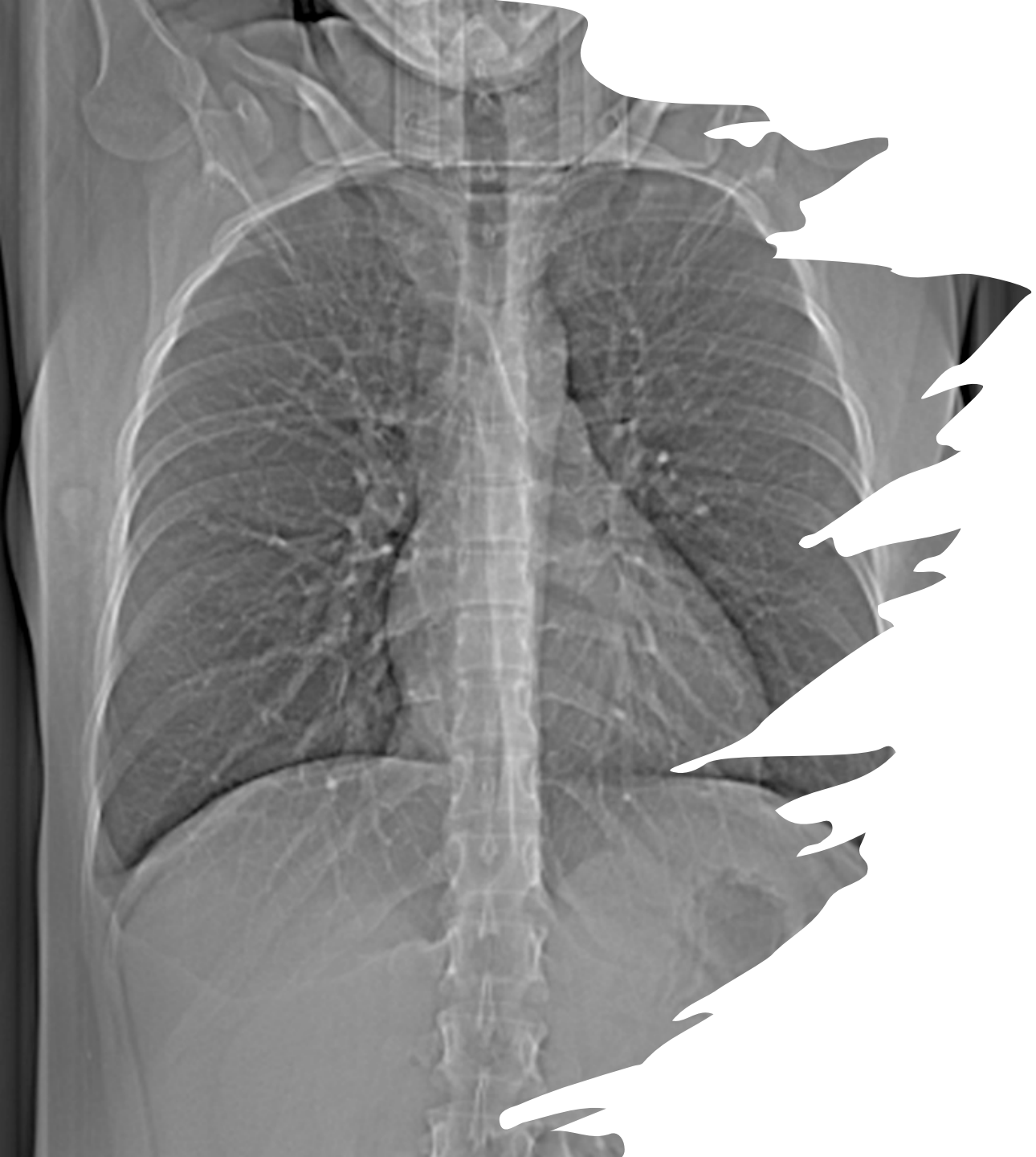
- At baseline and **every 3 years**
- **California now requires CT Scan for engineered stone workers**
- Exam also includes spirometry and TB testing


HUMAN HAIR
50-70 µm
(microns) in diameter
PM 2.5
Combustion particles, organic
compounds, metals, etc.
< 2.5 µm (microns) in diameter
90 µm (microns) in diameter
FINE BEACH SAND
SILICOSIS
Dust in alveoli

Why are masks insufficient?

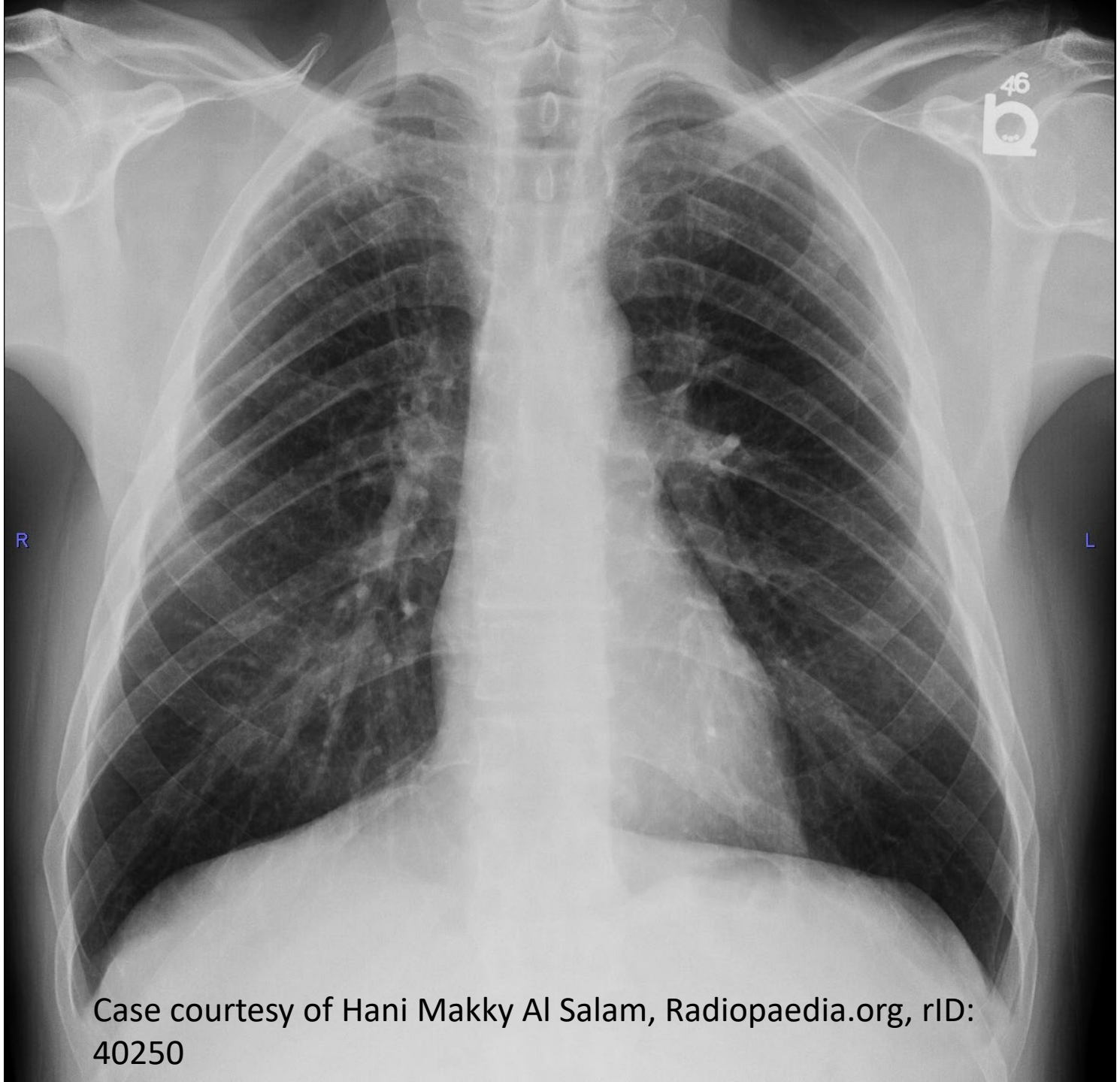
Hierarchy of Controls



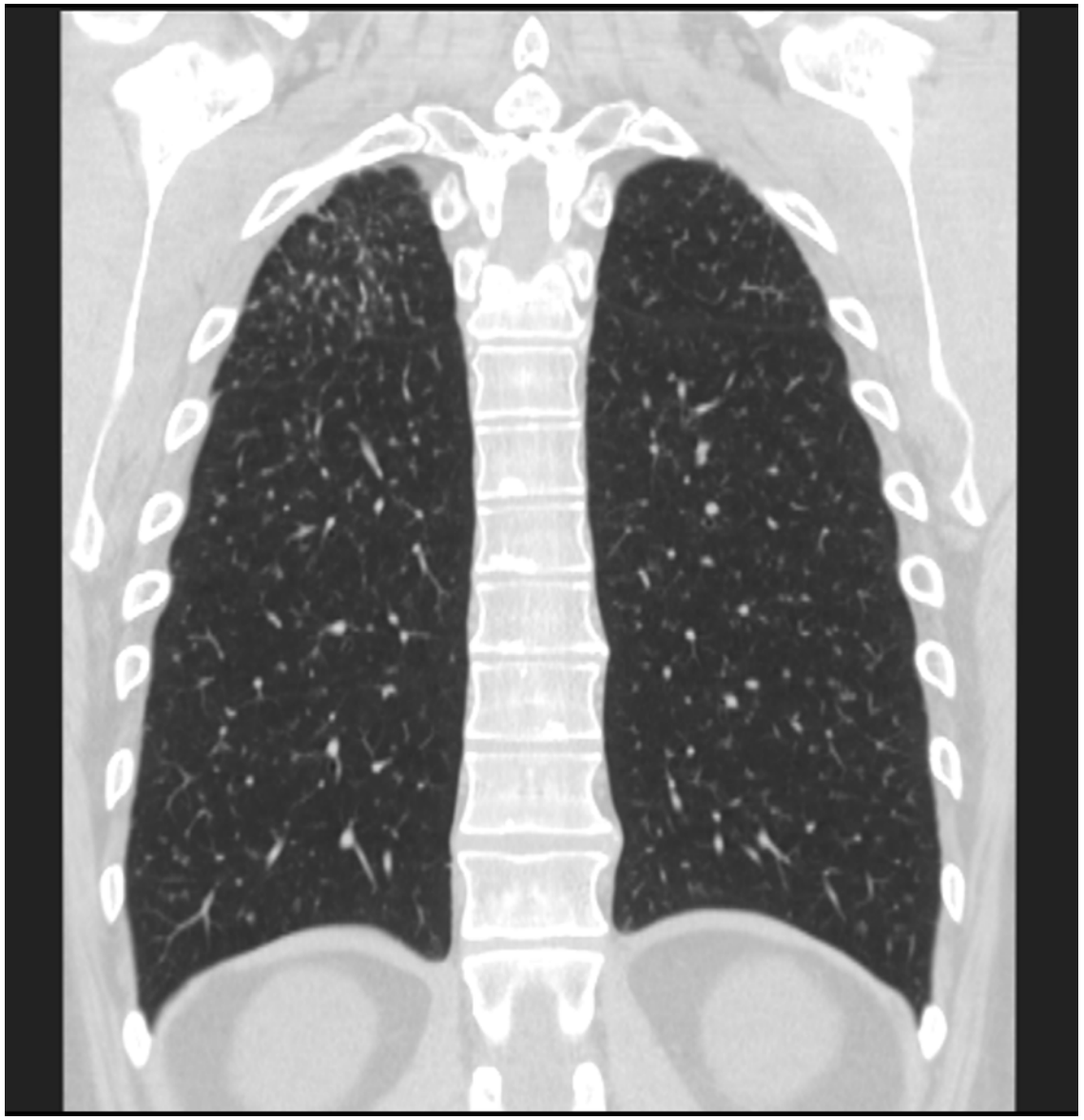


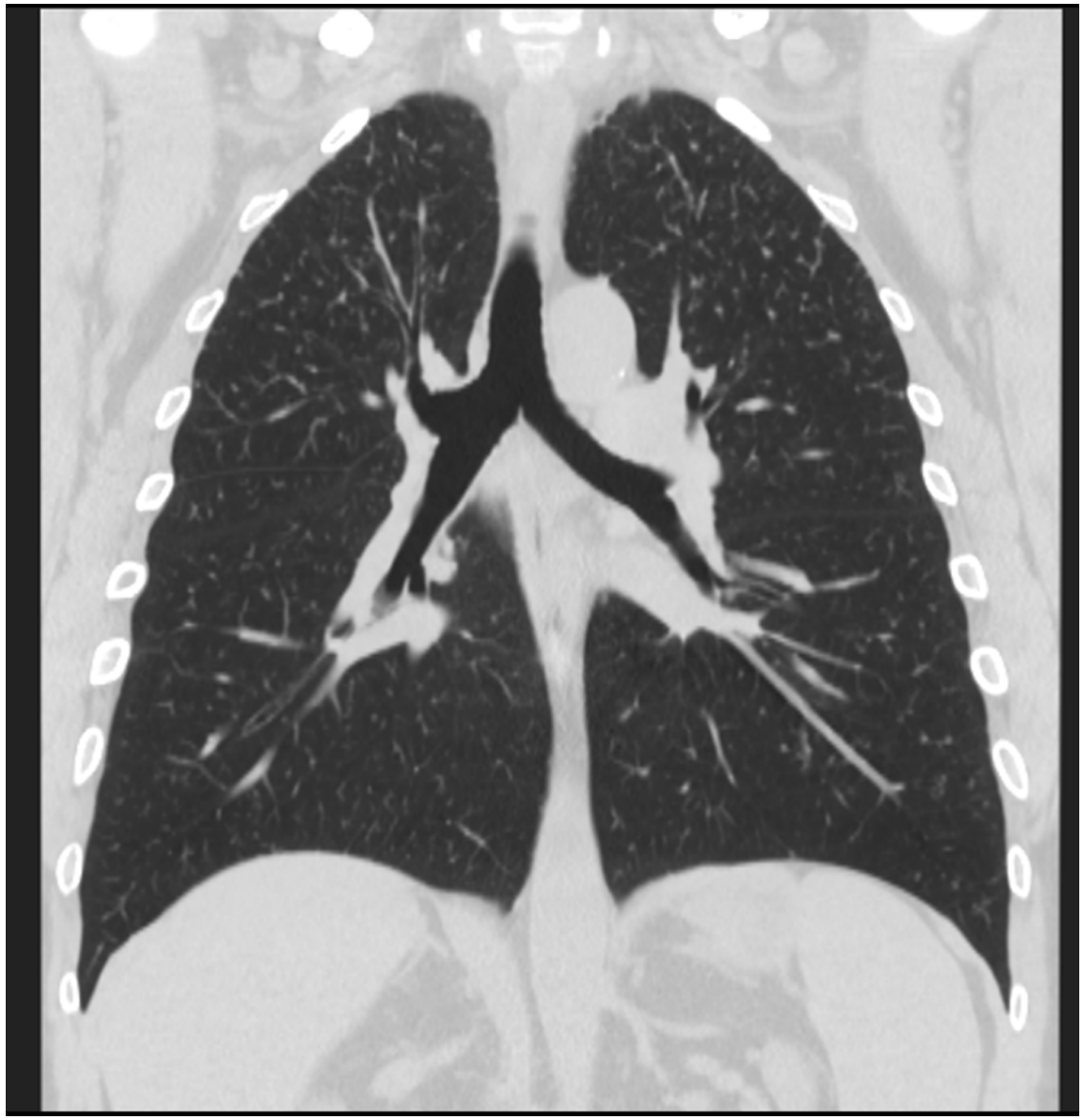
Chest X-ray vs CT Scan

- Two Australian case series (PMID: 31407419, 33115923)
  - 35-43% of fabricators with silicosis had normal chest X-ray but abnormal CT scan
- Italian case series (PMID: 32352423)
  - Those with abnormal CT scans
  - 42% Chest X-rays were abnormal
  - 33% of spirometry were abnormal



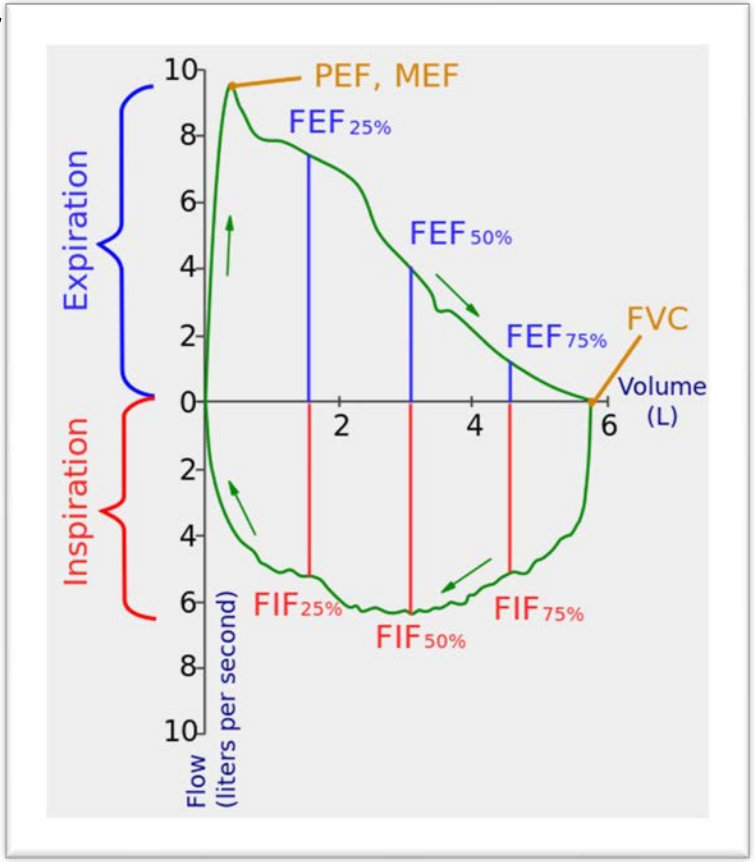
Case courtesy of Hani Makky Al Salam, Radiopaedia.org, rID: 40250





Spirometry vs Diffusion Capacity

- Italian case series (PMID: 32352423)
  - Of those with abnormal CT scans 33% had abnormal spirometry
  - 50% had abnormal diffusion capacity
- Coal miners
  - 9% of coal miners with normal FEV1, had abnormal DLCO
  - As radiology gets worse, the diffusion gets worse too



Almberg et al., “Relationship Between Radiographic Disease, Spirometry Findings, and Diffusion Capacity in a Population of Former U.S. Coal Miners.” Am J Respir Crit Care Med 2023;207:A4363

How to get screened?

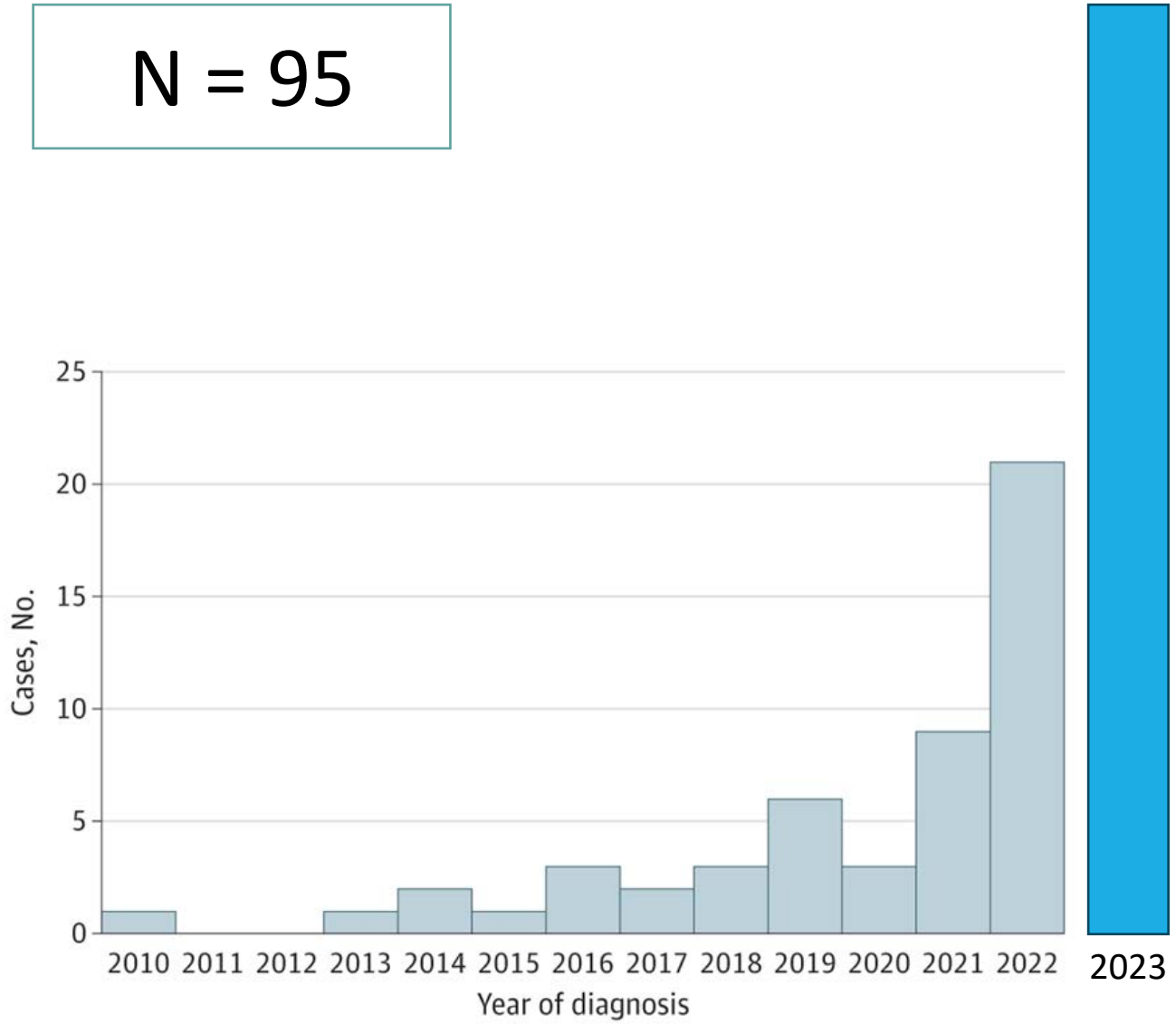
- Employer required to pay for screening
- Surasi et al, no Californian employers had paid for medical screening following questionnaire from OSHA Special Emphasis Panel in 2019
  - Currently assessing updated uptake by new OSHA program
- Many workers are being screened by lawyers and referred to medical centers or presenting to primary care providers for screening

Current Medical Screening Limitations

- CT scans and diffusion capacity more sensitive tests than current requirements
- Medical screening requirements need an update
- Need to make medical screening readily available

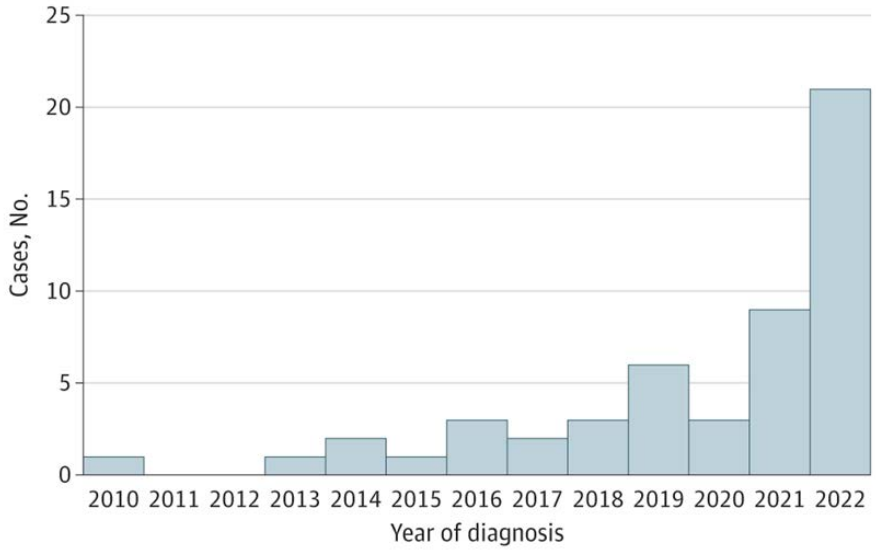
Updates on the California Outbreak

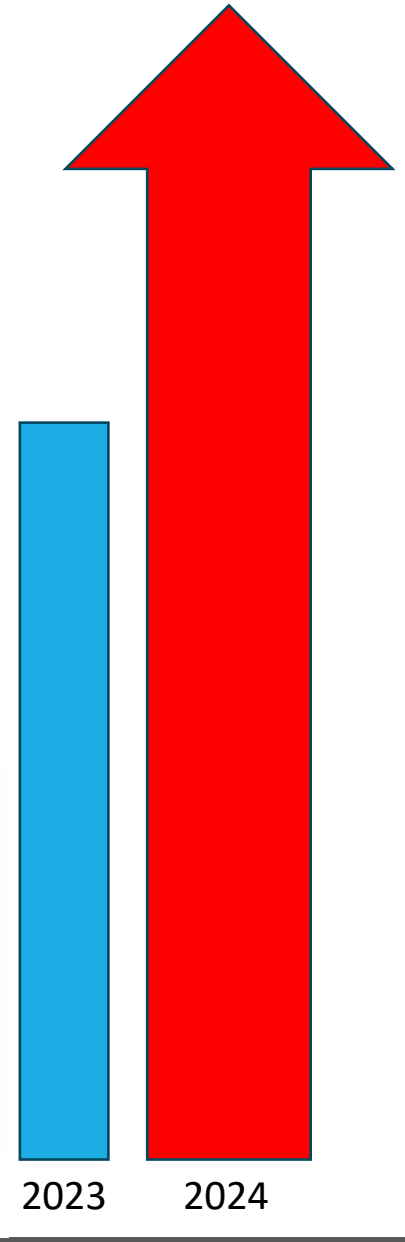
N = 95


25
20
15
10
5
0
Cases, No.
2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Year of diagnosis
2023

N = 215

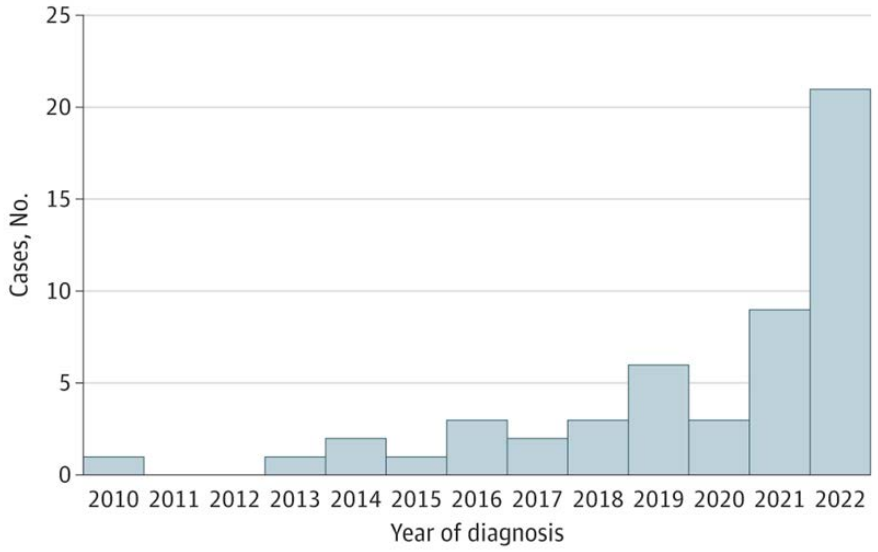
- At least 12 workers have died
- 26 have received lung transplants (18 within the last 1 year)

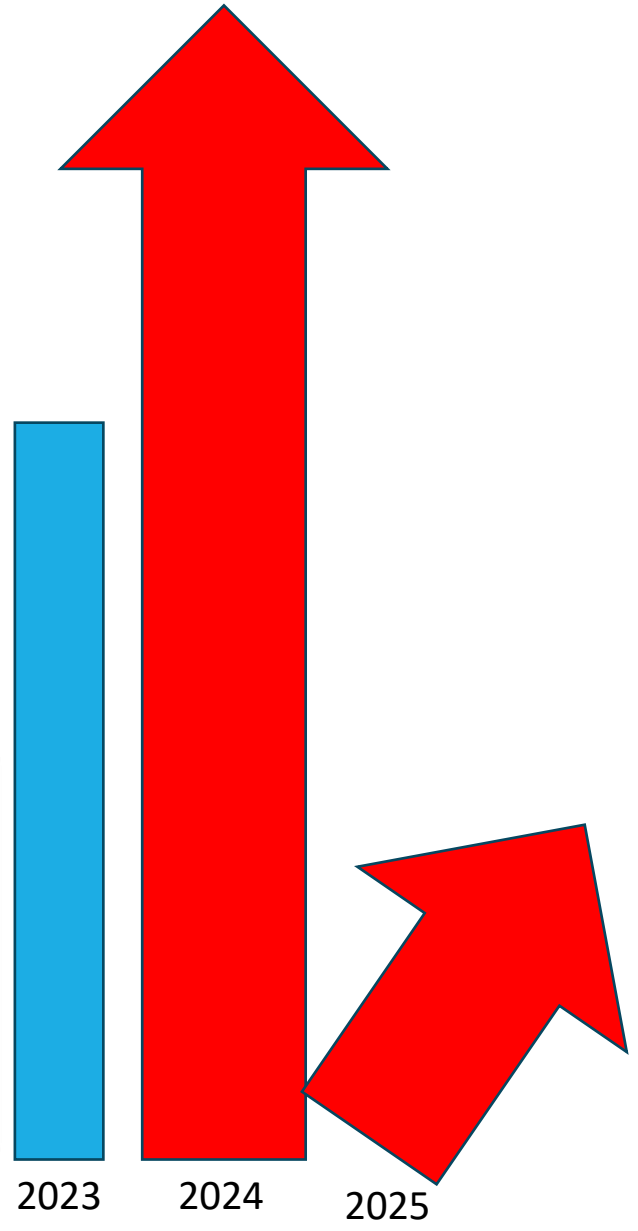




N = 251

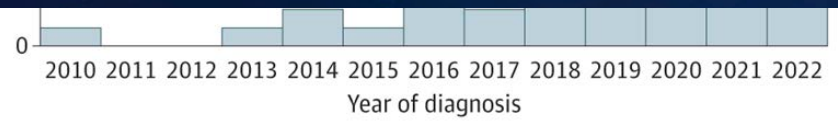
- At least 15 workers have died
- 29 have received lung transplants





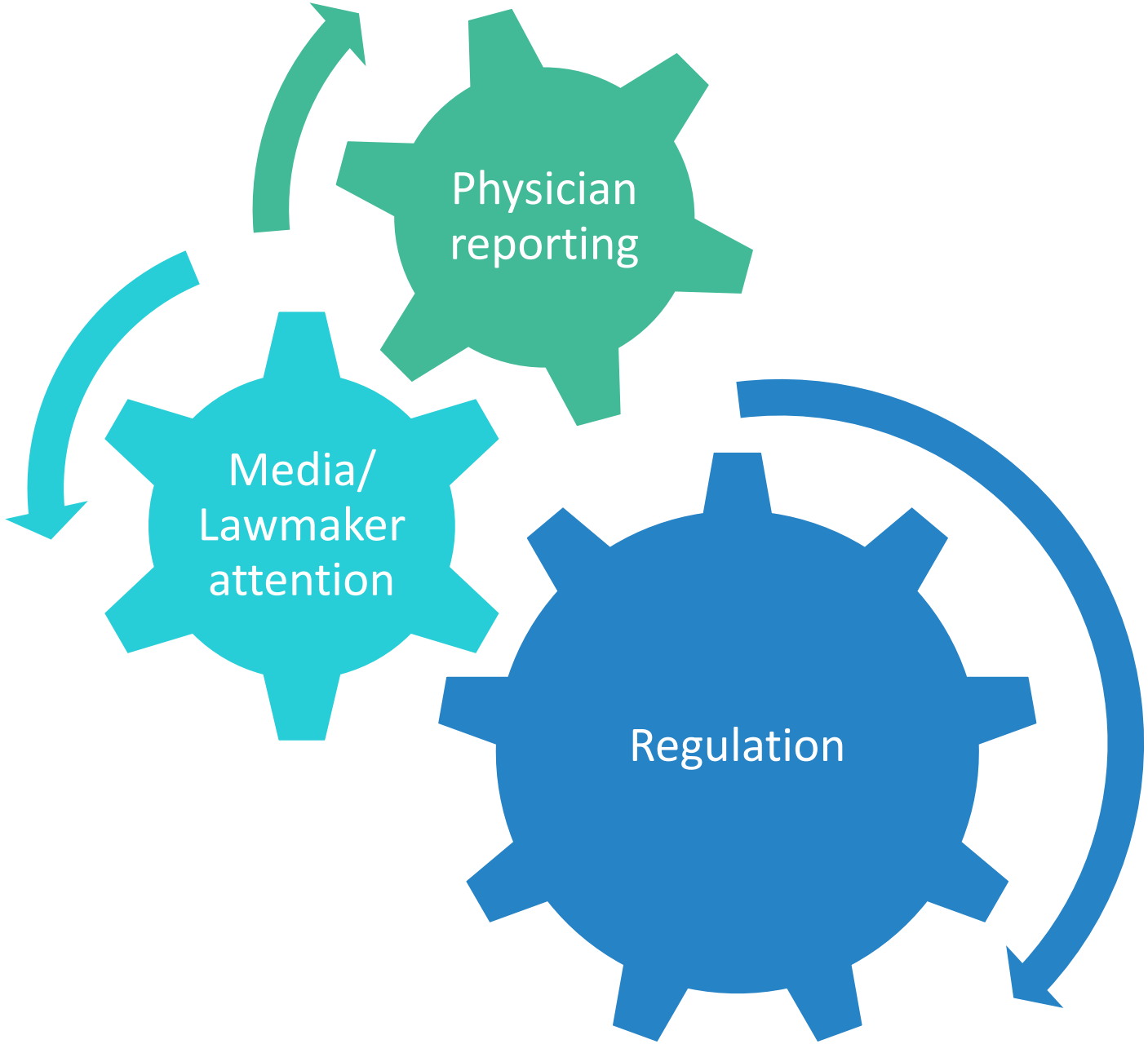
N = 251

- At l
- 29 k



2023 2024 2025

Advocating for change


Physician reporting
Media/ Lawmaker attention
Regulation

NEWS

ISRAEL-HAMAS WAR POLITICS U.S. NEWS WORLD BUSINESS HEALTH

Quartz countertops li
disease in w
m

npr

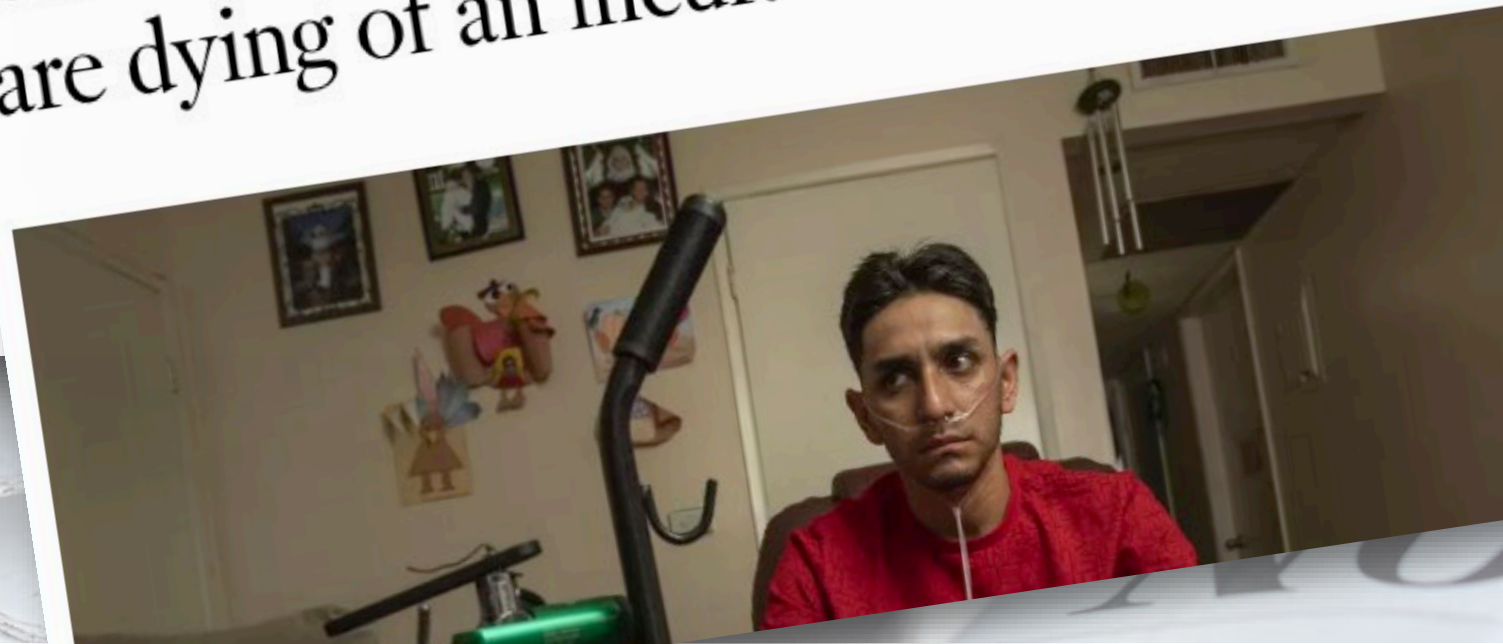
SILICOSIS IN U.S. COUNTERTOP WORKE

Young men making
facing lung damage
action

Los Angeles Times

CALIFORNIA

California workers who cut countertops are dying of an incurable disease



Community and Governmental Outreach

- June was “Silicosis Awareness Month” in LA County
- LA County – DPH to work with community outreach workers to visit shops in Pacoima area to make recommendations to LA County Board of Directors
- Meeting with State Representatives to discuss options from regulation to bans

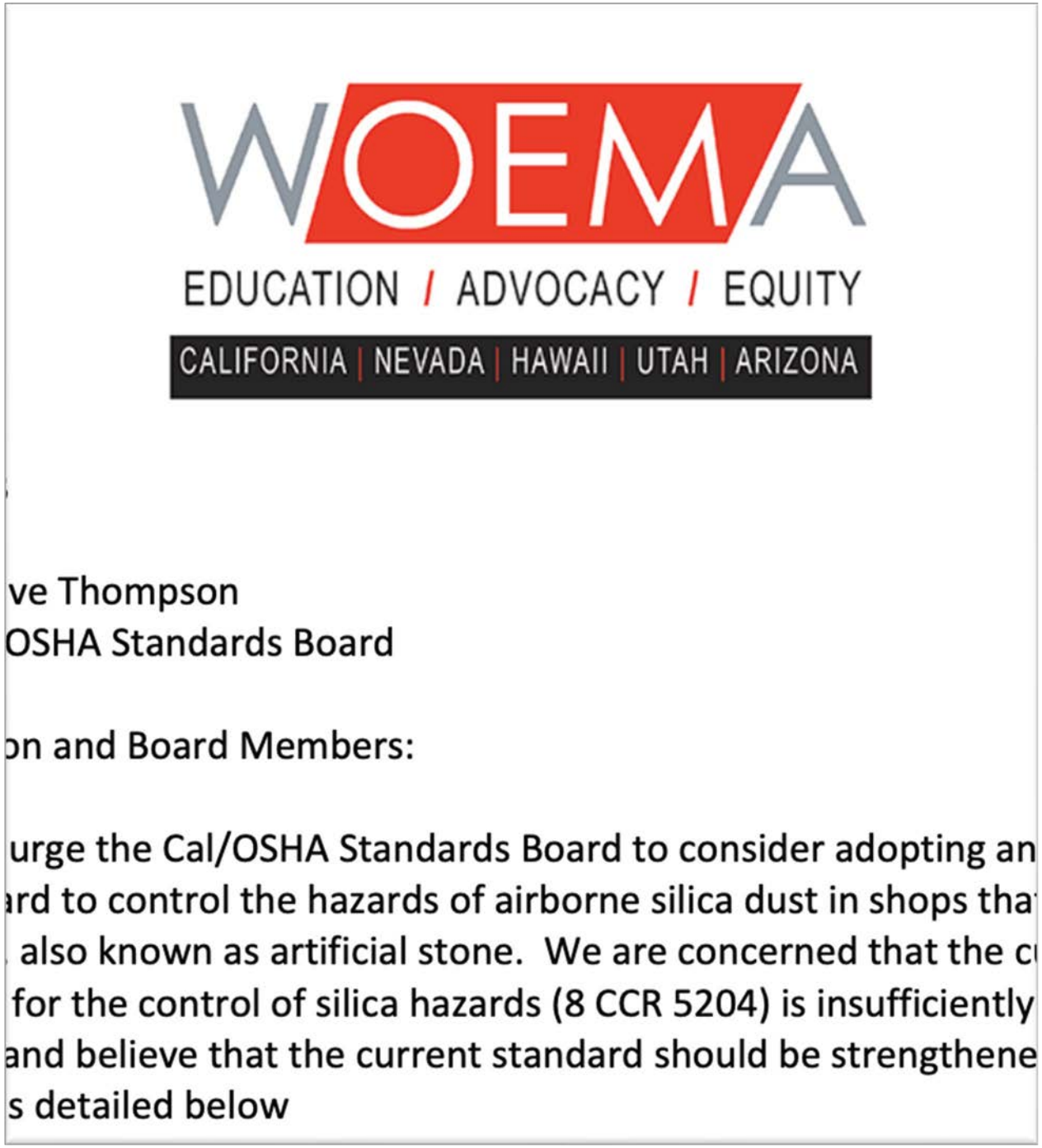
WORKPLACE

L.A. County Supervisors Take Initial Steps Toward a Ban on Artificial-Stone Countertops

by **Jim Morris** and **Kim Krisberg**

June 6, 2023

Gustavo Reyes Gonzalez, 32, has a severe case of silicosis from



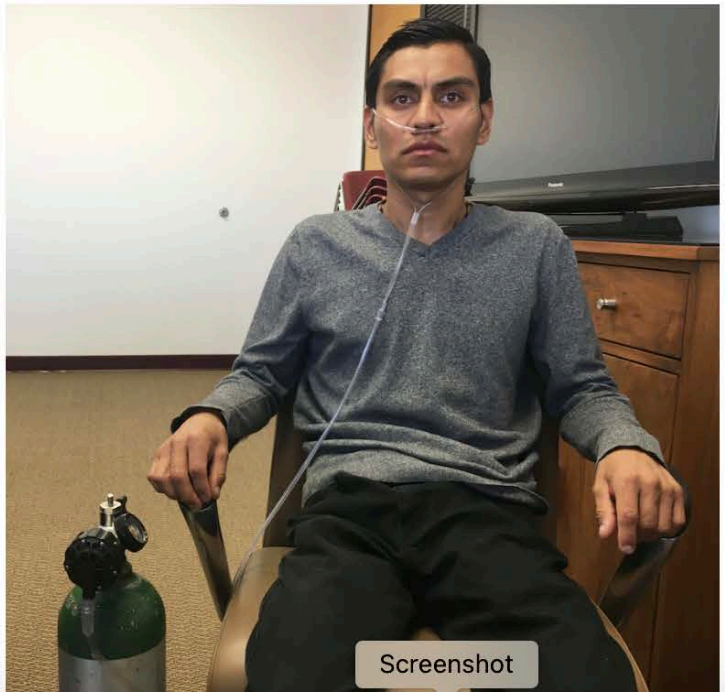
California state efforts

- CDPH
  - Surveillance
  - Research
- WOEMA:
  - Emergency Temporary Standard
  - Drafting Legislation
    - State congresswoman Luz Rivas
- Cal/OSHA: Special Emphasis Program

Jury Awards $52.4M in Case Against Artificial-Stone Countertop Makers

by **Jim Morris** August 8, 2024

In the first case of its type to go to trial in the United States, a Los Angeles County jury handed down a $52.4 million verdict Wednesday against three artificial-stone countertop manufacturers sued by a fabrication worker who developed the lung disease silicosis.



LATEST STORIES

We can’t fix health care if we’re not talking about it

Summary

- Engineered stone fabrication is toxic and causes a severe progressive lung disease called silicosis
- Affects a high-risk workforce of immigrant workers
- PPE is insufficient to control level of exposure
- CT scans are more sensitive than chest x-rays to identify early disease
- Advocate for increased regulation

Acknowledgements

Our patients

CDPH Occupational Health Branch

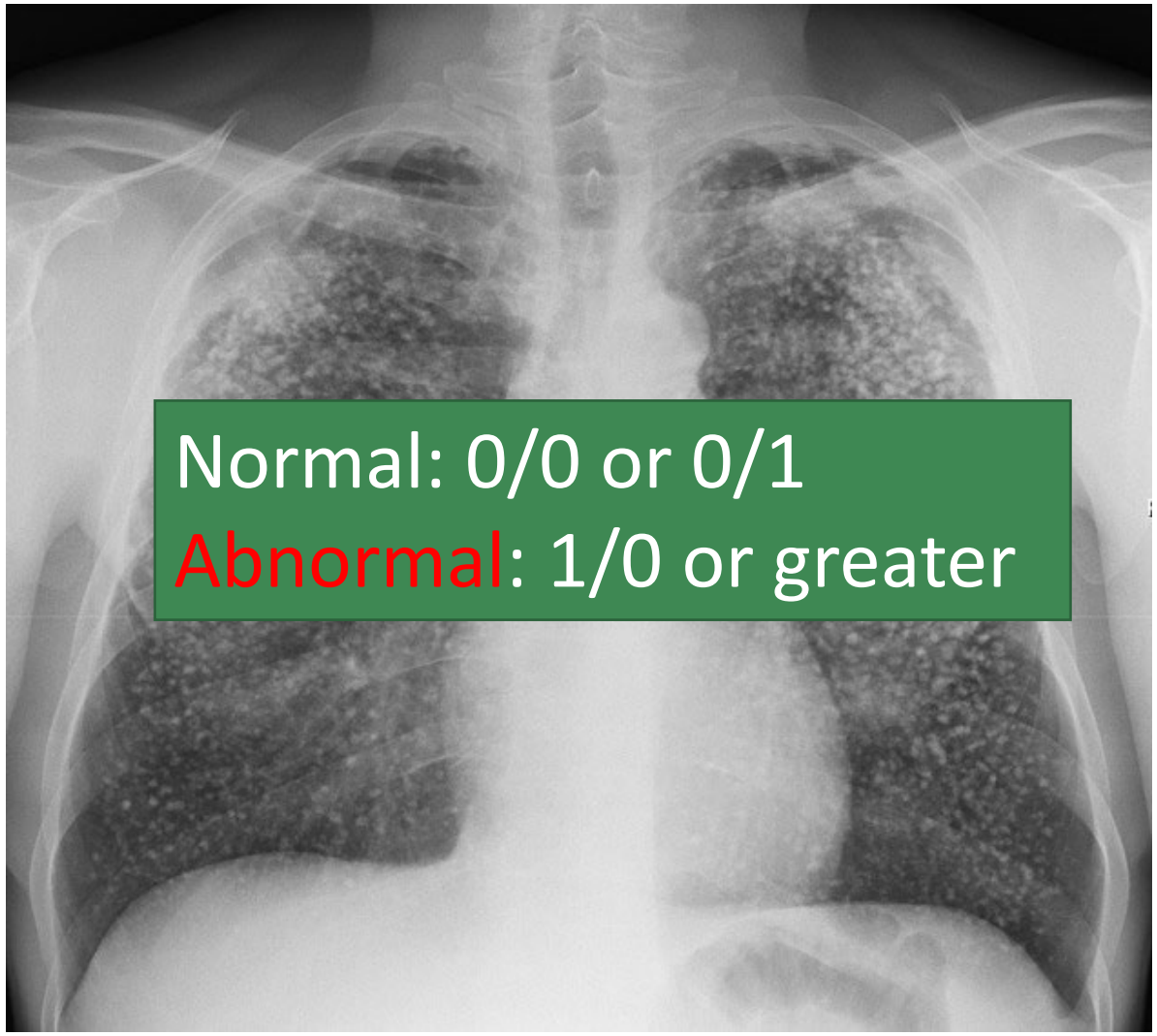
- Robert J Harrison
- Kristin Cummings
- Amy Heinzerling
- Jennifer Flattery

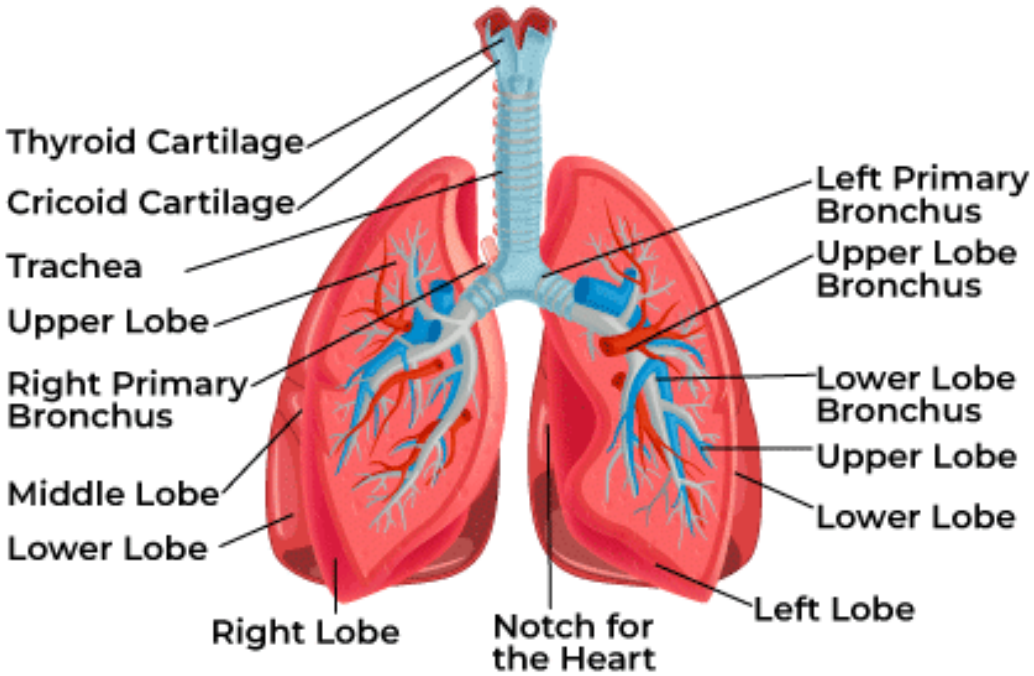
UCLA

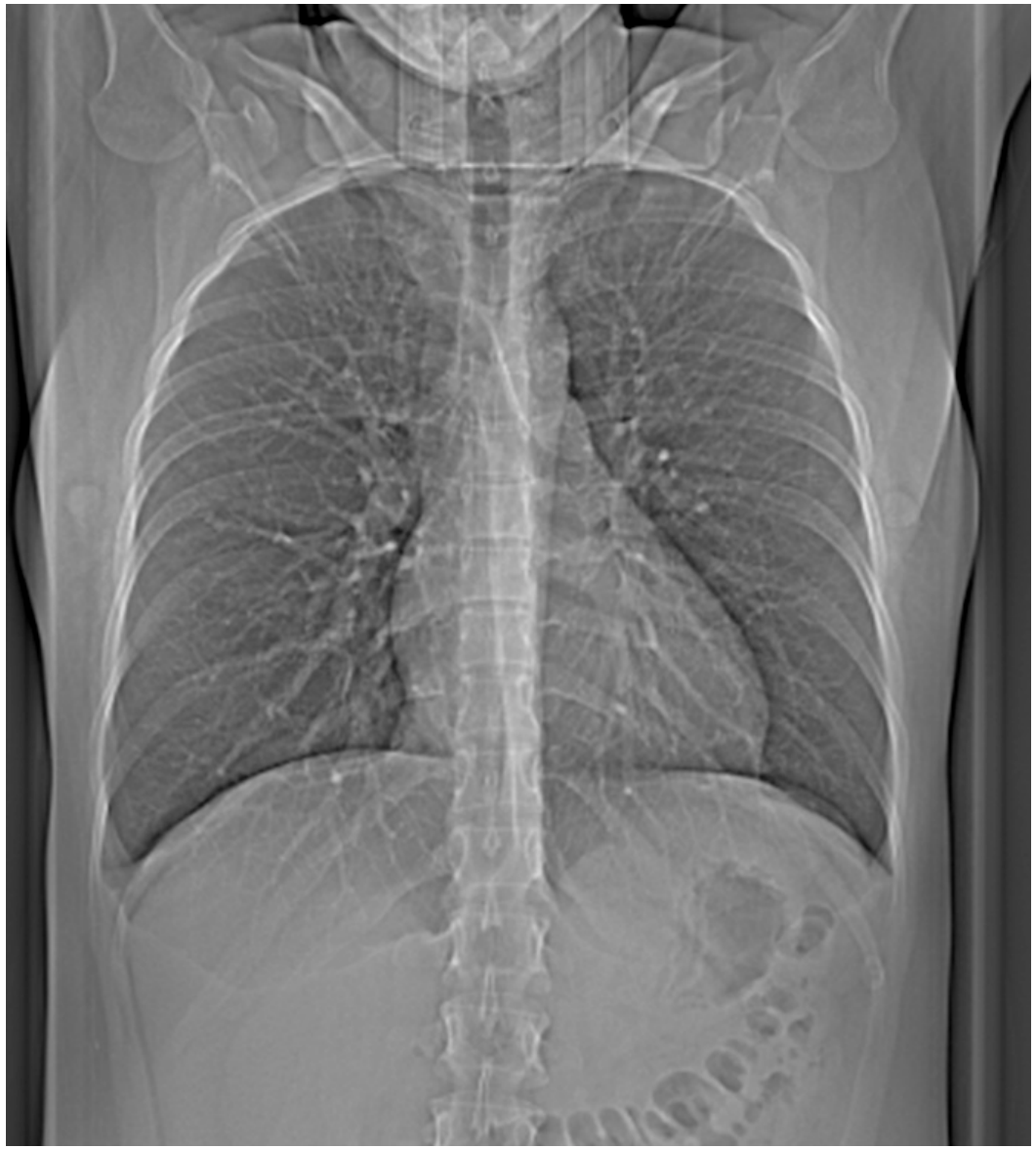
- Jane Fazio
- Nader Kamangar
- Karoly Viragh
- Nawal Afif

ILO B-read

- Pneumoconiosis classification system
- Small opacities rated on
  - Profusion (0-3)
  - Size
    - Small round: Size p (<1.5 mm), q (1.5-3mm), r (3-10mm)
    - Irregular small: s (<1.5mm), t (1.5-3mm), or u (3-10 mm)
- Large opacities (any opacity >1 cm)
  - A (< 5cm), B(5-RUL size), C (larger than B)

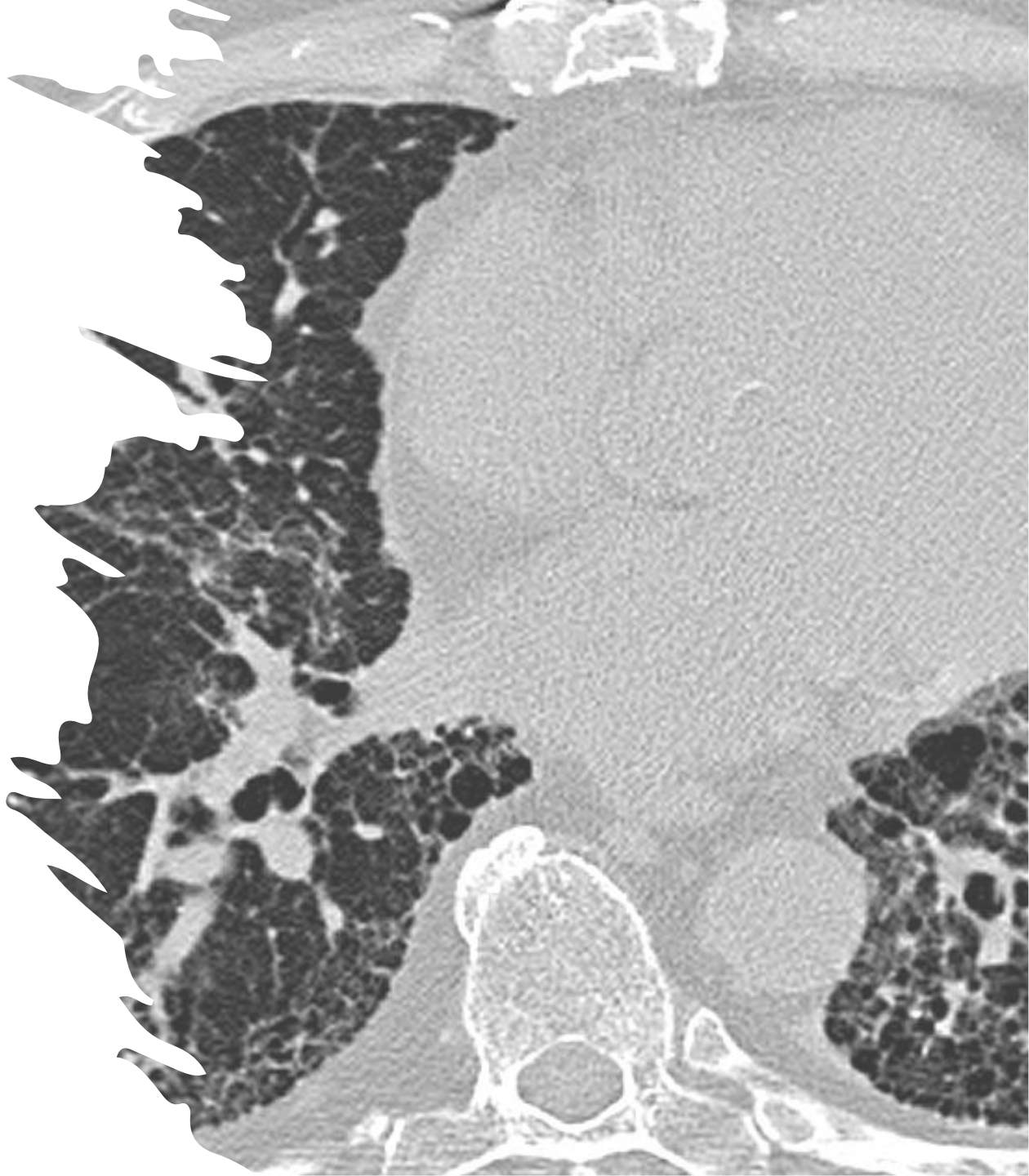


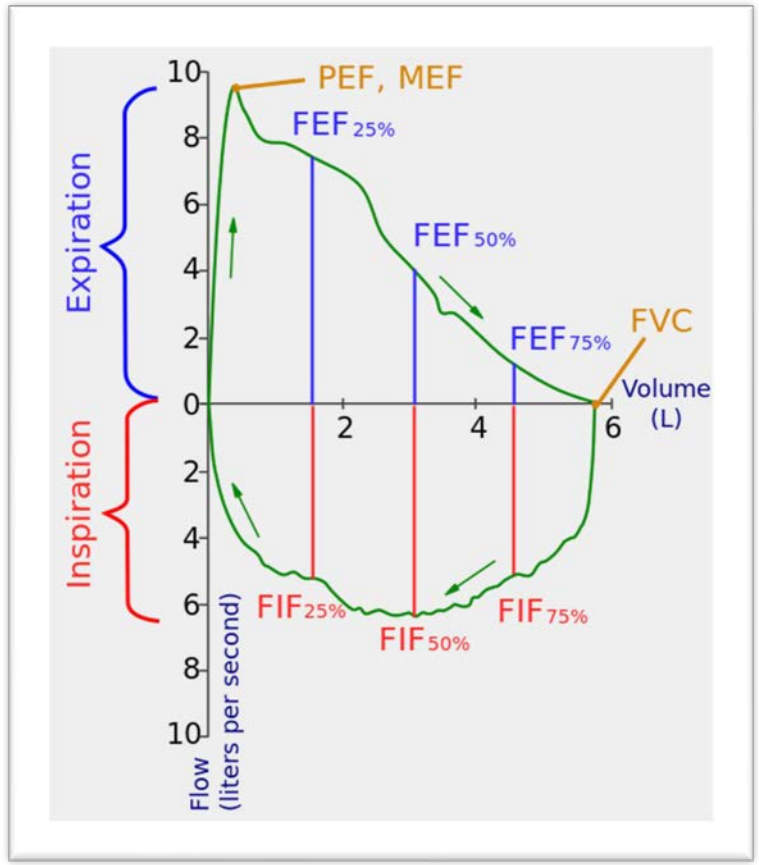

Thyroid Cartilage
Cricoid Cartilage
Trachea
Upper Lobe
Right Primary Bronchus
Middle Lobe
Lower Lobe
Right Lobe
Notch for the Heart
Left Primary Bronchus
Upper Lobe Bronchus
Lower Lobe Bronchus
Upper Lobe
Lower Lobe
Left Lobe

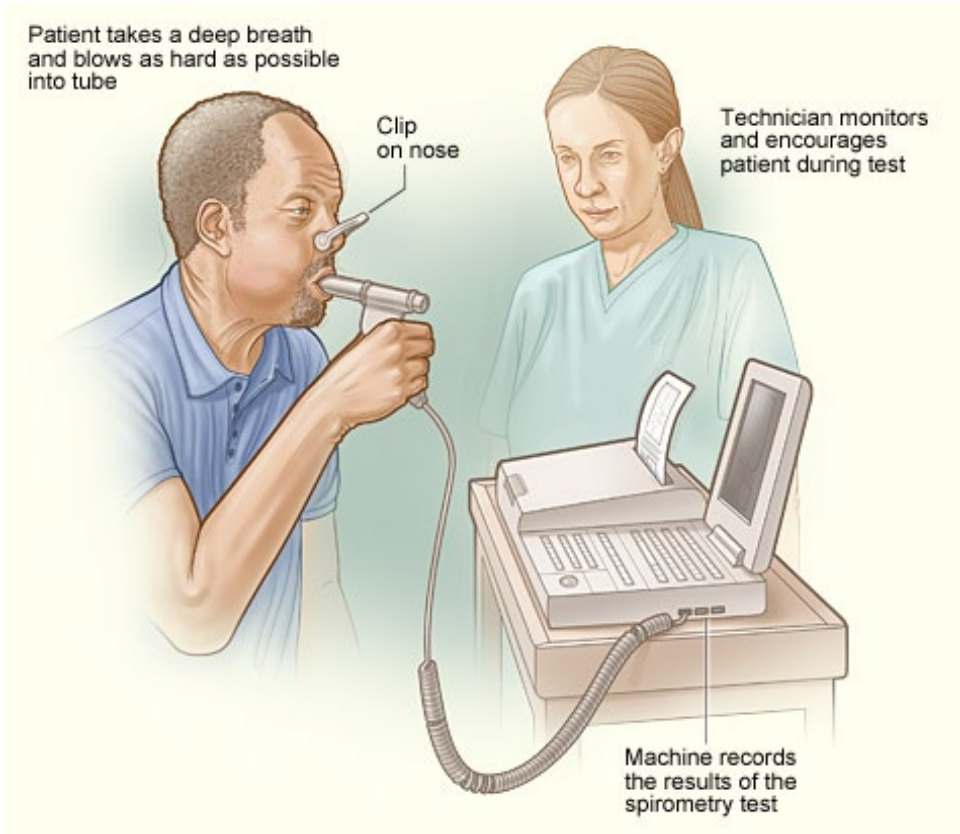


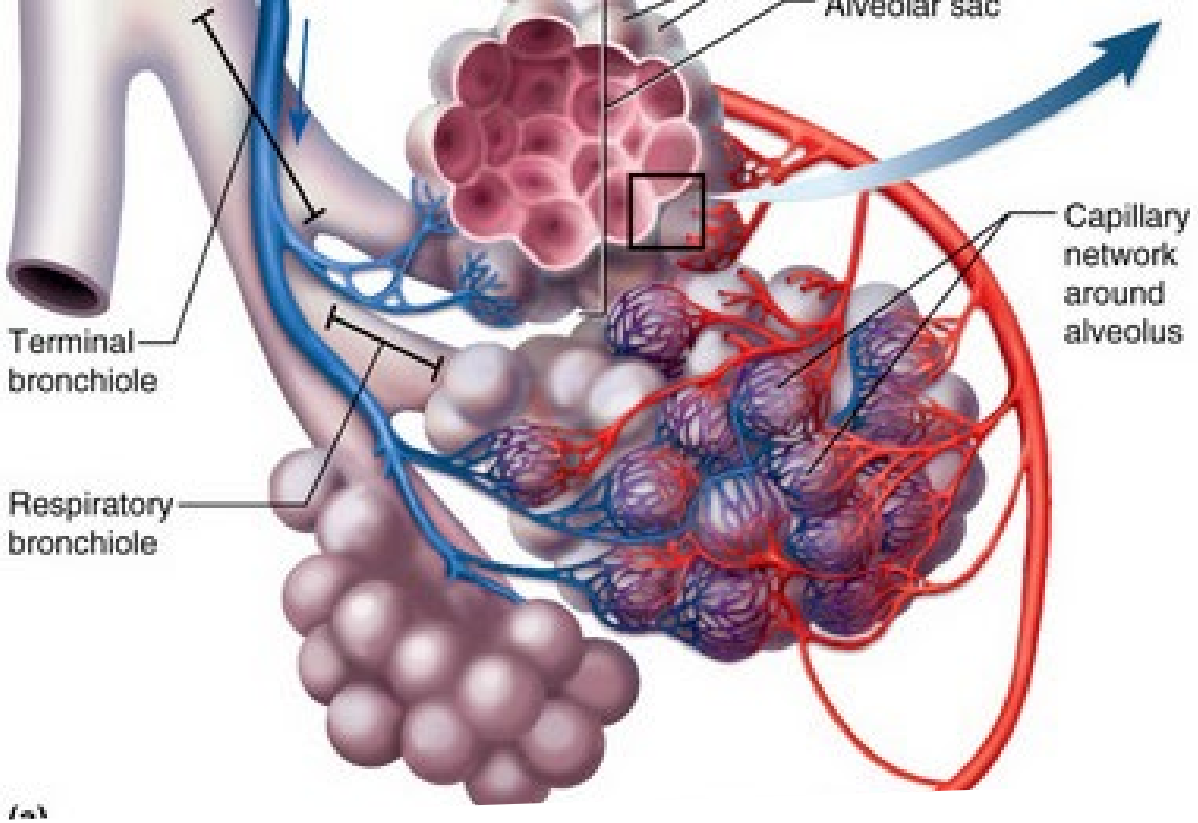
ICOERD classification

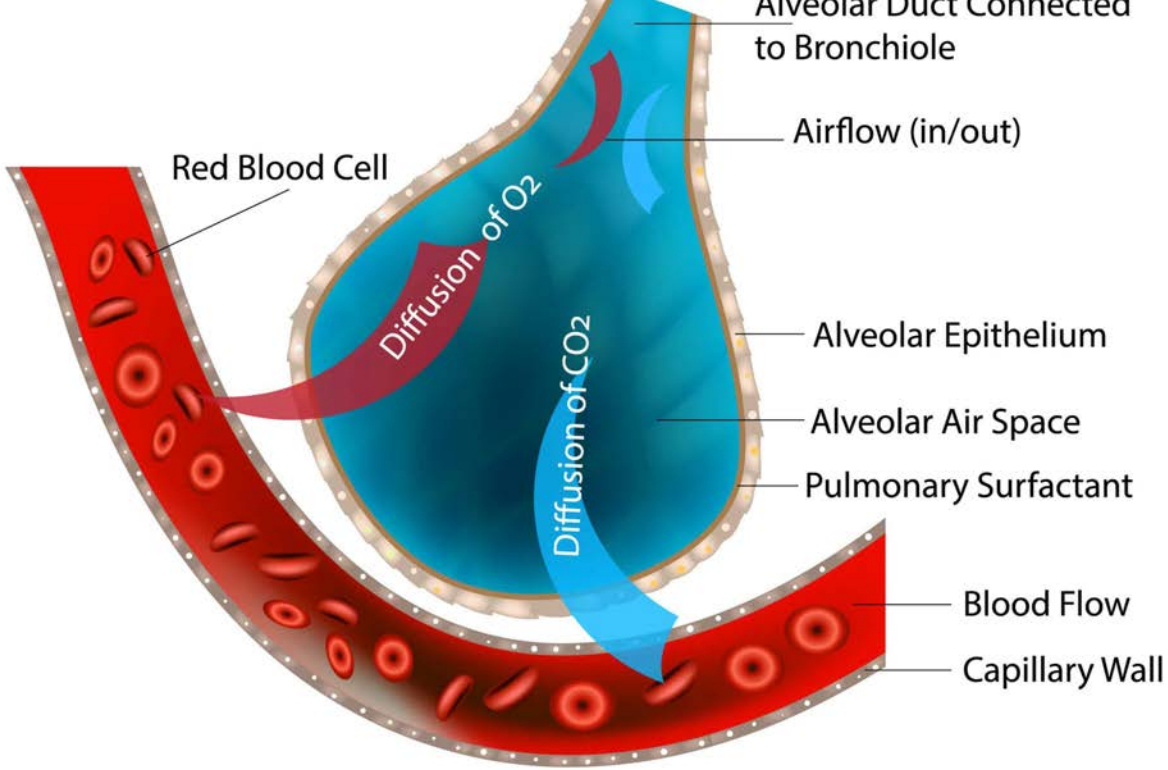
- 4-point categories
  - Grade rounds and irregular opacities in lungs
  - Also grades emphysema and ground glass (aka hazy) opacities
  - By lung zones
- Similar interobserver differences to ILO classification (PMID: 25810444)




PEF, MEF
FEF 25%
FEF 50%
FEF 75%
FVC
Expiration
Inspiration
Volume (L)
FIF 25%
FIF 50%
FIF 75%
Flow (liters per second)
10
8
6
4
2
0
2
4
6
8
10
2
4
6


Patient takes a deep breath and blows as hard as possible into tube
Clip on nose
Technician monitors and encourages patient during test
Machine records the results of the spirometry test





Diffusion Capacity

The diffusing capacity is a measurement of the rate of transfer of gas from the alveolus (air sac) to hemoglobin/blood.

New GINA Guidelines:

What You Need to Know

Reika Miyokawa, MD

Santa Clara Valley Medical Center

Disclosures

- I have the following relationships with ACCME defined ineligible companies: none
- I **WILL** discuss off-label use and/or investigational use of any drugs or devices.

WHAT IS ASTHMA?

- Chronic airway inflammation and hyper-responsiveness, leading to…
  1) Respiratory symptoms that vary over time and in intensity
  2) Variable expiratory airflow limitation

WHAT IS ASTHMA?

- Chronic airway inflammation and hyper-responsiveness, leading to…
  1) Respiratory symptoms that **vary** over time and in intensity
  2) **Variable** expiratory airflow limitation

  - Prevalence: >260 million worldwide
  - 500,000 asthma related deaths/year

ASTHMA IS A HETEROGENOUS DISEASE

Phenotypes:

- Allergic vs non-allergic
- Inflammatory biomarkers: Type 2 high vs Type 2 low (aka non-type 2)
- Time of onset: early vs late
- Asthma with persistent airflow limitation
- Asthma with obesity

WHO IS GINA?

- Established by WHO and National Heart, Lung, and Blood Institute
- **Aim:** "increase awareness about asthma and provide scientific evidence to improve worldwide asthma care"
- Global Strategy for Asthma Management and Prevention (aka **GINA report**) published annually

DIAGNOSIS & ASSESSMENT

DIAGNOSING ASTHMA

1) **Typical variable symptoms**

AND

2) **Confirmation of variable expiratory flow limitation**

Any of:

- (+) bronchodilator responsiveness
  - ↑ in FEV1 or FVC by ≥12% and ≥200 mL from baseline

  OR
  - ↑ in PEF by ≥20% (**new in 2024**)
- Excessive diurnal PEF variability over 2 weeks
- Improvement in lung function post-4 weeks of ICS use
- (+) positive bronchial challenge test
- Excessive lung function variation between visits

↓ **FEV1/FVC** no longer part of criteria (except for during bronchial challenge tests)

ASTHMA SEVERITY

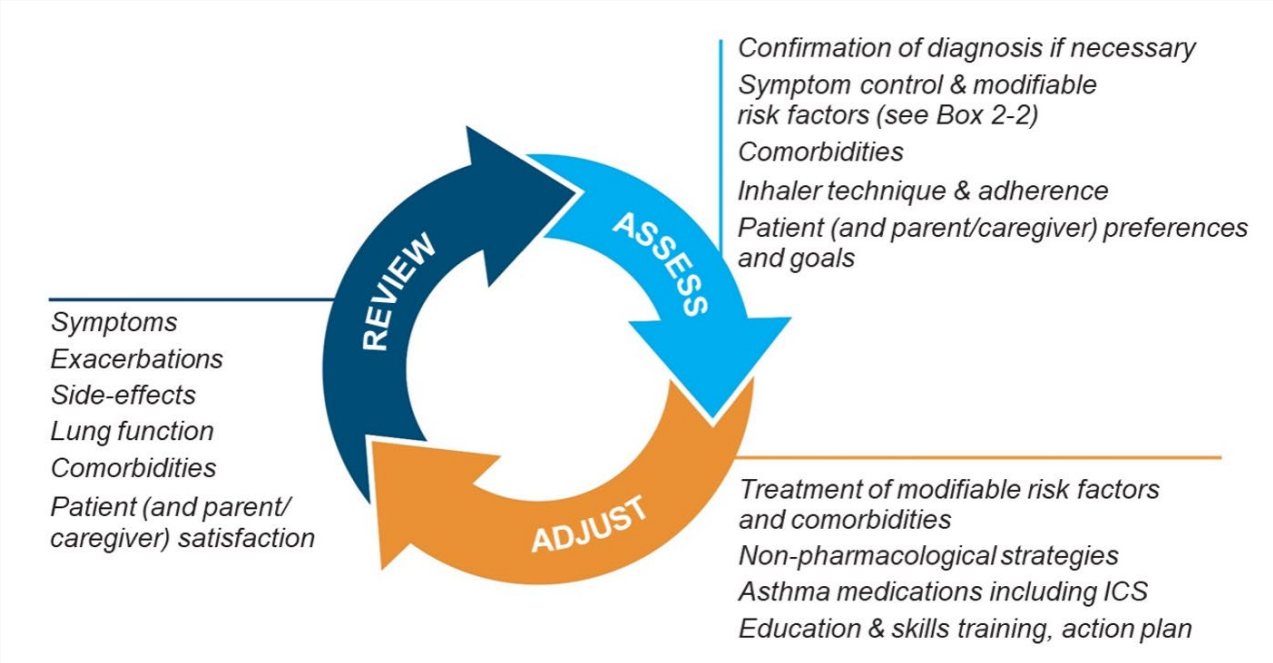
Assessed **retrospectively**!

- **Mild asthma**: well controlled with low intensity treatment (steps 1-2)
- **Moderate asthma**: well controlled with treatment steps 3-4
- **Severe asthma:** uncontrolled despite optimized treatment on high dose ICS-LABA, or requires high dose ICS-LABA to prevent uncontrolled symptoms

WHAT'S NEW IN STEP-UP THERAPY

TREATMENT GOALS

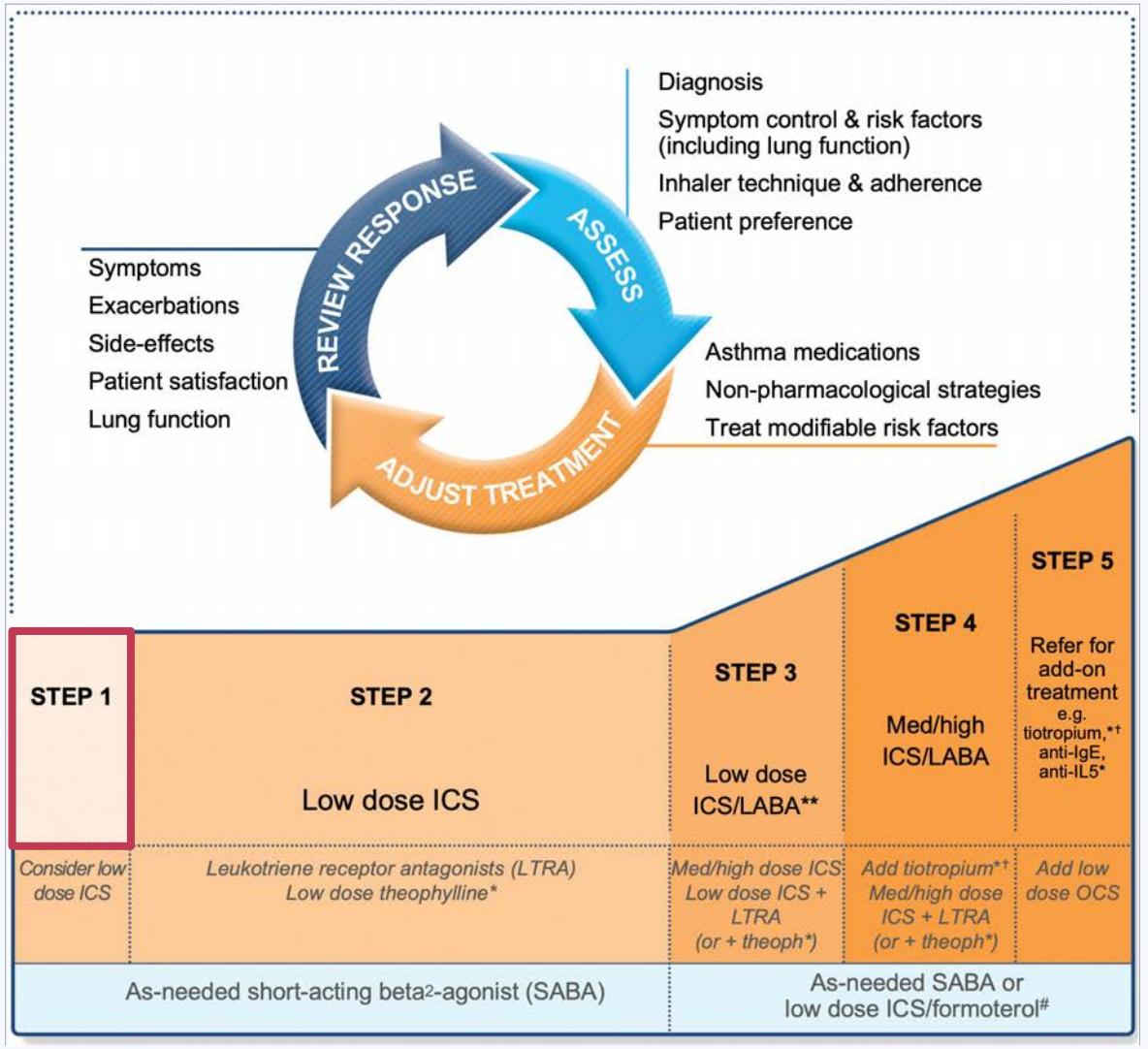
- **Long term symptom control**
  - Few or no symptoms
  - No sleep interruptions from asthma
  - No asthma related limitations on physical activity
- **↓ asthma related risks**
  - No exacerbations
  - ↑ lung function
  - ↓ systemic steroid use
  - ↓ side effects from asthma related medications



GINA Report 2024

TRADITIONAL TREATMENT STRATEGIES

STEP 1 THERAPY:
- Sx <2x/mon, no exacerbation RF
- **SABA prn**, no maintenance med



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

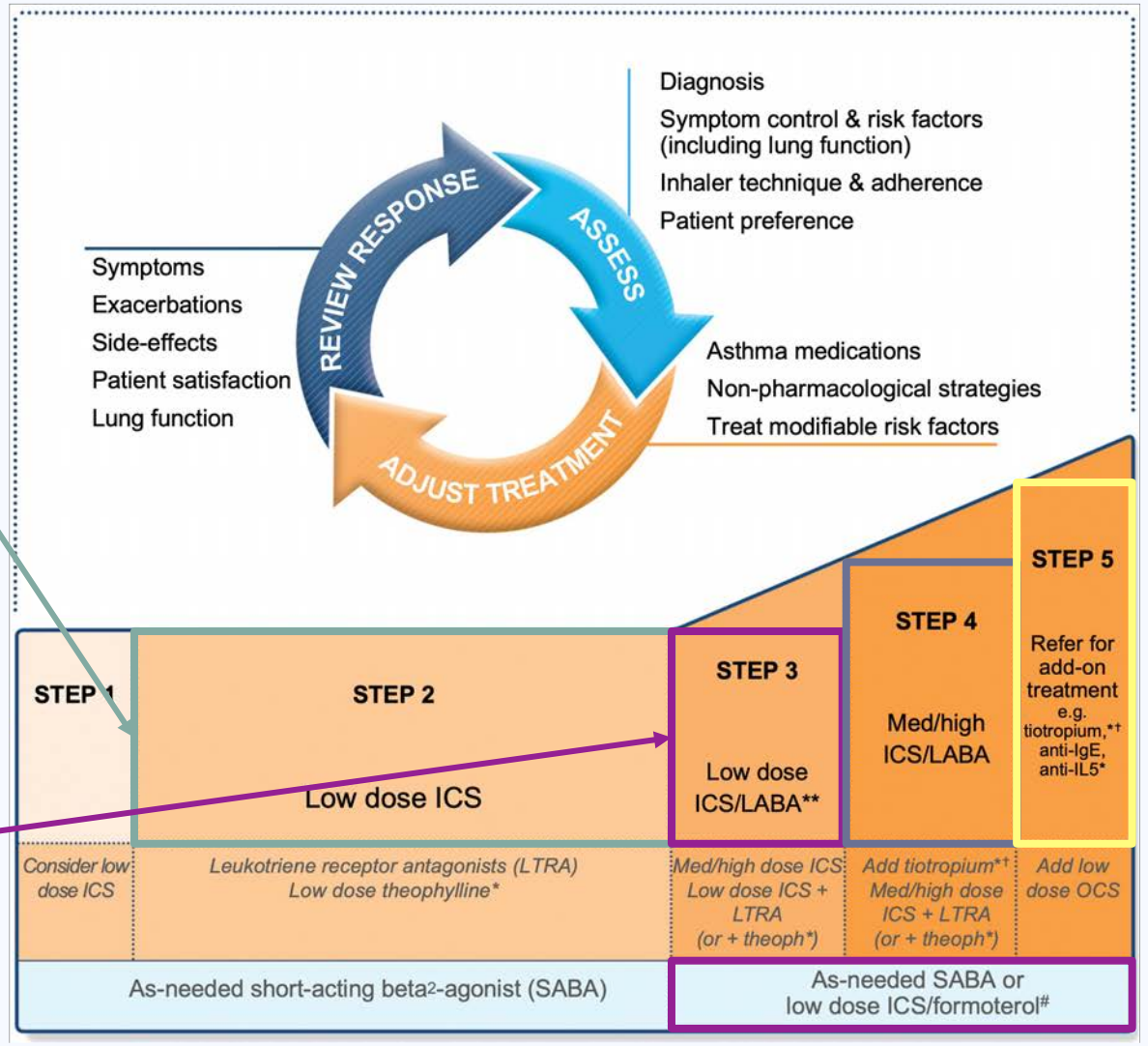
GINA Report 2018

TRADITIONAL TREATMENT STRATEGIES

STEP 1 THERAPY:
- Sx <2x/mon, no exacerbation RF
- **SABA prn**, no maintenance med

STEP 2 THERAPY:
- Sx >2x/mon or exacerbation RF
- **Low dose ICS maintenance** + **SABA prn**

STEP 3 THERAPY:
- ≥1 exacerbation/year
- **Low dose ICS/LABA maintenance** + **SABA prn** or **ICS/LABA prn**



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#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

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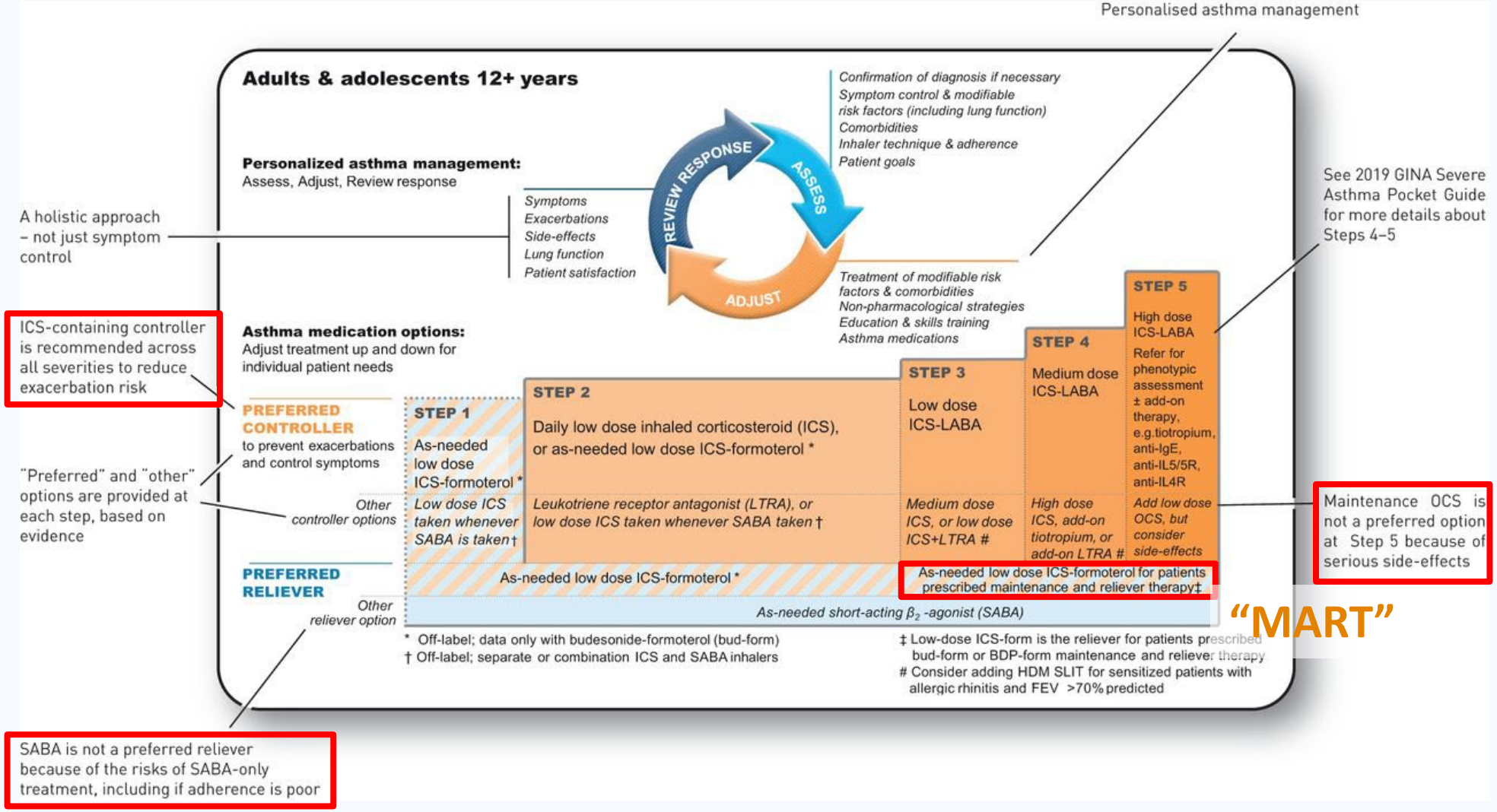
GINA Report 2018

UPDATES IN GINA 2019



WHY NOT SABA PRN?

MICSCONCEPTION: infrequent symptoms means low risk for morbidity/mortality

- "Mild asthma" consists of:
  - 30% of acute asthma exacerbations
  - 16% of near fatal asthma
  - 15% of fatal asthma

Regular use of SABA alone leads to:

- ↓ in bronchodilator response
- ↑ airway hyper-responsiveness and exercise induced bronchoconstriction
- ↑ allergic response
- ↑ eosinophilic inflammation

HOW ABOUT DAILY ICS?

Regular ICS use found to have:

- ↓ hospitalizations and asthma related deaths
- ↓ in severe exacerbations by 50%
- ↑ QOL

But…

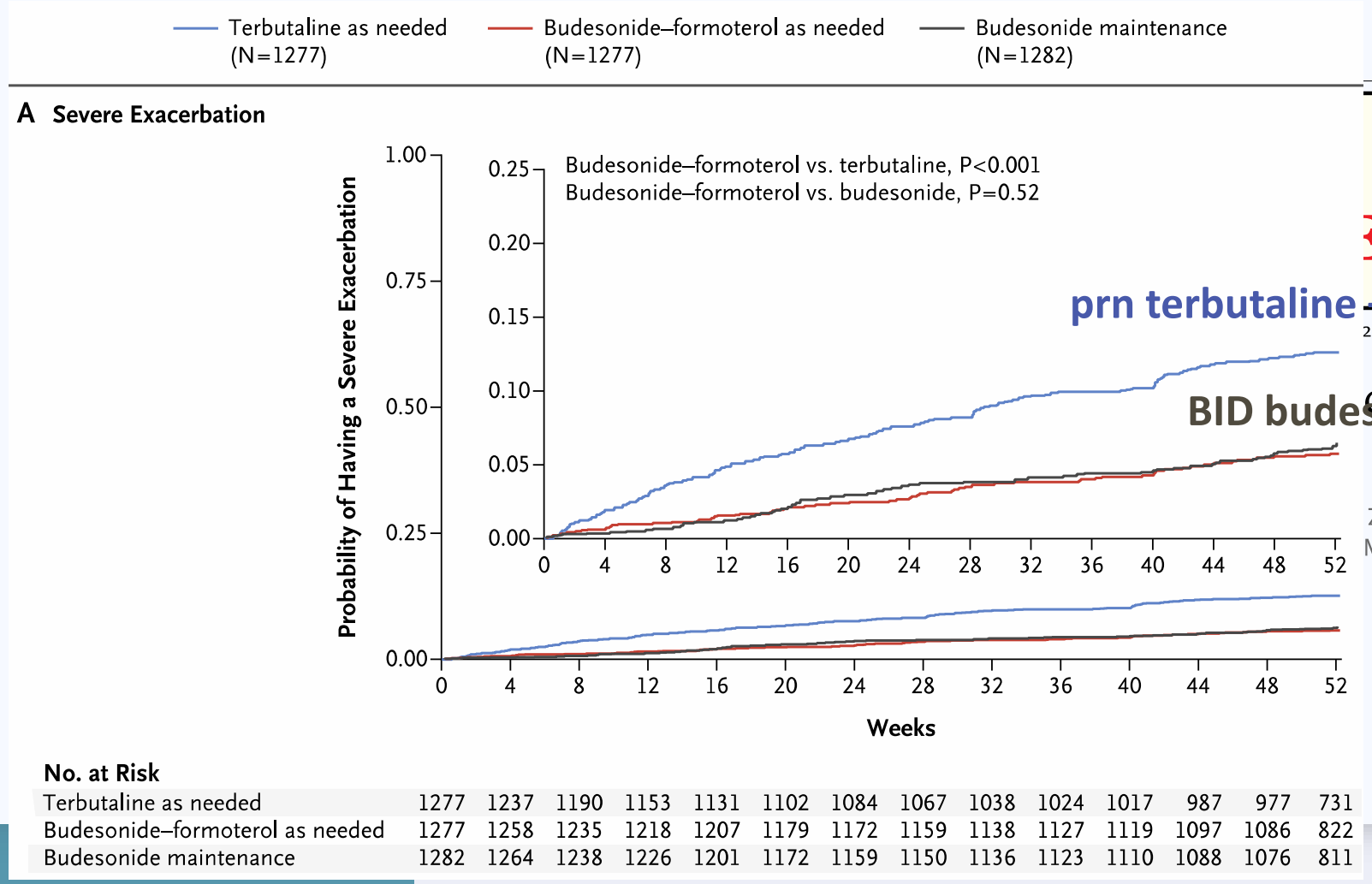
Only 25-35% of prescribed daily ICS were being used

Barriers to daily ICS use:

- Physician and patient concern for side effects
- Regular use of SABA prn without ICS in hospital settings
- Lack of perceived necessity
- Cost

ICS-FORMOTEROL PRN

SYGMA 1 TRIAL (2018):



prn terbutaline + BID placebo

BID budesonide 200 µg + prn terbutaline

prn budesonide 200 µg / formoterol 6 µg + BID placebo

Reprinted with permission from Massachussetts Medical Society

O'Byrne, P. et al. (2018). Inhaled combined Budesonide–formoterol as needed in mild asthma. New England Journal of Medicine, 378(20), 1865–1876.

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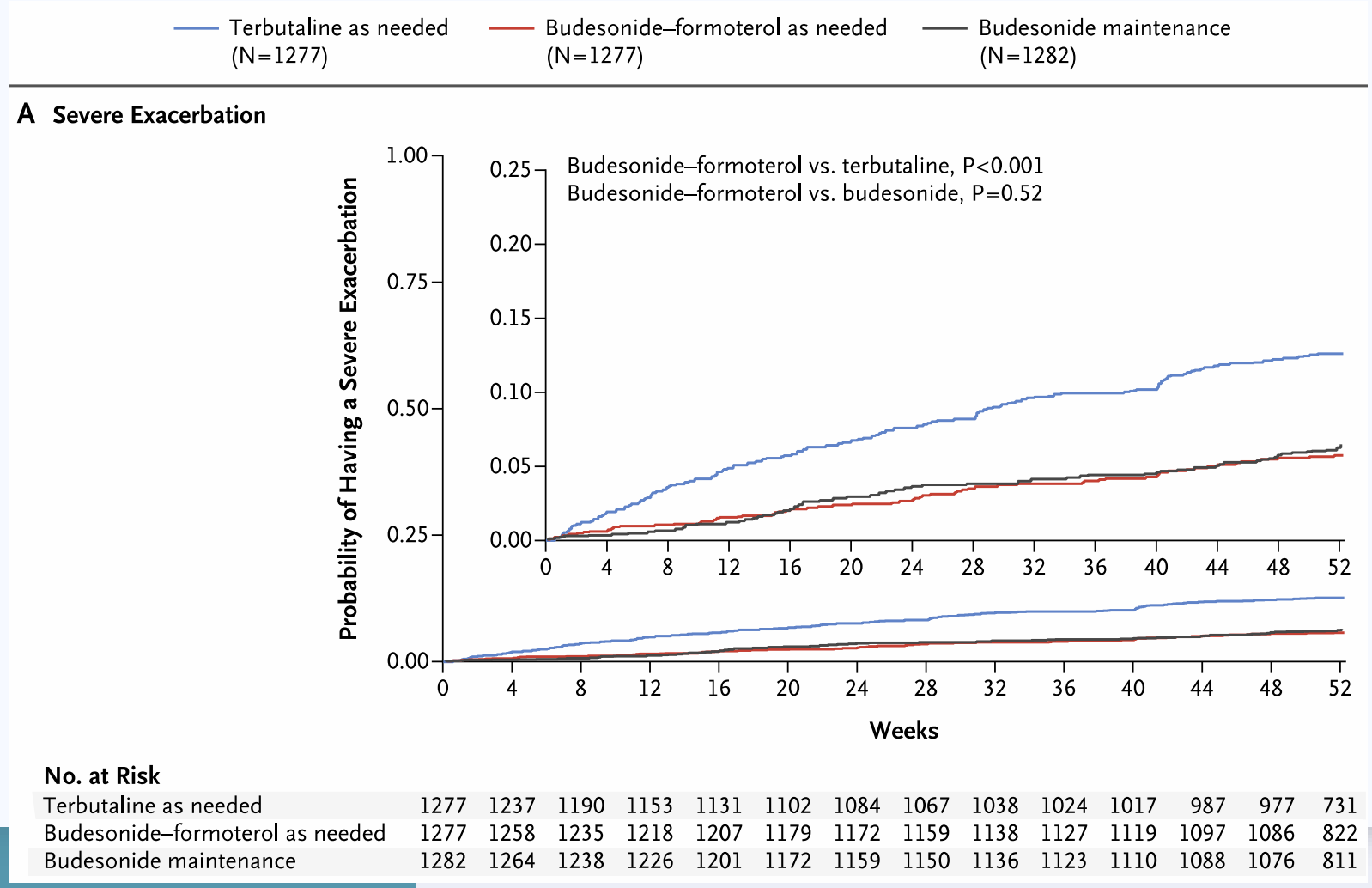
ICS-FORMOTEROL PRN

SYGMA 1 TRIAL (2018):



Rate of severe exacerbation:

- **prn SABA**: 0.2/year
- **prn ICS-formoterol**: 0.07/year
- **BID ICS**: 0.09/year

O'Byrne, P. et al. (2018). Inhaled combined Budesonide–formoterol as needed in mild asthma. New England Journal of Medicine, 378(20), 1865–1876.

ICS-FORMOTEROL PRN

SYGMA 1 TRIAL (2018):

In patients with mild asthma…

- prn ICS-LABA is superior to prn SABA alone in prevention of severe exacerbations
- prn ICS-LABA is not inferior to BID ICS in preventing mod-severe exacerbations (but is inferior in achieving well controlled asthma)
- prn ICS-LABA group used 1/5 of the median ICS dose compared to BID ICS group

GINA 2019: adolescents/adults with “mild asthma” should NOT be treated with prn SABA alone, and instead should receive ICS containing treatment as either reliever or maintenance therapy

MORE ON ICS-FORMOTEROL PRN

Low dose ICS-formoterol prn therapy leads to…

- ↓ severe exacerbations requiring systemic steroids compared to SABA prn
- ↓ ED visits and hospital admissions compared to SABA prn
- Non-inferior for severe exacerbations compared to maintenance ICS
- ↓ average ICS dose compared to maintenance low dose ICS

ORIGINAL ARTICLE

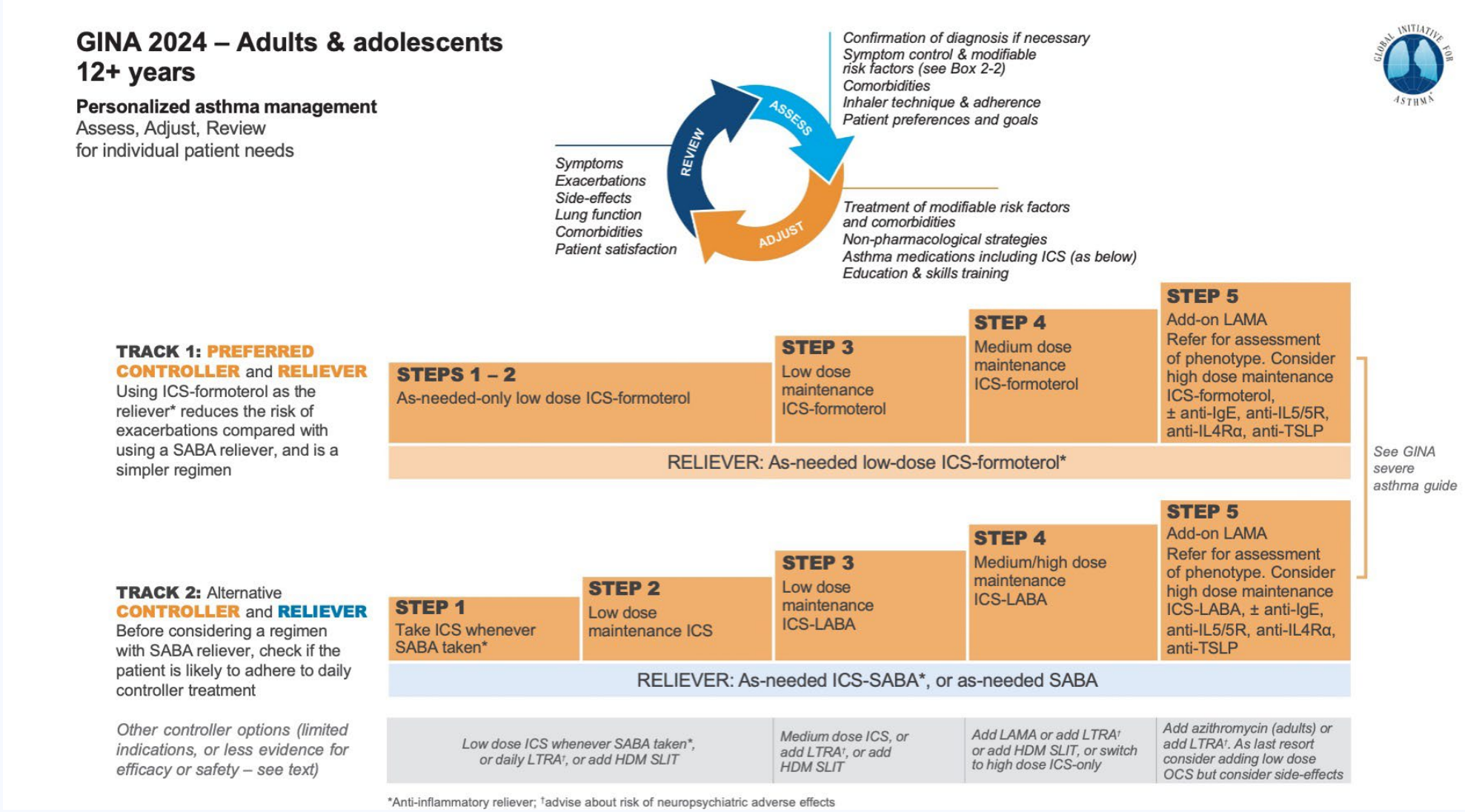
Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

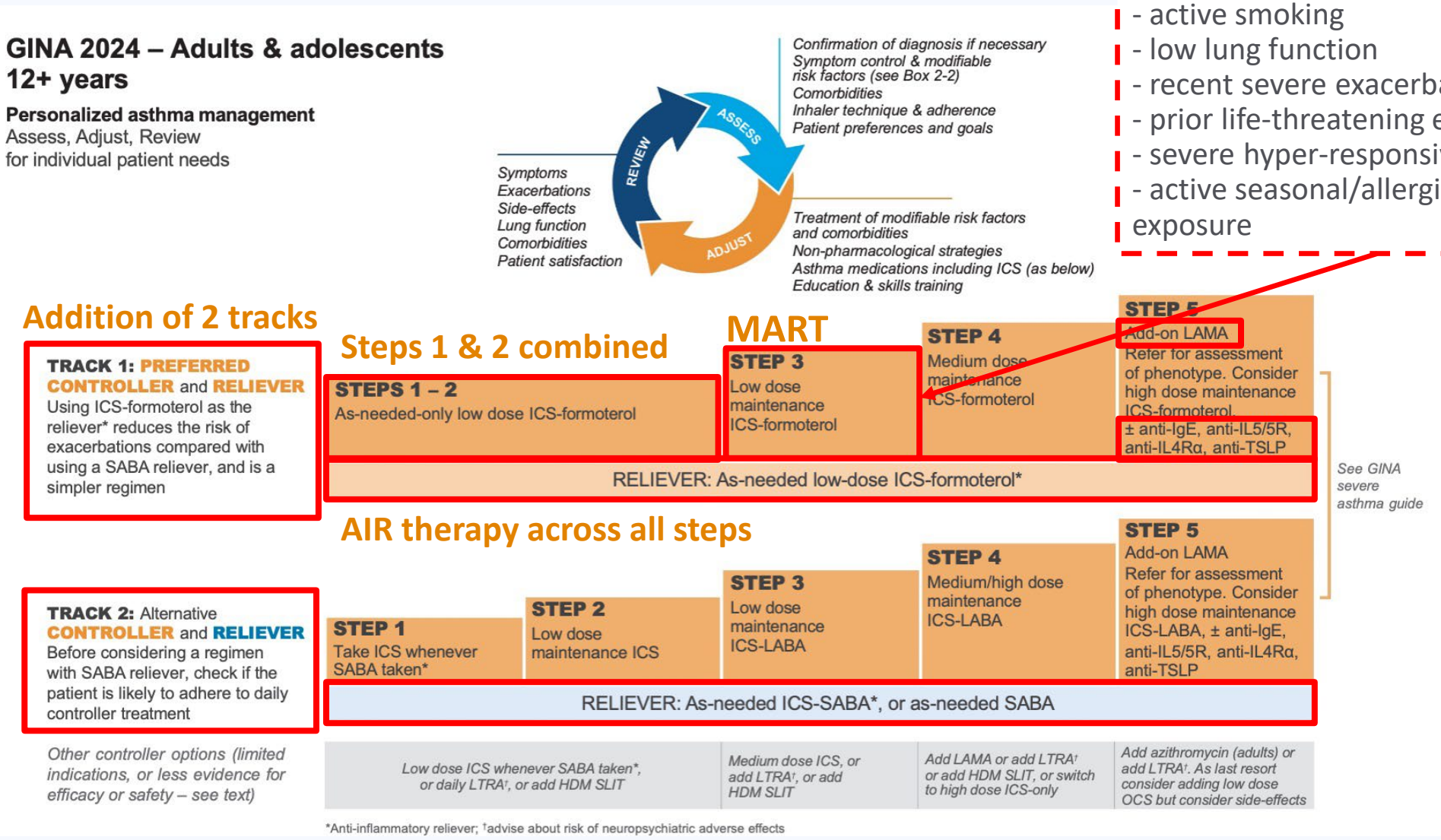
Jo Hardy, Christina Baggott*, James Fingleton, Helen K Reddel, Robert J Hancox, Matire Harwood, Andrew Corin, Jenny Sparks, Daniela Hall, Doñah Sabbagh, Saras Mane, Alexandra Vohlidkova, John Martindale, Mathew Williams, Philippa Shirtcliffe, Mark Holliday, Mark Weatherall, Richard Beasley, on behalf of the PRACTICAL study team†*

GINA 2024



GINA 2024

Straight to MART if:
- daily sx
- active smoking
- low lung function
- recent severe exacerbation
- prior life-threatening exacerbation
- severe hyper-responsiveness
- active seasonal/allergic trigger exposure



ICS-FORMOTEROL IN THE UNITED STATES

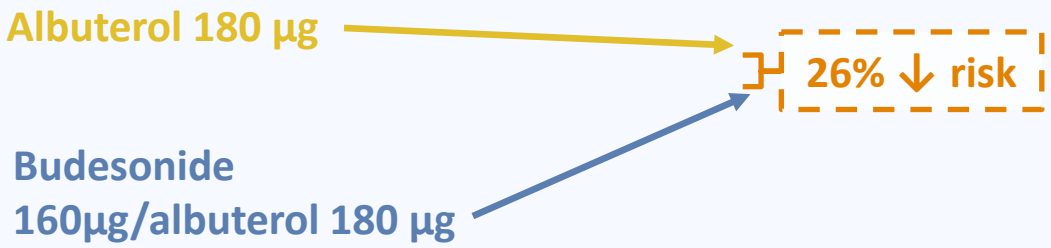
Available formularies:

- Budesonide-formoterol
- Mometasone-formoterol

Neither are FDA approved for use as AIR therapy

ICS-ALBUTEROL AS AIR THERAPY

- **BUDESONIDE-ALBUTEROL:** FDA approved 1/2023 as the first combination rescue inhaler for asthma
- **MANDALA (6/2022):**
  - Budesonide (160µg)-albuterol prn reduced severe asthma exacerbation risk in mod-severe asthma compared to albuterol prn



***Budesonide-albuterol CANNOT be used as MART**

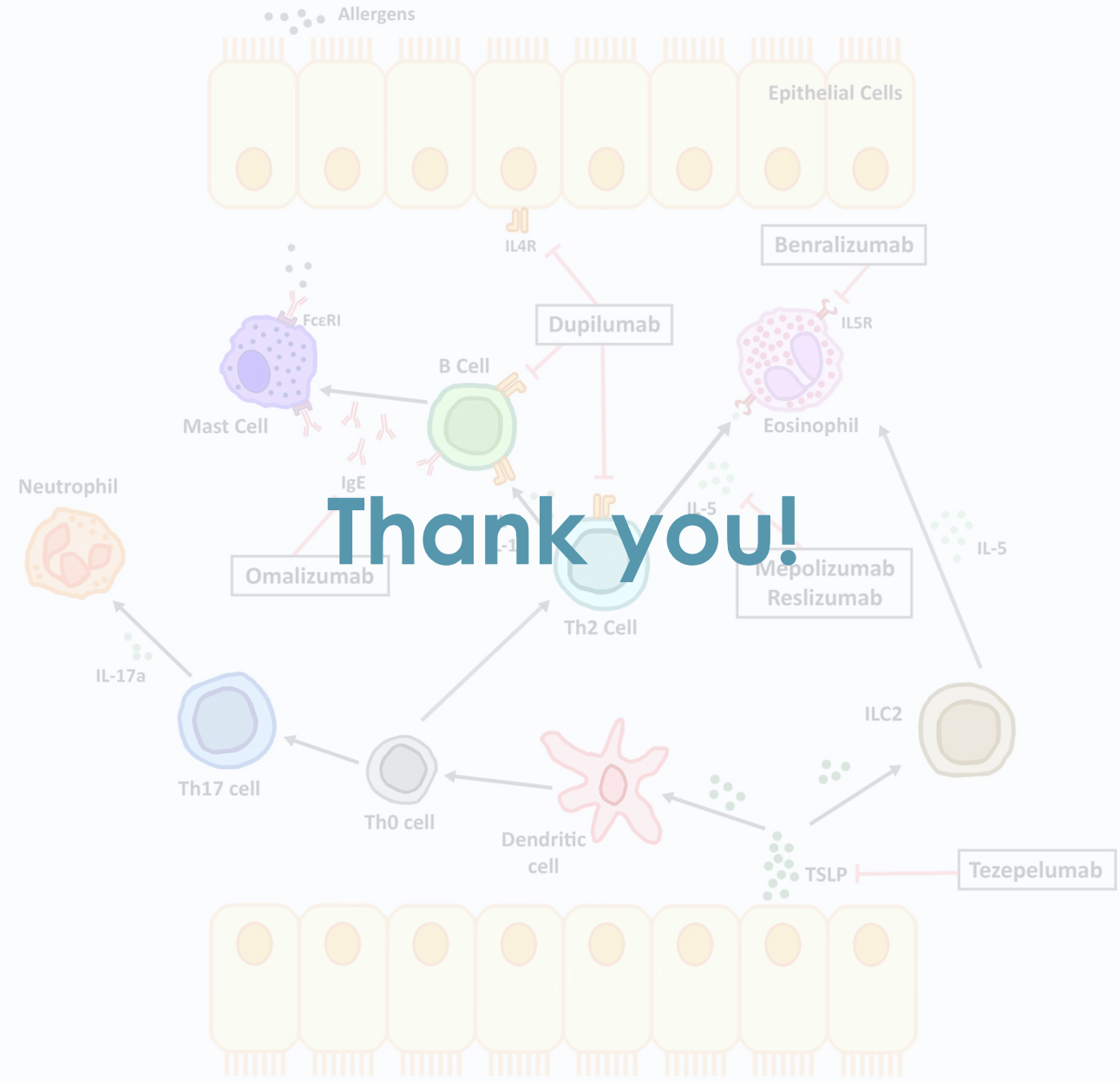
Papi, A. et al (2022). Albuterol–Budesonide fixed-dose combination rescue inhaler for asthma. New England Journal of Medicine, 386(22), 2071–2083.

GINA 2024: OTHER UPDATES

OTHER UPDATES FROM GINA 2024

Add-on therapies

- **Immunotherapy (SCIT, SLIT):** consider in allergic asthma
  - ↓ ICS and systemic steroid use, ↑ QOL, ↑ lung function
  - Should be initiated after good asthma control is achieved
- **Pulmonary rehabilitation:** consider in those with low exercise capacity or persistent airflow limitation
  - ↑ QOL, ↑ exercise capacity



Thank you!

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The role of Th2 inflammation in airways diseases

Praveen Akuthota, MD

University of California San Diego

Disclosures

- I have the following relationships with ACCME defined ineligible companies:

AstraZeneca, Connect Biopharma, Sanofi, Regeneron, GlaxoSmithKline, Amgen, Vida Ventures, Enveda

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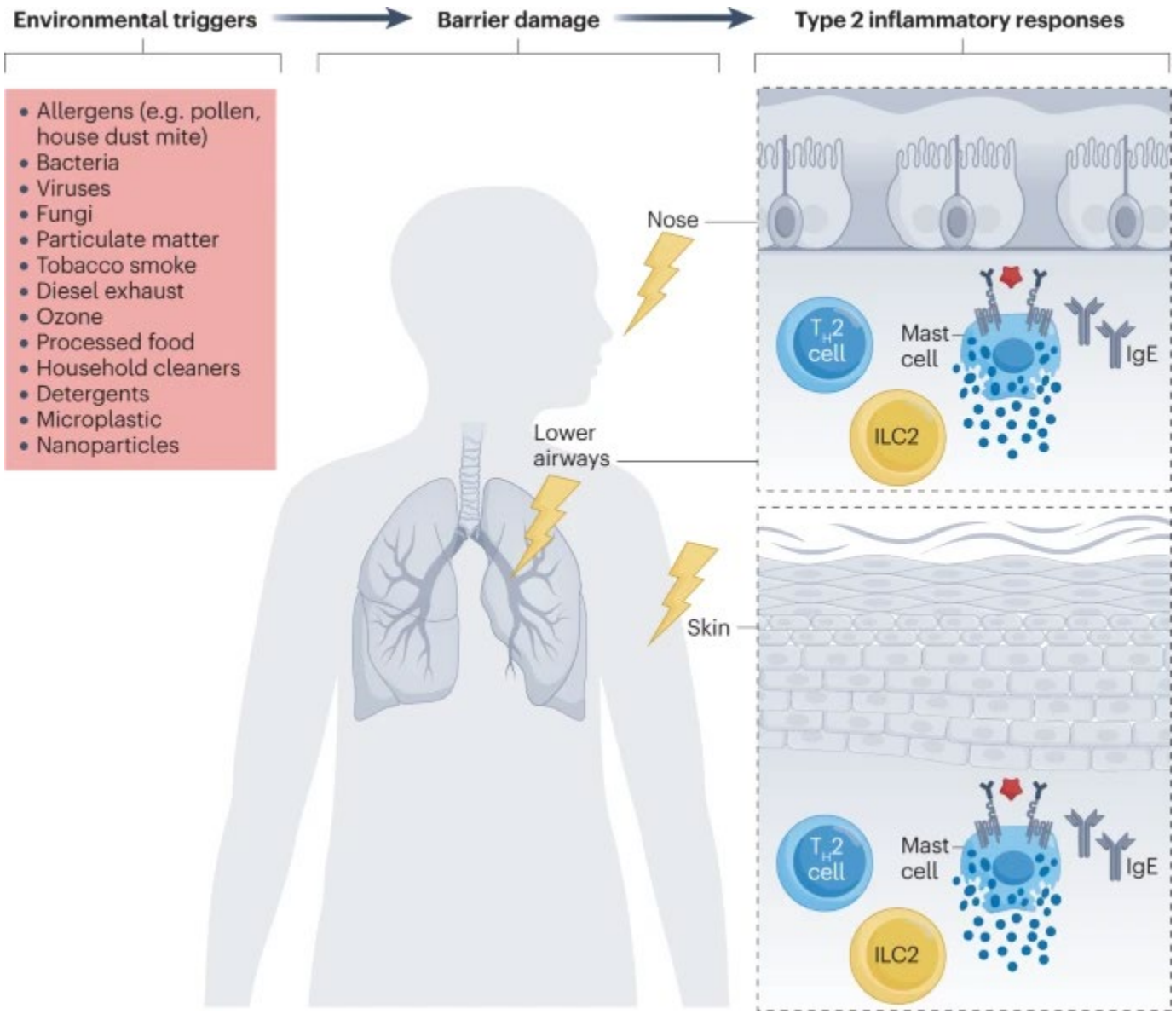
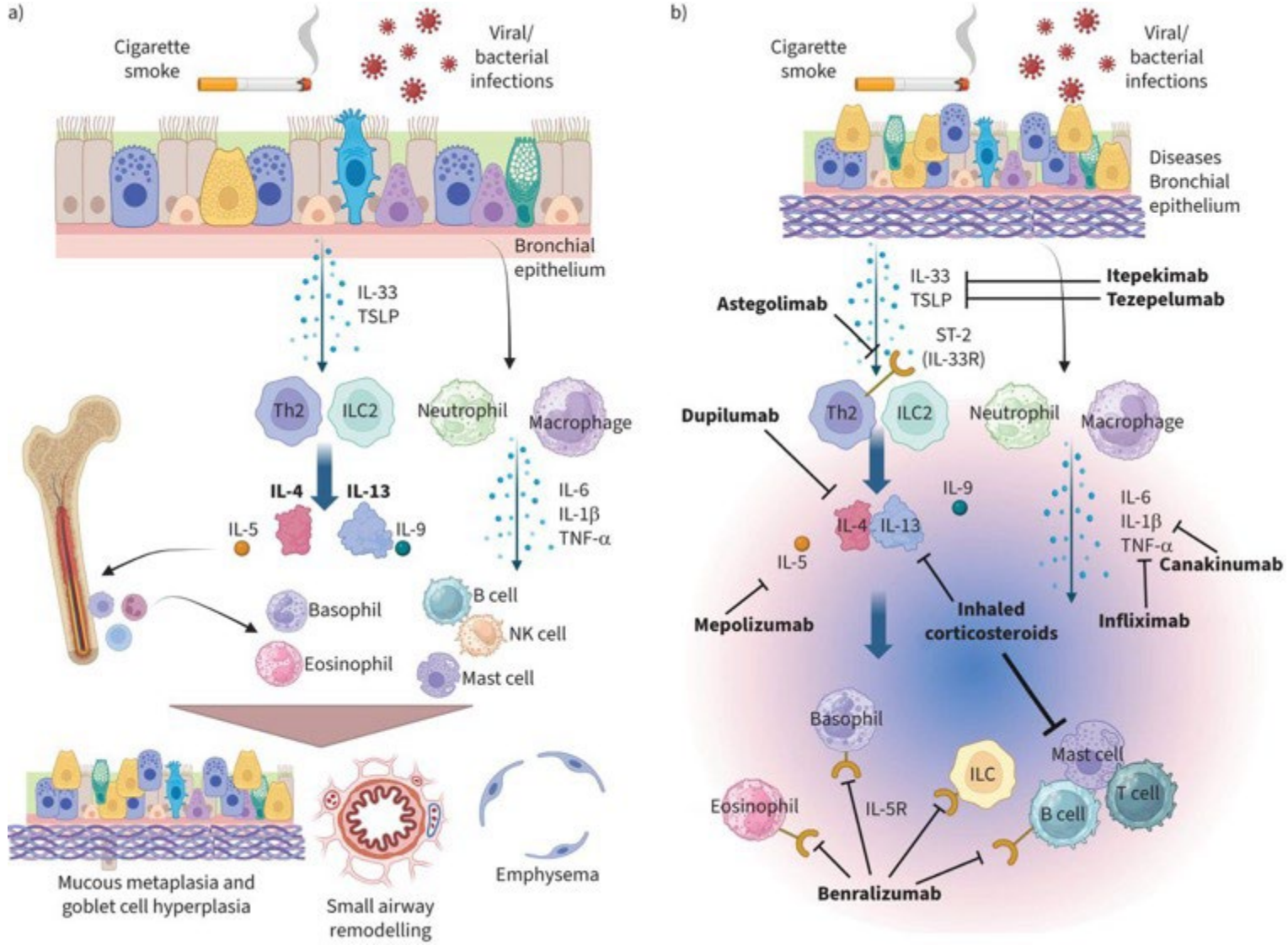


Type 2 Inflammation in Airways Disease: More Than Just Asthma?

Kolhir P et al, Nature Reviews Drug Discovery 2023

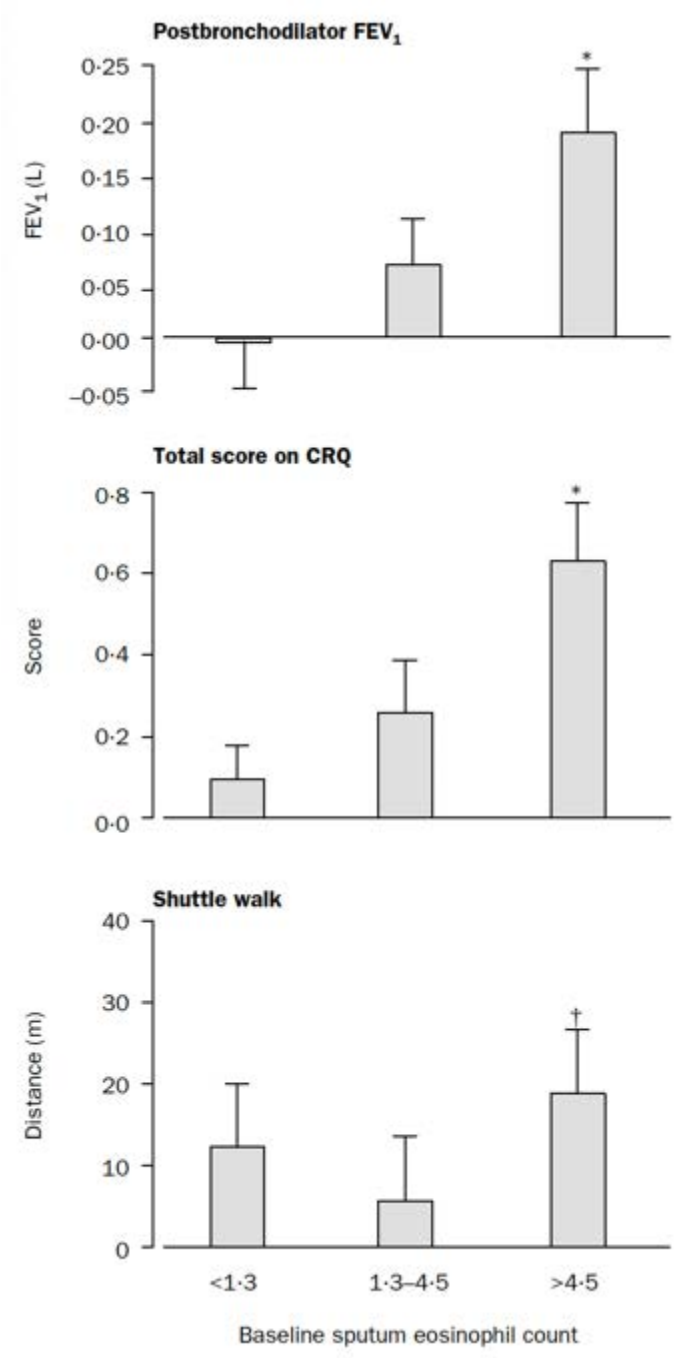
Polverino et al, ERJ, 2024

Type 2 Inflammation in COPD



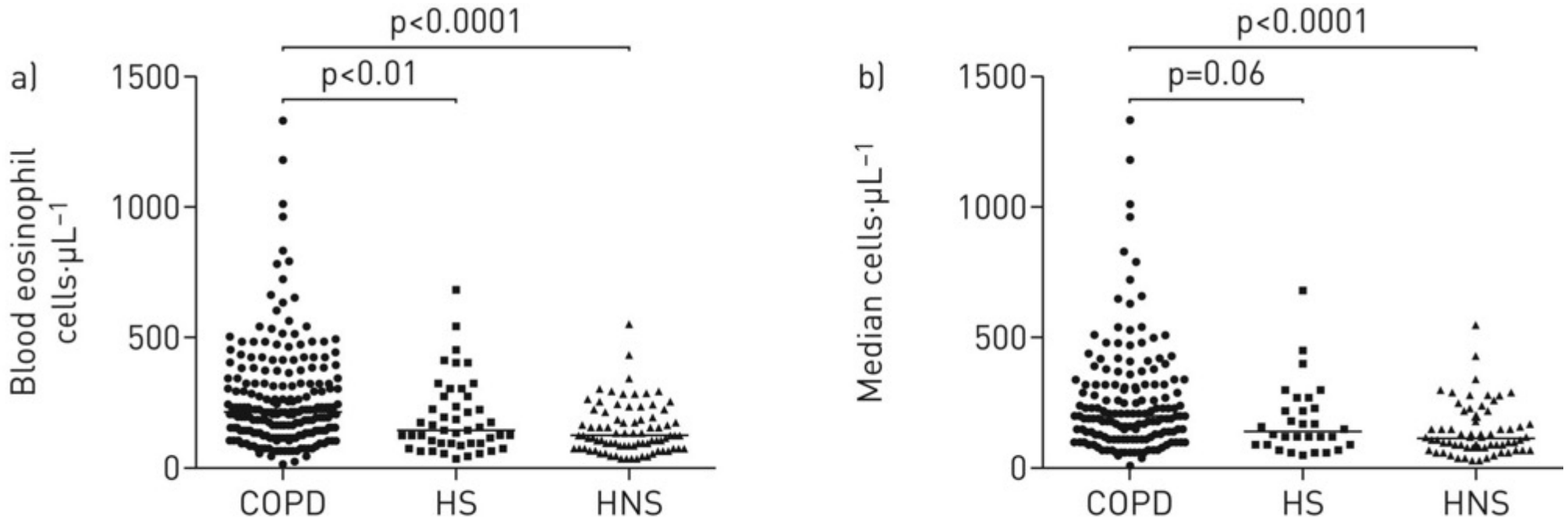
Sputum Eosinophilia as a Predictor of Treatment Response to OCS in COPD

Brightling C et al, Lancet, 2000



Blood Eosinophil Counts in COPD

Kolum et al, ERJ 2019

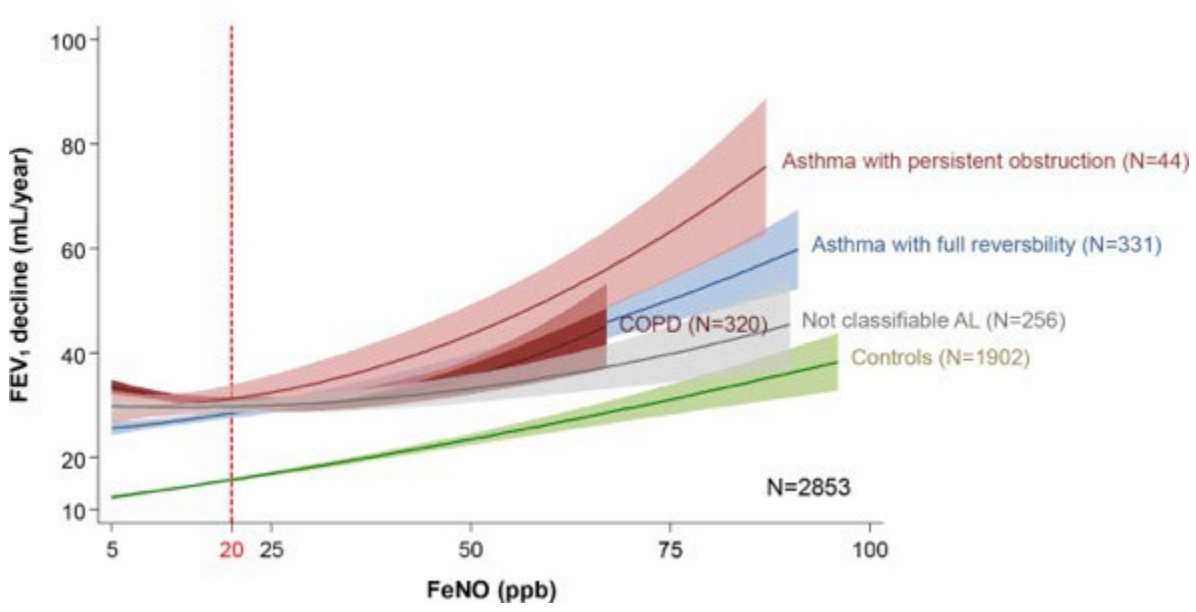


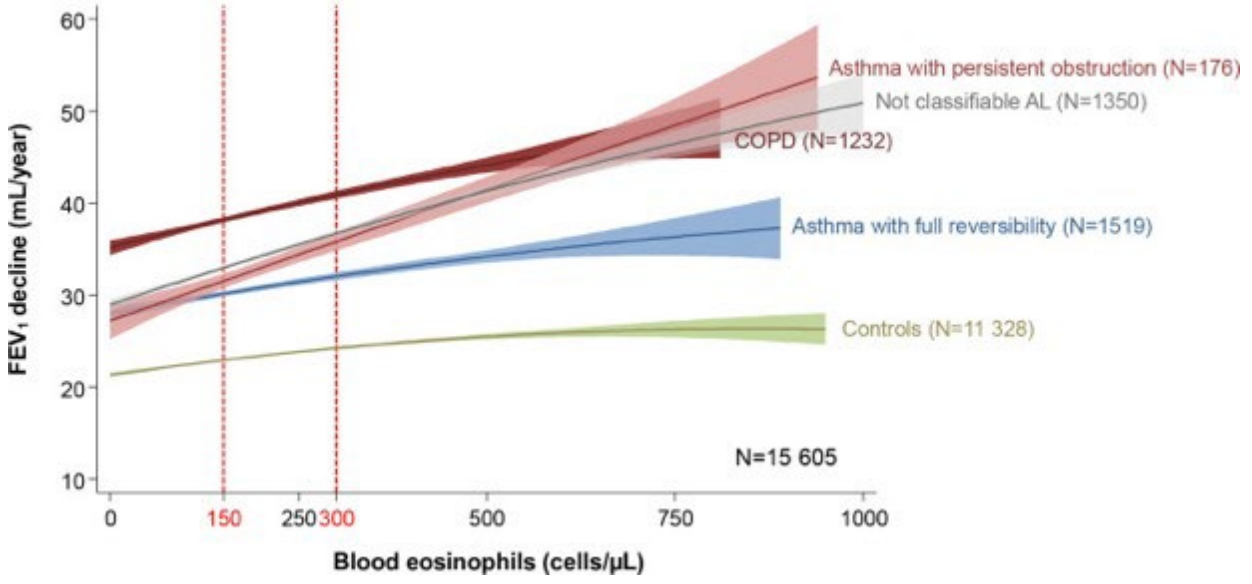
Median cells·μL⁻¹	210	140	120

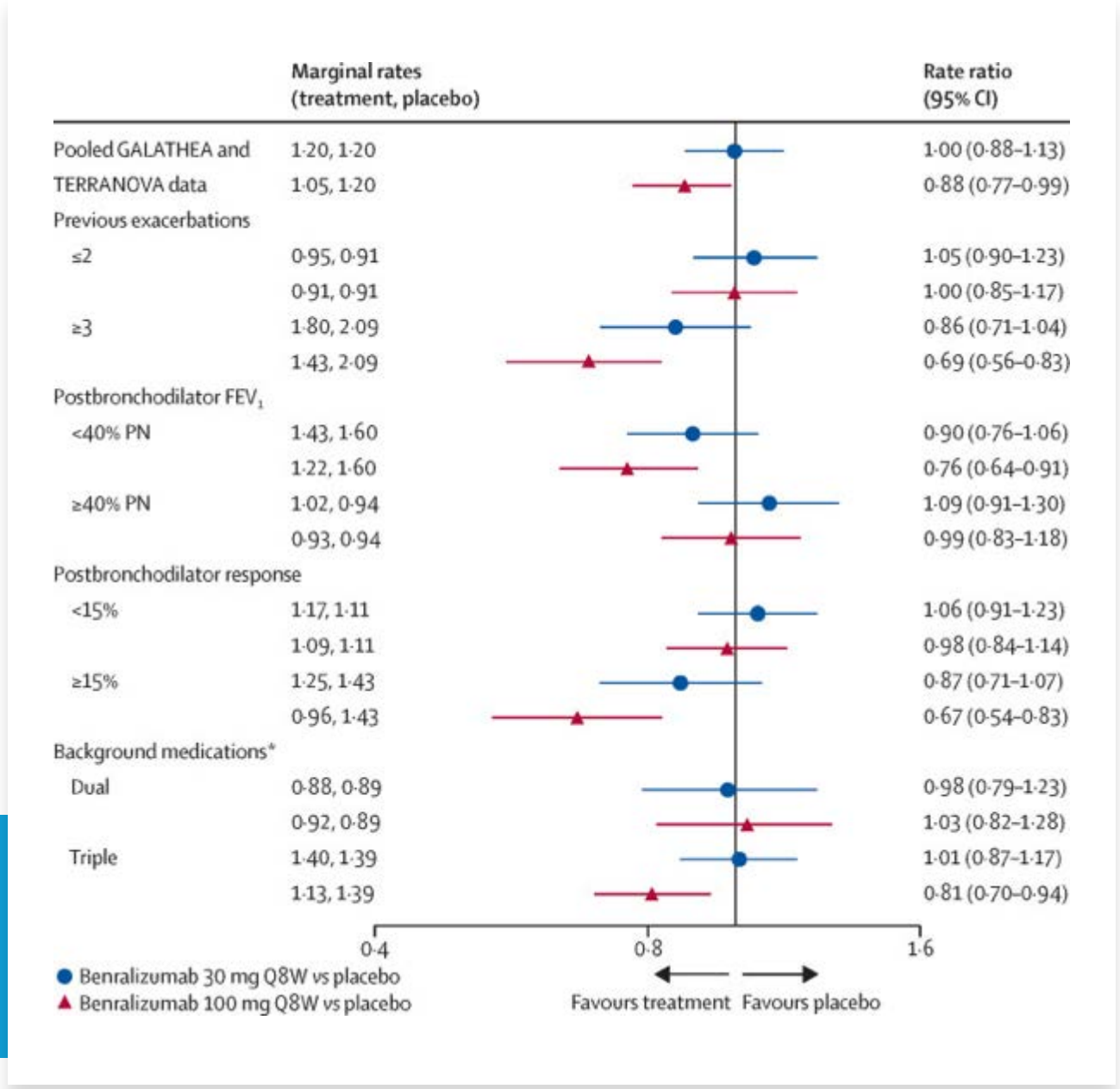
Median cells·μL⁻¹	200	140	115

Type 2 Inflammation and Lung Function Decline in Obstructive Airways Disease

Colak Y et al, Thorax 20124





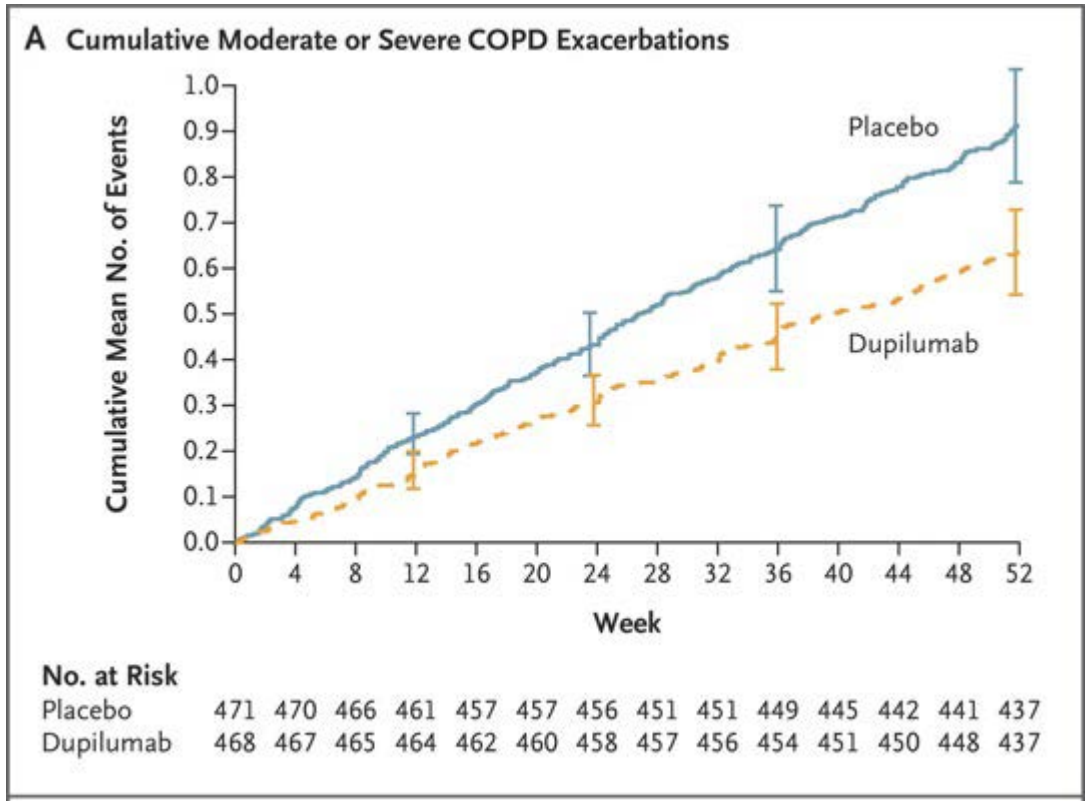


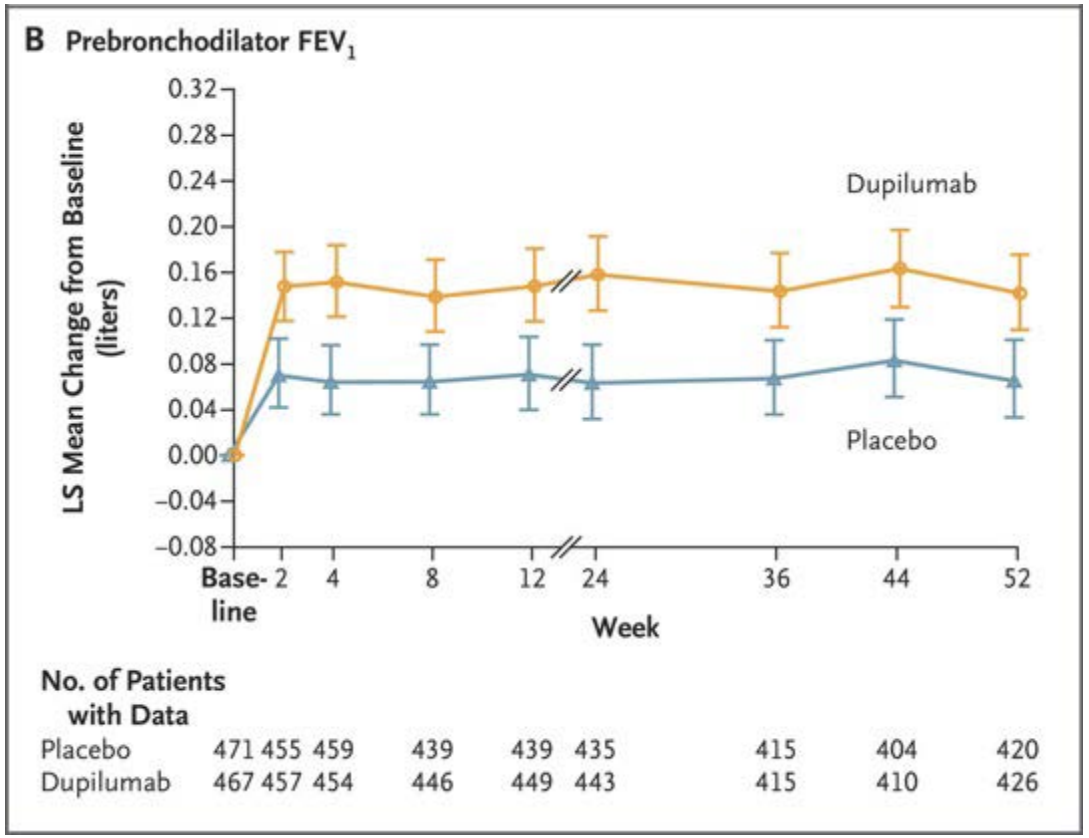
Eosinophil-Targeting Biologics in COPD

Criner GJ et al, Lancet Resp Med 2020

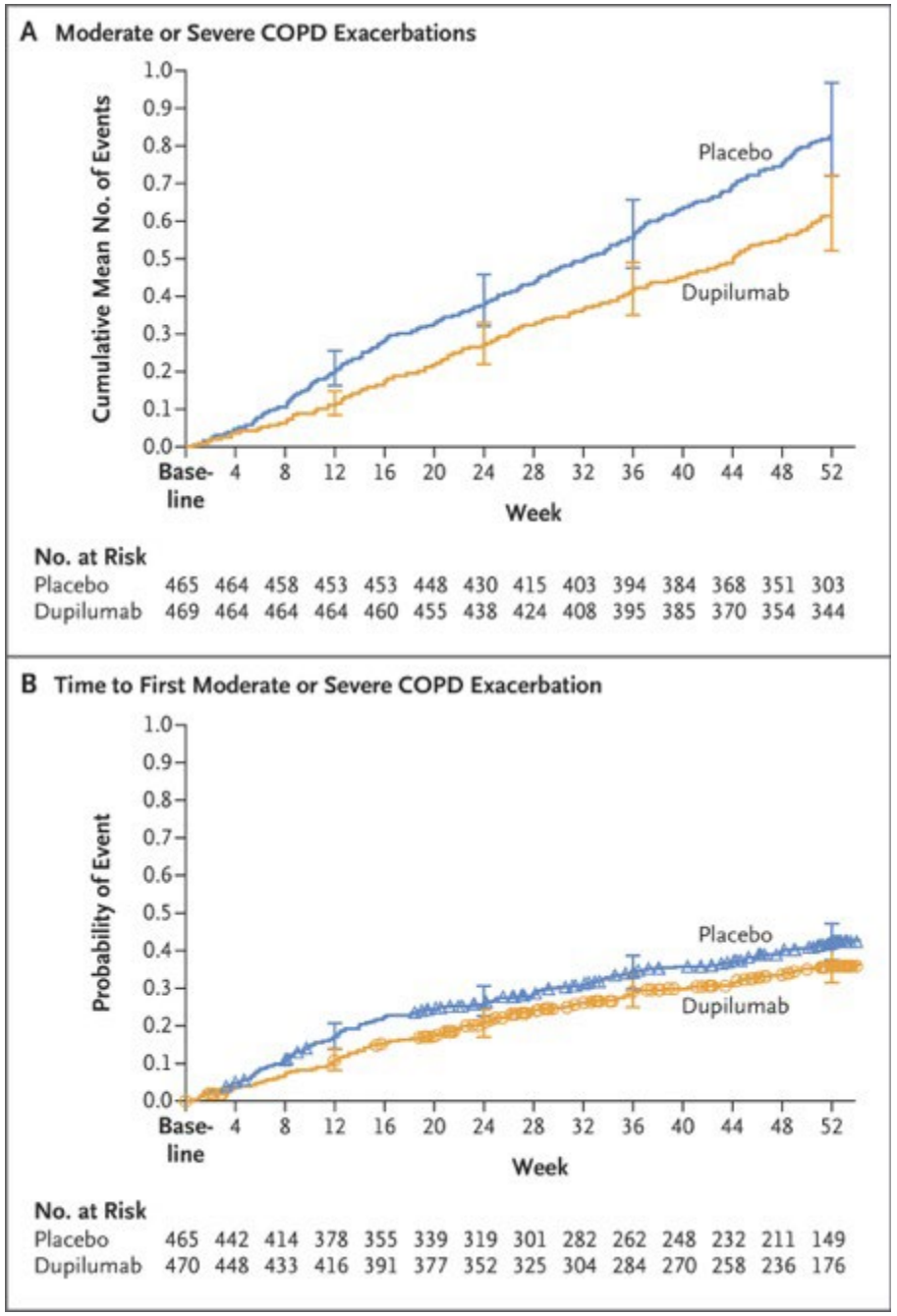
Dupilumab for COPD with Elevated Eosinophil Counts: BOREAS

Bhatt et al, NEJM 2023





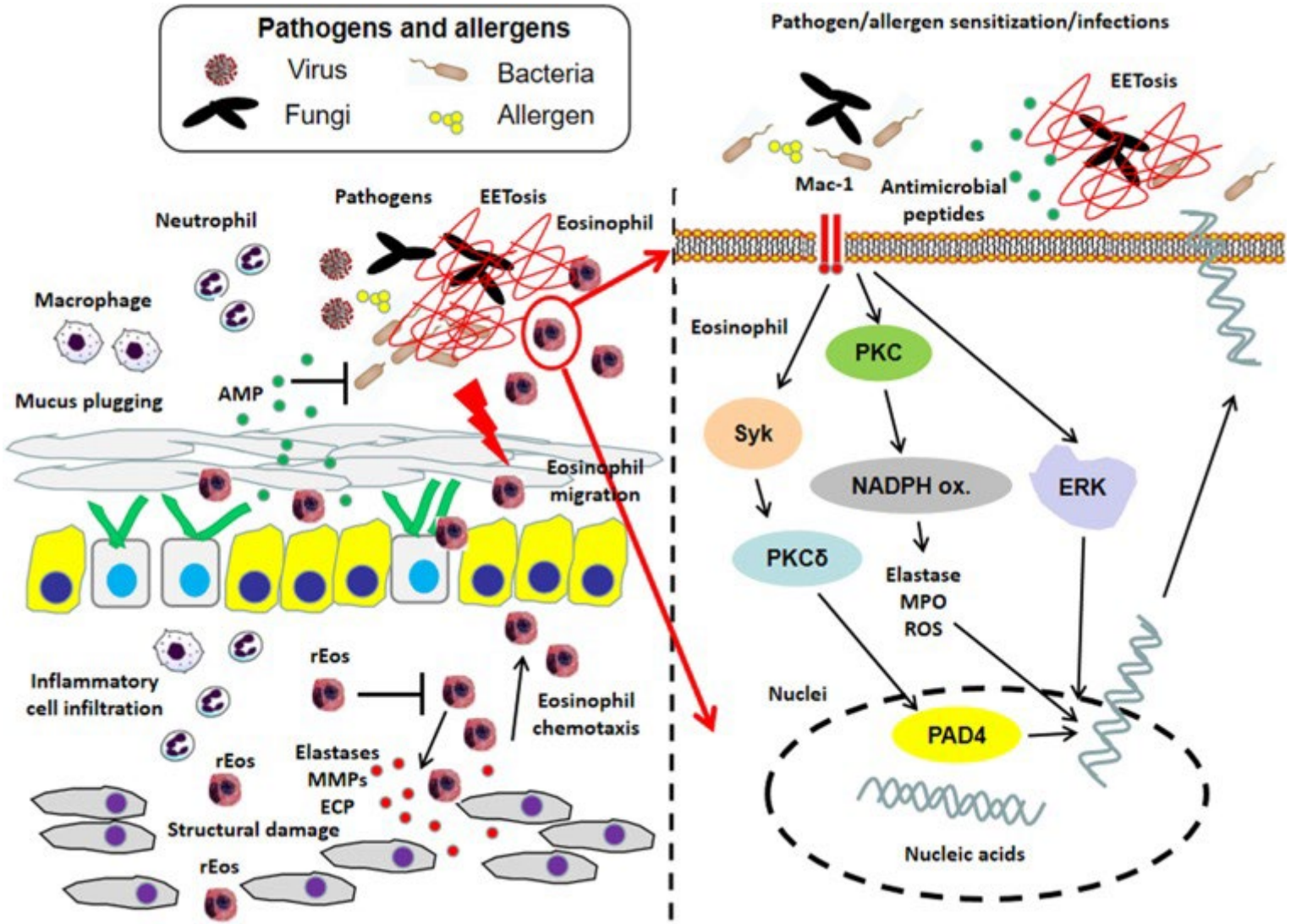
Dupilumab for COPD with Elevated Eosinophil Counts: NOTUS



Bhatt et al, NEJM 2024

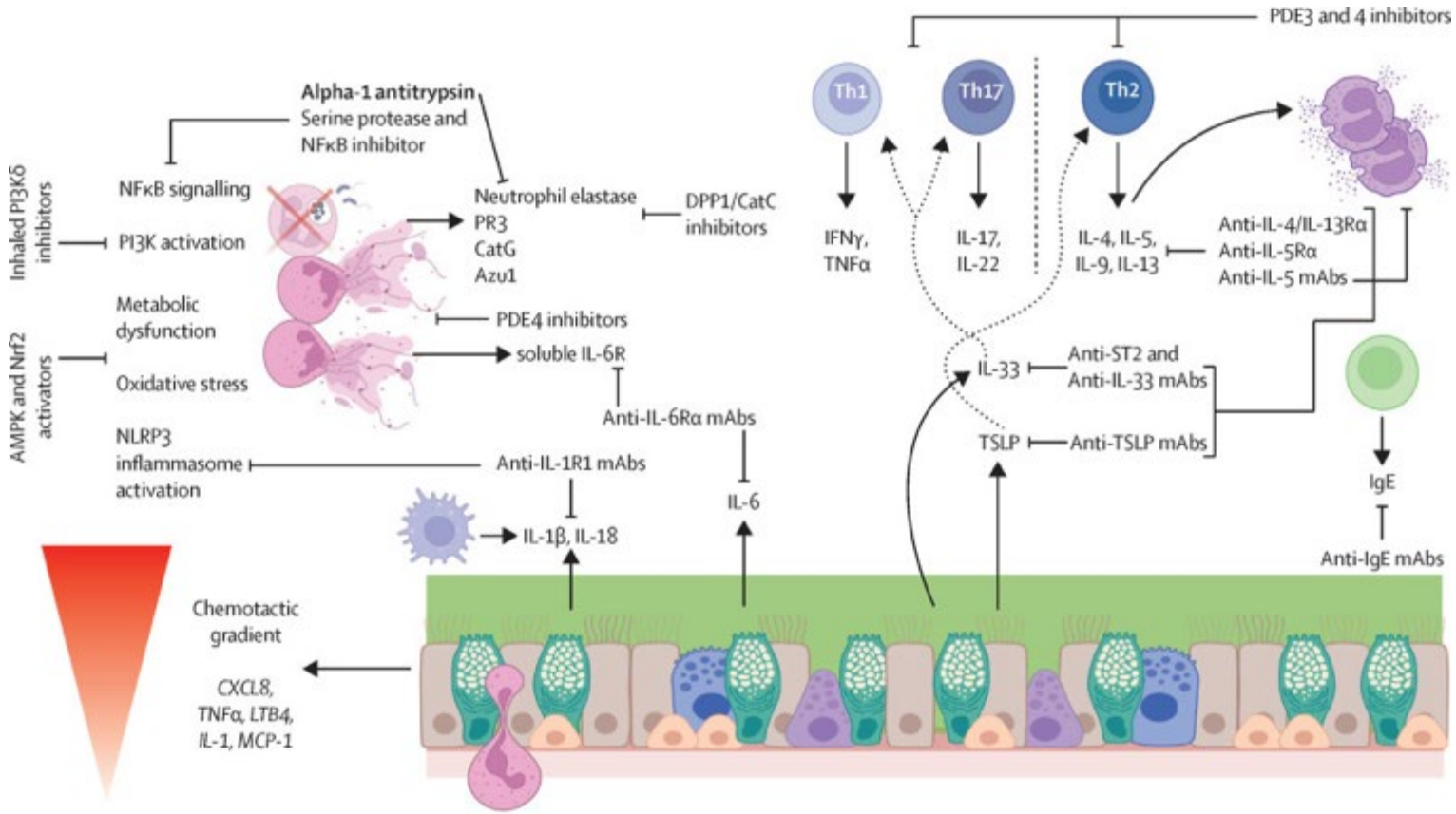
Guan et al. JACI:IP, 2023

The Potential Pathogenic Role of Eosinophils in Non-CF Bronchiectasis



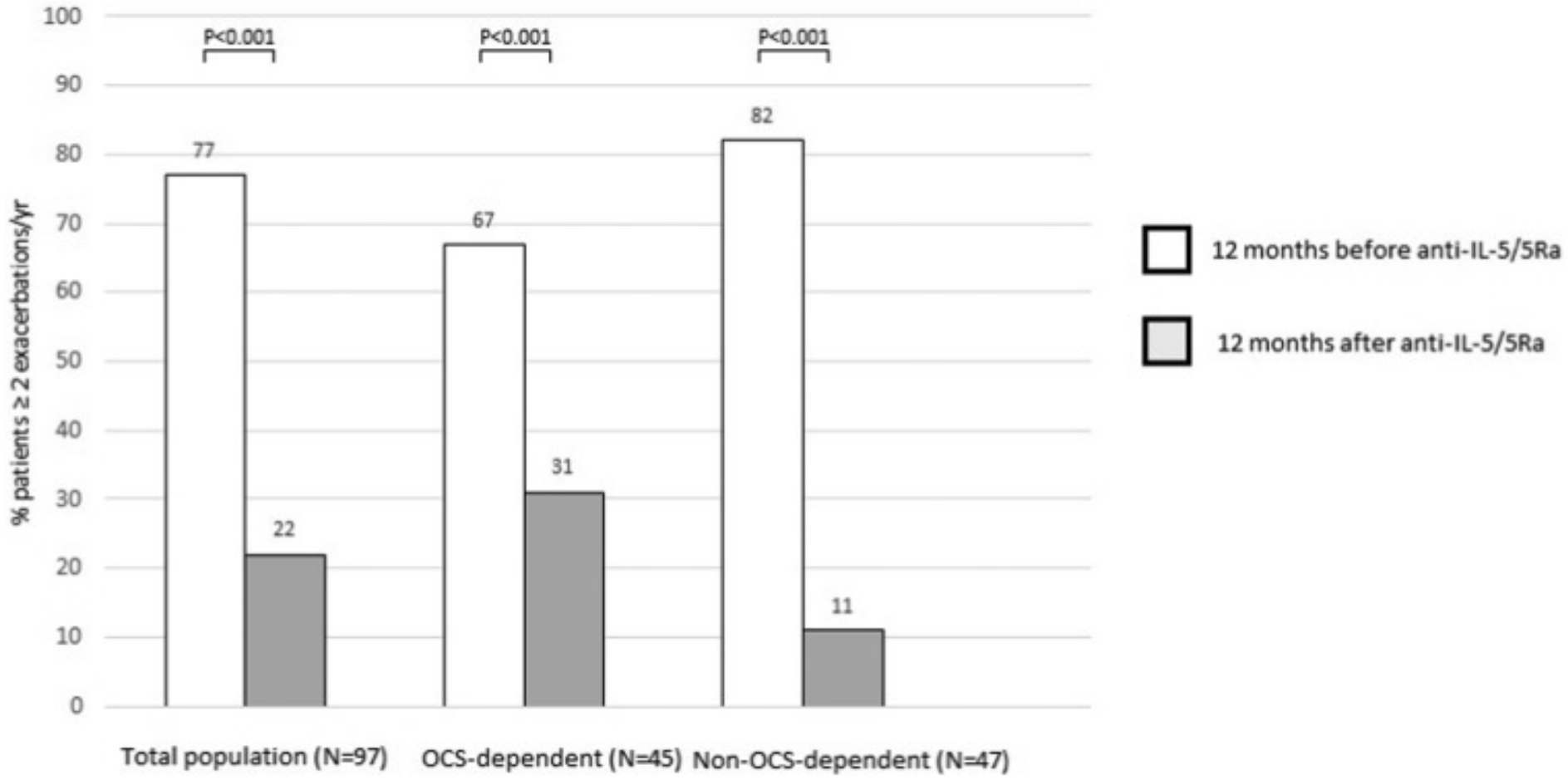
Long M et al, Lancet Resp Med, 2024

Bronchiectasis as an Inflammatory Disease



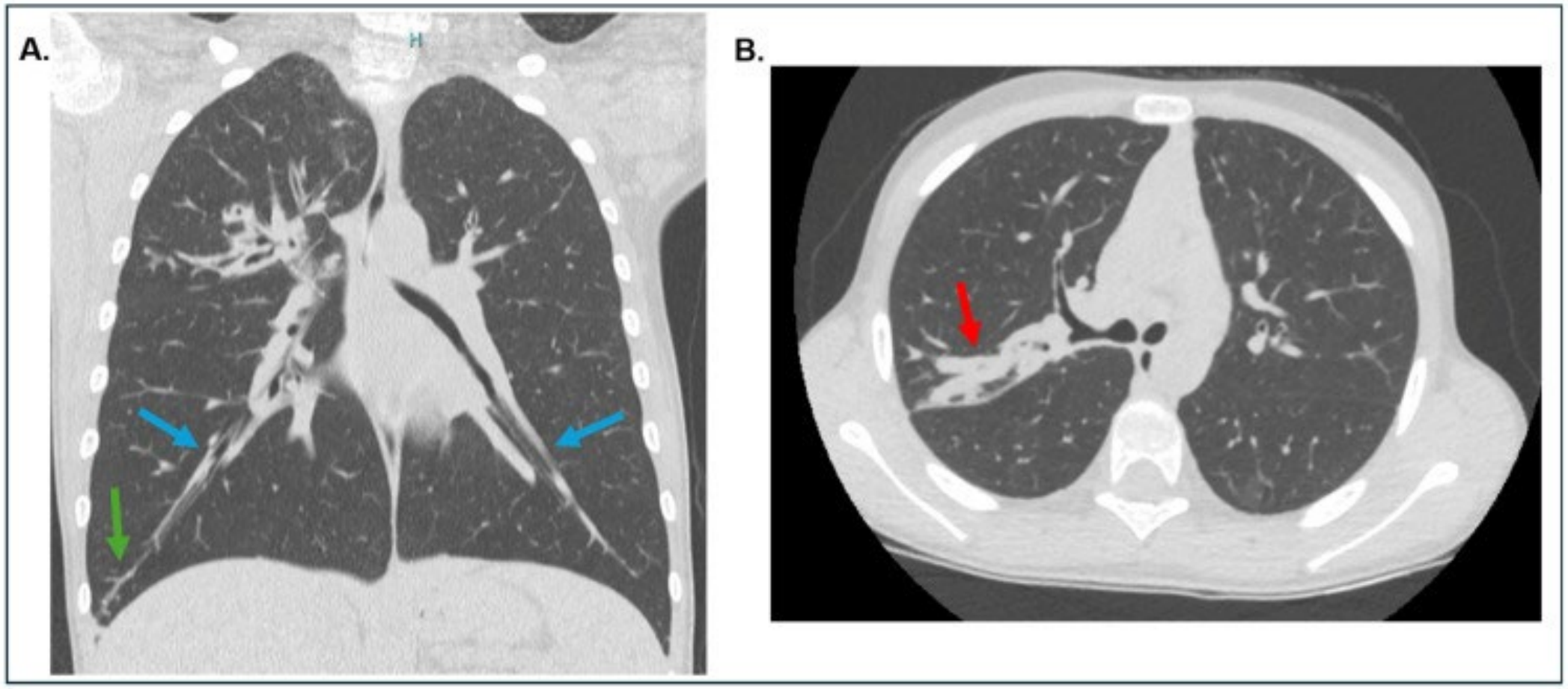
Exacerbation Reduction in Severe Eosinophilic Asthma with Concurrent Bronchiectasis

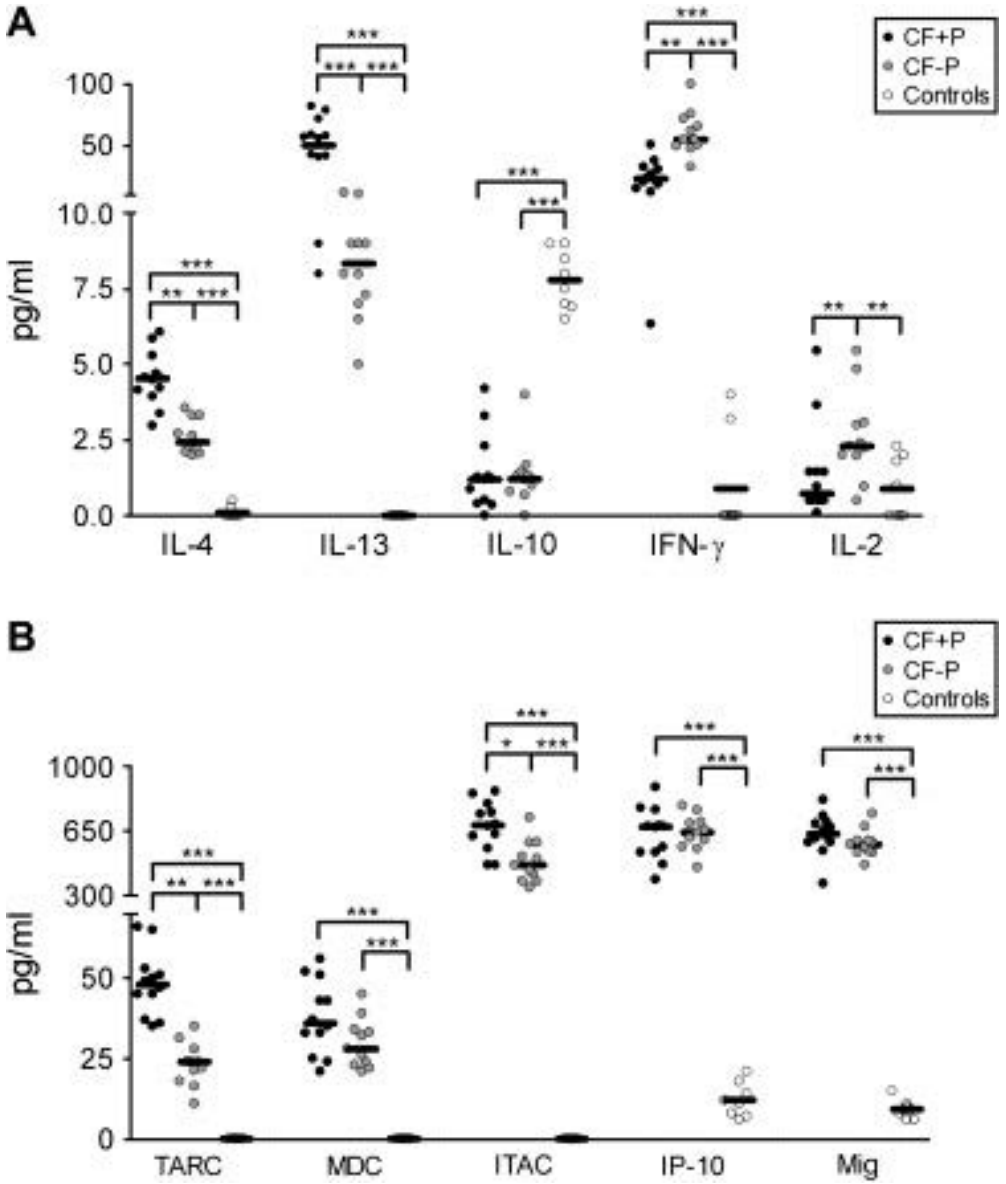
Bendien et al, JACI:IP, 2023



Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

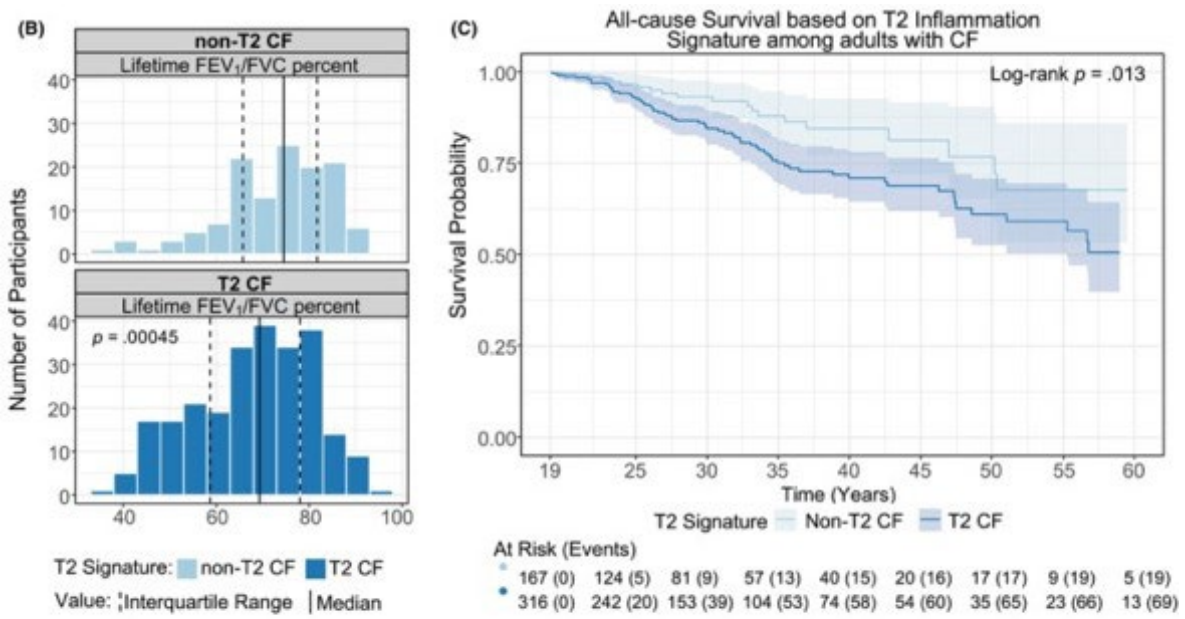
Chatterjee P et al, J Fungi, 2024





Type 2 Inflammation in Cystic Fibrosis

Hartl D et al, JACI, 2006

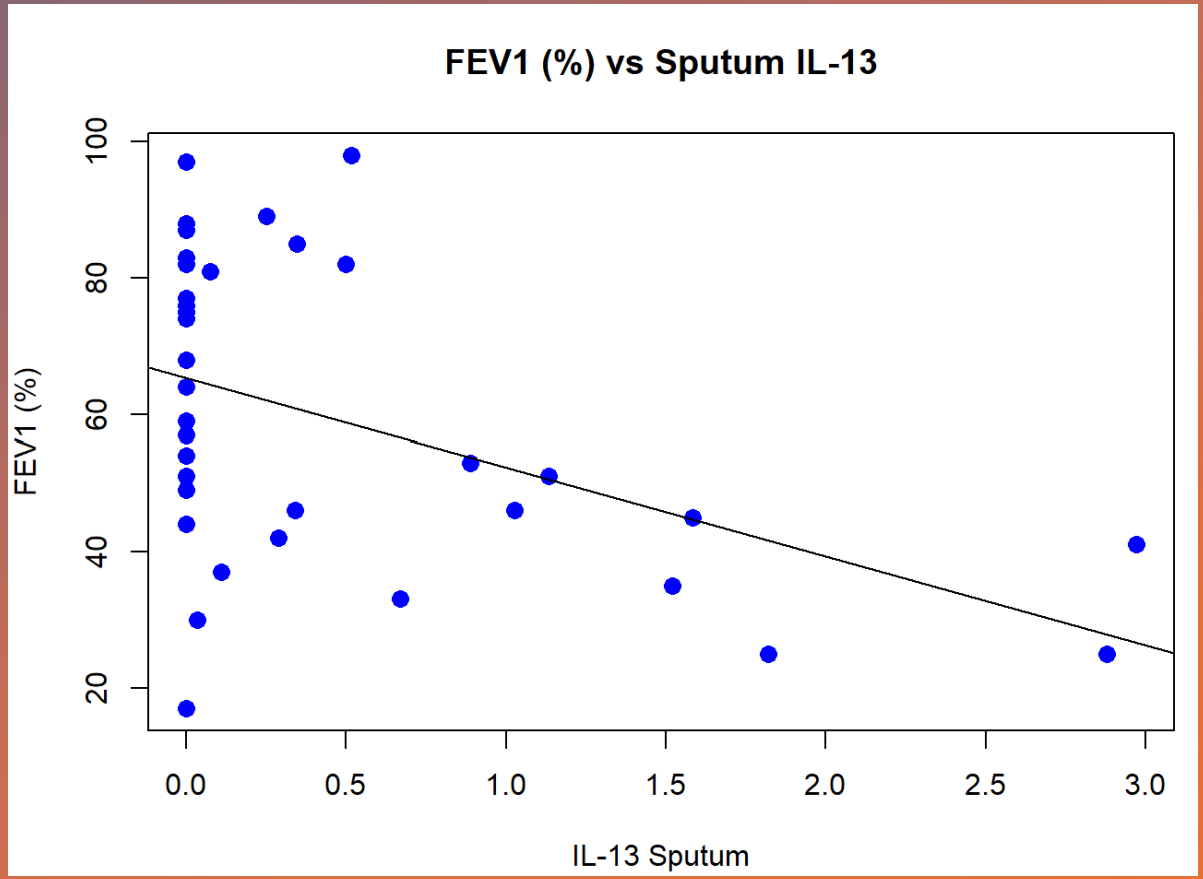


Type 2 Inflammation as a Predictor of Mortality in CF

Cook DP et al, Allergy, 2024

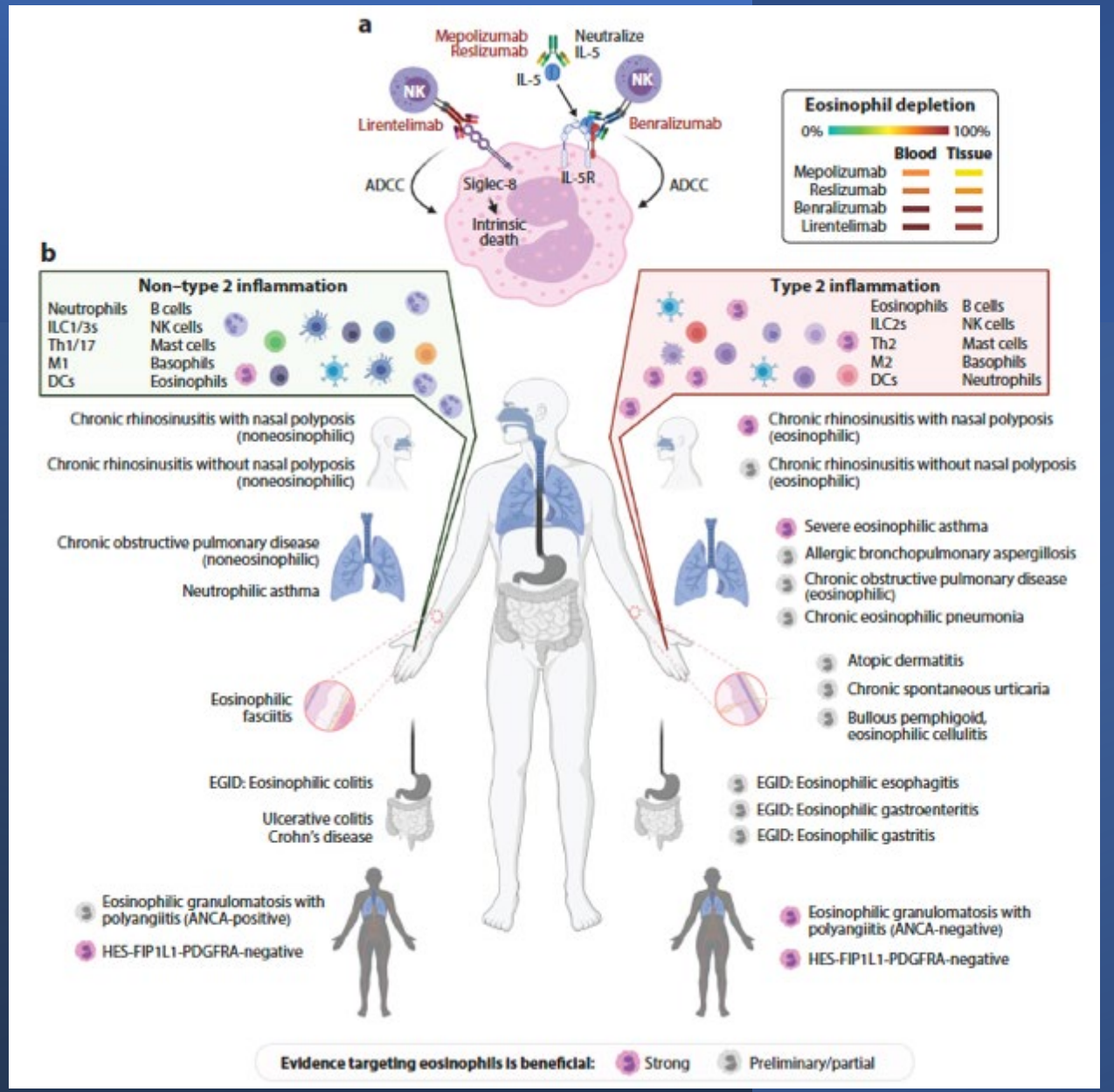
IL-13 levels in Sputum are Correlated Inversely with FEV1 in CF

Danelle Leverone and Jeff Barry,
presented at ATS 2024,
unpublished



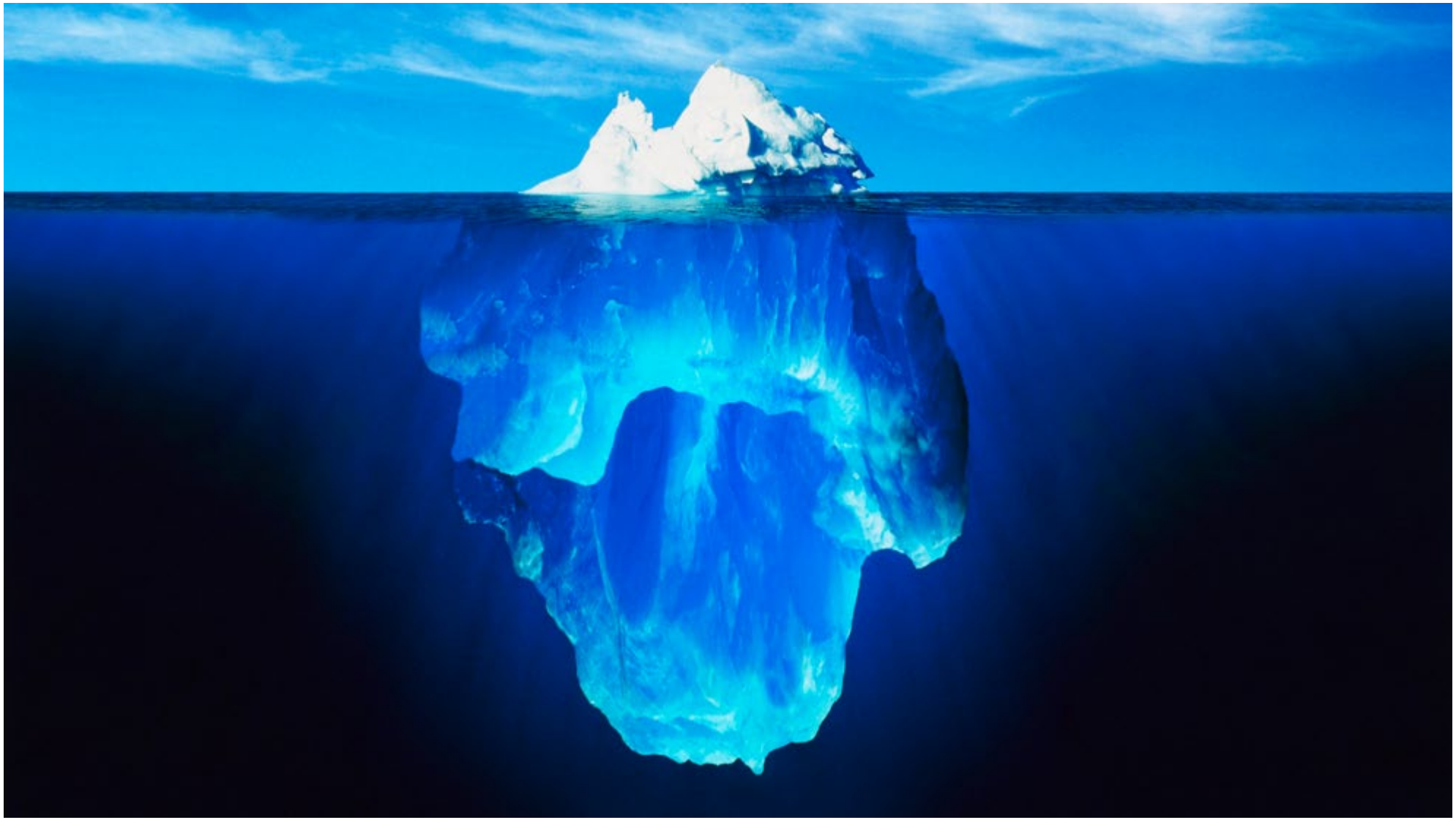
The Impact of Biologics Tell Us About the Relative Importance of Different Inflammatory Pathways in Disease:

e.g. ”Eosinophil Knockout Humans”



From: Jacobsen et al, Annual Review of Immunology, 2021

Questions?



Update on the Role of Biologics in Asthma and Atopic Disease

Monica Tang, MD
UCSF

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **Sanofi/Regeneron – Advisory Board**
- I **WILL** discuss off-label use and/or investigational use of any drugs or devices.

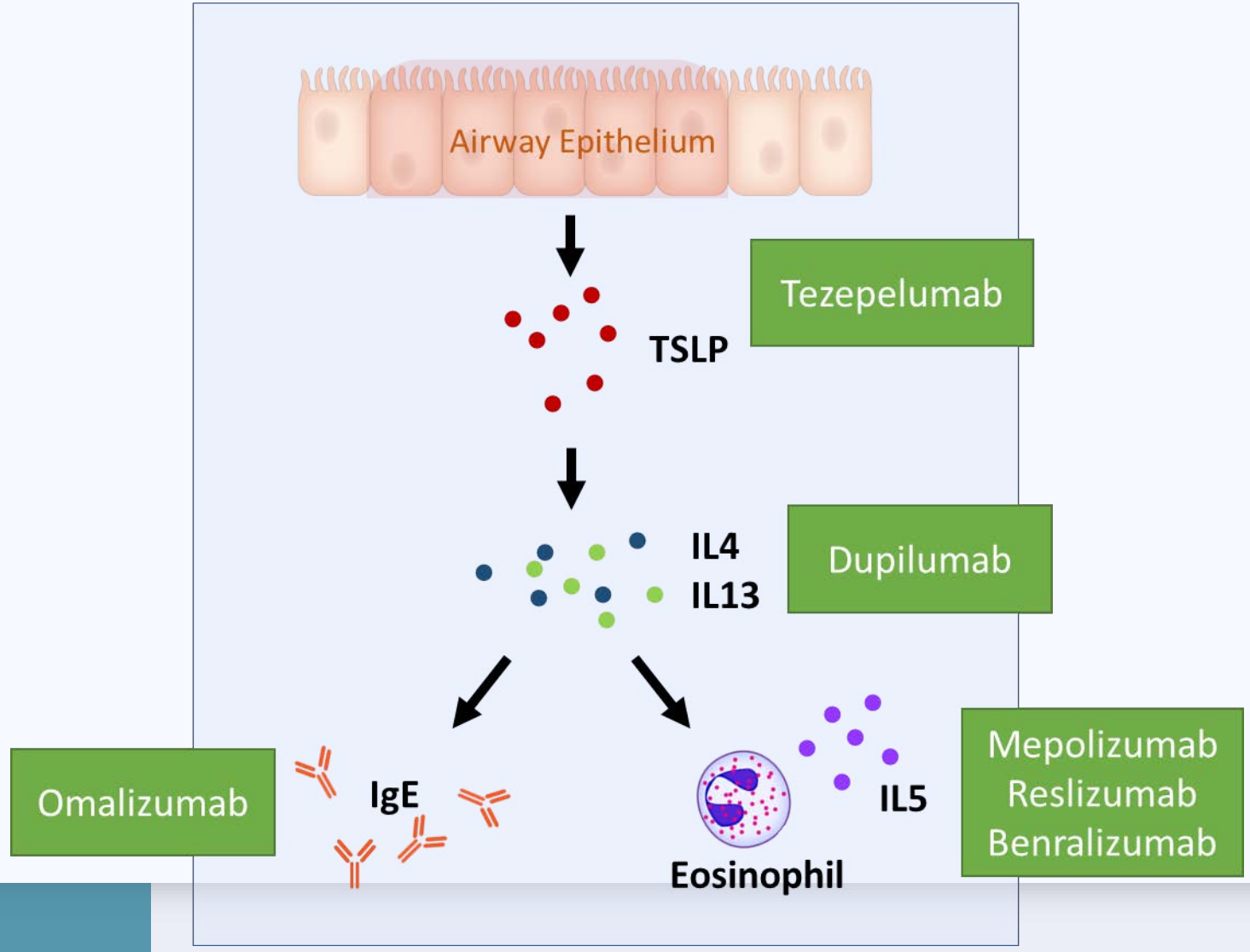
Outline

The use of biologics in asthma

The use of biologics in atopic disease

The novel use of biologics

Asthma Biologics



Original Article

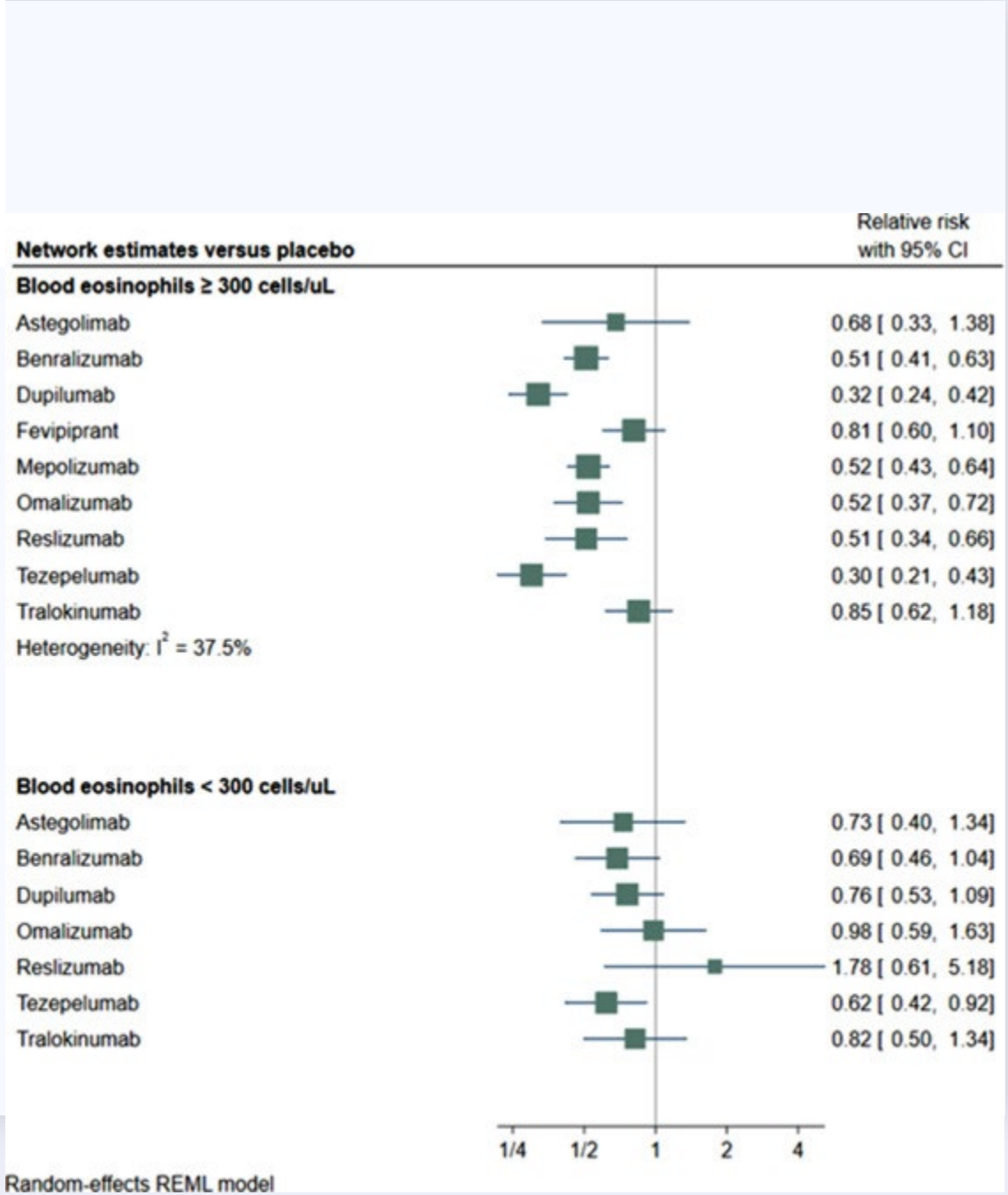
A comparison of the effectiveness of biologic therapies for asthma

A systematic review and network meta-analysis

Tyler Pitre, MD, MA*; Tanvir Jassal, BASc†; Albi Angjeli, BHSc‡; Vineeth Jarabana, BHSc§; Sricherry Nannapaneni, BHSc‡; Ayesha Umair, BHSc‡; Muizz Hussain, BHSc‖; Gareth Leung, BHSc, MSc¶; Sarah Kirsh, BSc†; Johnny Su, MD*; Kairavi Desai, BMSc‖; Jade Coyne, MD*,#; Sindu Mohan, MD*,#; Dena Zeraatkar, PhD†,**,††

Eosinophilic:
ALL biologics
reduce
exacerbations

Non-Eosinophilic:
NO biologics
reduce
exacerbations



Efficacy in Asthma

GRADE recommendation			
High certainty	Definitely more beneficial than standard care	Definitely more harmful than standard care	Definitely no different than standard care
Moderate certainty	Probably more beneficial than standard care	Probably more harmful than standard care	Probably no different than standard care
Low certainty	May be more beneficial than standard care	May be more harmful than standard care	May be no different than standard care
Very low certainty	We are very uncertain	We are very uncertain	We are very uncertain

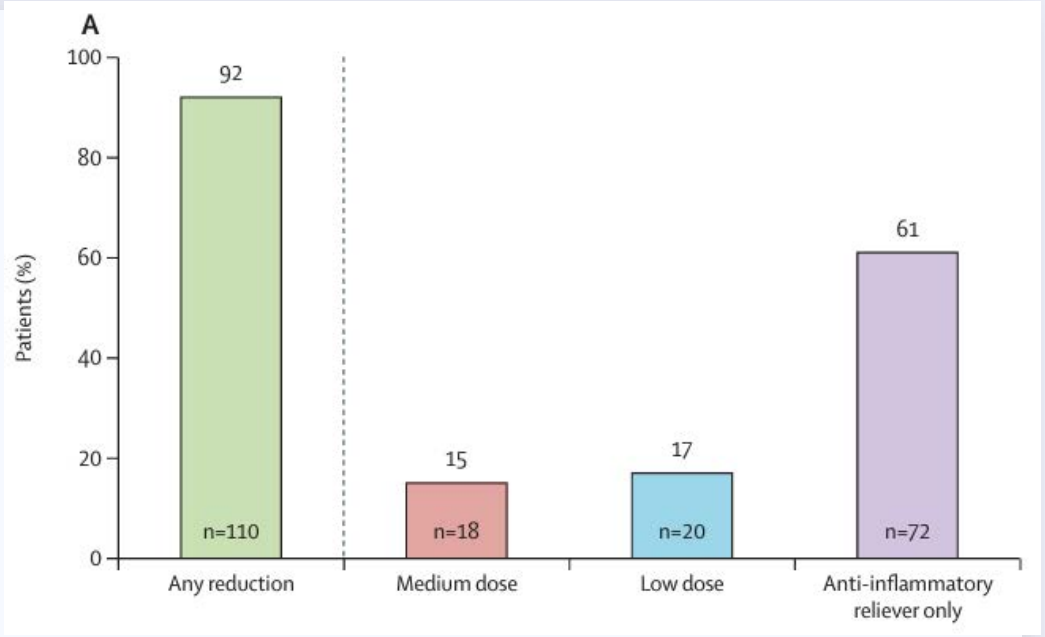
Drug	Asthma exacerbations		ACQ		FEV1 (L)		Hospital admissions	Corticosteroid sparing	Adverse events leading to discont.
Eosinophils	*≥ 300*	*< 300*	*≥ 300*	*< 300*	*≥ 300*	*< 300*	NA	NA	NA
Baseline risk	*470 per 1000*		*NA*		*NA*		*137 per 1000*	*560 per 1000*	*19 per 1000*
MCID/MID	*20%*		*-0.5*		*0.1 L*		*5%*	*20%*	*10%*
Tezepelumab	-329 (-366.6 to -272.6)	-173.9 (-277.3 to -23.5)‡	-0.4 (-0.61 to -0.19)‡	-0.23 (-0.36 to -0.09)	0.24 (0.16 to 0.32)	0.1 (0 to 0.19)¶	-110.97 (-120.56 to -94.53)‡	33.6 (-72.8 to 168)¶	-6.08 (-12.54 to 6.65)
Dupilumab	-319.6 (-357.2 to -272.6)	-112.8 (-225.6 to 51.7)‡	-0.73 (-0.98 to -0.48)‡	-0.2 (-0.42 to 0.02)	0.25 (0.21 to 0.29)	0.1 (0 to 0.2)¶	-97.27 (-124.67 to -4.11)‡	274.4 (123.2 to 464.8)¶	0.57 (-10.26 to 24.7)
Mepolizumab	-211.5 (-258.5 to -155.1)‡		-0.33 (-0.51 to -0.15)‡	0.49 (0.01 to 0.97)‡	0.1 (0.04 to 0.15)‡			341.6 (39.2 to 789.6)‡	-6.65 (-12.16 to 3.04)
Reslizumab	-230.3 (-282 to -164.5)‡	371.3 (-188 to 2002.2)¶††	-0.28 (-0.44 to -0.11)	0.12 (-0.09 to 0.33)	0.19 (0.12 to 0.25)	0.09 (-0.04 to 0.22)¶		128.8 (-84 to 436.8)¶	-6.65 (-11.21 to 0.38)
Benralizumab	-230.3 (-277.3 to -173.9)‡	-145.7 (-263.2 to 37.6)‡	-0.3 (-0.44 to -0.16)	-0.23 (-0.41 to -0.06)	0.14 (0.11 to 0.18)‡	0.04 (-0.05 to 0.13)‡	-17.81 (-41.1 to 10.96)	431.2 (162.4 to 800.8)‡	12.35 (-3.99 to 46.55)
Omalizumab	-225.6 (-296.1 to -131.6)‡	-9.4 (-192.7 to 296.1)¶	-0.25 (-0.5 to 0.01)‡*		0.09 (0.02 to 0.16)‡*		-84.94 (-105.49 to -47.95)‡	179.2 (84 to 285.6)‡	3.8 (-3.8 to 15.39)‡

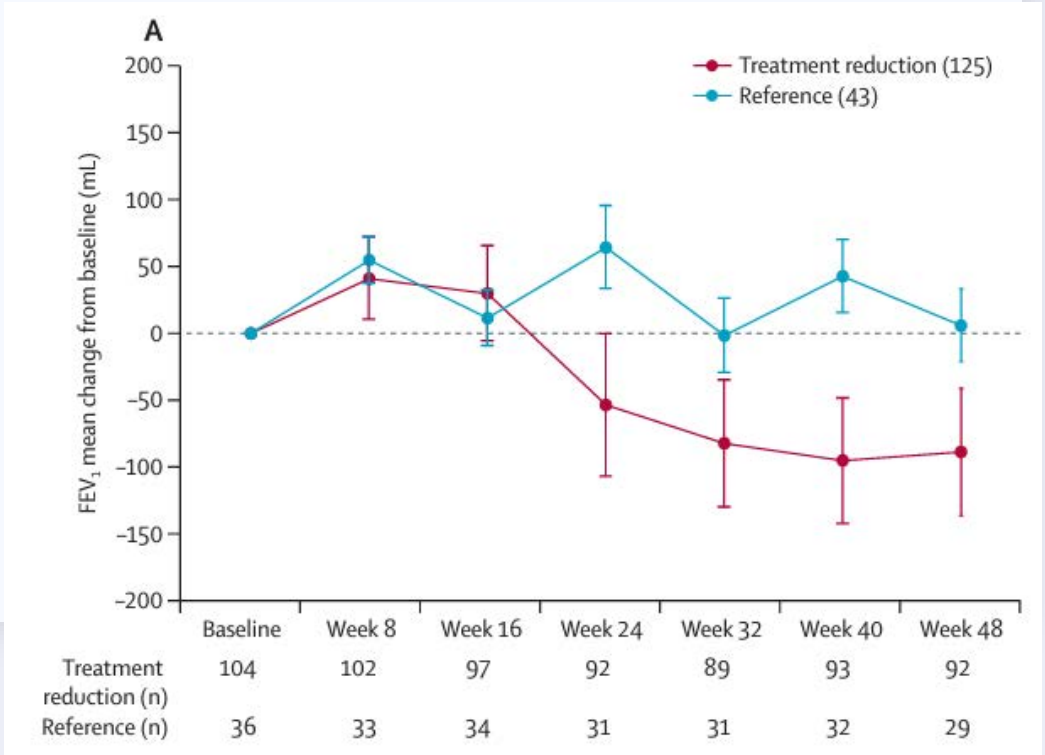
• Pitre T, et a
Immunol. 2

Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study

*David J Jackson, Liam G Heaney, Marc Humbert, Brian D Kent, Anat Shavit, Lina Hiljemark, Lynda Olinger, David Cohen, Andrew Menzies-Gow, Stephanie Korn, on behalf of the SHAMAL Investigators**

- Phase 4, randomized, open label, active-controlled study
- n=208, Randomly assigned (3:1) to reduce or continue their ICS-formoterol.
- 92% reduced their dose, most to as needed only.
- However, those who reduced their dose had a decline in FEV1 (especially on anti-inflammatory reliever therapy only).





CHEST COMMENTARY | VOLUME 164, ISSUE 4, P831-834, OCTOBER 2023 Download Full Issue

Are We Ready for Asthma Remission as a Clinical Outcome?

Njira L. Lugogo, MD • Arjun Mohan, MD • Praveen Akuthota, MD • Simon Couillard, MD • Sarah Rhoads, MD • Michael E. Wechsler, MD, MMsc

Criteria for Remission	Dupilumab		Benralizumab			Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/ CALIMA Phase 3	2022[4] ANDHI Phase 3b	2023[5] XALOC-1	2022[6,7] NAVIGATOR Phase 3	2022[8] REDES	2022[9] CHRONICLE	2022[10] Danish Registry
Absence of symptoms[a,b] **and**	ACQ-5 < 1.5	ACQ-5 < 1.5	ACQ-6 < 1.5" or ≤ 0.75	ACQ-6 < 1.5" or ≤ 0.75	ACQ-5 < 1.5 or ACT ≥ 16	ACQ-6 ≤ 1.5[a,b]	ACT ≥ 20	Majority ≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function **and**	Post-BD FEV_1pp ≥ 80%	Post-BD FEV_1 ≥ 80% *OR* pre-BD FEV_1 ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Not included	Pre-BD FEV_1pp > 80% *OR* Pre-BD FEV_1 > 20% from baseline; FEV1 > 95% of baseline**	Not included	Not included	Post-BD FEV_1pp ≥ 80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	26.3%"	28.7%	43%	14%*- 28.5%**	37%	35%	19%

Predictors of response/treatment success in asthma

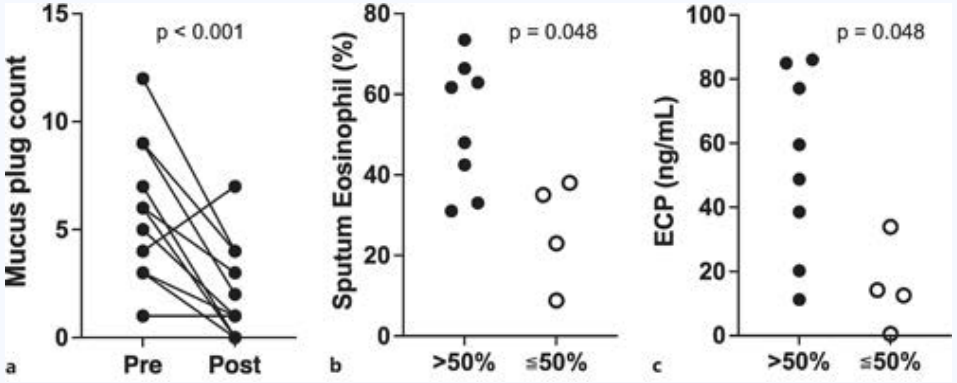
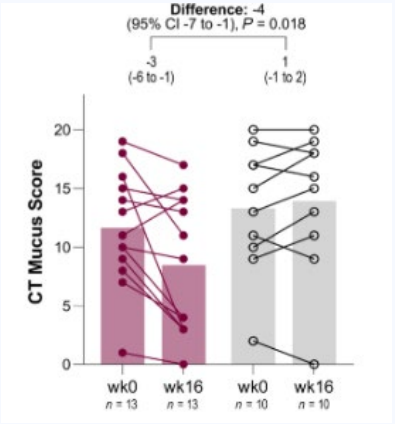
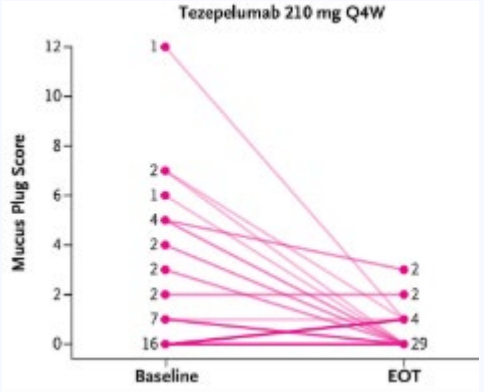
Biologic	Disease Characteristics	Biomarkers
Omalizumab	Allergic disease Childhood onset CRSwNP Severe disease Lower FEV1	Blood eosinophil ≥ 250 cells/uL FeNO ≥ 20 ppb Serum periostin ≥ 50 ng/mL High sputum IL-13 VOCs, Plasma lipid biomarkers
Mepolizumab	Lower BMI Later age of onset CRSwNP Frequent exacerbations Lower maintenance OCS dose	Baseline blood eosinophil count High sputum eosinophils Breakthrough exacerbations due to high FeNO or high CRP (infections)
Reslizumab	CRSwNP	Blood eosinophil ≥ 400 cells/uL
Benralizumab	CRSwNP Frequent exacerbations OCS dependent FEV1<65%	Baseline blood eosinophil count
Dupilumab	Older age	Blood eosinophil ≥ 150-300 cells/uL FeNO ≥ 25-50 ppb IgE > 157 IU/mL
Tezepelumab		Higher baseline blood eosinophils Higher baseline FeNO
Overall	Childhood onset Fewer exacerbations Poor asthma control Not OCS dependent	Better clinical response with controlled airway eosinophils (may be discordant with blood and may be distinct eosinophil subpopulations)

Blood eosinophils

FeNO

• Gyawali B, Georas SN, Khurana S. Biologics in severe asthma: a state-of-the-art review. Eur Respir Rev. 2025 Jan 8;34(175):240088. doi: 10.1183/16000617.0088-2024. PMID: 39778920; PMCID: PMC11707604.

Targeting mucus plugs

Biologic	Study	Outcome
Benralizumab	Sakai et al. Int Arch Allergy Immunol 2023 Case series (n=12)	
Dupilumab	Svenningsen et al. AJRCCM 2023	 ↑ in FEV1 and ACQ-6 ↑^{120}Xe ventilation MRI
Tezepelumab	Nordenmark et al. NEJM Evid 2023	 ↑correlated with pre-BD FEV1 and air trapping ↑correlated with blood eosinophil, FeNO, plasma and BAL EDN

Biologic use in other atopic disorders

Which biologics are approved for additional indications?

	Target	Indication
Omalizumab Xolair	IgE	Chronic urticaria Nasal polyps Food allergy
Mepolizumab Nucala	IL-5	EGPA HES Nasal polyps
Reslizumab Cinqair	IL-5	
Benralizumab Fasenra	IL-5R	EGPA
Dupilumab Dupixent	IL-4Ra (IL4/IL13)	Atopic dermatitis Nasal polyps Eosinophilic esophagitis Prurigo nodularis Eosinophilic COPD
Tezepelumab Tezspire	TSLP	

Eosinophilic COPD – Dupilumab (2024)

Biologic	Study	n	Inclusion	Exac	FEV1 (L)	QOL SGRQ >4	Symptoms E-RS-COPD	AEs
Dupilumab 300 mg q2wk	BOREAS	939	• Blood eos >300 cells/uL • Recurrent exacerbations despite ICS/LABA/LAMA • Chronic bronchitis sx	0.70 (0.58, 086)	0.08 (0.04, 0.13)	1.4 (1.1-1.9)	-1.1 (-1.8, -0.4)	Similar
	NOTUS	935		0.66 (0.54, 0.82)	0.06 (0.01, 0.11)	1.2 (0.9, 1.6)	-0.6 (-1.4, 0.2)	Similar
	Pooled	1847		0.69 (0.60, 0.79)	0.08 (0.05, 0.11)	1.3 (1.1, 1.6)	-0.9 (-1.4, -0.4)	Similar

- Note that studies are ongoing with anti-IL5/IL5R/anti-TSLP therapy as initial studies had less stringent selection criteria for an eosinophilic phenotype and did not demonstrate as consistent an effect in all outcomes.

Eosinophilic esophagitis – Dupilumab (2022)

Biologic	Study	Clinical symptoms	Histologic remission	Safety
Dupilumab 300 mg qwk	Dellon et al. NEJM 2022	DSQ -12.32 (-19.11, -5.54) DSQ -9,.92 (-14.81, -5.02)	55 (40-71) 54 (41-66)	n=9

EGPA - Mepolizumab (2017) and Benralizumab (2024)

Biologic	Study	Remission BVAS 0 Pred ≤4 mg/d	Relapse	Complete prednisone withdrawal	AEs
Mepolizumab 300 mg q4wk	MIRRA (n=136) NEJM 2017	32%	56%	18%	Any 97% vs 94% Serious 18% vs 26% Systemic reaction 6% vs 1%
Mepolizumab 300 mg q4wk	LAP (n=100) JACI 2024 Safety extension		6% asthma 3% EGPA		3% d/c due to AEs
Mepolizumab 300 mg q4wk	MANDARA (n=140) NEJM 2024	56%	30%	26%	Any 96%, serious 13%
Benralizumab 30 mg q4wk		58%	30%	41%	Any 90%, serious 6%

Efficacy in hypereosinophilic syndrome

Biologic	Study	Disease Flare	Adverse events
Mepolizumab 300 mg q4wk	HES Mepolizumab Phase III (n=108)	0.28 (0.12-.0.64)	Similar

CRSwNP - Dupilumab (2019), Omalizumab (2020), and mepolizumab (2021)

	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 33.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

- Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. J Allergy Clin Immunol. 2022 Apr;149(4):1286-1295. doi: 10.1016/j.jaci.2021.09.009. Epub 2021 Sep 17. PMID: 34543652.

Eczema – Dupilumab (2017), Tralokinumab (2021), Lebrikizumab (2024), Nemolizumab (2024)

	Atopic Dermatitis Severity EASI (0–72)	Patient-Reported AD Severity POEM (0–28)	Itch NRS (0–10)	Sleep Disturbance NRS (0–10)	Eczema-Related Quality of Life DLQI (0–30)	Atopic Dermatitis Flares	Any Adverse Event	Serious Adverse Event
	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CI)	RD (95%CI)	RD (95%CI)
Baseline	29.00	20.87	7.10	5.30	14.74	139 per 1000	592 per 1000	22 per 1000
Astegolimab	4.47 (-5.17 to 14.10)		0.66 (-1.20 to 2.54)			-64 (-122 to 133)	-169 (-377 to 71)	37 (-19 to 591)
Benralizumab	0.13 (-10.79 to 10.99)							
Dupilumab 300mg Q2W (Standard Dose)	-10.72 (-12.30 to -9.19)	-7.05 (-7.64 to -6.50)	-2.14 (-2.38 to -1.90)	-1.84 (-2.26 to -1.42)	-4.56 (-5.18 to -3.98)	-74 (-83 to -64)	-20 (-50 to 10)*	-11 (-14 to -7)
Fezakinumab	-4.98 (-13.97 to 4.02)						-52 (-312 to 188)	34 (-19 to 539)
Itepekimab	-3.82 (-11.33 to 3.68)		-1.30 (-2.74 to 0.13)			-55 (-105 to 57)		-13 (-21 to 55)
Lebrikizumab 250mg Q2W (Standard Dose)	-9.10 (-12.36 to -5.84)	-6.10 (-9.40 to -2.76)	-1.77 (-2.32 to -1.24)	-1.59 (-2.09 to -1.08)	-3.92 (-5.55 to -2.31)	-73 (-124 to 108)	70 (-48 to 171)*	-15 (-20 to 12)
Mepolizumab	-3.48 (-9.89 to 2.93)	-4.21 (-7.30 to -1.13)	-1.30 (-3.03 to 0.41)				-507 (-582 to -124)	-2 (-21 to 489)
Nemolizumab	-3.40 (-7.36 to 0.52)	-4.77 (-7.24 to -2.35)	-2.16 (-2.88 to -1.44)	-1.78 (-2.41 to -1.16)	-1.95 (-3.40 to -0.49)	3 (-42 to 66)	38 (-52 to 121)	4 (-13 to 51)
Omalizumab	0.17 (-6.81 to 7.23)	-0.51 (-3.59 to 2.51)			-4.01 (-6.76 to -1.22)	-20 (-104 to 194)	80 (-317 to 325)	0 (-15 to 45)
Tezepelumab	-2.13 (-6.98 to 2.68)		-0.57 (-1.95 to 0.81)				-66 (-258 to 118)	-8 (-18 to 32)
Tralokinumab 300mg Q2W (Standard Dose)	-6.45 (-8.67 to -4.27)	-4.47 (-5.37 to -3.58)	-1.08 (-1.51 to -0.65)	-0.93 (-1.36 to -0.49)	-2.36 (-3.21 to -1.51)	-57 (-72 to -40)	-1 (-43 to 40)*	-8 (-13 to 1)
Ustekinumab	1.58 (-5.01 to 8.27)		0.03 (-1.69 to 1.76)		-0.60 (-2.82 to 1.67)	-87 (-121 to 0)	-102 (-337 to 137)	-5 (-21 to 191)

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from placebo	Possibly not clearly different from placebo
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

• Chu AWL et al. Systemic treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023 Dec;152(6):1470-1492. doi: 10.1016/j.jaci.2023.08.029. Epub 2023 Sep 9. PMID: 37678577.

Chronic urticaria – Omalizumab (2014)

Biologic	Study	Symptom score	Complete response (UAS7=0)	Safety
Omalizumab 150-300 mg q4wks	Zhao et al. JACI 2016	WIS -5.72 (-6.65, -4.79) WWS -6.18 (-7.24, -5.11)	4.55 (3.33, 6.23)	Similar

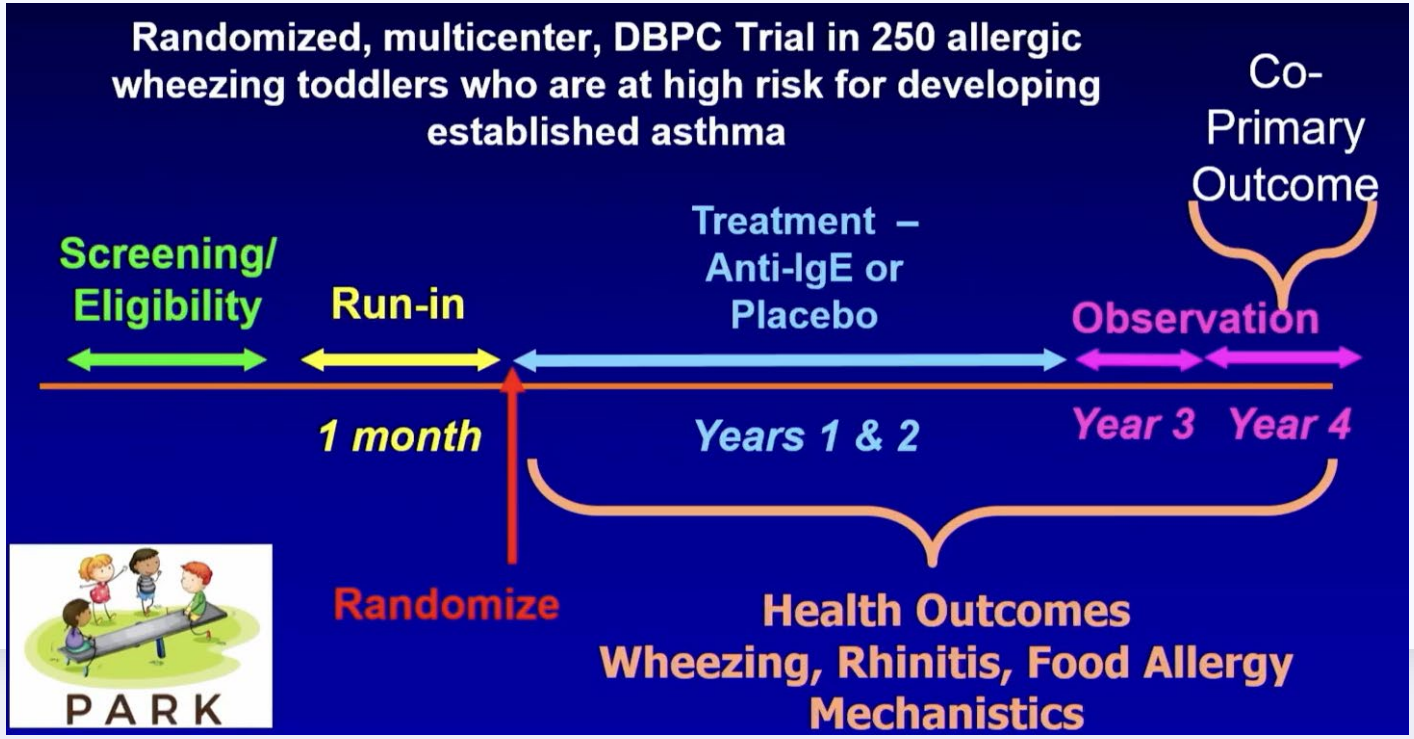
Food Allergy – Omalizumab (2025)

Biologic	Study	Increase reaction threshold	Safety
Omalizumab Based on IgE and weight	OUTMATCH Phase III (n=118)	60% (47-70) consumed >600 mg peanut	Similar, no SAE

Biologics coming soon…

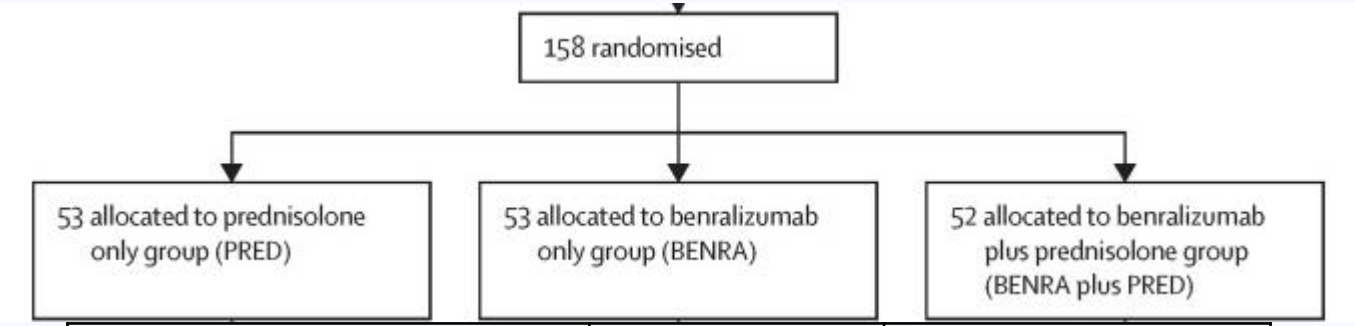
Preventing Asthma in High Risk Kids (PARK)

- Hypothesis: Early blockade of IgE and IgE mediated responses with omalizumab will prevent the development and reduce the severity of asthma in those at high risk for developing asthma



Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial

Sanjay Ramakrishnan, Richard E K Russell, Hafiz R Mahmood, Karolina Krassowska, James Melhorn, Christine Mwasuku, Ian D Pavord, Laura Bermejo-Sanchez, Imran Howell, Mahdi Mahdi, Stefan Peterson, Thomas Bengtsson, Mona Bafadhel

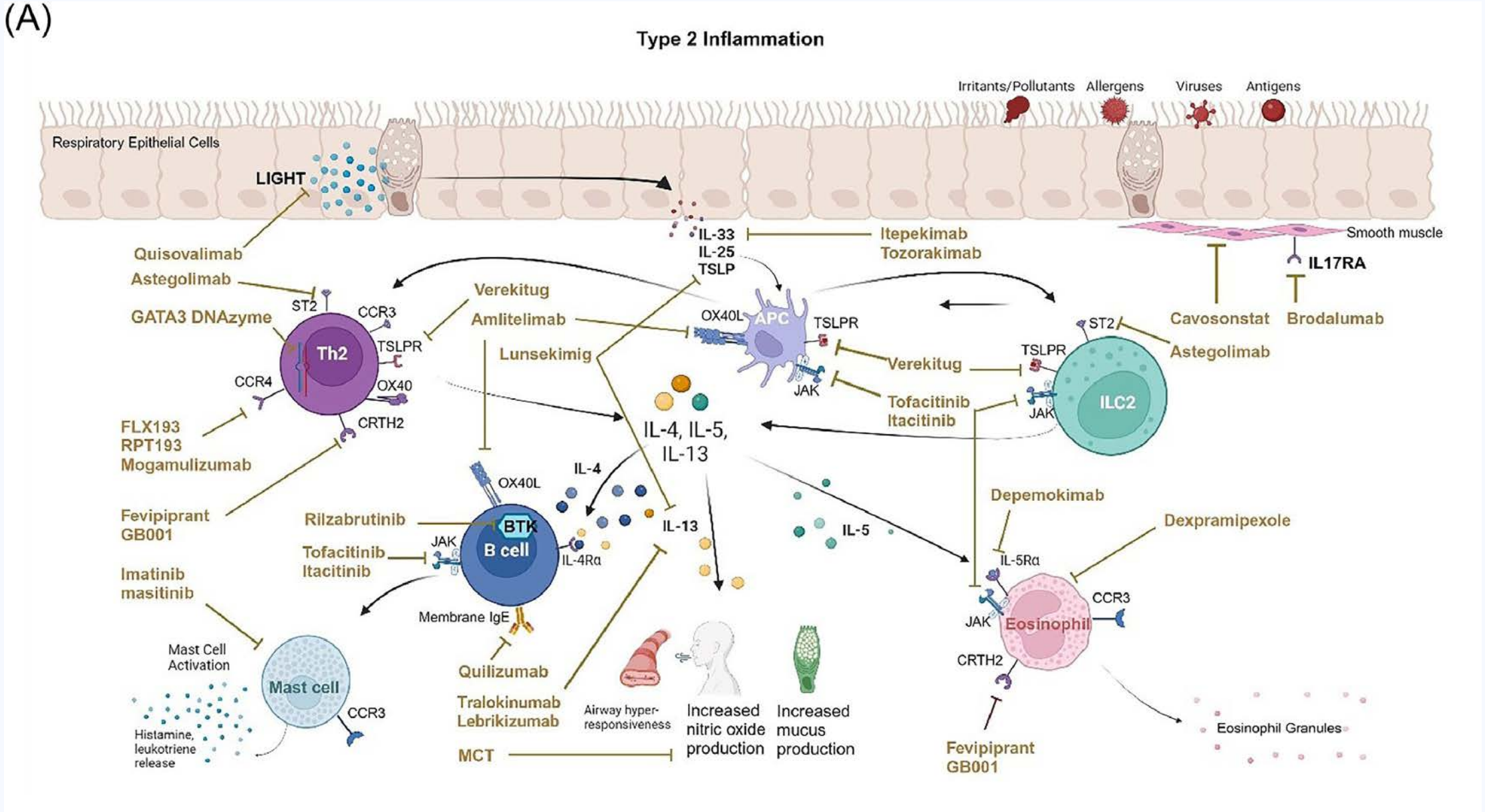


	PRED (n=53)	**Pooled-BENRA (n=105)**
Treatment failure at 90 days (Death, Admission, Retreatment)	39 (74%)	47 (45%)
OR (95%CI)	.0·26 (0·13 to 0·56) P= 0·0005	
Change in total VAS symptoms at day 28	103 (75 to 132)	152 (131 to 173)
Least-square mean difference	49 (14 to 84) P=0.0065	

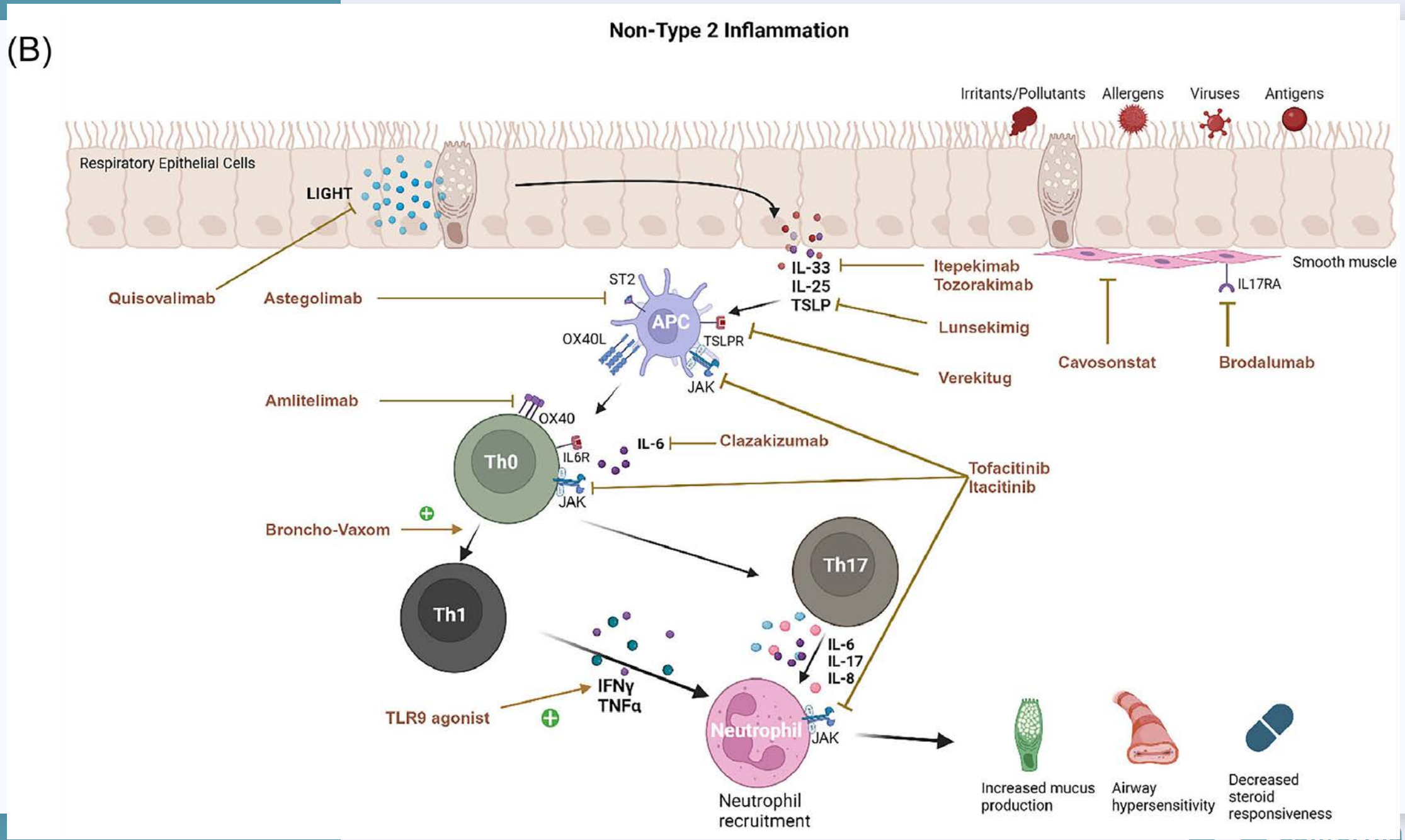
Novel asthma treatments

Novelty	Therapies
Ultra-long-acting	Depemokimab – anti-IL-5 q6mo Verekitug – anti-TSLPR q6mo, currently in Phase II trials (VALIANT), estimated completion 11/2026
Combined	Lunsekimig – anti-IL-13/anti-TSLP, currently in Phase II trial (AIRCULES/AIRLYMPUS), estimated completion 11/2027
Inhaled	AZD4604 – JAK1 inhibitor, currently in Phase IIb trial (AJAX), estimated completion 09/2025 Frevecitinb – pan-JAK inhibitor Early trials are ongoing, but challenges include high levels of protease in the lungs which may degrade inhaled therapy and difficulty translating from preclinical animal to clinical human models

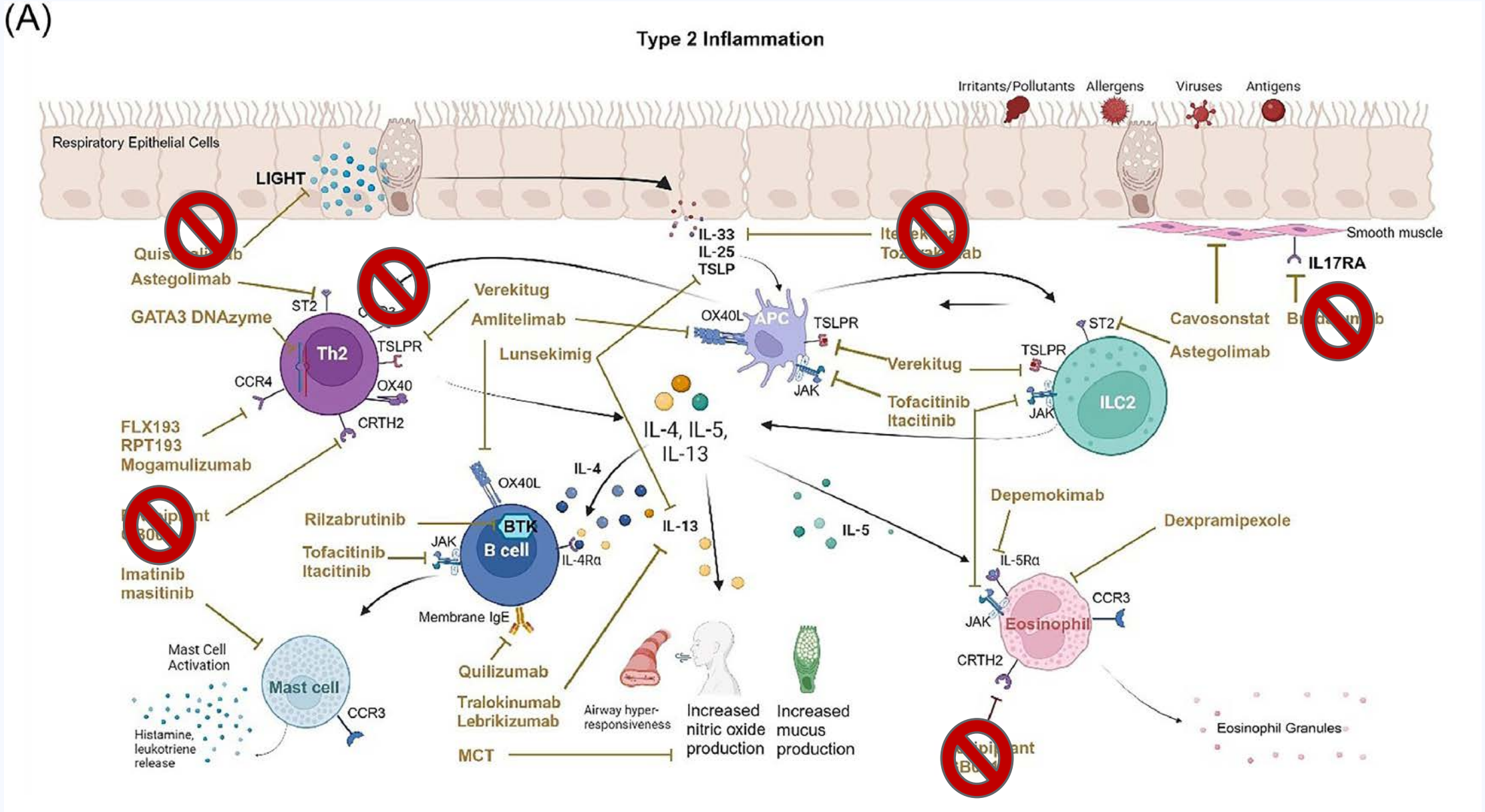
• Seluk L, Davis AE, Rhoads S, Wechsler ME. Novel asthma treatments: Advancing beyond approved novel step-up therapies for asthma. Ann Allergy Asthma Immunol. 2025 Jan;134(1):9-18. doi: 10.1016/j.anai.2024.09.016. Epub 2024 Oct 10. PMID: 39393433.



• Seluk L, Davis AE, Rhoads S, Wechsler ME. Novel asthma treatments: Advancing beyond approved novel step-up therapies for asthma. Ann Allergy Asthma Immunol. 2025 Jan;134(1):9-18. doi: 10.1016/j.anai.2024.09.016. Epub 2024 Oct 10. PMID: 39393433.



• Seluk L, Davis AE, Rhoads S, Wechsler ME. Novel asthma treatments: Advancing beyond approved novel step-up therapies for asthma. Ann Allergy Asthma Immunol. 2025 Jan;134(1):9-18. doi: 10.1016/j.anai.2024.09.016. Epub 2024 Oct 10. PMID: 39393433.



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Summary

- The use of biologics have advanced a goal of asthma treatment to potentially achieve remission
- Biologics can be used in other diseases driven by type 2 inflammation, pathology may matter more than disease.

Targeting Clinical Remission When Treating Asthma

Shazia Lutfeali, MD
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Overall Position

Remission has long been a goal of treatment in other chronic diseases

In asthma, “remission” has historically been used to describe spontaneous cessation of disease activity (for example, during adolescence)

Asthma control is the current long-term asthma treatment goal

However, biologic treatments targeting specific pathways now allow for greater asthma control

Treatment-induced asthma remission is a realistic goal and should be targeted as such

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Terminology

- **Asthma control**: Current symptom control plus risk of future adverse outcomes

Box 2-2. GINA assessment of asthma control at clinical visits in adults, adolescents and children 6–11 years

A. Recent asthma symptom control (but also ask the patient/caregiver about the whole period since last review#)

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA* reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.

Measure FEV_1 at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

★ **Clinical remission**: No asthma symptoms, no exacerbations, optimization/stabilization of lung function ≠ cure

- **Complete (pathophysiological) remission**: No asthma symptoms, no exacerbations, normal lung function, resolution of asthma-related inflammation and/or negative bronchial hyperresponsiveness

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Remission Is Possible

- Questionnaire-based study from Finland
- Patients with early (0-11 years), intermediate (12-39 years), and late (40-69 years) onset physician-diagnosed asthma
- Remission defined by no asthma symptoms or asthma medication usage for 12 months

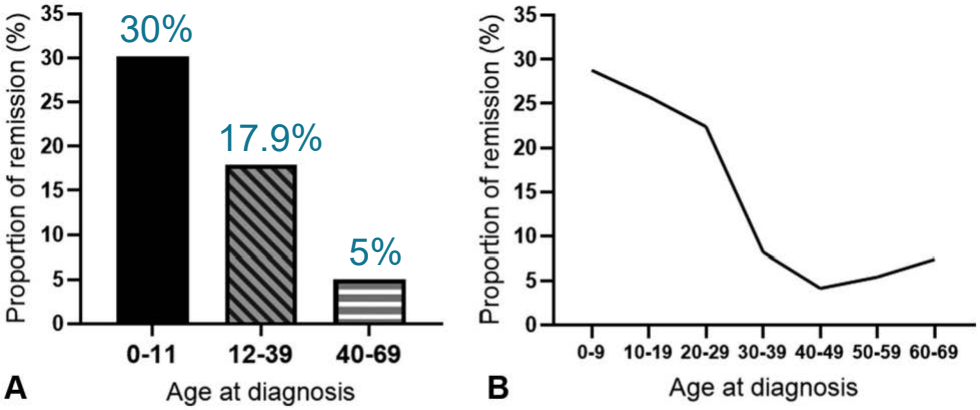

FIGURE 2. Remission (%) in subjects with physician-diagnosed asthma in groups defined by age at asthma diagnosis. In (**A**) is shown the proportion of remission in subjects with early (0-11), intermediate (12-39 years) and late-diagnosed (40-69 years) asthma. In (**B**) is shown the proportion of remission in subjects divided into 10-year groups by age at asthma diagnosis.

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Honkamäki J et al. J Allergy Clin Immunol Pract. 2021 May;9(5):1950-1959.e4. doi: 10.1016/j.jaip.2020.12.015. Epub 2020 Dec 15. PMID: 33338683.

Remission is Possible (cont.)

Remission in Recently Diagnosed Adult-Onset Asthma[1]

200 adult patients with recently diagnosed (<1 year) asthma

↓

170 patients assessed at 5-year follow up

→

27 patients **(15.9%)** experienced clinical remission*

*No asthma symptoms for ≥ 1 year and no asthma medications for ≥ 1 year

Remission of Childhood Asthma in Early Adulthood[2]

1041 children with mild-moderate persistent asthma between 5-12yrs of age

↓

879 patients assessed at first follow up between 18-23yrs of age

→

229 patients **(26.0%)** experienced clinical remission*

*FEV1/FVC ≥ 80%, no asthma exacerbations in the prior year, no use of asthma medications in the prior year, no reported asthma symptoms in the prior year

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[1]Westerhof GA et al. J Allergy Clin Immunol. 2018 Jan;141(1):104-109.e3. doi: 10.1016/j.jaci.2017.03.034. Epub 2017 Apr 22. PMID: 28438546.
[2]Wang et al. J Allergy Clin Immunol. 2019 May;143(5):1752-1759.e6. doi: 10.1016/j.jaci.2018.09.038. Epub 2018 Nov 14. PMID: 30445065; PMCID: PMC7061344.

Asthma Studies Assessing Remission

Study	Terminology	Study design	Parameters	Measures
Westerhof et al (2018)[29]	Clinical remission	Prospective, longitudinal ADONIS study New onset asthma*	2	All measured for ≥1 year (at 5-year follow-up) 1. No asthma symptoms 2. No asthma medication
Tupper et al (2021)[30]	Clinical remission	Danish longitudinal TRAIL study Asthma diagnosis†	2	All measured within the last year 1. No asthma medications 2. No asthma symptoms (GINA 2017 definition)
Pavord et al (2021)[31]	Clinical remission	*Post hoc* analysis of the LIBERTY ASTHMA QUEST clinical trial Uncontrolled moderate-to-severe asthma‡ Add-on dupilumab	3	All measured at week 24 or week 52 1. No exacerbations 2. ACQ-5: <1.5 3. Post-BD FEV_1: ≥80%
Castro et al (2022)[32]	Clinical remission	NAVIGATOR clinical trial Asthma diagnosis§ Add-on tezepelumab	6	Measured at week 52 1. No exacerbations 2. No OCS use 3. ACQ-6: ≤0.75 4. Pre-BD FEV_1: >20% ↑‖ or >80% predicted 5. PGI-S: no/minimal/mild/very mild symptoms‖6. CGI-C: much/very much improved
Pavord et al (2023)[33]	Clinical remission	*Post hoc* analysis of the observational REDES study Severe uncontrolled eosinophilic asthma Add-on mepolizumab	3 and 4	3-component Measured for 52 weeks 1. No exacerbations Measured at week 52 2. No OCS use 3. ACT: ≥20 4-component Measured for 52 weeks 1. No exacerbations Measured at week 52 2. No OCS use 3. ACT: ≥20 4. Post-BD FEV_1: ≥80%
Menzies Gow et al (2022)[34]	Clinical remission	*Post hoc* analysis of the SIROCCO, CALIMA, and ZONDA clinical trials Severe, uncontrolled asthma¶ Add-on benralizumab and stable dose of background medication#	4	All measured at 6 months and 12 months for SIROCCO and CALIMA 1. No exacerbations 2. No OCS use 3. ACQ-6: <1.5 Or 3. ACQ-6: ≤0.75 (stringent criteria) 4. Pre-BD FEV_1: ≥100 mL ↑‖
Maglio et al (2023)[35]	Clinical remission	Retrospective observational study Mepolizumab or benralizumab	4	All measured at 6 months and 12 months 1. No exacerbations 2. No OCS use 3. ACT: ≥20 4. Pre-BD FEV_1: 80% predicted
Brusselle et al (2023)[36]	Clinical remission	*Post hoc* analysis of the observational, single-arm, prospective REALITI-A study Severe asthma Newly prescribed mepolizumab	3	Measured at 0, 52, and 104 weeks after mepolizumab initiation 1. No OCS use 2. ACQ-5: <1.5 Measured during the 12 months before treatment and 24-month follow-up period 3. No exacerbations
Pelaia et al (2023)[37]	Clinical remission	Retrospective, multicenter, observational study Outpatients with severe type 2 asthma Dupilumab	4	All measured at 6 months 1. ACT: ≥20 2. FEV_1 ≥80% predicted 3. No exacerbations 4. No OCS use
Moermans et al (2023)[38]	Remission	Observational study Patients with severe asthma Mepolizumab or reslizumab	5	All measured at 1 year 1. No OCS 2. No exacerbations 3. ACQ: <1.5, ACT: >19, or both 4. FEV_1 ≥80% predicted, FEV_1 ≥10% improvement‖, or both 5. Blood eosinophil count: <300 cells/μL

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How is Asthma Remission Assessed?

Clinical Symptoms	No exacerbations	Lung Function	Medication Requirement	Normalization of Asthma Pathophysiology
• Duration of sustained absence of symptoms • Validated instruments (ACQ, ACT, AIRQ) • Use of bronchodilators	• Systemic corticosteroid use • ED visits or hospitalizations • Unscheduled office visits due to asthma • Missed work or school days due to asthma	• Normalization, stabilization, or optimization of lung function	• Controller medication use • Rescue medication use	• Asthma biomarkers • Broncho-provocation test • Histology

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Four Possible Levels of Remission

Clinical Remission on Treatment

For ≥12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

Complete Remission on Treatment

Clinical remission plus the following:

- Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FENO, and/or other relevant measures), **and**
- In appropriate research settings: Current negative bronchial hyperresponsiveness

Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

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Menzies-Gow A et al. J Allergy Clin Immunol. 2020 Mar;145(3):757-765. doi: 10.1016/j.jaci.2019.12.006. Epub 2019 Dec 19. PMID: 31866436.

Workgroup Consensus

Consensus of an American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology, and American Thoracic Society workgroup on definition of clinical remission in asthma on treatment

Michael Blaiss, MD[*]; John Oppenheimer, MD[†,‡]; Mark Corbett, MD[§]; Leonard Bacharier, MD[‖]; Jonathan Bernstein, MD[¶]; Tara Carr, MD[#]; Bradley Chipps, MD[**]; Simon Couillard, MD, MSc[††] Erick Forno, MD, MPH[‡‡]; Torie Grant, MD, MHS[§§]; Njira Lugogo, MD[‖‖]; Kathleen May, MD[¶¶]; Eric Schauberger, DO, PhD[##]

Asthma Clinical Remission on Treatment Criteria

1. **NO** exacerbations requiring a physician visit, emergency care, hospitalization, and/or systemic corticosteroid for asthma
2. **NO** missed work or school over a 12-month period due to asthma-related symptoms
3. Stable and optimized pulmonary function results on all occasions, when measured over a 12-month period, with ≥2 measurements during the year
4. Continued use of controller therapies (ICS, ICS/LABA, leukotriene receptor antagonist) ONLY at low-medium dose of ICS, or less, as defined by most recent GINA strategy
5. ACT>20, AirQ<2, ACQ<0.75 on all occasions measured in the previous 12-month period, with ≥2 measurements during the year
6. Symptoms requiring 1-time reliever therapy (SABA, ICS-SABA, ICS-LABA) no more than once per month

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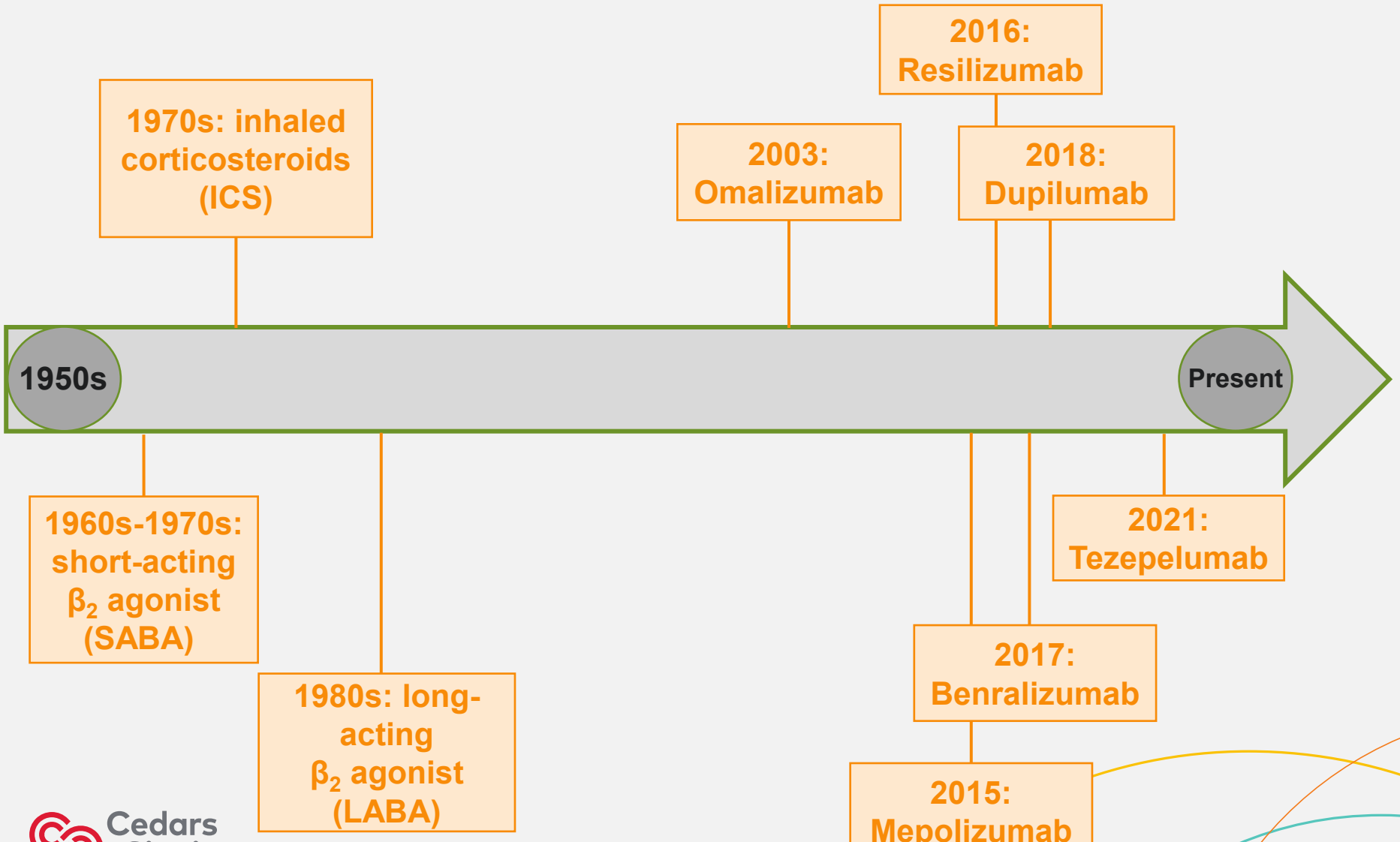
Adapted from: Blaiss Met al. Ann Allergy Asthma Immunol. 2023 Dec;131(6):782-785. doi: 10.1016/j.anai.2023.08.609. Epub 2023 Sep 8. PMID: 37690606.

Asthma Therapies Timeline



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Biologics and Asthma Remission

- Prevent asthma exacerbations, have oral steroid-sparing effects, improve lung function, and improve symptom control/quality of life

- How effective are they at inducing remission?

Criteria for Remission	Dupilumab		Benralizumab			Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/ CALIMA Phase 3	2022[4] ANDHI Phase 3b	2023[5] XALOC-1	2022[6,7] NAVIGATOR Phase 3	2022[8] REDES	2022[9] CHRONICLE	2022[10] Danish Registry
Absence of symptoms[a,b] **and**	ACQ-5 < 1.5	ACQ-5 < 1.5	ACQ-6 < 1.5" or ≤ 0.75	ACQ-6 < 1.5" or ≤ 0.75	ACQ-5 < 1.5 or ACT ≥ 16	ACQ-6 ≤ 1.5[a,b]	ACT ≥ 20	Majority ≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function **and**	Post-BD FEV_1pp ≥ 80%	Post-BD FEV_1 ≥ 80% *OR* pre-BD FEV_1 ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Not included	Pre-BD FEV_1pp > 80% *OR* Pre-BD FEV_1 > 20% from baseline; FEV1 > 95% of baseline**	Not included	Not included	Post-BD FEV_1pp ≥ 80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	26.3%"	28.7%	43%	14%^- 28.5%**	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted. ^ Includes agreement between physicians and patient assessments of control (clinical global impression of change CGI-C; Patient Global Impression of Severity)

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Jackson DJ Poster presented at AAAAI 2023 San Antonio TX USA 6. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 7. Wechsler, M ERS 2023 Milan, Italy (Unpublished) 8. Ribas DC et al. Drugs 2021;81(15):1763-1774. 9. Chipps, B et al. JACI 2022;149:Suppl AB147 10. Hansen S et al ERJ 2022;60:3553

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Lugogo NL et al. Chest. 2023 Oct;164(4):831-834. doi: 10.1016/j.chest.2023.04.028. PMID: 37805244; PMCID: PMC10925539.

Clinical remission attainment, definitions, and correlates among patients with severe asthma treated with biologics: a systematic review and meta-analysis Amy Shackleford, Liam G Heaney, Charlene Redmond, P Jane McDowell, John Busby

In the current analysis, among patients receiving biologics, clinical remission was defined within a period of 12 consecutive months as the absence of exacerbations and SCS use, at least 50% of ACT scores of 20 or more points in the latest 6 months, and subspecialist report of asthma control in the latest 6 months

There were 611 evaluable patients with biologic use for at least 12 months and complete data (Table II). At enrollment, the biologics received by these patients were omalizumab (28.2%), benralizumab (25.7%), mepolizumab (18.7%), dupilumab (12.4%), and reslizumab (2.6%). No patients included in this analysis received tezepelumab.

The median per-patient duration of biologic use (summed across biologics if more than 1 biologic was used) was 39.6 months

The median time from biologic initiation to remission was 30.2 months

The point prevalence of remission increased from 22.3% in months 12 to 13 to 34.3% in months 47 to 48.

Adults with controlled (ACQ-5 < 1.5) severe eosinophilic asthma on high dose ICS who had been initiated on benralizumab

Predictors of Remission

- Elevated blood eosinophils and FeNO associated with on-treatment remission[1]
- What about patients without T2-predominant biomarkers?

	Achieved Remission*			Did NOT Achieve Remission*		
	0-24 wks (n = 126)	>24-52 wks (n = 141)	>52-104 wks (n = 127)	0-24 wks (n = 244)	>24-52 wks (n = 228)	>52-104 wks (n = 247)
FeNO (ppb)						
<25	38.7%	37.1%	39.8%	45%	46.4%	44.5%
25 to <50	28.2%	30.7%	28.5%	27.5%	27.2%	28.6%
≥50	33.1%	32.1%	31.7%	27.5%	26.3%	26.9%
Blood Eosinophils (cells/µl)						
<150	19%	19.9%	22%	27.5%	28.1%	26.3%
150 to <300	31%	29.8%	30.7%	35.7%	37.3%	36%
≥300	50%	50.4%	47.2%	36.9%	34.6%	37.7%

*Remission defined as an ACQ-6 total score ≤1.5, stable lung function (pre-BD FEV1 >95% of baseline) and no exacerbations or use of oral corticosteroids

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[1]Chipps BE et al. J Allergy Clin Immunol Glob. 2024 Oct 30;4(1):100365. doi: 10.1016/j.jacig.2024.100365. PMID: 39659738; PMCID: PMC11629328.
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Conclusions

- Paradigm shift in asthma treatment goals is needed
- Studies have shown that asthma remission is possible with use of biologic therapies
- Definition of asthma remission is evolving, but criteria have been proposed
- Therefore, remission can be targeted even as definitions are being validated and refined
- Further research is needed to demonstrate that targeting remission in asthma leads to better outcomes for patients

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Quotes from GINA 2024

"The concept of clinical remission on treatment is consistent with the long-term goal of asthma management promoted by GINA, to achieve the best possible long-term asthma outcomes for each patient"

"Research in patients who have (or have not) experienced clinical or complete remission of asthma, either off treatment or on treatment, provides important opportunities for understanding … underlying mechanisms of asthma, and for developing new approaches to asthma prevention and management"

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Cedars Sinai

Thank you!

Cedars Sinai

Con: Clinical Remission is not possible in asthma

Nicholas Kenyon, MD, MAD

University of California, Davis

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- Regeneron, advisory board
- Astra Zeneca, research study
- Patents #11,813,050 and #10,111,606 and #10,067,119 and #9,398,881 and PCT/US2017/063,018 and PCT/US2017/023908 are assigned to UC Davis and licensed to SensIT Ventures,

- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Con Discussion

1. Is clinical remission possible in asthma?

    -Yes, as defined

2. Does clinical remission represent a new level of success in managing our asthma patients?

    -Probably not

3. Should this be a focus of our care?

    -No

Do we know what remission is?

- Cancer Remission – "Cancer remission can be partial, complete, or spontaneous. For cancer to be in remission, a decrease in cancer signs for at least a month must be observed. Cancers in remission, however, may come back or recur."

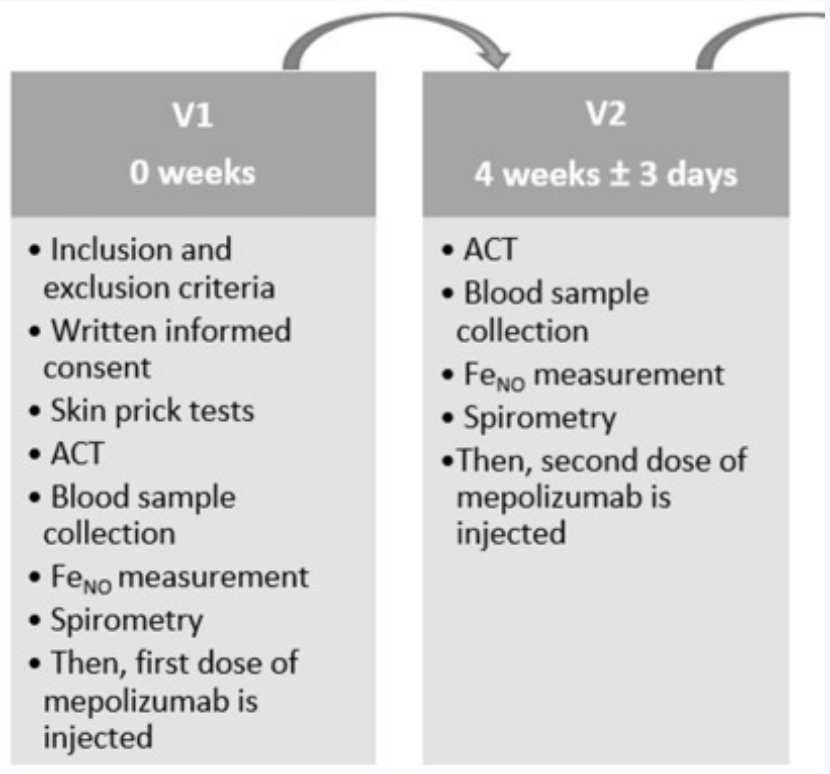
- Rheumatoid Arthritis Remission – "Rheumatoid arthritis is generally considered a chronic, lifelong condition… Doctors and people living with RA may both have remission as a goal. But they might not agree on exactly what remission means and what it looks like. You may think of remission as freedom from symptoms, while your doctor will follow a more technical medical definition."

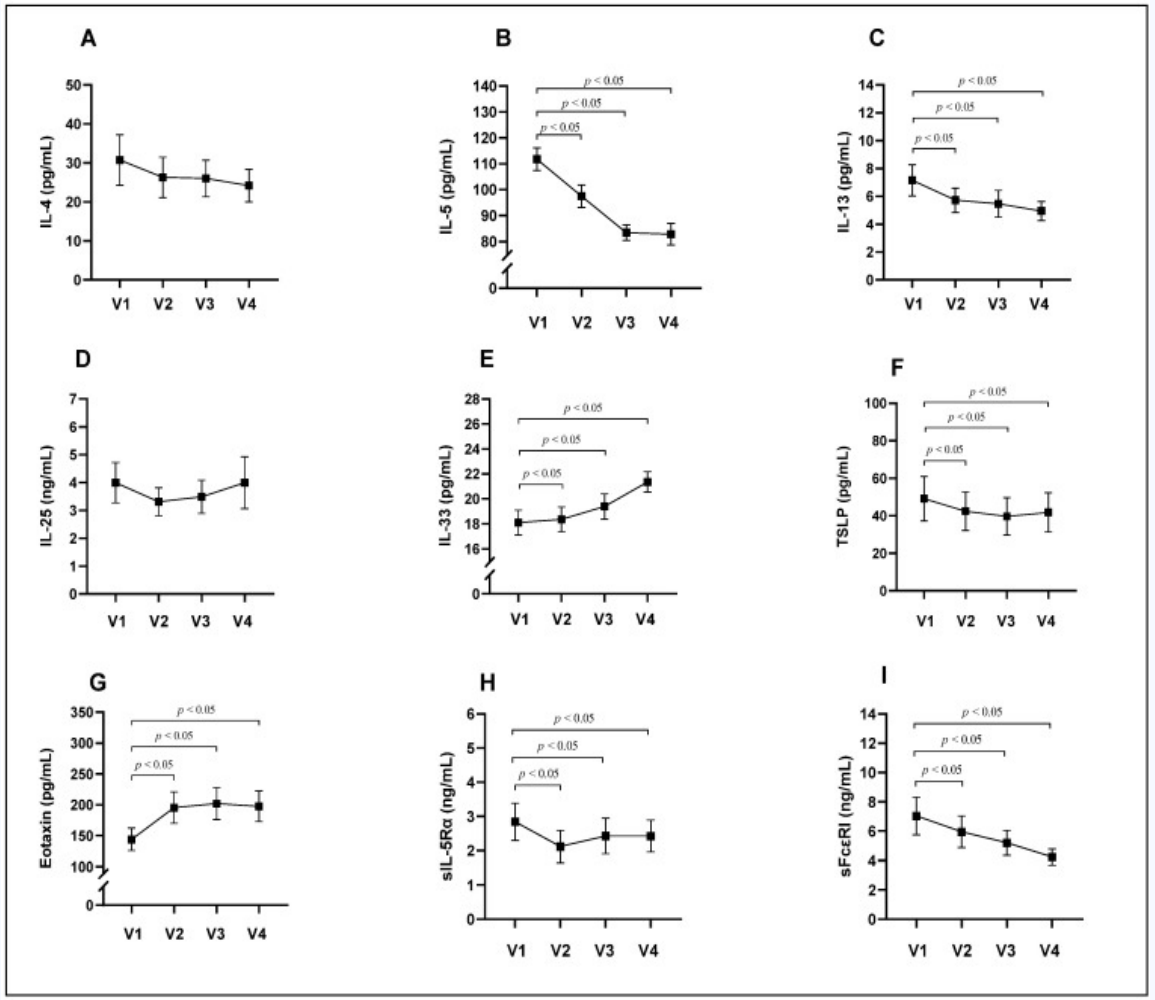
Clinical remission in asthma

Clinical Remission on Treatment	Clinical Remission off Treatment
For ≥12 months: • Sustained absence of significant asthma symptoms based on validated instrument, **and** • Optimization and stabilization of lung function, **and** • Patient and HCP agreement regarding disease remission, **and** • No use of systenic corticosteriod therapy for exacerbation treatment or long-term disease control	Same criteria maintained without asthma treatment for ≥12 months
Complete Remission on Treatment	**Complete Remission off Treatment**
Clinical remission plus the following: • Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FENO, and/or other relevant measures), **and** • In appropriate research settings: Current negative bronchial hyperresponsiveness	Same criteria maintained without asthma treatment for ≥12 months

Menzies Gow et al. JACI 2020

Clinical remission and inflammatory biomarkers

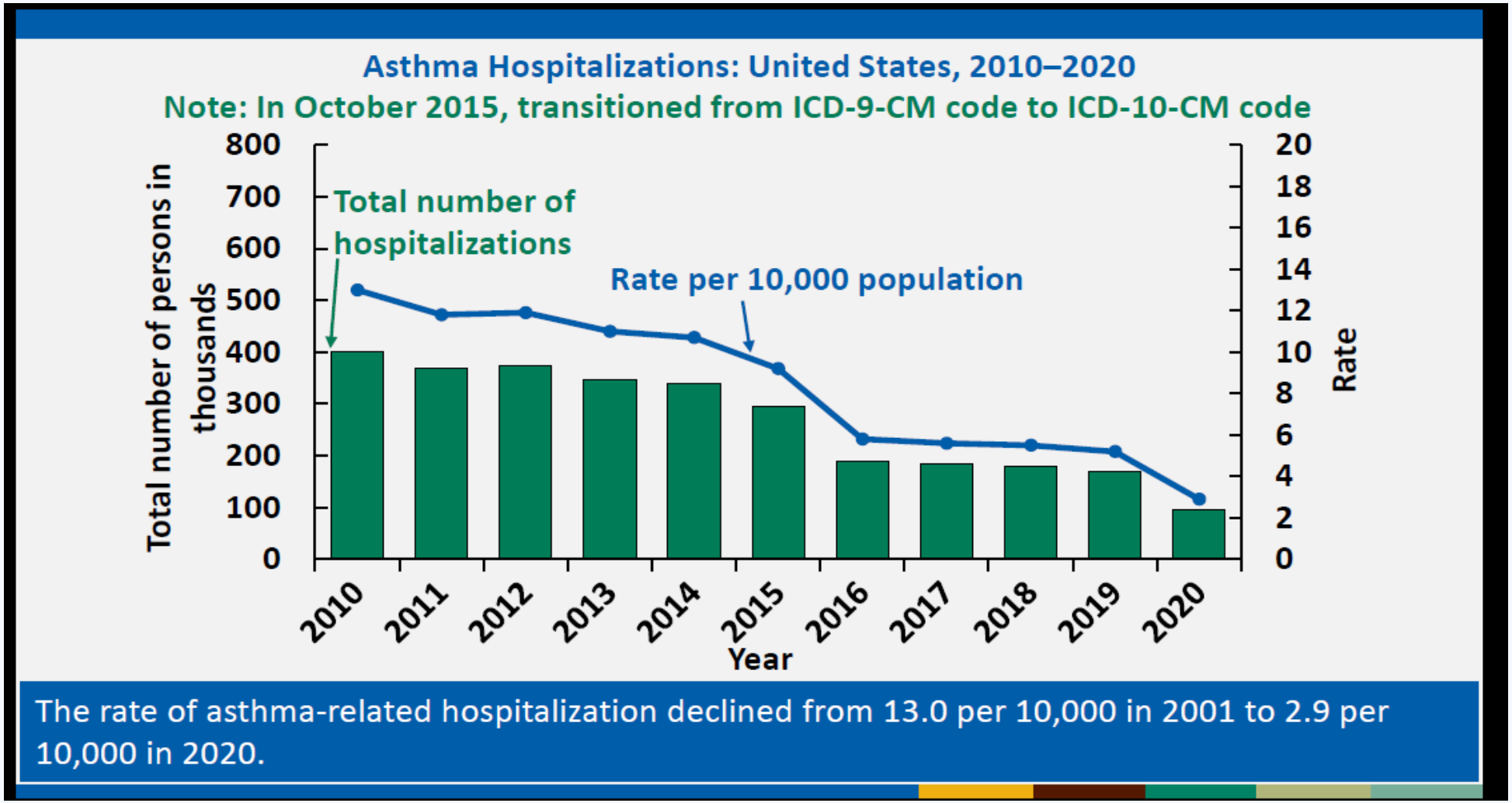




Palacionyte et al Diagnostics 2024

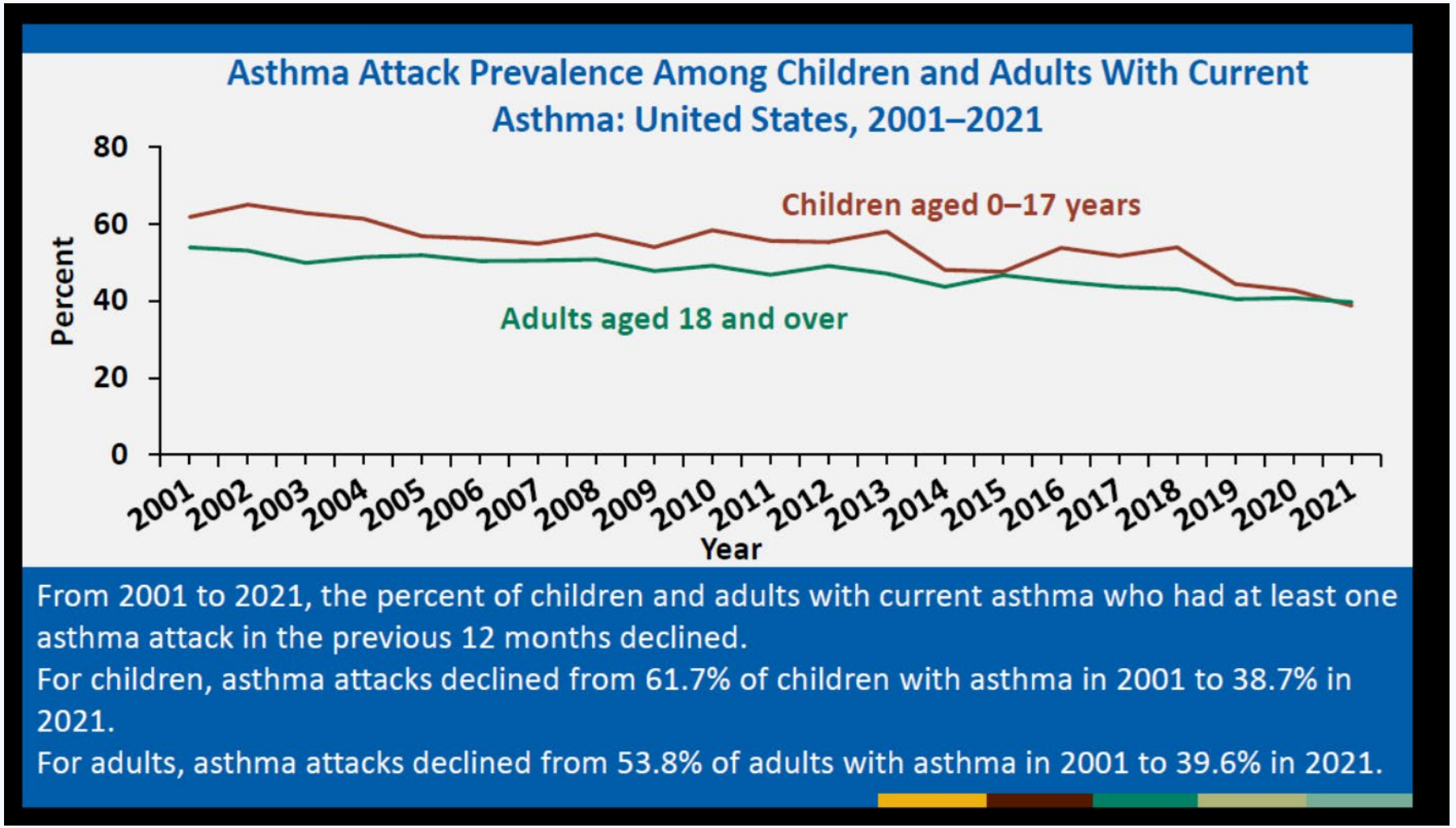
California Thoracic Society
ATS Chapter Serving California and Arizona

We have managed asthma risk better.



CDC 2023

Asthma exacerbations are fairly persistent.



CDC 2023

We can't alter natural and manmade asthma precipitants.

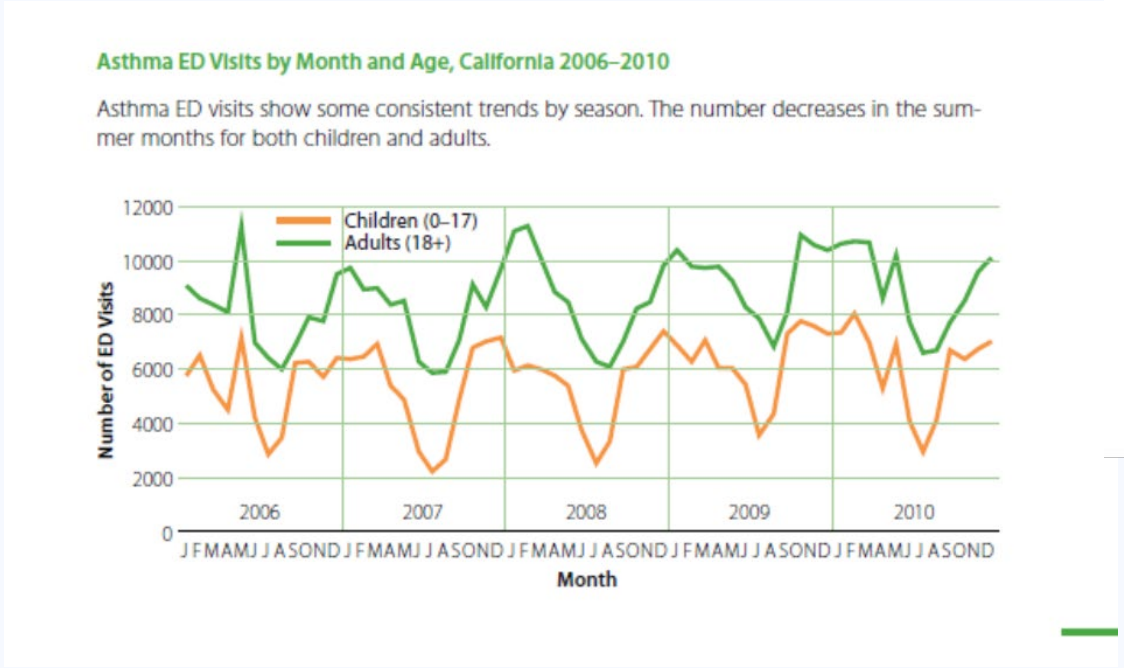
Respiratory viruses

Wildfires

Indoor / outdoor pollutants

- Volatile organic compounds/VOCS

Occupational exposures



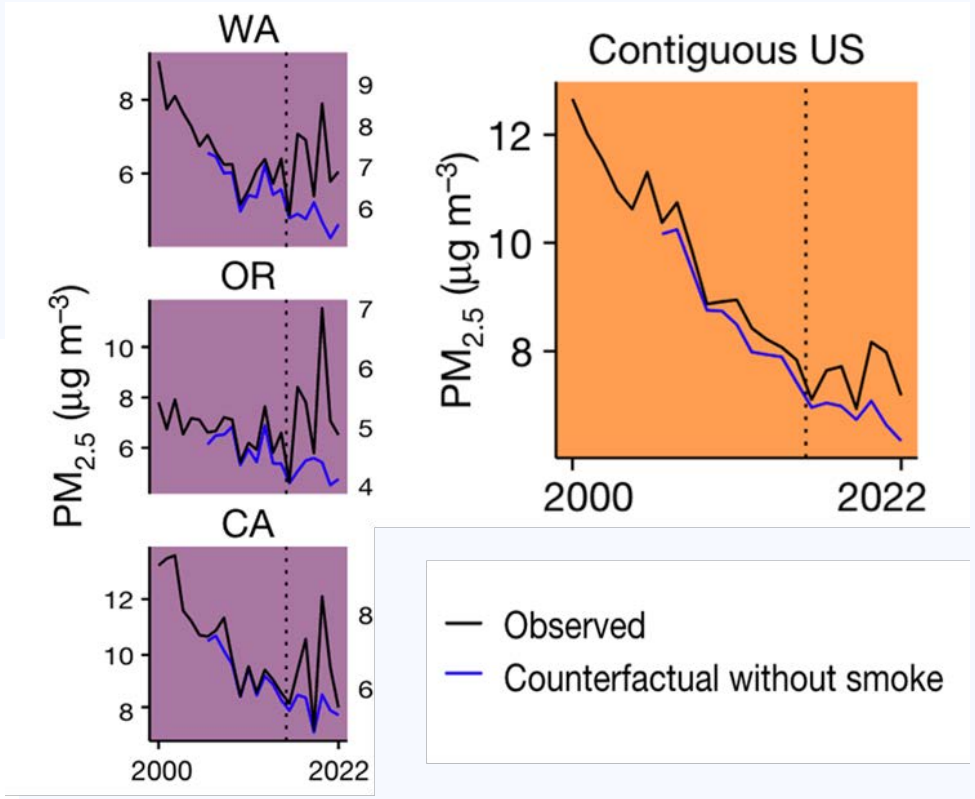
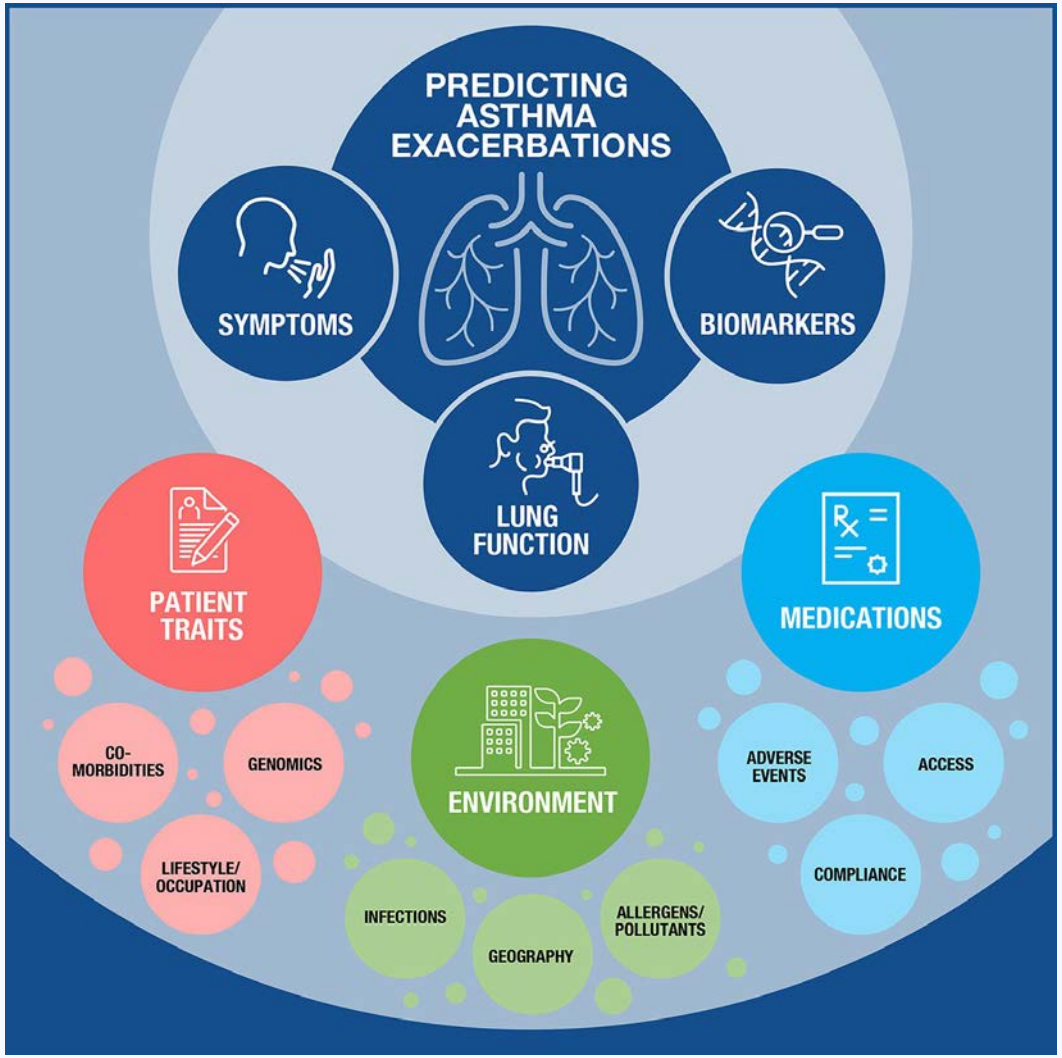


Figure 1: Effect of wildfire smoke on ambient PM2.5 levels nationally

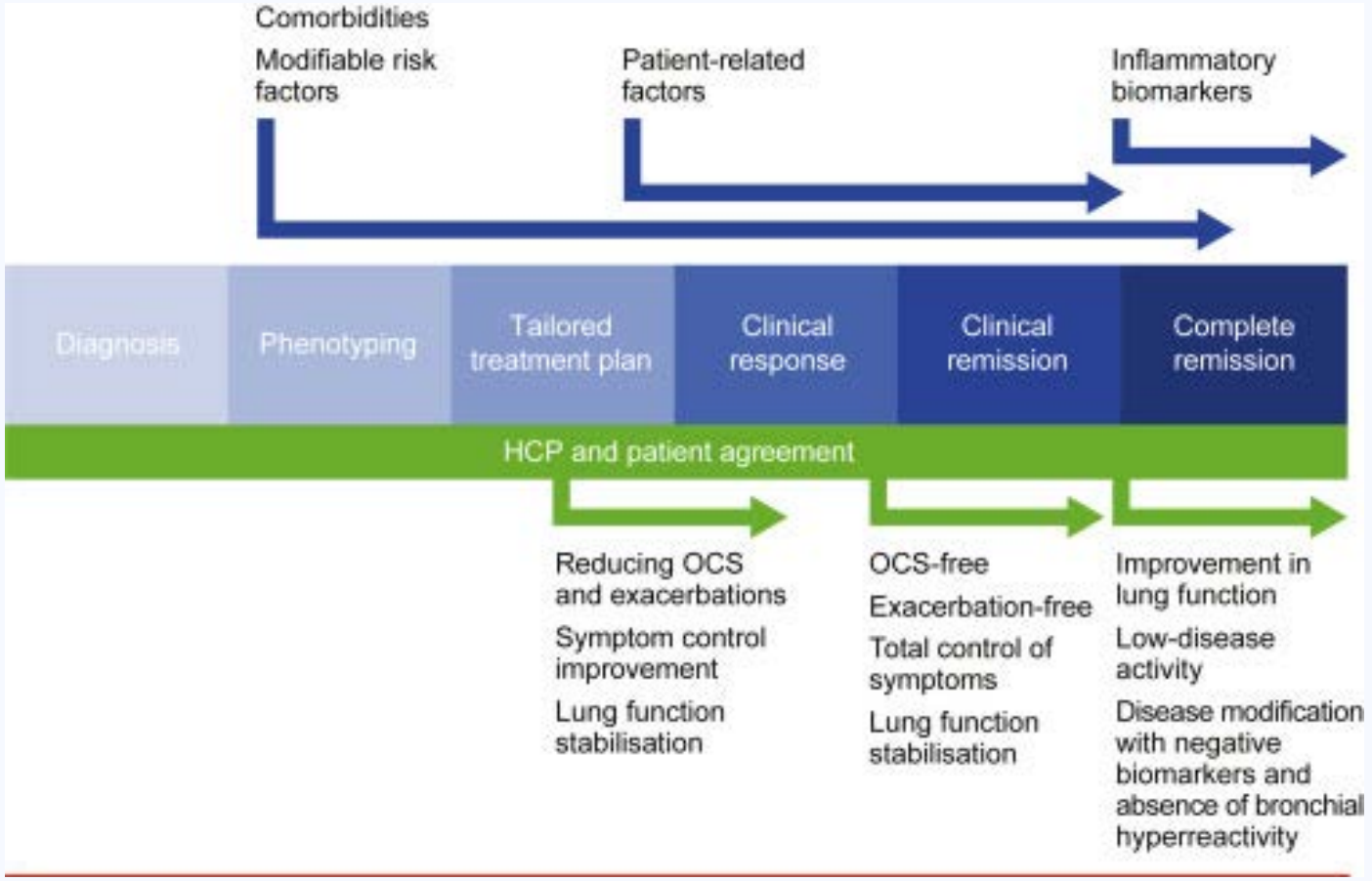
CDPH; Burke et al. Nature. 2023

Can we predict asthma exacerbations ? Maybe in the future with AI/ML.



Molfino et al. Adv Ther. 2023.

Continuum of care in asthma



Busse et al. JACI 2024

What issues will we face with our patients if we focus on clinical remission?

- Miscommunication.
  - "Your asthma is in remission, but your asthma is still there…so don't change anything."
- Disillusionment
  - "I thought this drug was going to cure me."
- Potential insurance and reapproval issues with standard of care medications.
  - "I was doing so well that I stopped all of my other medications."

Summary

1. Is clinical remission possible in asthma?

    -Yes, as defined

2. Does clinical remission represent a new level of success in managing our asthma patients?

    -Probably not

3. Should this be a focus of our care?

    -No

From ILA to PPF: Understanding the ILD Alphabet Soup

Toby Maher

Professor of Medicine and Director of Interstitial Lung Disease Unit.

Keck Medicine of USC.

Disclosures

- I have the following relationships with ACCME defined ineligible companies:

Abbvie, Amgen, AstraZeneca, Bayer, Biogen Idec,
Blade Therapeutics, BMS, Boehringer Ingelheim, Endeavor,
F. Hoffmann-La Roche, Galápagos NV, Galecto, GlaxoSmithKline, Gossamer Bio,
Merck, Pfizer, Pliant, Redx, Trevi, Three Lakes Partners, UCB, United Therapeutics,
Vicore

- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

JAMA | Review

Interstitial Lung Disease
A Review

Toby M. Maher, MD, MSc, PhD

IMPORTANCE Interstitial lung disease (ILD) consists of a group of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea that frequently results in end-stage respiratory failure. In the US, ILD affects approximately 650 000 people and causes approximately 25 000 to 30 000 deaths per year.

OBSERVATIONS The most common forms of ILD are idiopathic pulmonary fibrosis (IPF), which accounts for approximately one-third of all cases of ILD, hypersensitivity pneumonitis, accounting for 15% of ILD cases, and connective tissue disease (CTD), accounting for 25% of ILD cases. ILD typically presents with dyspnea on exertion. Approximately 30% of patients with ILD report cough. Thoracic computed tomography is approximately 91% sensitive and 71% specific for diagnosing subtypes of ILDs such as IPF. Physiologic assessment provides important prognostic information. A 5% decline in forced vital capacity (FVC) over 12 months is associated with an approximately 2-fold increase in mortality compared with no change in FVC. Antifibrotic therapy with nintedanib or pirfenidone slows annual FVC decline by approximately 44% to 57% in individuals with IPF, scleroderma associated ILD, and in those with progressive pulmonary fibrosis of any cause. For connective tissue disease–associated ILD, immunomodulatory therapy, such as tocilizumab, rituximab, and mycophenolate mofetil, may slow decline or even improve FVC at 12-month follow-up. Structured exercise therapy reduces symptoms and improves 6-minute walk test distance in individuals with dyspnea. Oxygen reduces symptoms and improves quality of life in individuals with ILD who desaturate below 88% on a 6-minute walk test. Lung transplant may improve symptoms and resolve respiratory failure in patients with end-stage ILD. After lung transplant, patients with ILD have a median survival of 5.2 to 6.7 years compared with a median survival of less than 2 years in patients with advanced ILD who do not undergo lung transplant. Up to 85% of individuals with end-stage fibrotic ILD develop pulmonary hypertension. In these patients, treatment with inhaled treprostinil improves walking distance and respiratory symptoms.

CONCLUSIONS AND RELEVANCE Interstitial lung disease typically presents with dyspnea on exertion and can progress to respiratory failure. First-line therapy includes nintedanib or pirfenidone for IPF and mycophenolate mofetil for ILD due to connective tissue disease. Lung transplant should be considered for patients with advanced ILD. In patients with ILD, exercise training improves 6-minute walk test distance and quality of life.

JAMA. doi:10.1001/jama.2024.3669
Published online April 22, 2024.

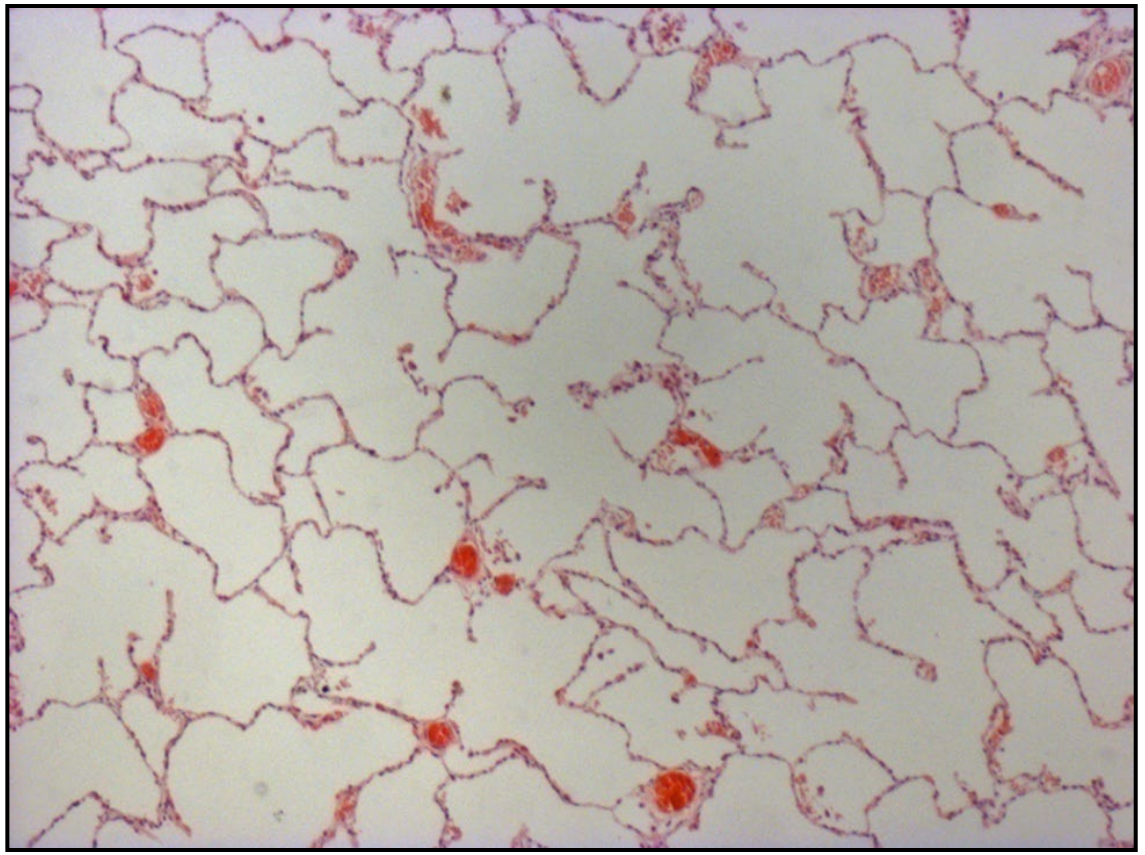
Multimedia

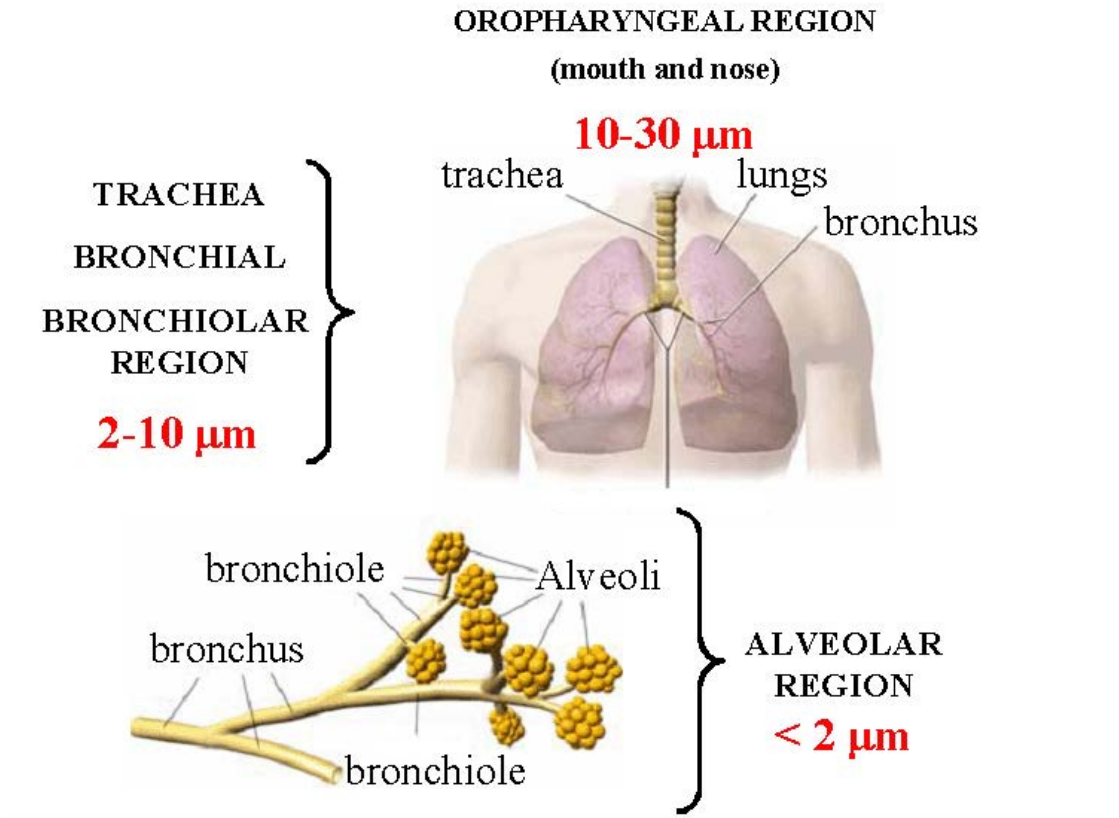
CME at jamacmelookup.com

Author Affiliations: University of Southern California, Los Angeles; National Heart and Lung Institute, Imperial College, London, UK.

Corresponding Author: Toby M. Maher, MD, MSc, PhD, University of Southern California, 1510 San Pablo St, Ste 514, Los Angeles, CA 90033 (tobymahe@usc.edu).

Section Editor: Kristin Walter, MD, Deputy Editor.




OROPHARYNGEAL REGION
(mouth and nose)
10-30 µm
TRACHEA
BRONCHIAL
BRONCHIOLAR REGION
2-10 µm
trachea
lungs
bronchus
bronchiole
Alveoli
bronchus
bronchiole
ALVEOLAR REGION
< 2 µm

Guidelines – 2011, 2018, 2022…

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernand
Thomas V. Colby, Jean-François Cordier, Kevin R. Flah
Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Dem
Masahito Ebina, David M. Hansell, Takeshi Johkoh, Do
Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson,
Barbara S. Griss, Shandra L. Protzko, and Holger J. S
on Idiopathic Pulmonary Fibrosis

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIET
RESPIRATORY SOCIETY (JRS), AND THE LATIN AMERICAN THOR
DIRECTORS, NOVEMBER 2010, THE ERS EXECUTIVE COMMITTEE,
THE ALAT EXECUTIVE COMMITTEE, NOVEMBER 2010

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Idiopathic
An Official ATS/ERS/JRS/A

Ganesh Raghu, Martine Remy-Jardin, J
Juergen Behr, Vincent Cottin, Sonye K.
Arata Azuma, Thomas J. Bice, Demosth
Yoshikazu Inoue, R. Gisli Jenkins, Takes
George Mansour, Andrew G. Nicholson,
William D. Travis, Simon L. F. Walsh, an
Respiratory Society, Japanese Respirat

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AM
SOCIETY (JRS), AND LATIN AMERICAN THORACIC SOC

Check for updates

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

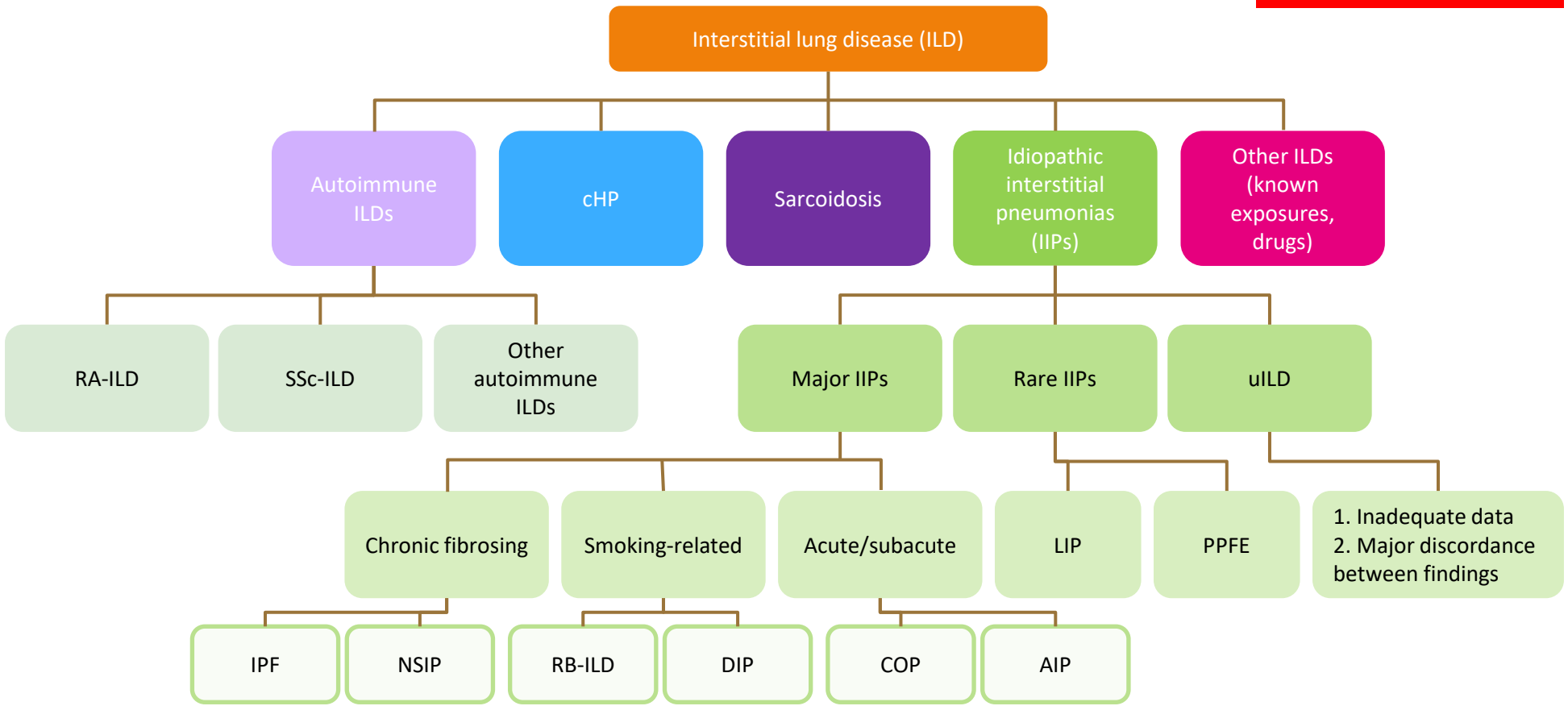
Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

This Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, June 2001 and by The ERS Executive Committee, June 2001

Interstitial Lung Abnormalities



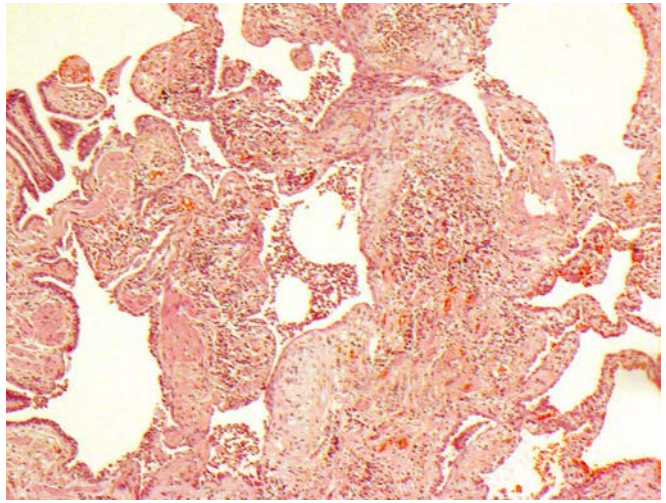
AIP, acute interstitial pneumonia; ATS, American Thoracic Society; COP, cryptogenic organising pneumonia; ERS, European Respiratory Society; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis;
LIP, lymphocytic interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis

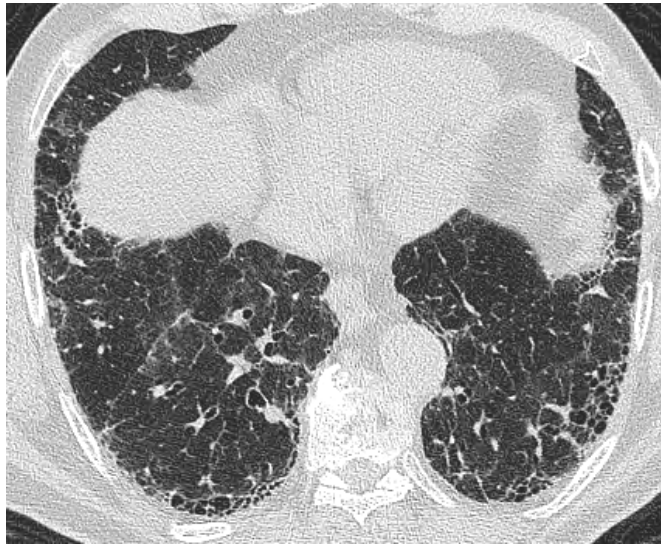
Adapted from: ATS/ERS. *Am J Respir Crit Care Med.* 2002;165:277–304; Ryerson CJ, Collard HR. *Curr Opin Pulm Med.* 2013;19:453–459; Travis WD, et al. *Am J Respir Crit Care Med.* 2013;188:733–748; Cottin V, et al. *Eur Respir Rev.* 2018;27:pii180076

ILD PATTERNS

Usual interstitial Pneumonia (UIP)

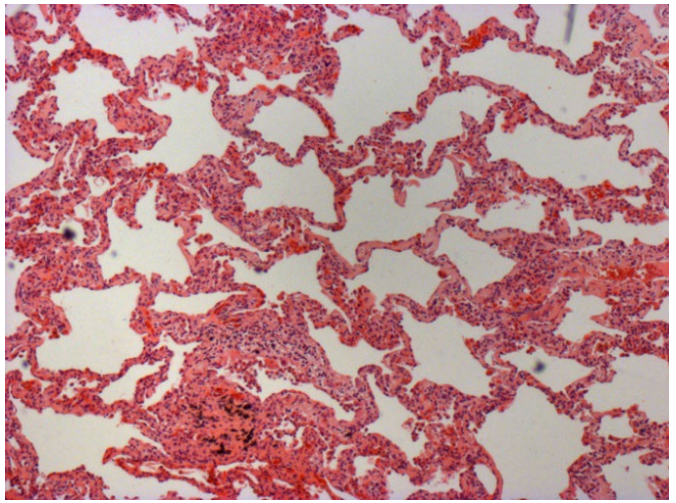
- IPF, rheumatoid-ILD, asbestosis, scleroderma-ILD, HP, sarcoidosis
- Poor prognosis: untreated median survival is approximately 3-4 y from diagnosis

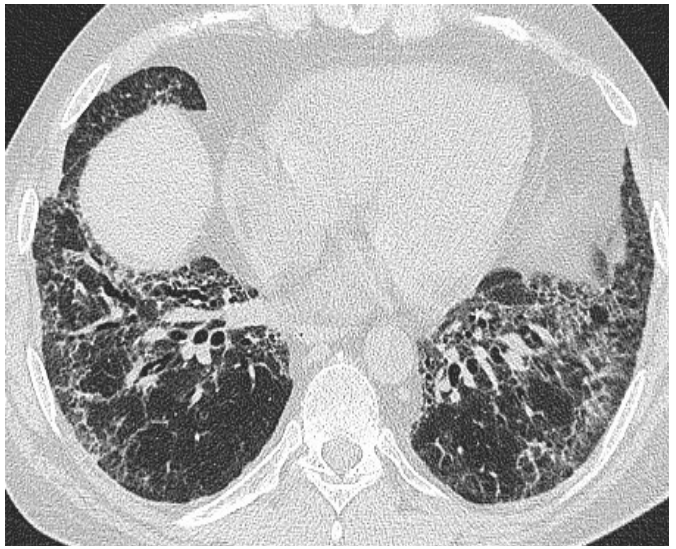




Non-Specific Interstitial Pneumonia (NSIP)

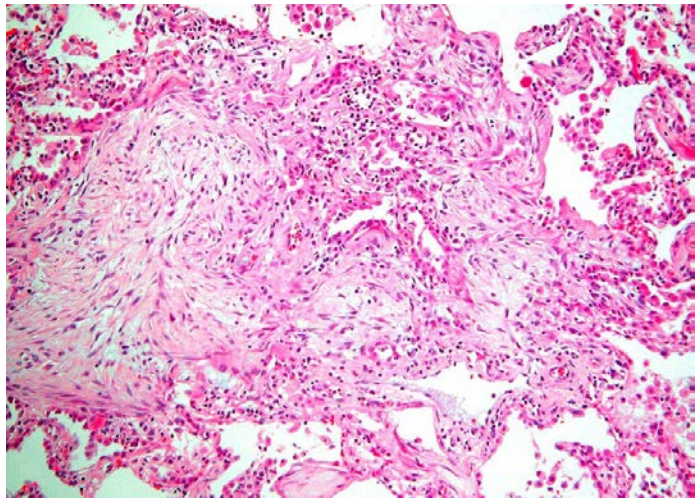
- iNSIP, scleroderma-ILD, rheumatoid-ILD, drug-induced ILD, smoking-induced ILD
- Intermediate prognosis: untreated median survival is approximately 8-10 y from diagnosis

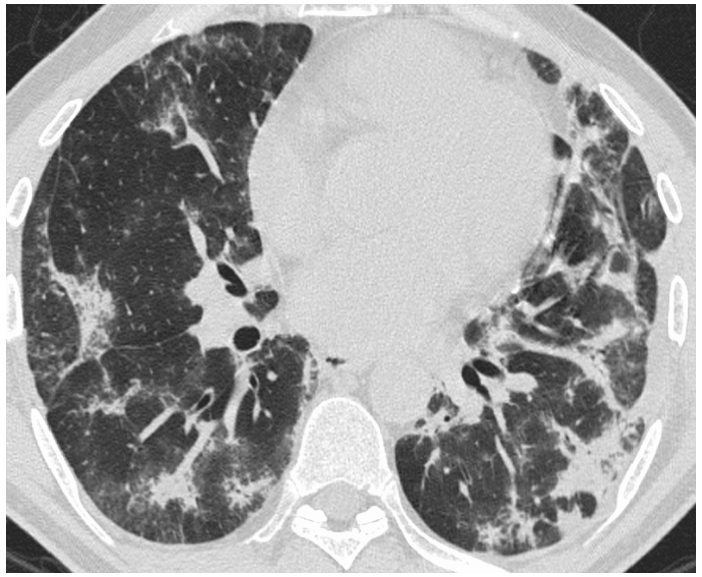




Organizing Pneumonia (OP)

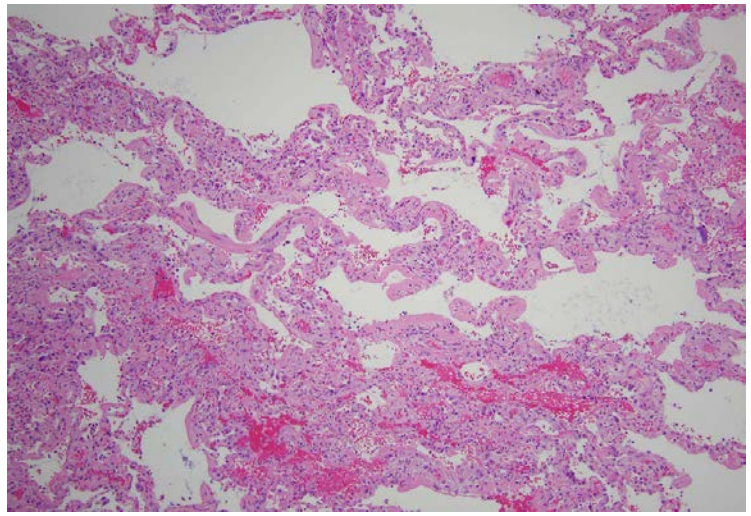
- COP, IIM associated ILD, drug-induced ILD, rheumatoid-ILD, vasculitis
- Good prognosis: often responds well to immunomodulatory therapy; however, some individuals with secondary OP progress to pulmonary fibrosis

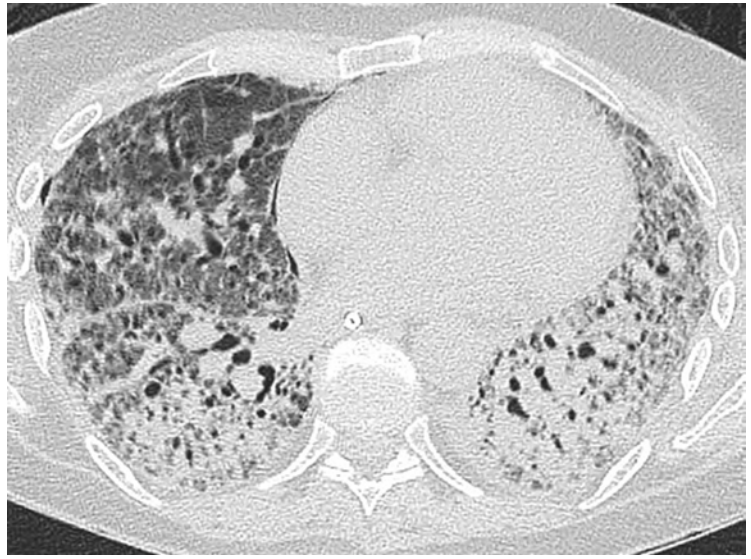




Acute Interstitial Pneumonia (AIP)

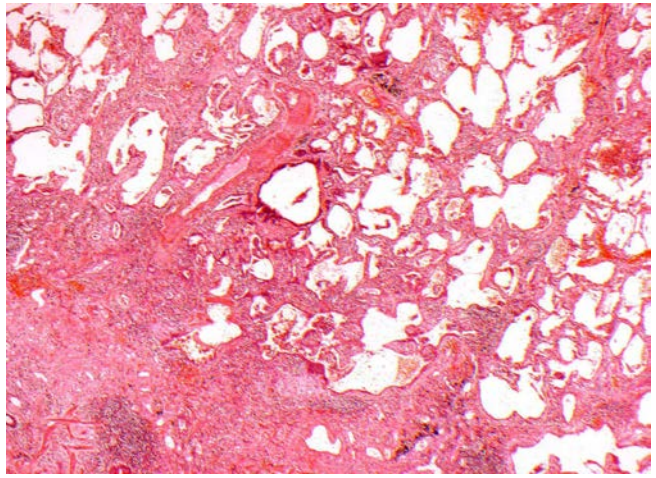
- ARDS, AIP, IIM (especially MDA5+) associated ILD, acute exacerbations of existing ILD
- Very poor prognosis: median survival is 2.2 months

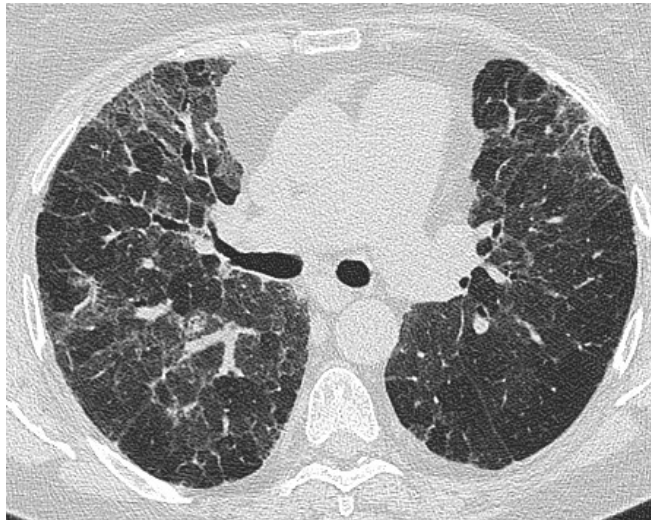




Bronciolocentric interstitial pneumonia (BIP)/ Hypersensitivity pneumonitis

- Good prognosis: nonfibrotic HP, frequently resolves without significant sequelae
- Intermediate prognosis: fibrotic HP





The multi-disciplinary team

Idiopathic Interstitial Pneumonia

What Is the Effect of a Multidisciplinary Approach to Diagnosis?

Kevin R. Flaherty, Talmadge E. King, Jr., Ganesh Raghu, Joseph P. Lynch III, Thomas V. Colby, William D. Travis, Barry H. Gross, Ella A. Kazerooni, Galen B. Toews, Qi Long, Susan Murray, Vibha N. Lama, Steven E. Gay, and Fernando J. Martinez

Division of Pulmonary and Critical Care Medicine and Department of Radiology, University of Michigan Health System, and Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; University of California, San Francisco, San Francisco, California; University of Washington, Seattle, Washington; Mayo Clinic, Scottsdale, Arizona; and Armed Forces Institute of Pathology, Washington, DC

(Received in original form February 3, 2004; accepted in final form July 11, 2004)

Supported in part by National Institutes of Health NHLBI grant P50HL46487, NIH/NCRR 3 MO1 RR00042-3353, NIH/NIA P60 AG08808-06, NHLBI, 1 K24 HL04212, and 1 K23 HL68713.

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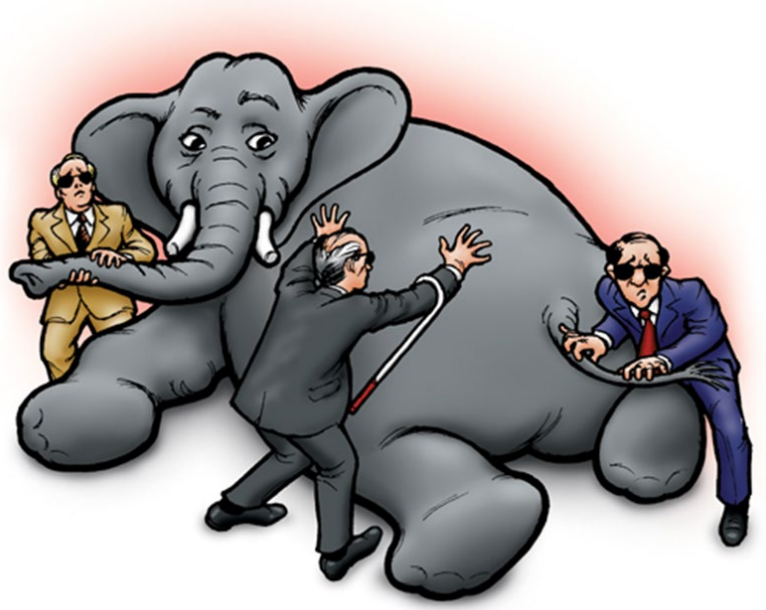
Am J Respir Crit Care Med Vol 170. pp 904–910, 2004
Originally Published in Press as DOI: 10.1164/rccm.200402-147OC on July 15, 2004
Internet address: www.atsjournals.org



Investigation of Suspected ILD

History and Clinical Examination

↓

Chest X-ray and Spirometry

↓

Confirm ILD

- Blood tests
- HRCT
- MDT assessment

↓

Confident Diagnosis?

↓ No

Consider BAL
(if non-diagnostic)

↓

lung biopsy (VATS/Cryobiopsy)

↓

MDT Assessment

↓ Yes

Assess Severity

- Full lung function
- 6 minute walk
- Overnight oximetry

Exclude complications

- Echocardiogram

Disease specific Investigations e.g.

- PET scan, 24 hour urinary calcium (sarcoid)
- Pituitary MRI (Langerhan's Histiocytosis)
- Tuberous sclerosis genotyping (LAM)

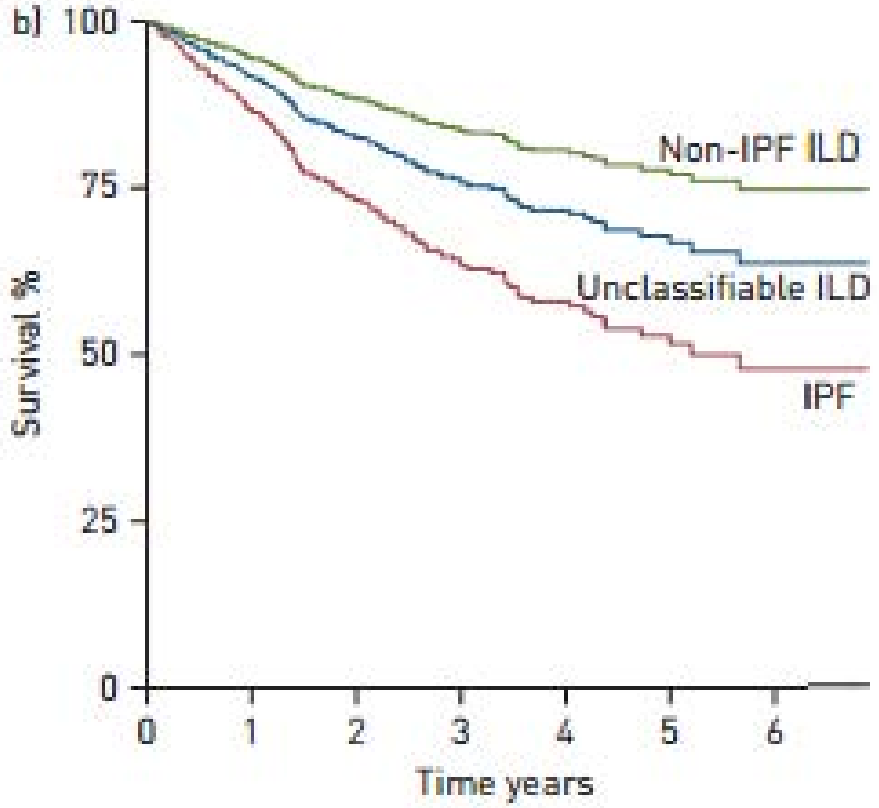
Maher TM Clinics in Allergy and Immunology 2012

Not all fibrotic ILD is classifiable

Prevalence and prognosis of unclassifiable interstitial lung disease

Christopher J. Ryerson[1], Thomas H. Urbania[2], Luca Richeldi[3], Joshua J. Mooney[4], Joyce S. Lee[4], Kirk D. Jones[5], Brett M. Elicker[2], Laura L. Koth[4], Talmadge E. King Jr[4], Paul J. Wolters[4] and Harold R. Collard[4]

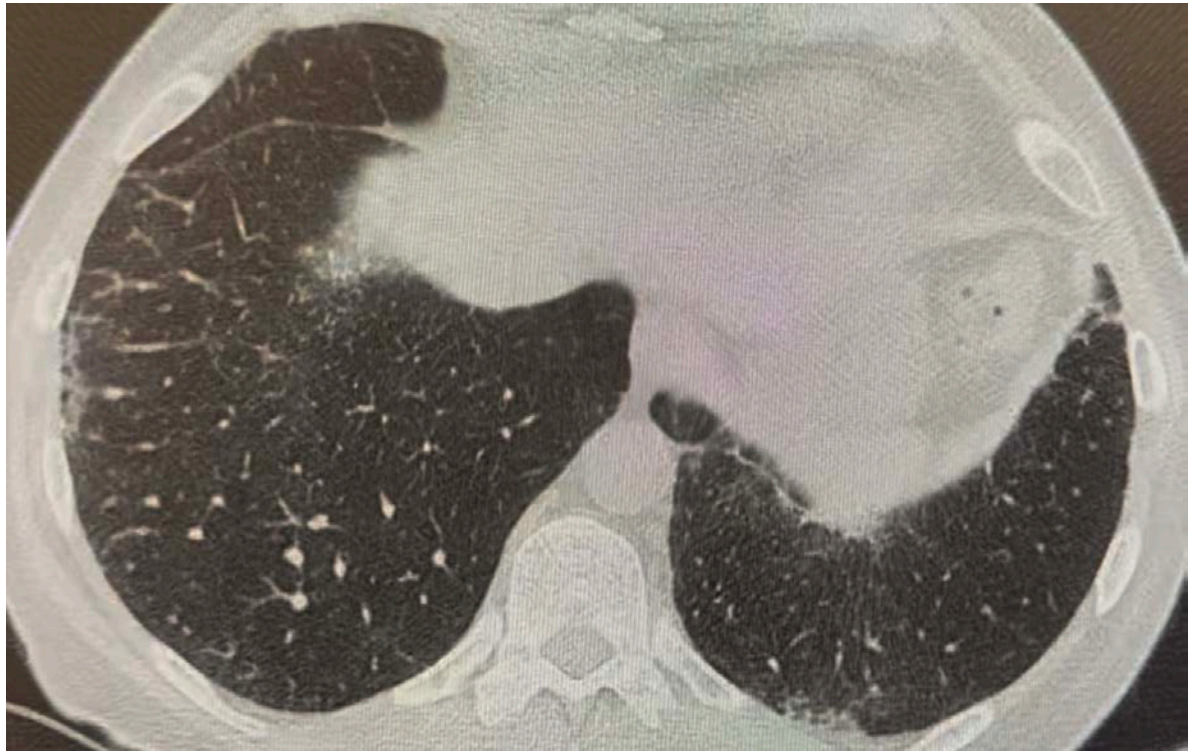
Affiliations: [1]Dept of Medicine, University of British Columbia, Vancouver, BC, Canada. [2]Dept of Radiology, University of California San Francisco, CA, [4]Dept of Medicine, University of California San Francisco, CA, and [5]Dept of Pathology, University of California San Francisco, CA, USA. [3]Center for Rare Lung Diseases, University of Modena and Reggio Emilia, Modena, Italy.



INTERSTITIAL LUNG ABNORMALITIES

Case History

- 54 year old man
- No respiratory symptoms
- Undergoing renal transplant assessment for end-stage diabetic nephropathy
- Ex smoker – 20 pk years
- Clinical exam unremarkable
- FVC 3.8 L, 106% predicted
- Tlco 94% predicted



What are interstitial lung abnormalities?

What are interstitial lung abnormalities (ILAs)?

- Incidental identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts
- Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)
- In individuals in whom interstitial lung disease is not suspected

Hatabu et al Fleischner Society Position Paper LRM 2020

What are NOT ILAs?

Imaging findings restricted to:

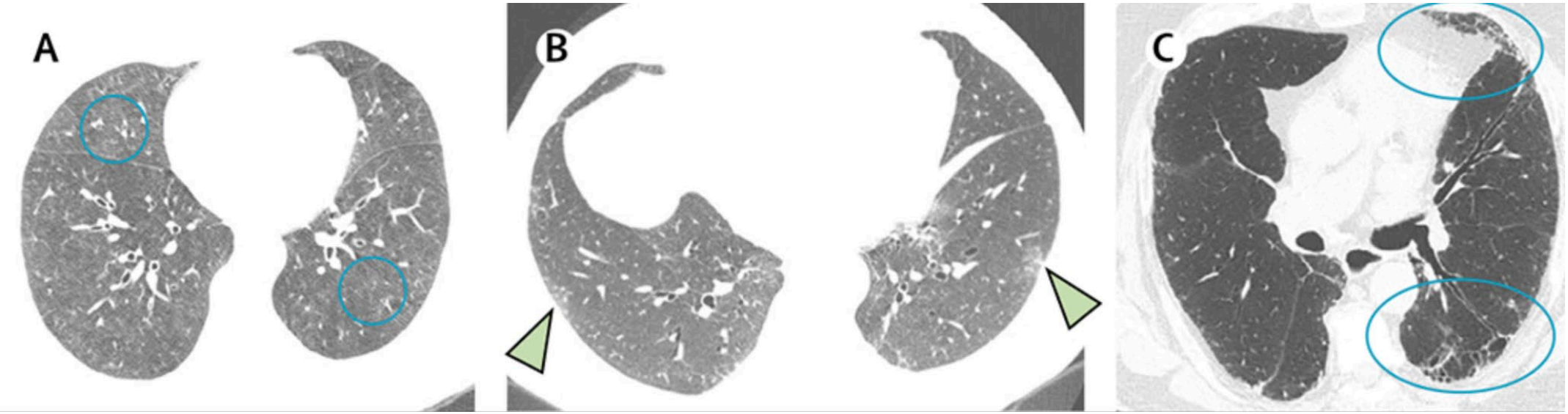
- Dependent lung atelectasis
- Focal paraspinal fibrosis in close contact with thoracic spine osteophytes (figure 2A)
- Smoking-related centrilobular nodularity in the absence of other findings (figure 2B)
- Mild focal or unilateral abnormality (figure 2C)
- Interstitial oedema (eg, in heart failure)
- Findings of aspiration (patchy ground-glass, tree in bud; figure 2C)

Preclinical and clinical identification:

- Preclinical interstitial abnormalities identified during screening of high-risk individuals (eg, those with rheumatoid arthritis, scleroderma, occupational exposure, familial interstitial lung disease)
- Findings in patients with known clinical interstitial lung disease

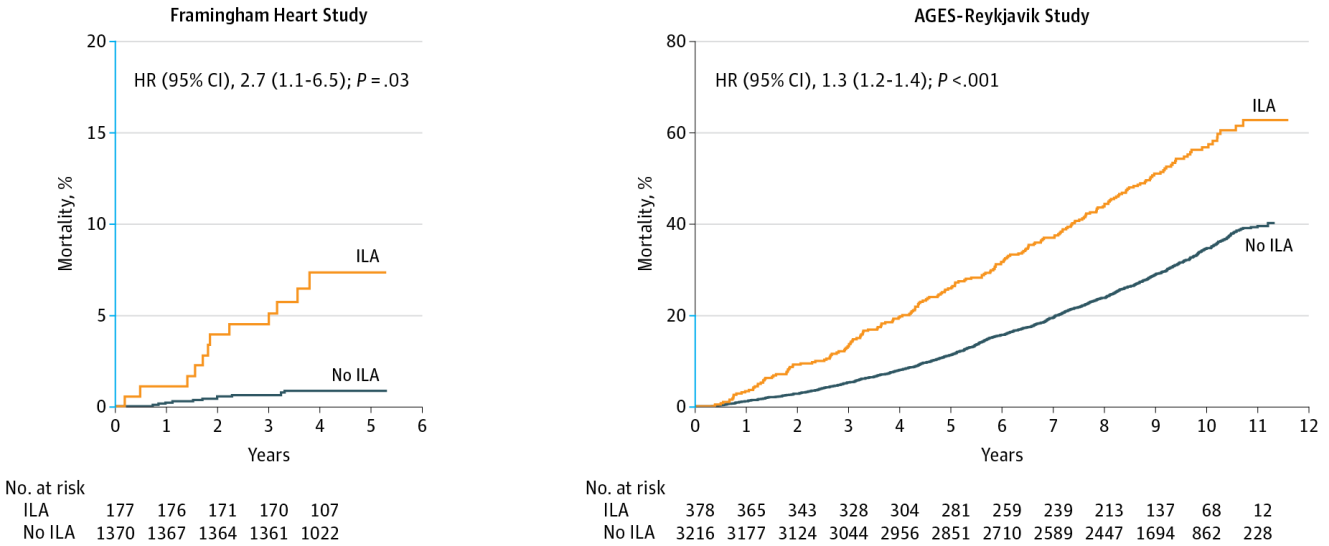
Hatabu et al Fleischner Society Position Paper LRM 2020

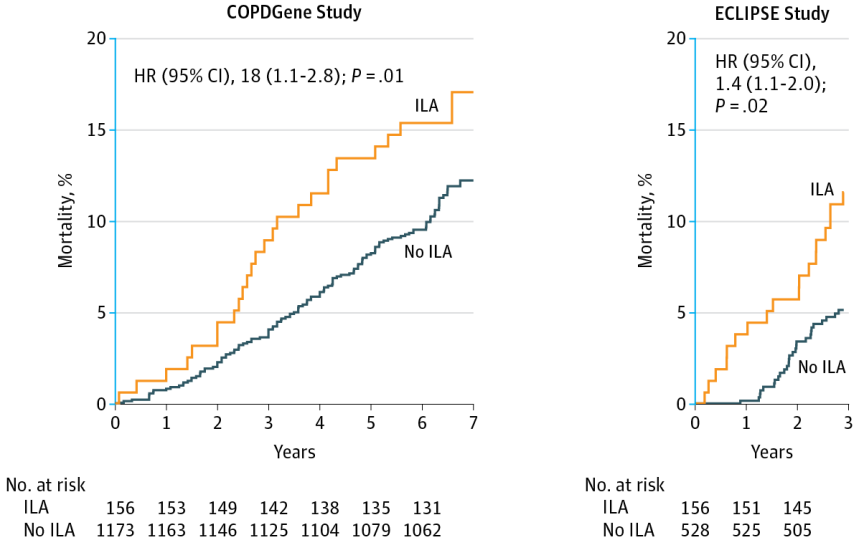
Types of ILA



Hatabu et al Fleischner Society Position Paper LRM 2020

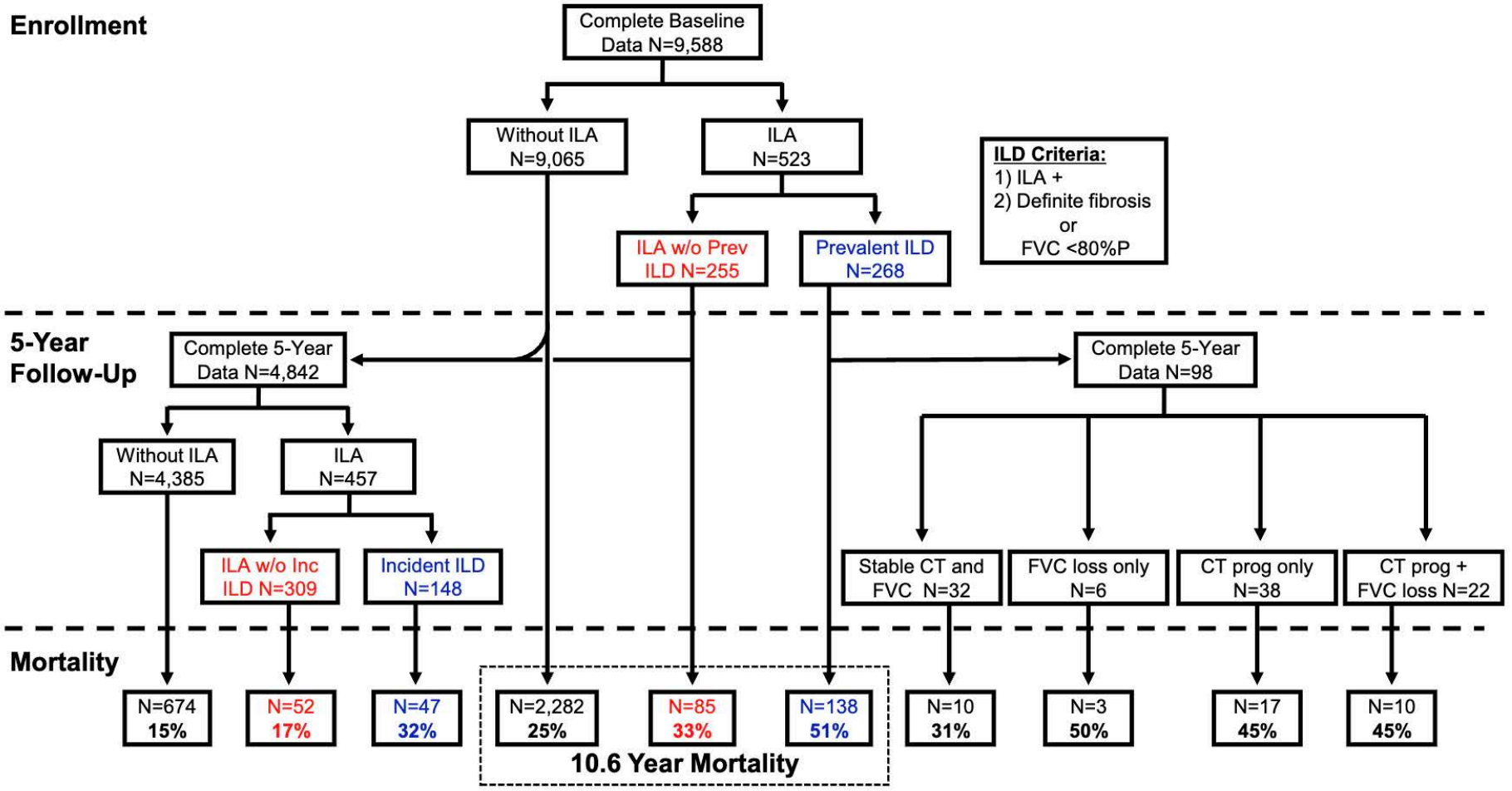
Relevance of ILA





Putman et al JAMA 2016

Distinguishing ILA from ILD



Rose et al AJRCCM 2024

Predictors of worse outcome with ILA

- Fibrotic change (honeycomb cysts, reticulation with traction bronchiectasis)
- Family history
- Genetic mutations (MUC5B, TERT, RTEL)
- Short telomeres
- CT progression over 12 months
- >10% FVC decline over 12 months
- Protein biomarkers

Predictors of worse outcome with ILA

- Fibrotic change (honeycomb cysts, reticulation with traction bronchiectasis)
- Family history
- Genetic mutations (MUC5B, TERT, RTEL)
- Short telomeres
- CT progression over 12 months
- >10% FVC decline over 12 months
- Protein biomarkers

My Clinical Approach to ILA*

- Exclude ILD (history of known cause of ILD, e.g. RA, respiratory symptoms, physiological impairment).
- Obtain baseline PFTs and HRCT
- Assess for change in PFTs (at 6 and 12 months) and CT (at 12 months)
- If stable PFTs and CT then follow annually with PFTs
- If PFT and/or CT worsening manage as ILD

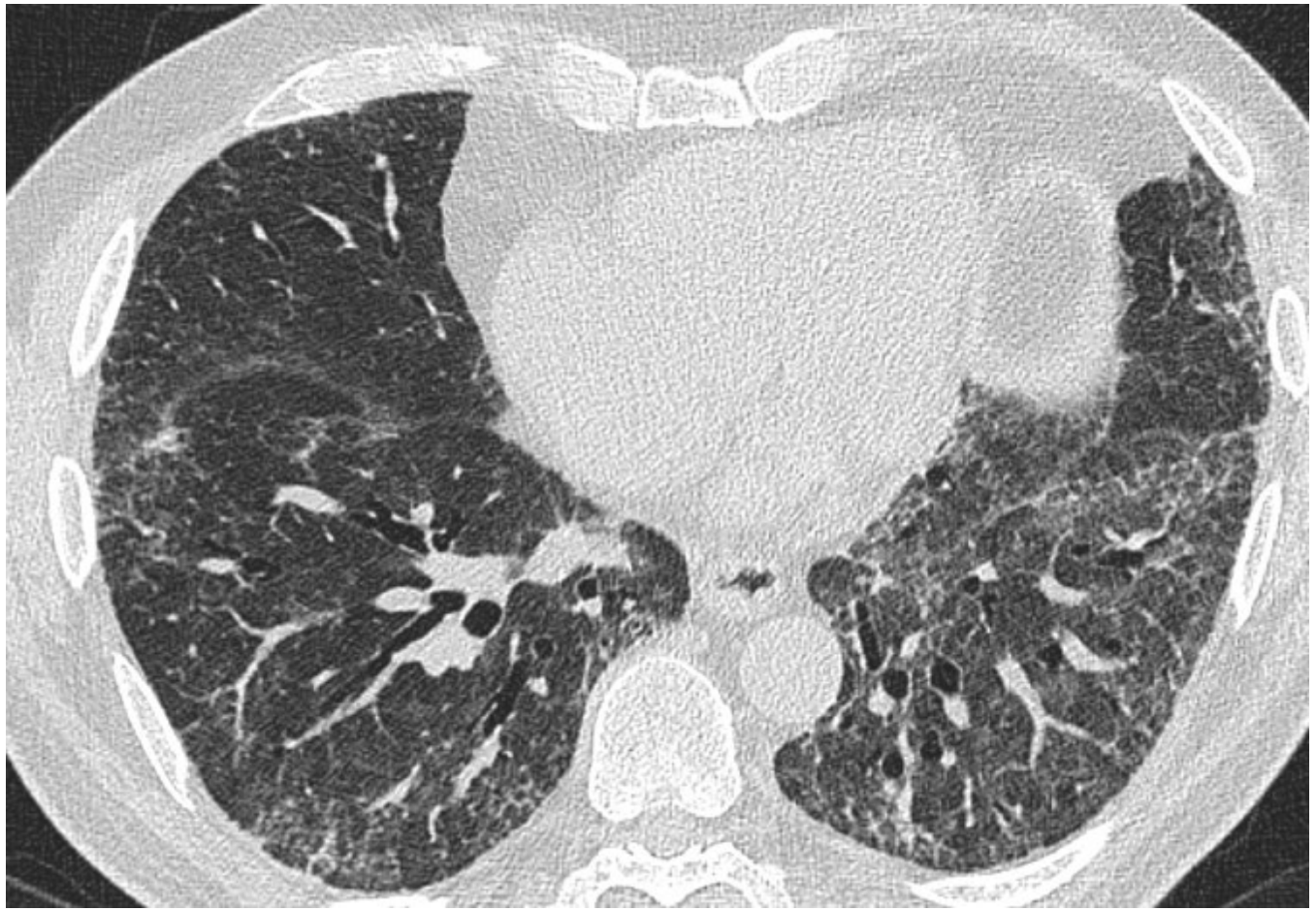
*ATS Guidelines expected in next 12 – 18 months

PROGRESSIVE PULMONARY FIBROSIS

Case history (2013)

- 57-year-old man
- 6-month history of progressive exertional dyspnoea
- At presentation, was breathless climbing one flight of stairs
- Minor cough
- No extrathoracic symptoms of note
- No exposure history
- No clubbing
- Bilateral basal crepitations
- Serology - weakly positive ANA and RhF
- Rheumatology assessment – no definable CTD or RA

CT scan (2013)



Further investigations

- FVC – 76% predicted
- Tlco 44% predicted
- Bronchoscopy – BAL 43% lymphocytosis
- Patient declined biopsy

MDT assessment

- Likely IPAF with mixed cellular and fibrotic NSIP
- Treated with reducing dose of oral corticosteroids and intravenous cyclophosphamide

Cyclophosphamide is not licensed for treatment of ILD.

Follow-up

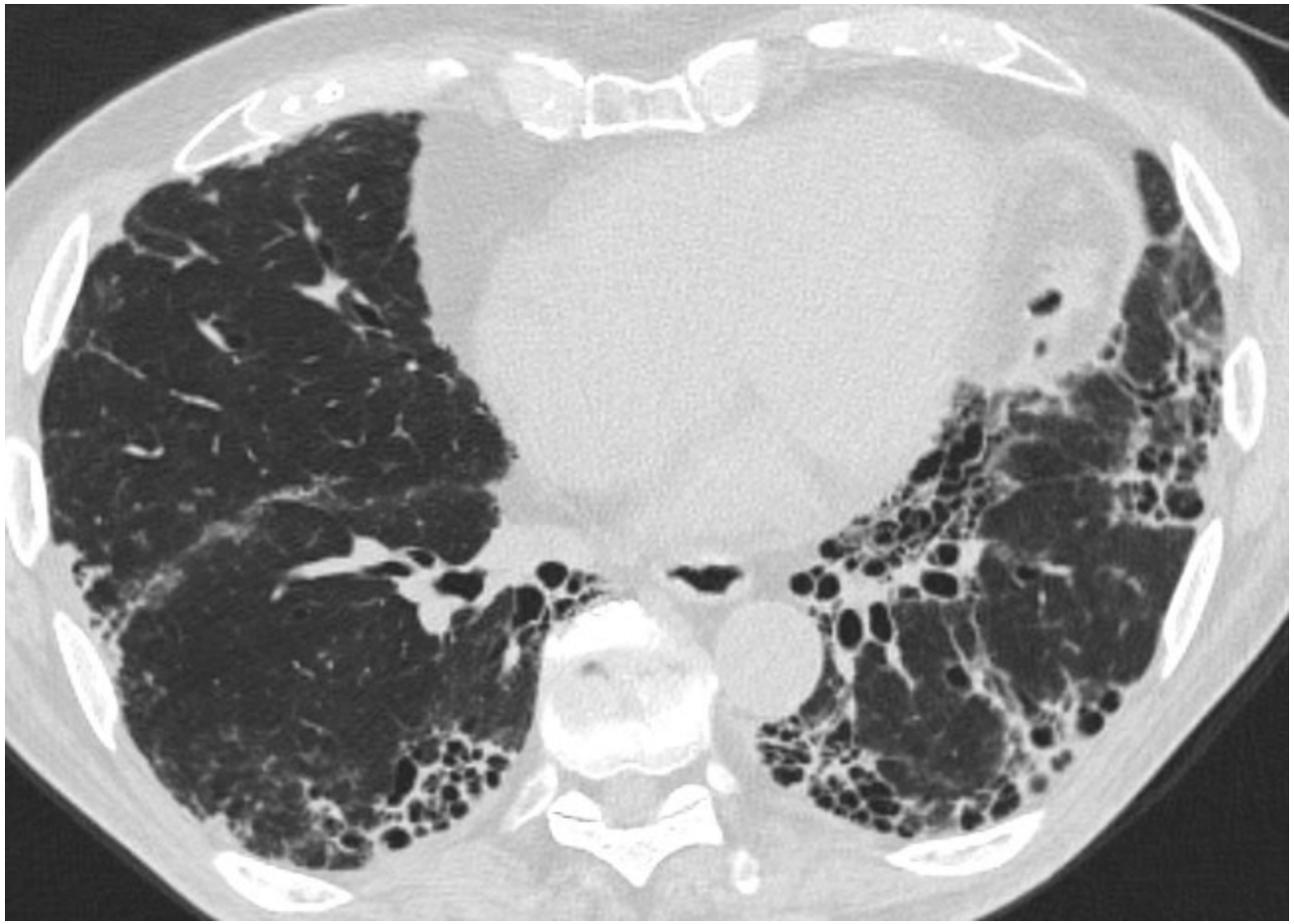
- Excellent response to treatment
- Exertional dyspnoea improved and returned to unrestricted activity
- Weaned and discontinued corticosteroids after 12 months
- Attended follow-up for three years (until 2016) and remained stable with minimal change on CT

Next presentation in 2021

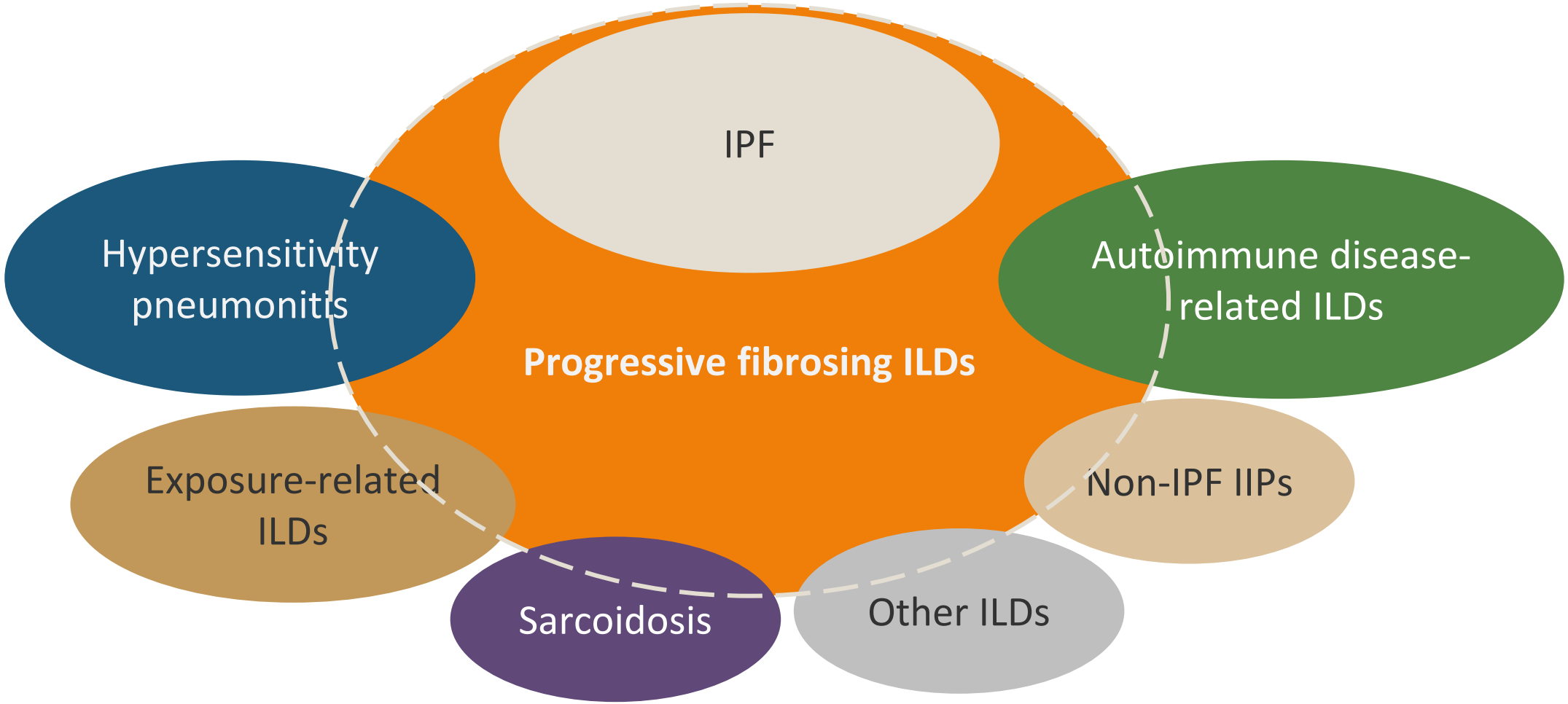
- In 2019, diagnosed with RA after presenting with classic joint symptoms, elevated anti CCP antibodies and raised Rh-F
- Had been treated with methotrexate and then rituximab
- Between 2019 and 2021, developed progressive exertional dyspnoea
- Exercise tolerance was approximately 2 flights of stairs
- FVC was 91% predicted in 2016, 85% predicted in 2019, and had dropped to 73% predicted by 2021

Methotrexate and rituximab are not licensed for treatment of ILD.

Repeat CT 2021

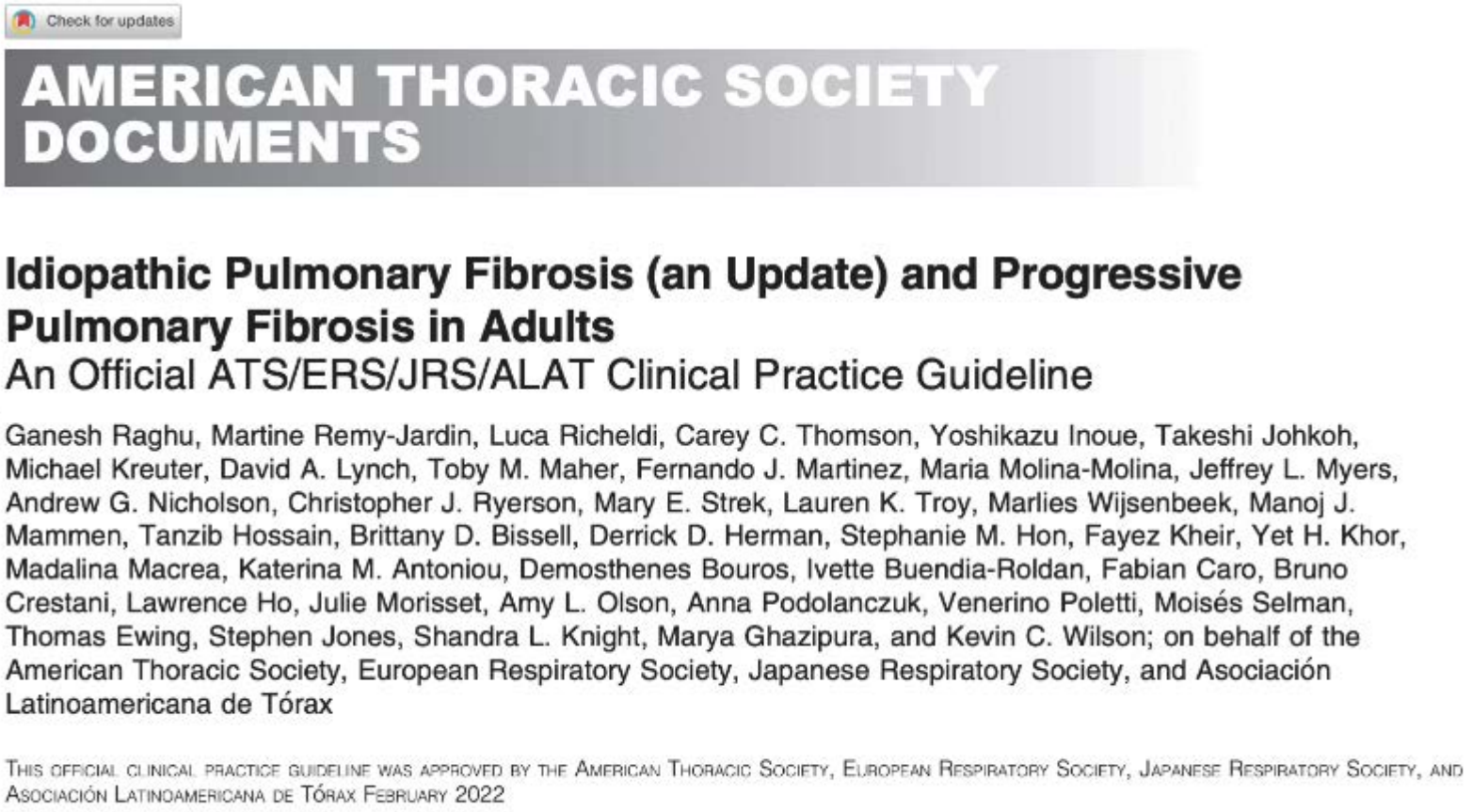


PF-ILDs



IIP, idiopathic interstitial pneumonia.

ATS/ERS/JRS/ALAT guideline



Check for updates

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Raghu G, et al. *Am J Respir Crit Care Med.* 2022;205:e18-e47.

INBUILD trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

Flaherty KR, et al. *N Engl J Med.* 2019;381:1718-1727.

Definitions of PPF

Guideline published by ATS/ERS/JRS/ALAT[1]

≥2 of the following occurring within 1 year:

- Absolute decline in FVC % predicted >5% and/or absolute decline in DLco % predicted >10%
- Worsened symptoms
- Radiological progression

INBUILD trial[2]

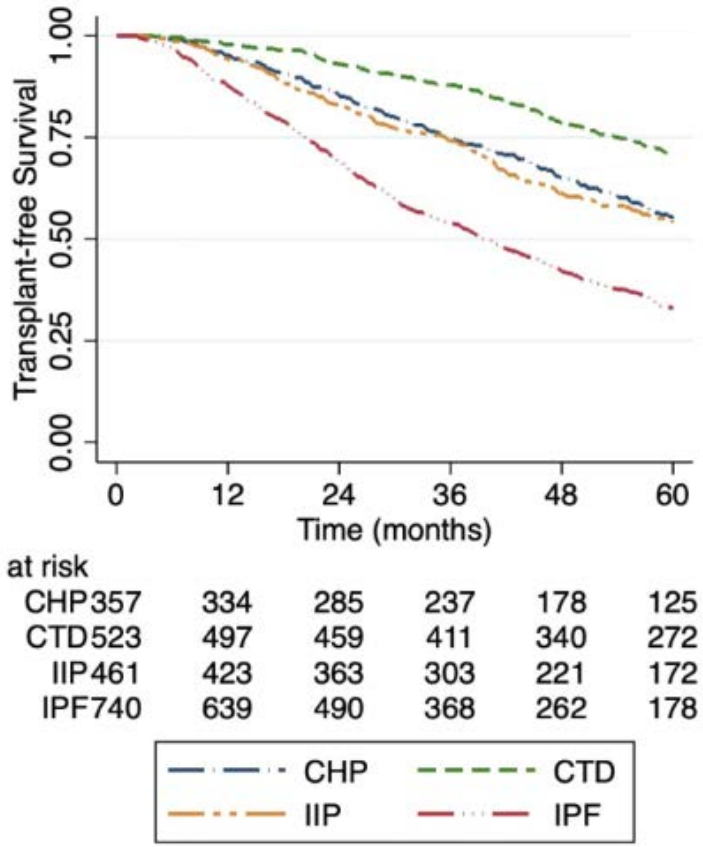
≥1 of the following occurring within 2 years:

- Relative decline in FVC % predicted ≥10%
- Relative decline in FVC % predicted ≥5–<10% and radiological progression and/or worsened symptoms
- Radiological progression and worsened symptoms

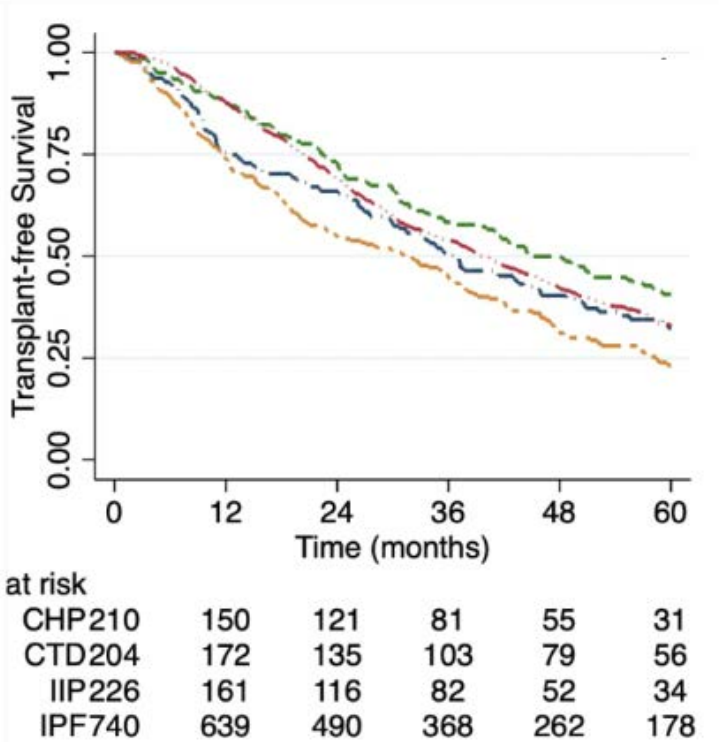
1. Raghu G, et al. *Am J Respir Crit Care Med*. 2022;205:e18-e47;
2. Flaherty KR, et al. *N Engl J Med.* 2019;381:1718-1727.

Outcomes in ILD following progression

Outcome by ILD sub-type



Outcome for PPF by ILD sub-type



Pugashetti JV, et al. *Am J Respir Crit Care Med.* 2023;207:69-76.

Can we predict who will develop PPF?

ORIGINAL ARTICLE

Combination of BAL and Computed Tomography Differentiates Progressive and Non-progressive Fibrotic Lung Diseases

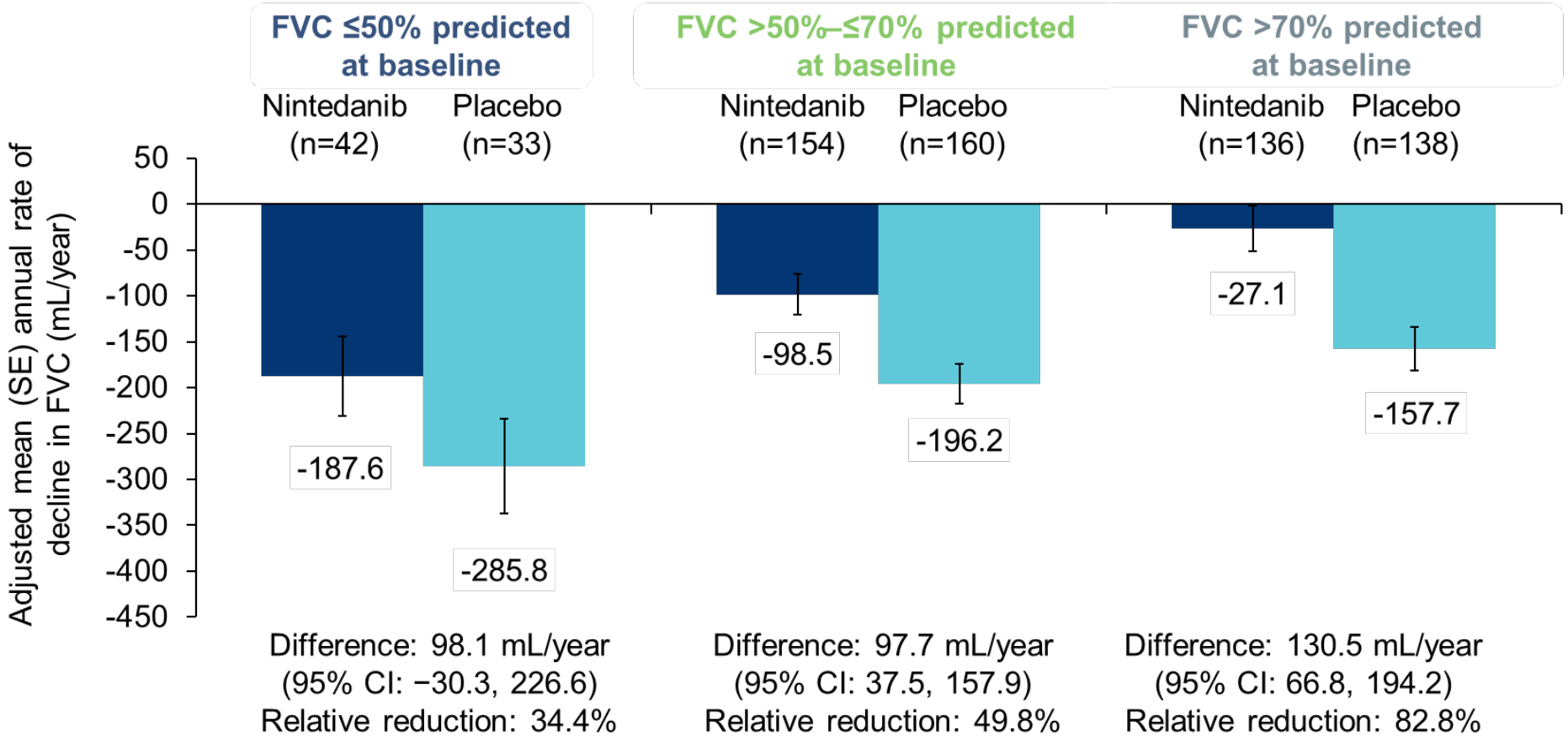
Joseph L. Barnett[1], Toby M. Maher[2], Jennifer K. Quint[3], Alex Adamson[3], Zhe Wu[3,5], David J. F. Smith[3,5], Bhavin Rawal[4], Arjun Nair[7], Simon L. F. Walsh[3], Sujal R. Desai[3,4], Peter M. George[3,4], Maria Kokosi[3,5], Gisli Jenkins[3,5], Vasilis Kouranos[3,5], Elisabetta A. Renzoni[3,5], Alex Rice[3,6], Andrew G. Nicholson[3,6], Felix Chua[3,5], Athol U. Wells[3,5], Philip L. Molyneaux[3,5*‡], and Anand Devaraj[3,4*‡]

[1]Department of Radiology, Royal Free Hospital, London, United Kingdom; [2]Keck School of Medicine, University of Southern California, Los Angeles, California; [3]National Heart and Lung Institute, Imperial College, London, United Kingdom; [4]Department of Radiology, [5]Interstitial Lung Disease Unit, and [6]Department of Histopathology, Royal Brompton Hospital, Guy's and St Thomas' National Health Service Foundation Trust, London, United Kingdom; and [7]Department of Radiology, University College Hospital, London, United Kingdom

	Univariable Analysis		
Variable	**OR (CI)**	***P* Value**	**Adjusted *P* Value***
CT fibrosis extent	1.05 (1.03–1.08)	<0.001	<0.001
CT UIP pattern	1.57 (1.21–2.04)	0.001	0.001
Lymphocyte proportion	0.95 (0.92–0.97)	<0.001	0.001

Barnett JL, et al. *Am J Respir Crit Care Med.* 2023;208:975-982.

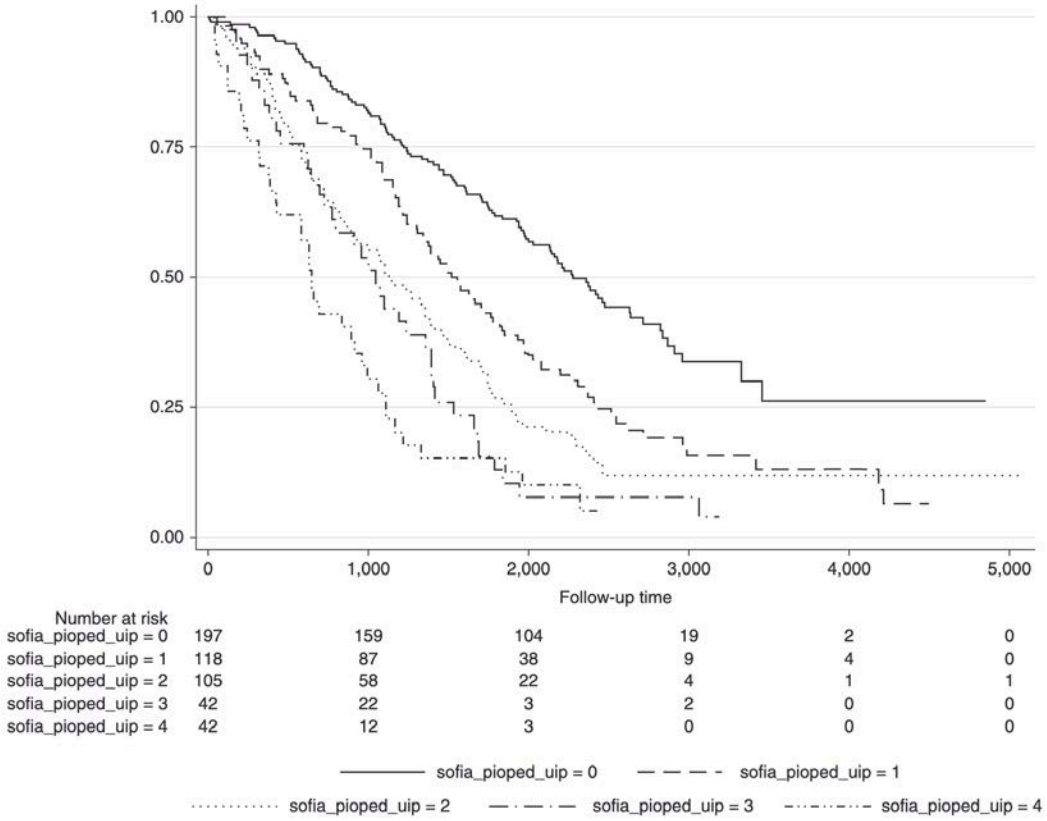
FVC decline by disease severity in INBUILD



1. Valenzuela C, *et al*. Live presentation at ERS 2020 virtual congress: Presentation no. 4577; 2. Flaherty KR, et al. *N Engl J Med*. 2019;381:1718-1727.

Deep Learning–based Outcome Prediction in Progressive Fibrotic Lung Disease Using High-Resolution Computed Tomography

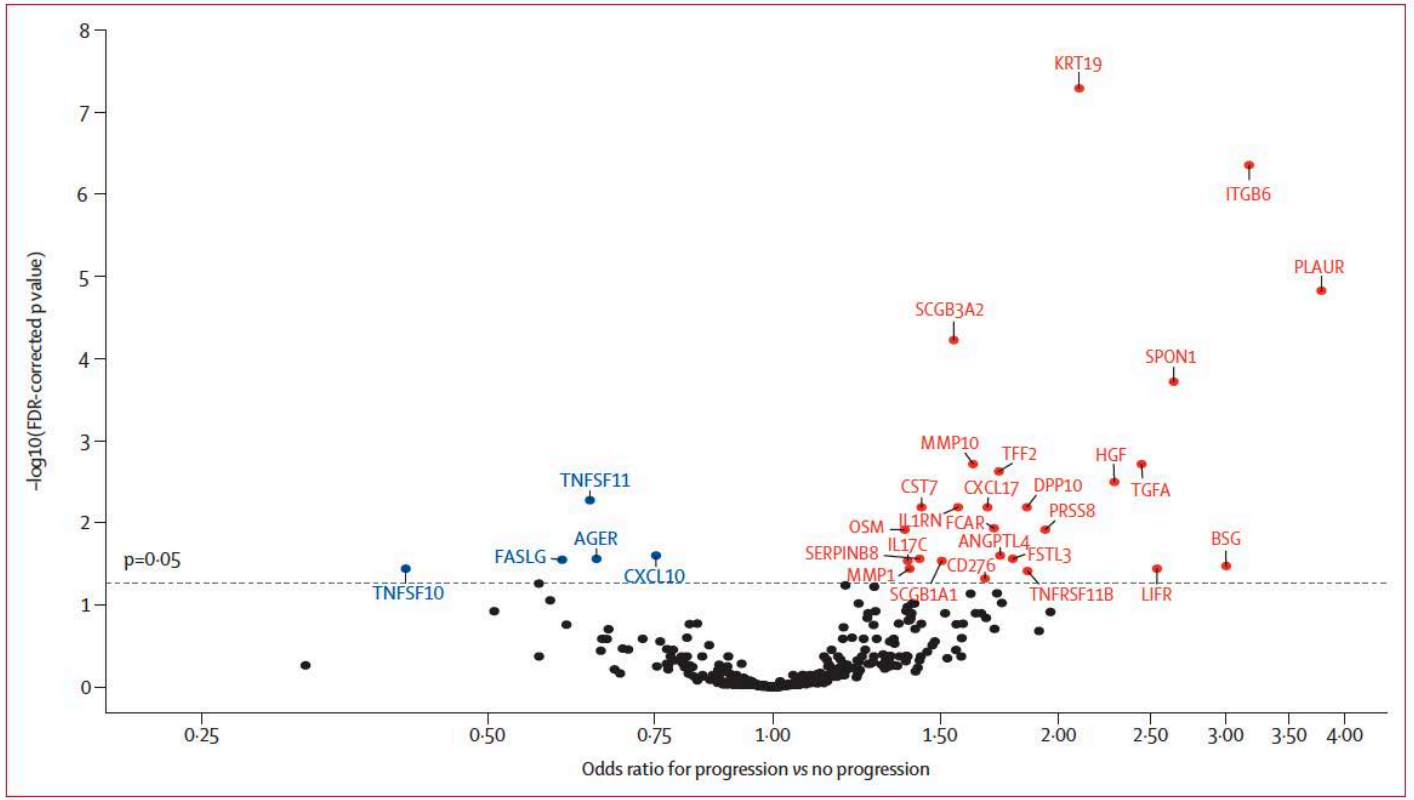
Simon L. F. Walsh[1], John A. Mackintosh[2], Lucio Calandriello[3], Mario Silva[4], Nicola Sverzellati[4], Anna Rita Larici[3], Stephen M. Humphries[5], David A. Lynch[5], Helen E. Jo[6], Ian Glaspole[7], Christopher Grainge[8], Nicole Goh[9,10,11], Peter M. A. Hopkins[2,12], Yuben Moodley[13], Paul N. Reynolds[14], Christopher Zappala[15], Gregory Keir[16], Wendy A. Cooper[17,18], Annabelle M. Mahar[17], Samantha Ellis[19], Athol U. Wells[1,20], and Tamera J. Corte[6]



Walsh SLF, et al. *Am J Respir Crit Care Med.* 2022;20:883-891.

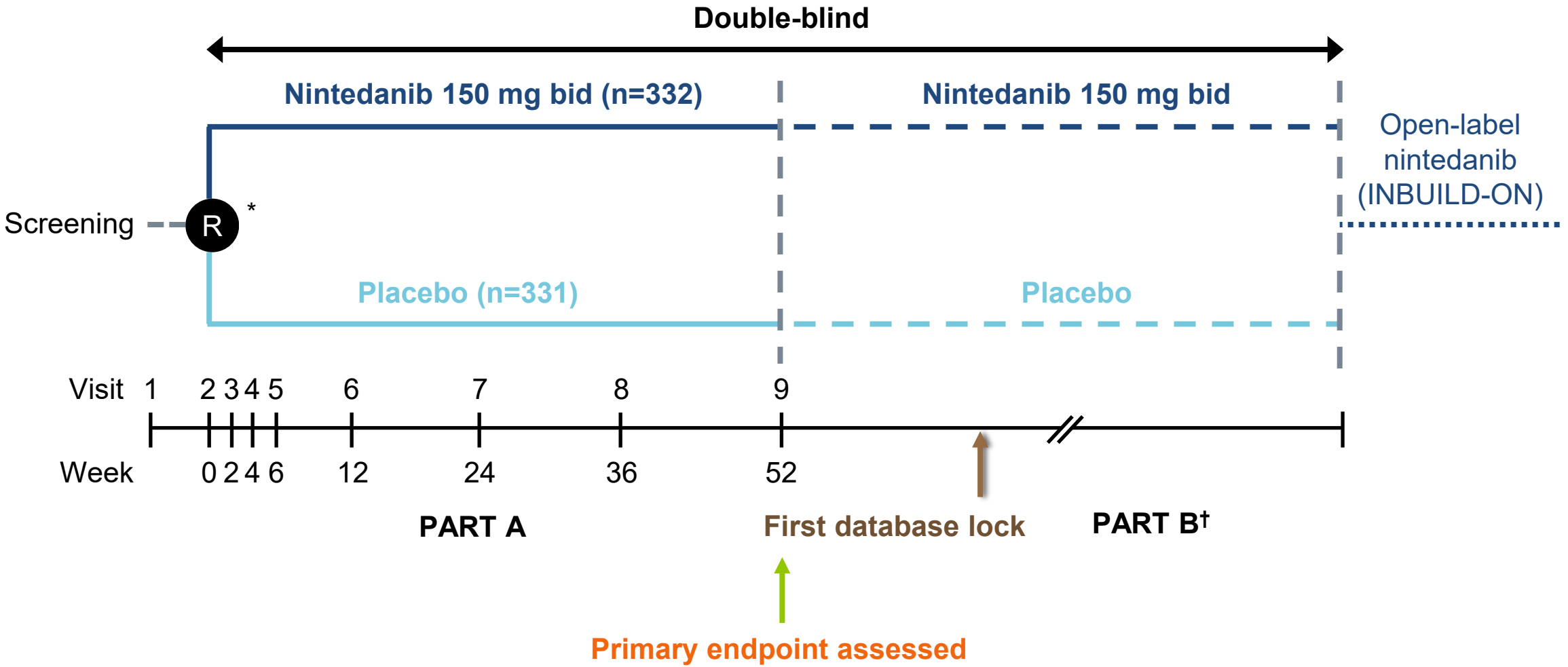
Proteomic biomarkers of progressive fibrosing interstitial lung disease: a multicentre cohort analysis

Willis S Bowman, Chad A Newton, Angela L Linderholm, Megan L Neely, Janelle Vu Pugashetti, Bhavika Kaul, Vivian Vo, Gabrielle A Echt, William Leon, Rupal J Shah, Yong Huang, Christine Kim Garcia, Paul J Wolters, Justin M Oldham



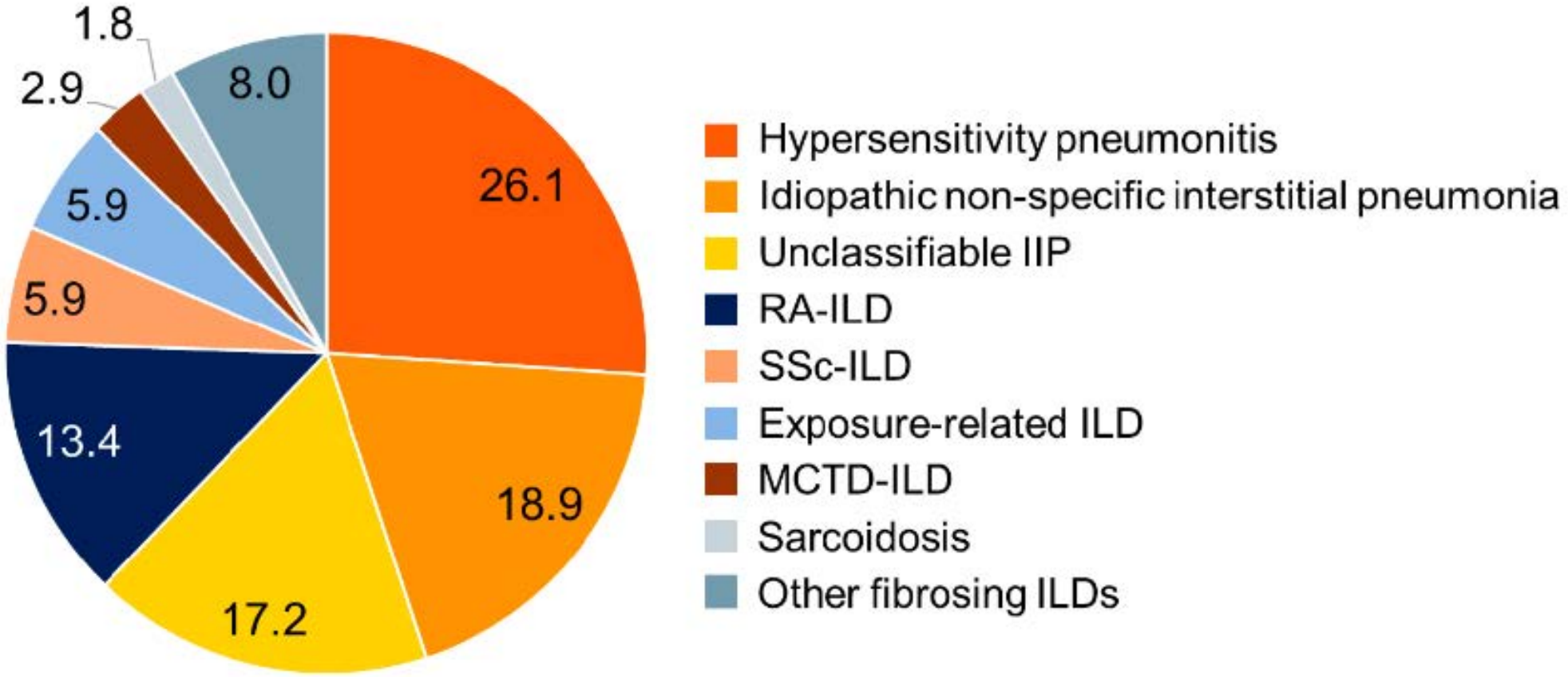
Bowman WS et al. *Lancet Respir Med.* 2022;10:593-602.

The INBUILD trial

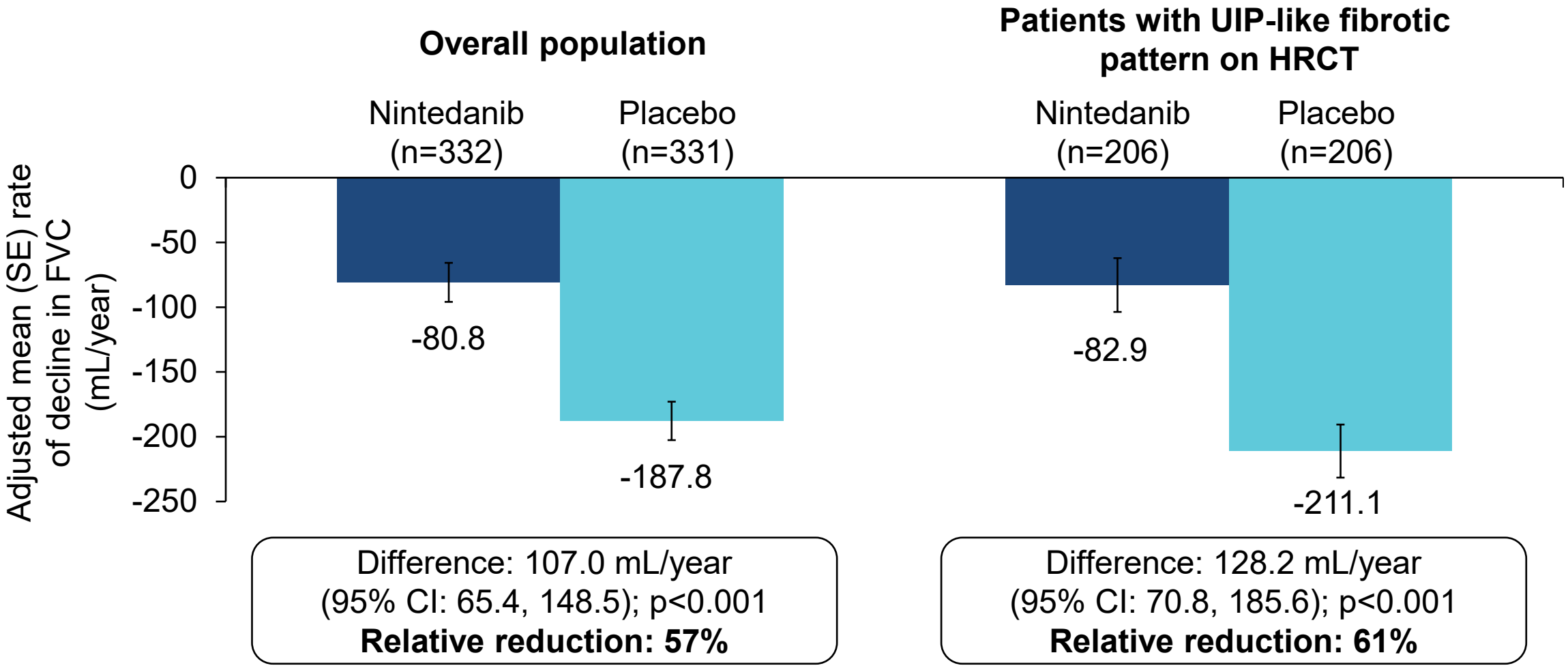


*Randomisation was stratified by HRCT pattern (UIP-like fibrotic pattern only or other fibrotic patterns) based on central review.
†Visits occurred every 16 weeks until end of treatment.
bid, twice daily; R, randomisation; UIP, usual interstitial pneumonia.
Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

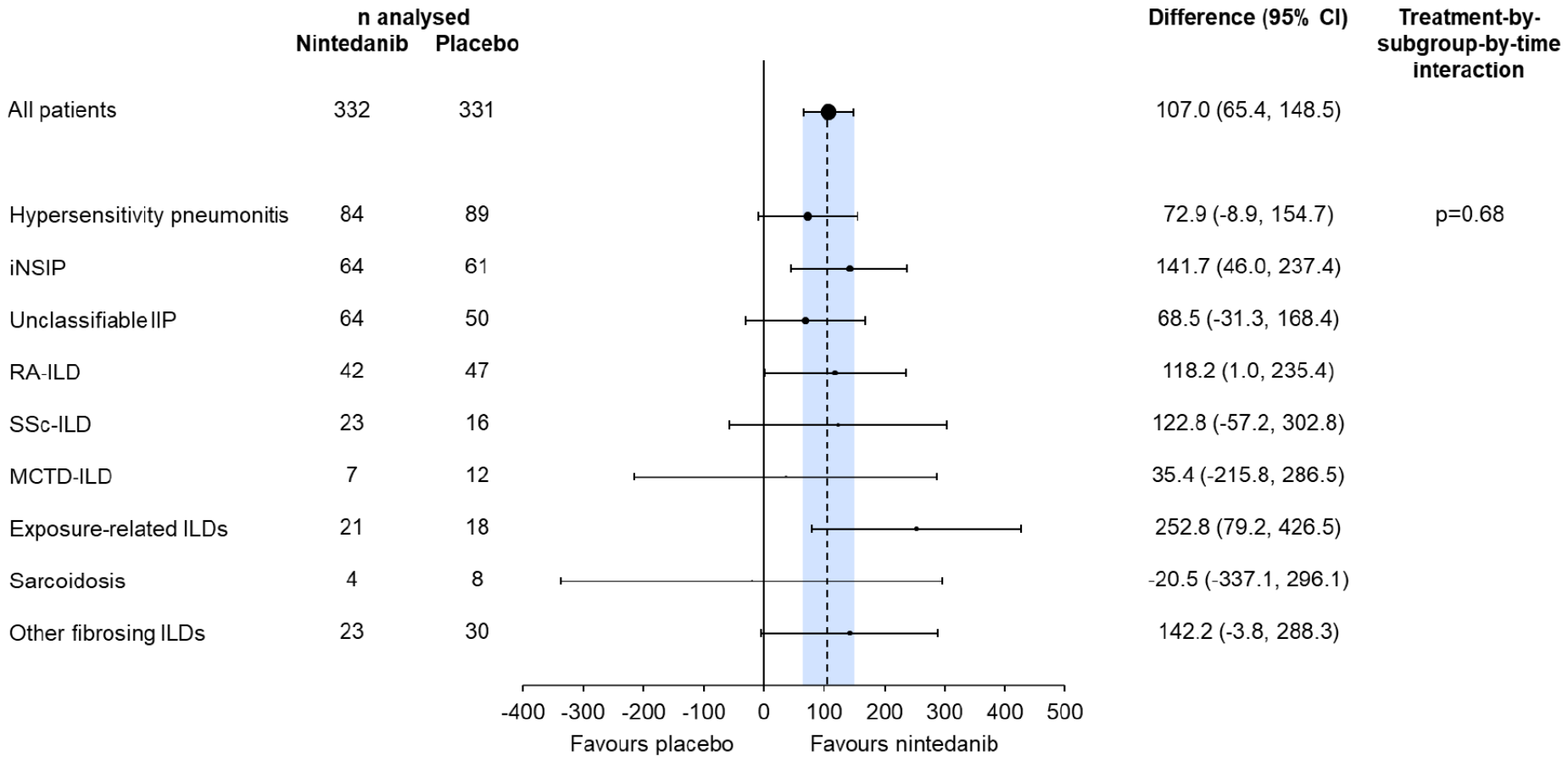
INBUILD trial: clinical diagnoses



Rate of decline in FVC over 52 weeks in INBUILD trial



Absolute difference in FVC between groups in INBUILD.



Wells AU et al Lancet Respir Med 2020

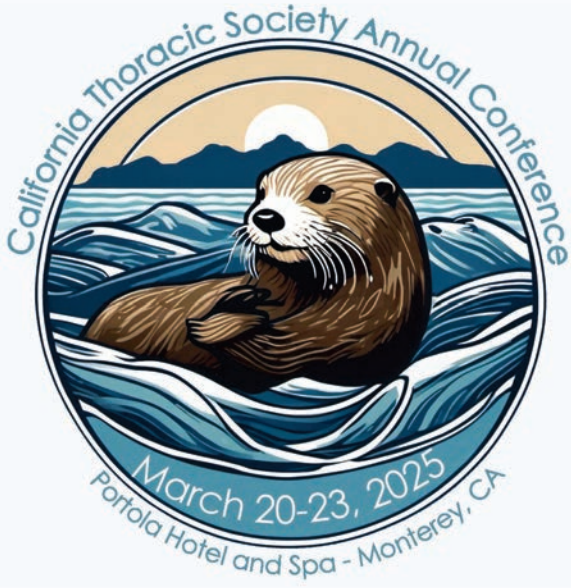
Most frequently reported adverse events (irrespective of causality) in overall population

	Nintedanib (n=332)	Placebo (n=331)
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of ILD	16 (4.8)	39 (11.8)
Weight decreased	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)

Data are n (%) of patients with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake for patients who discontinued trial drug before week 52). Adverse events based on MedDRA preferred terms that were reported in >11% of patients in either treatment group are shown. Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

Conclusions

- ILD pattern helps to define both likely diagnosis and prognosis
- ILD patterns overlap and can be seen across different diseases
- Interstitial lung abnormalities can be found in up to 10% of otherwise healthy over 60s
- Progression is more likely with fibrotic change, family history and short-term progression
- Progressive pulmonary fibrosis can be seen across ILDs, portends a poor prognosis and should trigger consideration for anti-fibrotic therapy.



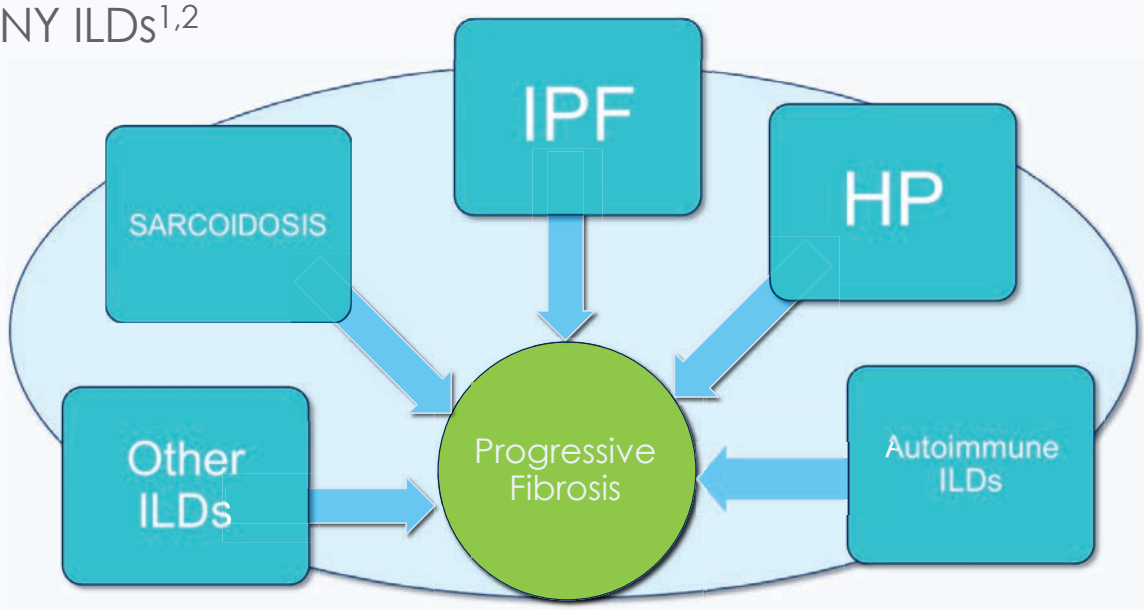
Imaging patterns in Interstitial Lung Disease

Lila Pourzand, M.D.
Ronald Reagan UCLA Medical Center
David Geffen School of Medicine at UCLA

Disclosures

- **Many of the slides for this presentation was shared with me by my mentor,**
- **Dr. Robert Suh. Otherwise, no disclosure.**
- **I WILL NOT discuss off-label use and/or investigational use of any drugs or devices.**

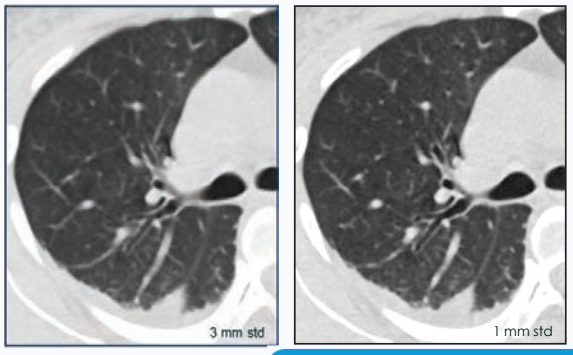
LUNG FIBROSIS CAN BE A FINAL COMMON PATHWAY FOR MANY ILDs[1,2]



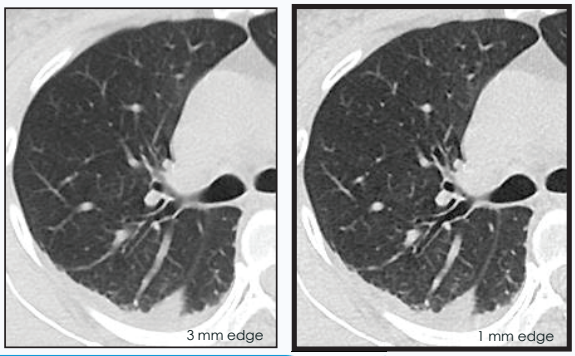
1. Galvin JR et al. *Radiology*. 2010;255(3):692-706. 2. Salvatore M et al. *J Am Board Fam Med*. 2018;3(1):151-162

VARIATION OF PARAMETERS FOR CHEST HRCT

NON-HIGH RESOLUTION

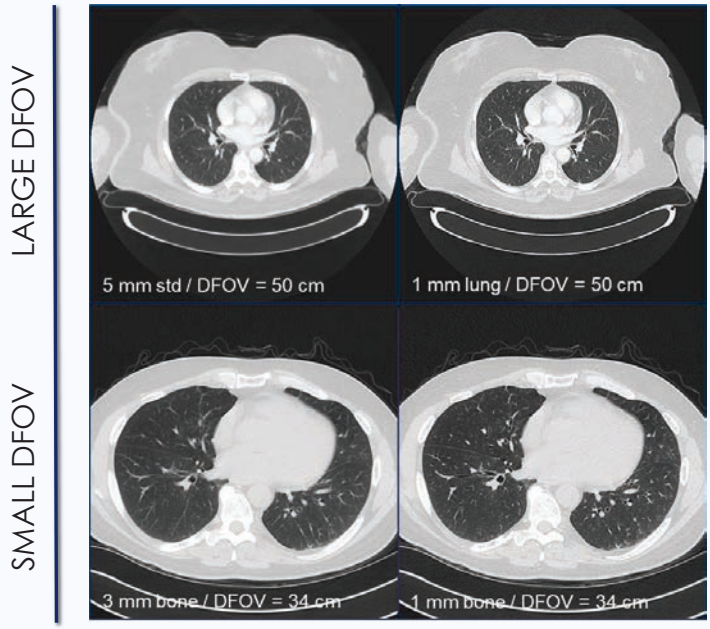


HIGH RESOLUTION



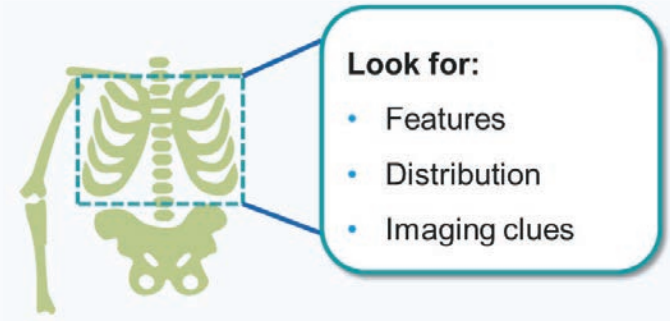
Thin-section HRCT scans with high-resolution algorithms are favored for improved contrast and spatial resolution

VARIATION OF PARAMETERS FOR CHEST HRCT



California Thoracic Society
ATS Chapter Serving California and Arizona

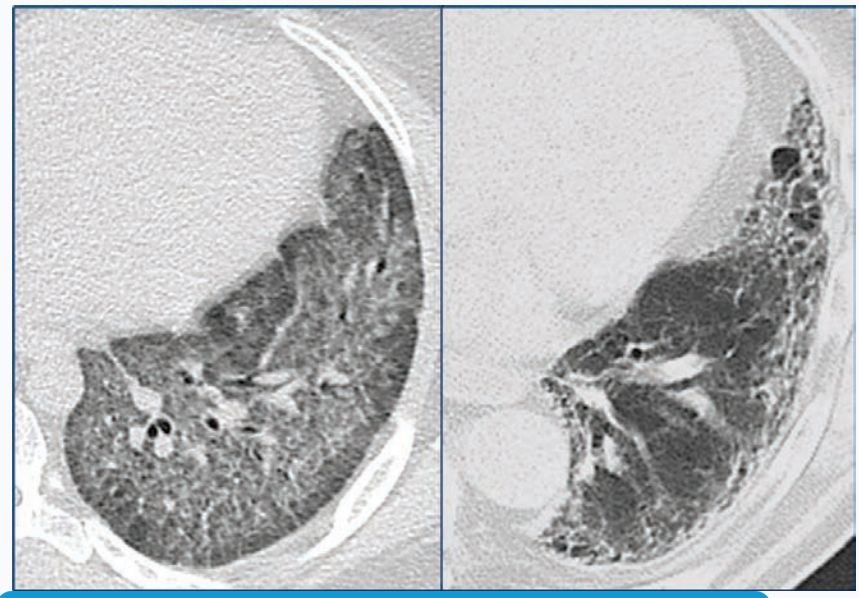
EVALUATING AN HRCT SCAN



The imaging features and how they are distributed can point to diagnostic patterns

FEATURES	**Indicative of ILD (fibrosis)**
	Honeycombing
	Traction bronchiectasis
	Reticulation
	Other features of ILD
	Ground glass opacity
	Air space consolidation
	Air trapping
	Nodular opacities
DISTRIBUTION	Upper or lower
	Central/peribronchovascular
	Peripheral/subpleural

EVALUATING AN HRCT SCAN



Axial distribution: Left image- central or peri broncho-vascular distribution. Right image- subpleural distribution

FEATURES	**Indicative of ILD (fibrosis)**
	Honeycombing
	Traction bronchiectasis
	Reticulation
	Other features of ILD
	Ground glass opacity
	Air space consolidation
	Air trapping
	Nodular opacities
DISTRIBUTION	Upper or lower
	Central/peribronchovascular
	Peripheral/subpleural

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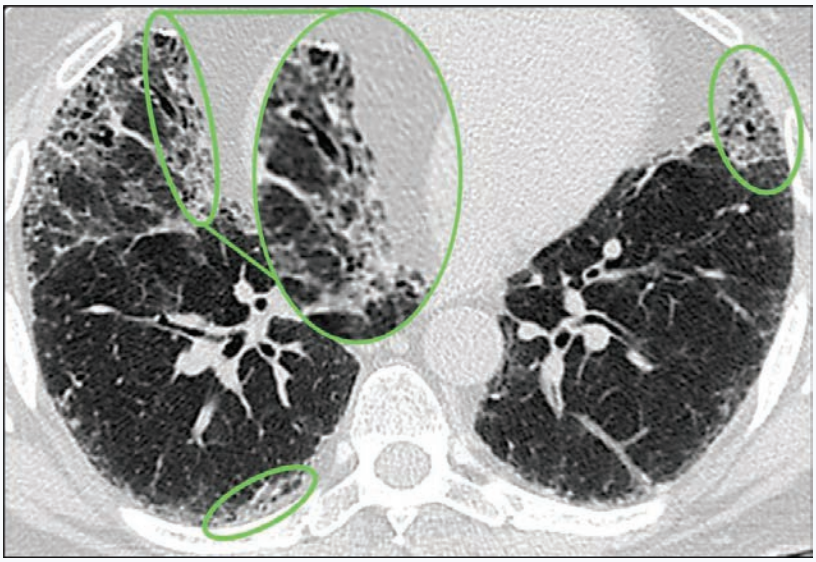
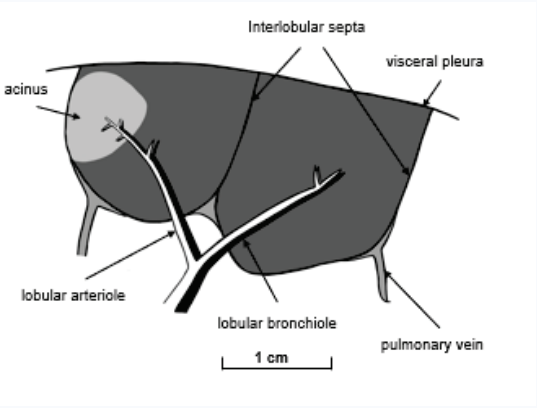
HRCT FEATURES OF ILD

INDICATIVE OF ILD: RETICULATION

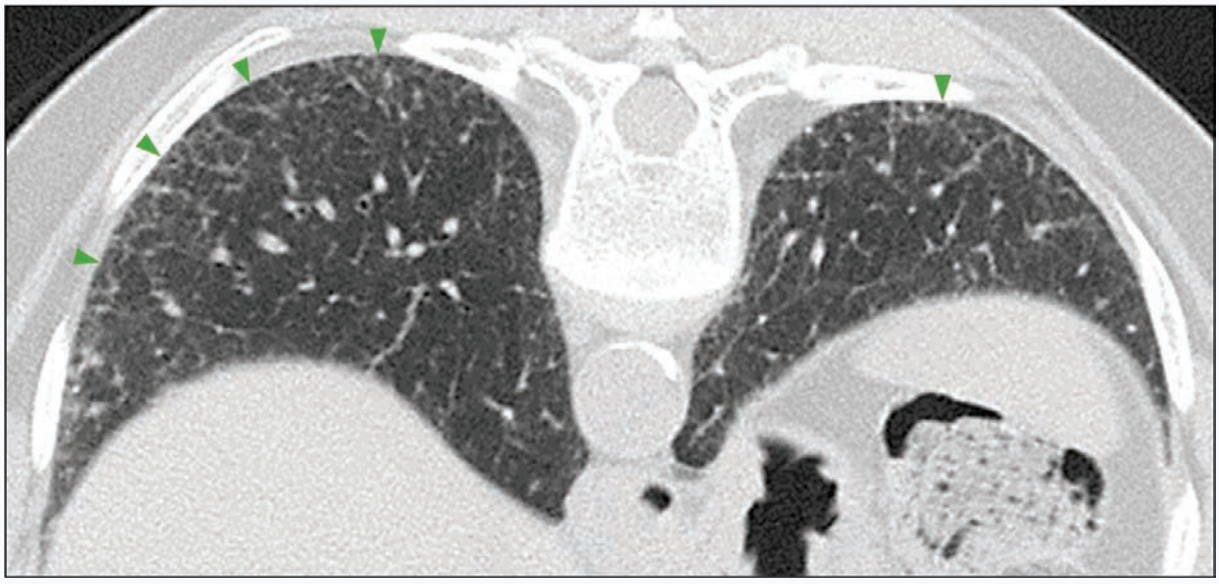


secondary pulmonary lobule[1]



• Image redraw courtesy of and used with permission from Chloe Suh. Webb WR. *Radiology*. 2006;239(2):322-338.

INDICATIVE OF ILD: RETICULATION (CONT'D)



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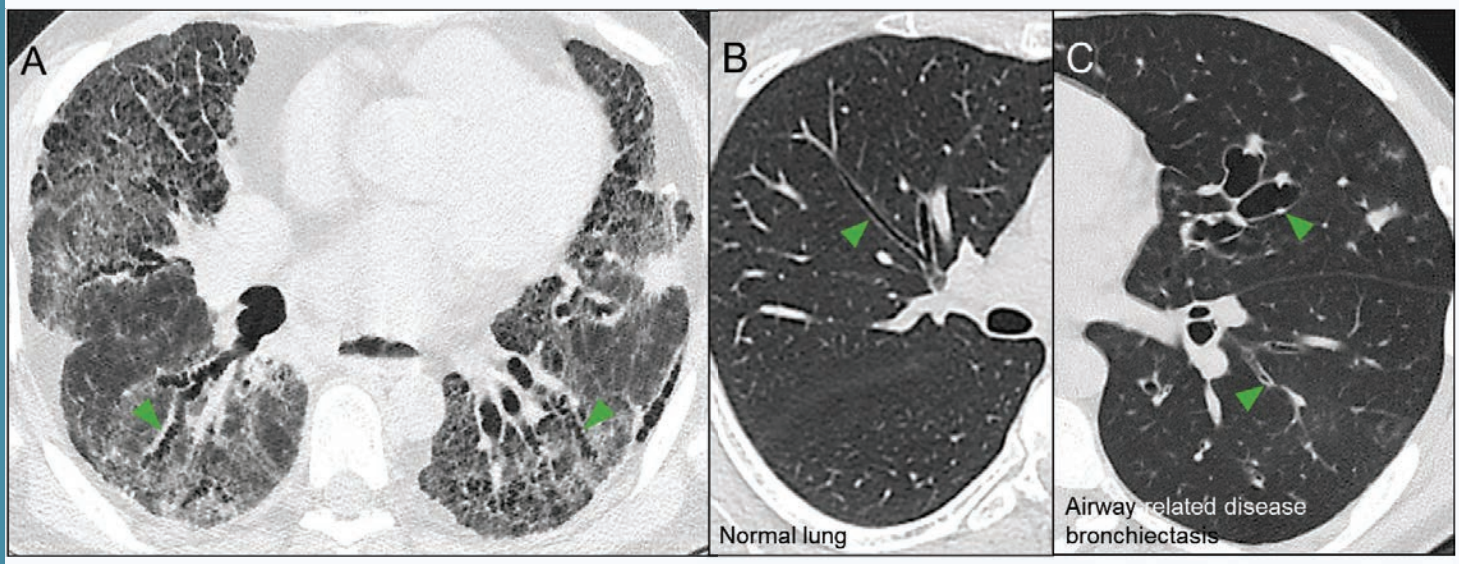
INDICATIVE OF FIBROSIS: TRACTION BRONCHIECTASIS



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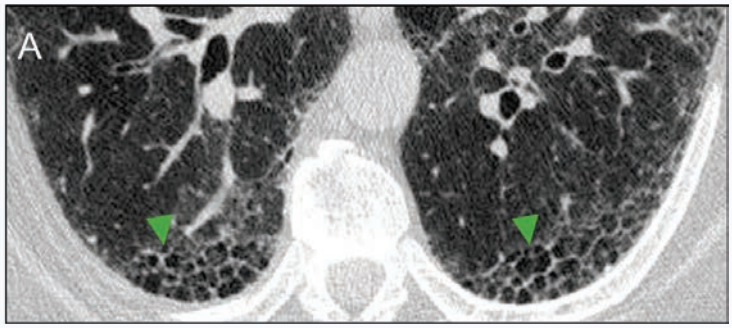
INDICATIVE OF FIBROSIS: HONEYCOMBING



- *70-80% of cases of UIP*
- *Strongest indicator of UIP on CT*
- *Median survival*
  - *UIP with honeycombing: 2.1 years*
  - *UIP without honeycombing: 5.8 years*

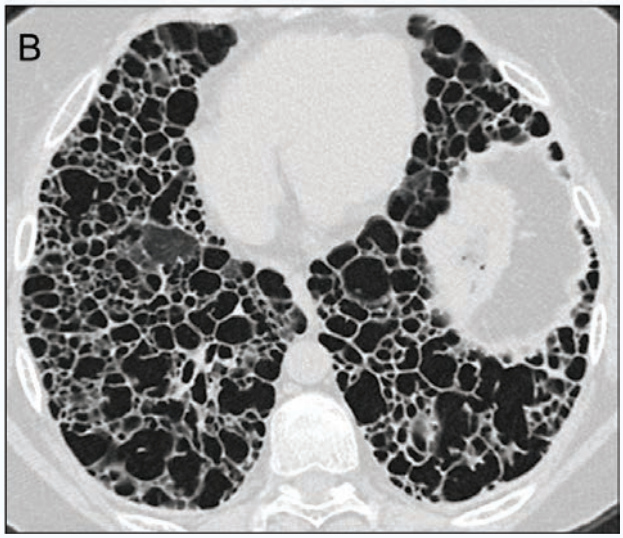
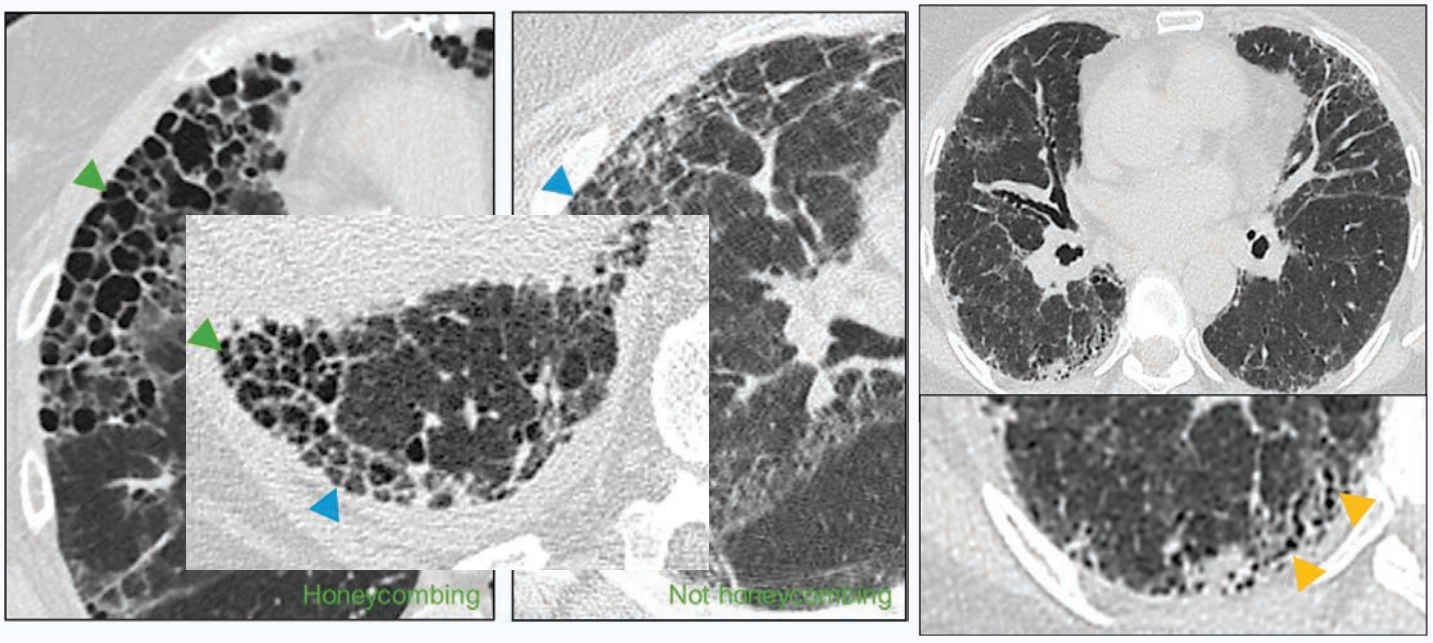


Image A courtesy of and used with permission from Jonathan Goldin, MD, PhD.

Hunninghake et al. *Chest* 2003;124:1215-1223.
Elliot et al. *JCAT* 2005;29:339-345.
Flaherty et al. *Thorax* 2003;58:143-148.

HONEYCOMBING v. RETICULATION OR TRACTION BRONCHIECTASIS



▲ Traction bronchiectasis

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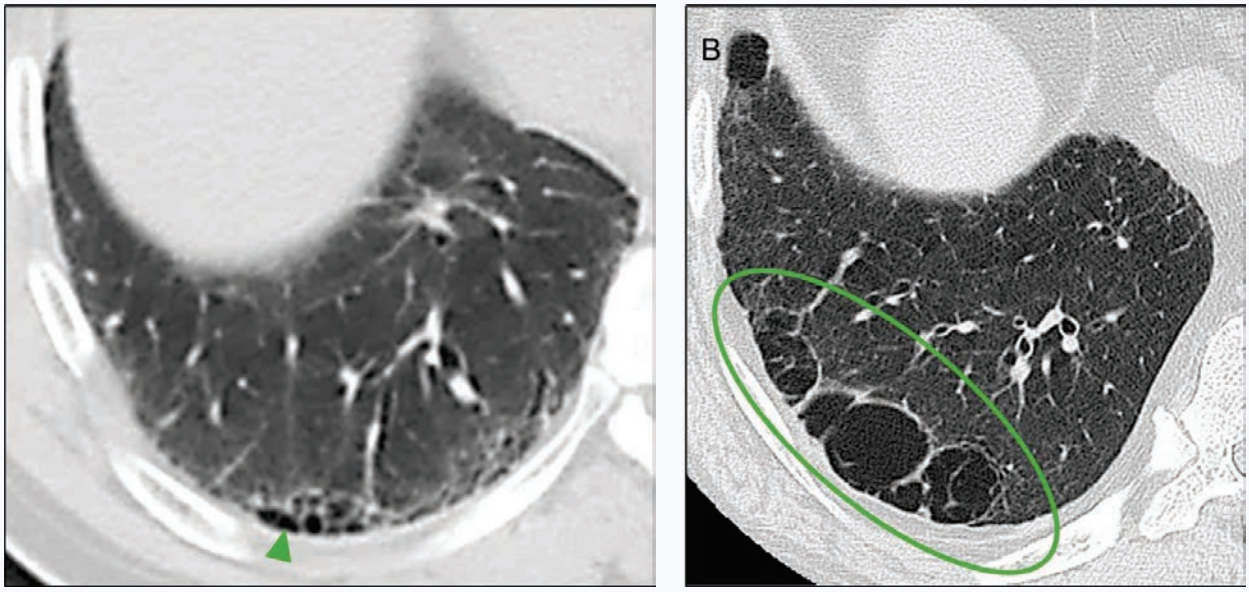
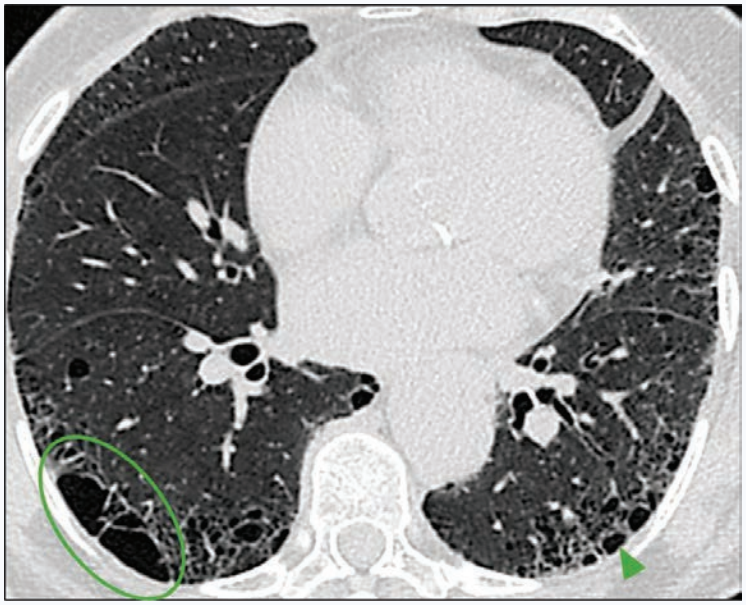
EARLY HONEYCOMBING v. PARASEPTAL EMPHYSEMA

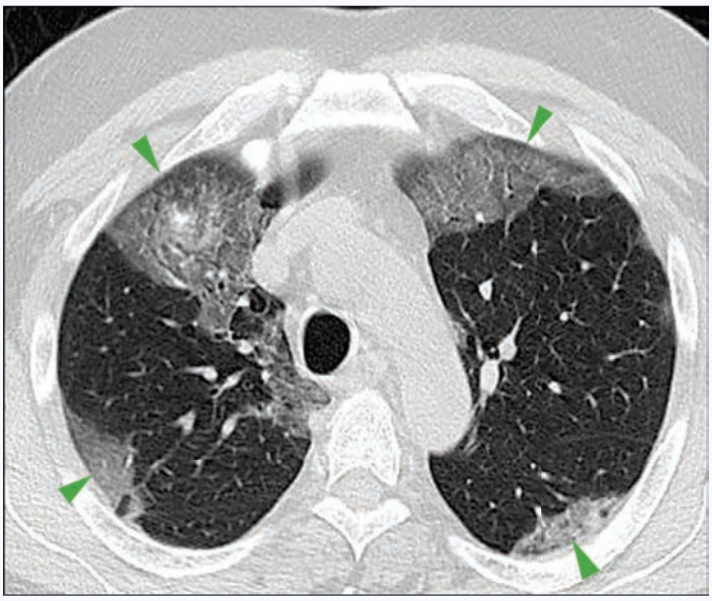


OVERLAPPING IMAGING SIGNATURES: CPFE



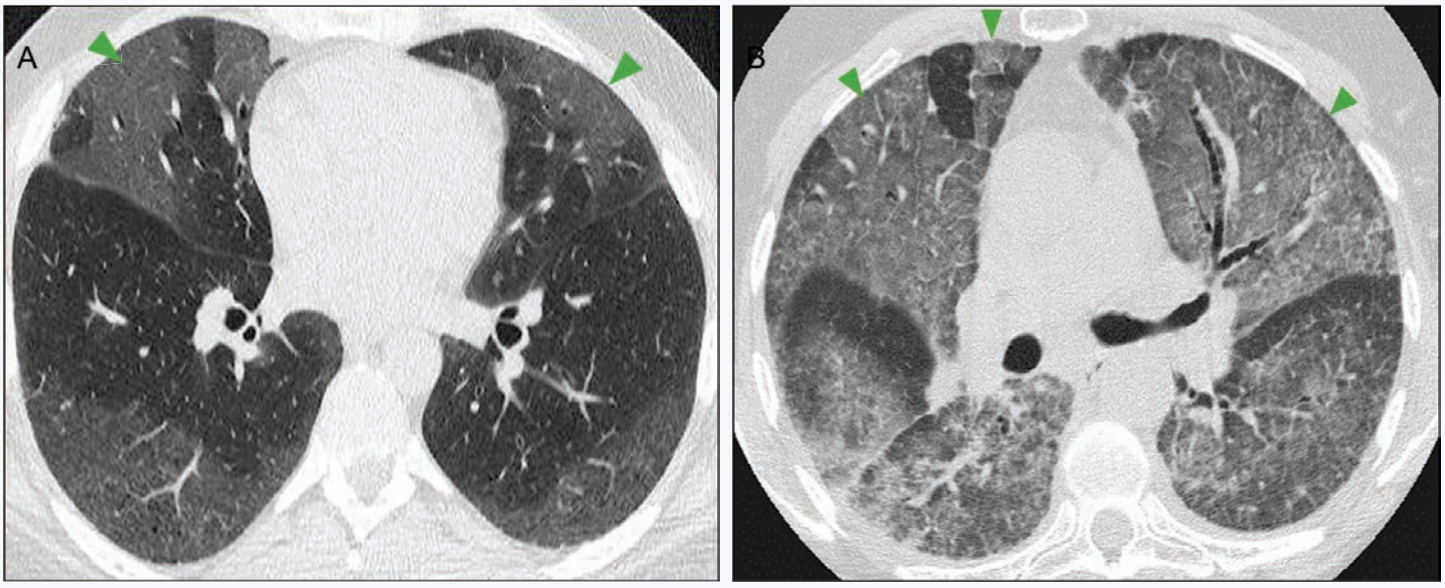
CPFE, combined pulmonary fibrosis and emphysema

OTHER FEATURES OF ILD: GROUND GLASS OPACITY

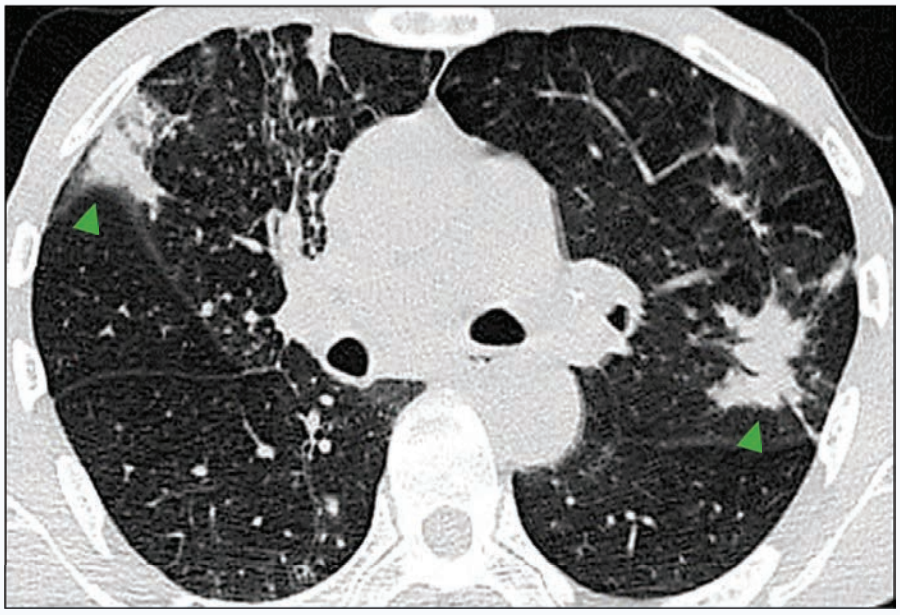


HRCT image courtesy of and used with permission from Sudhakar Pipavath, MD.

OTHER FEATURES OF ILD: GROUND GLASS OPACITY



OTHER FEATURES OF ILD: CONSOLIDATION



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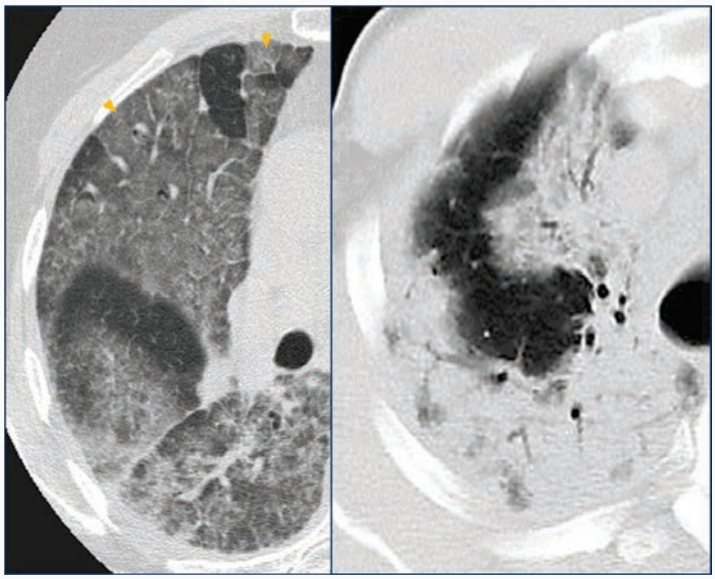
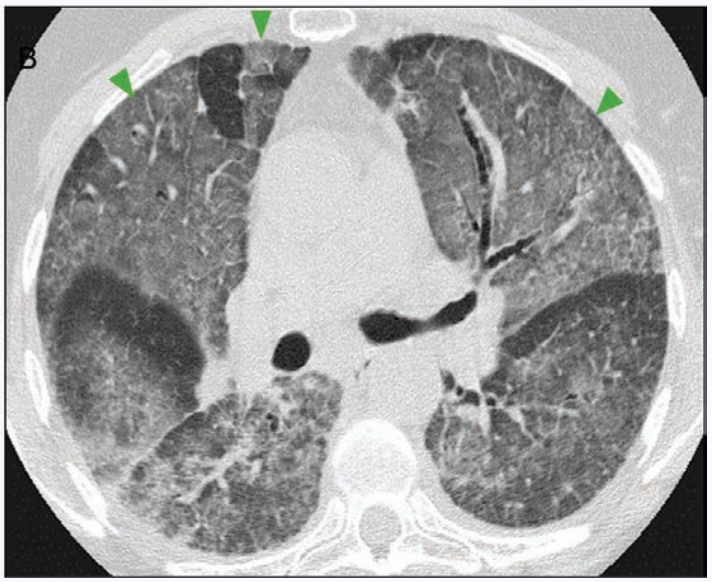
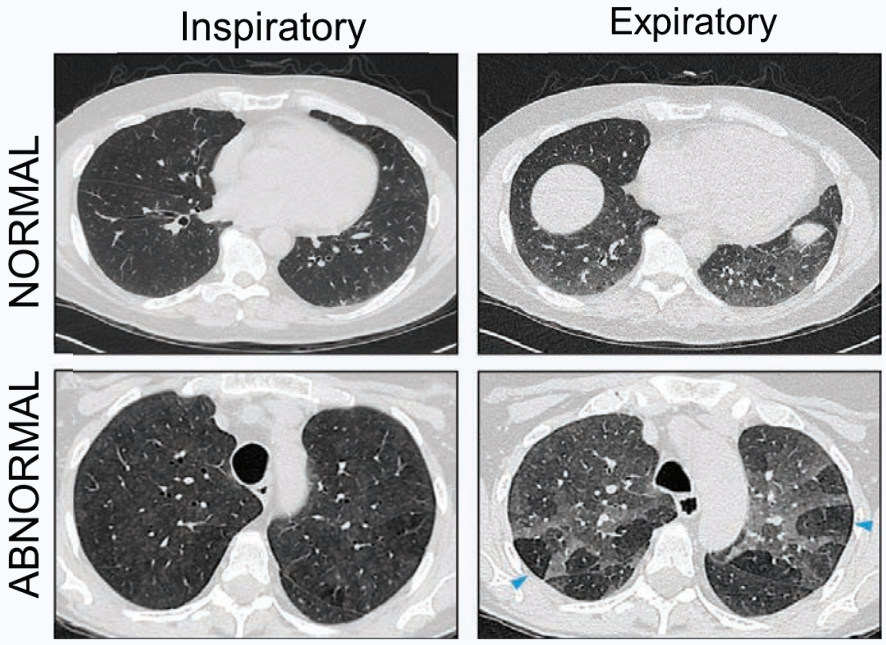
OTHER FEATURES OF ILD: GROUND GLASS OPACITY v. CONSOLIDATION

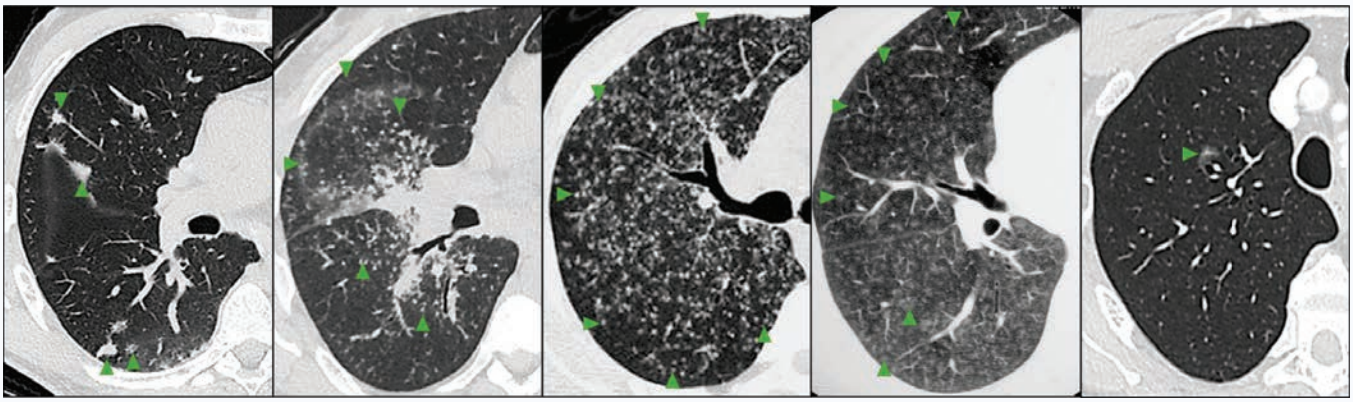




OTHER FEATURES OF ILD: AIR TRAPPING



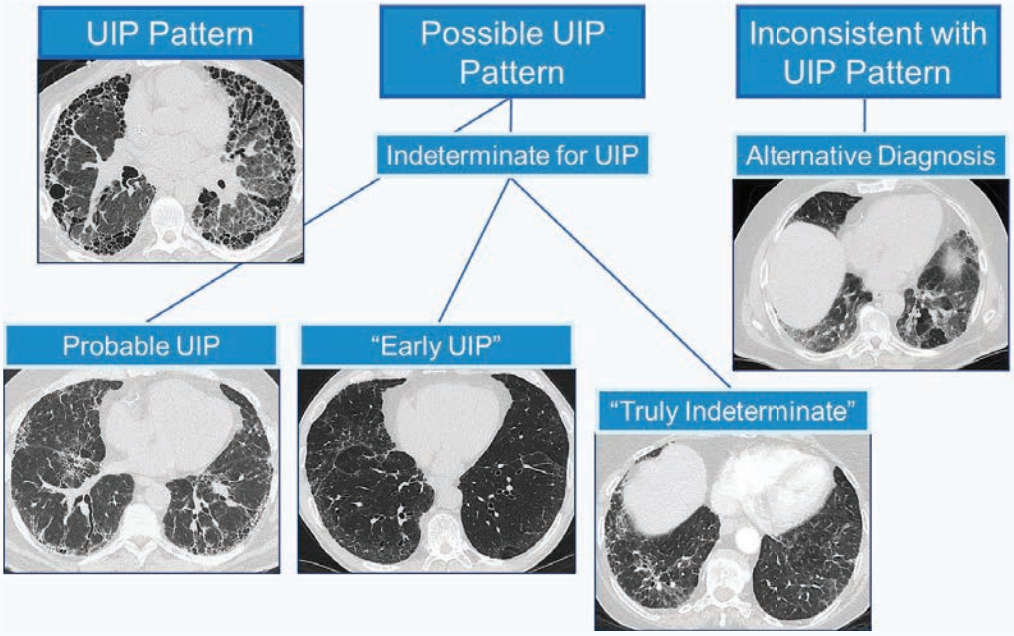
OTHER FEATURES OF ILD: NODULAR OPACITIES



Nodules | Micronodules | Solid nodules | Ground glass nodules | Part-solid nodule

HRCT PATTERNS OF ILD

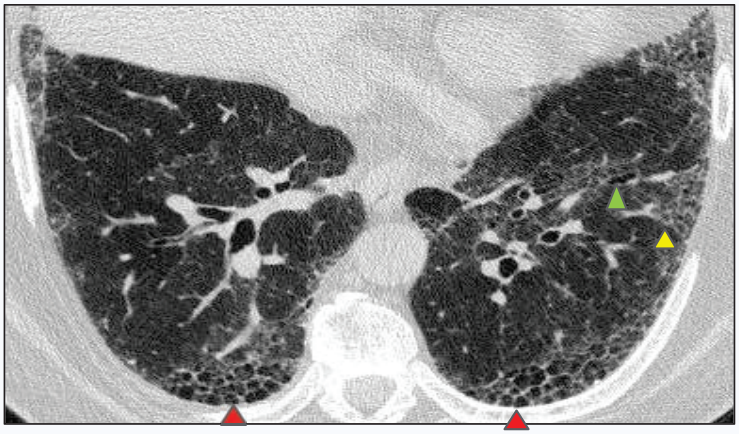
HRCT: UPDATED SCANNING PATTERNS



1. Raghu G et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | HP | OP



Typical Distribution[1]:
- Subpleural
- Basal predominance
- Occasional upper lobe involvement

HRCT features[1]:
- Honeycomb cysts ▲
- Traction bronchiectasis ▲
- Reticulation ▲

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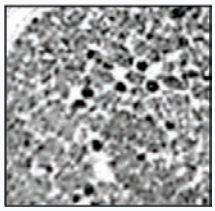
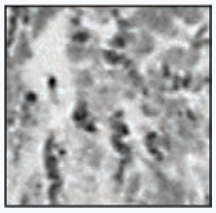
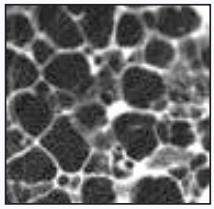
PROGRESSION OF HRCT ABNORMALITIES IN UIP



Reticulation



Reticulation and
traction bronchiectasis



Honeycombing/
end-stage lung fibrosis

Disease
progression

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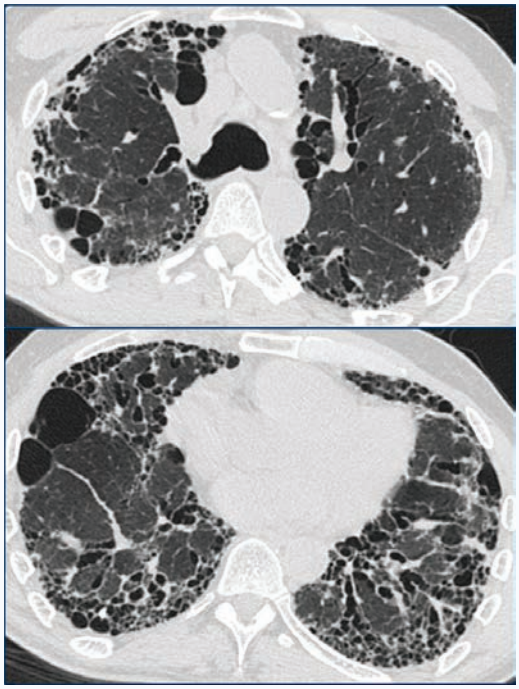
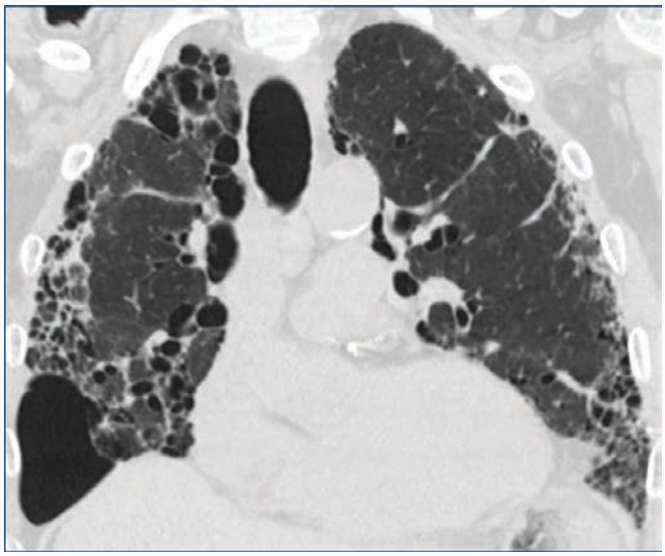
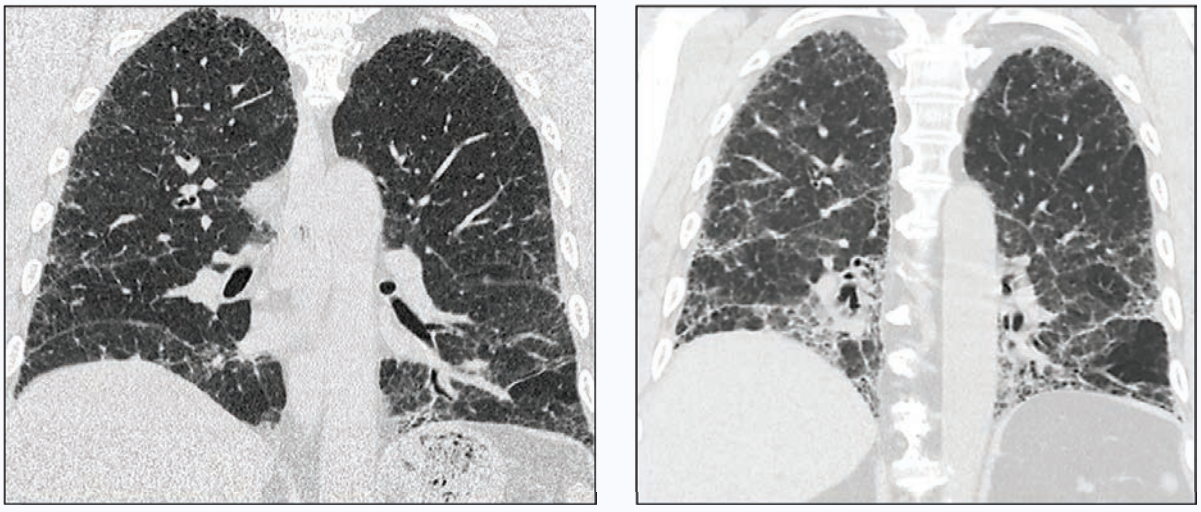
UIP PATTERN





UIP: PROGRESSION OVER TIME



Year 0

Year 3

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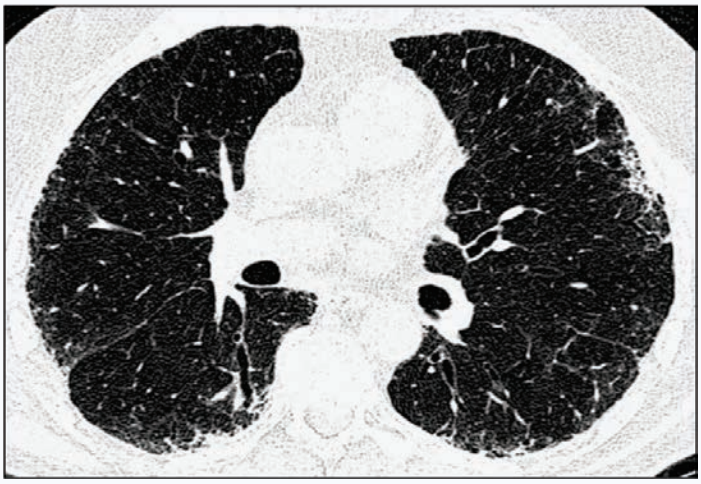
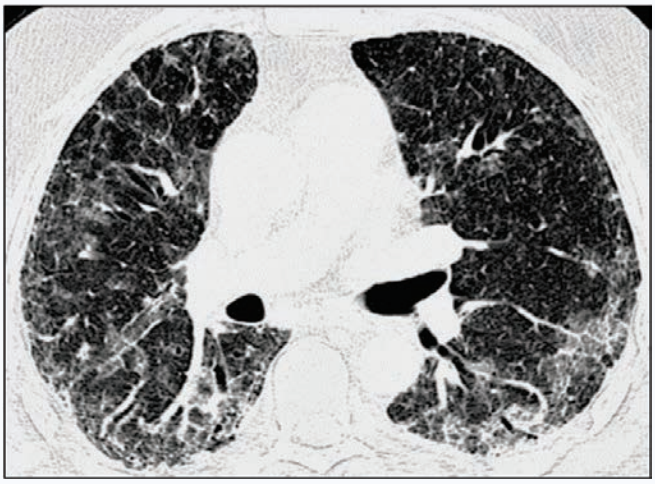
ACUTE EXACERBATIONS IN PATIENTS WITH UIP

BASELINE



5 MONTHS LATER

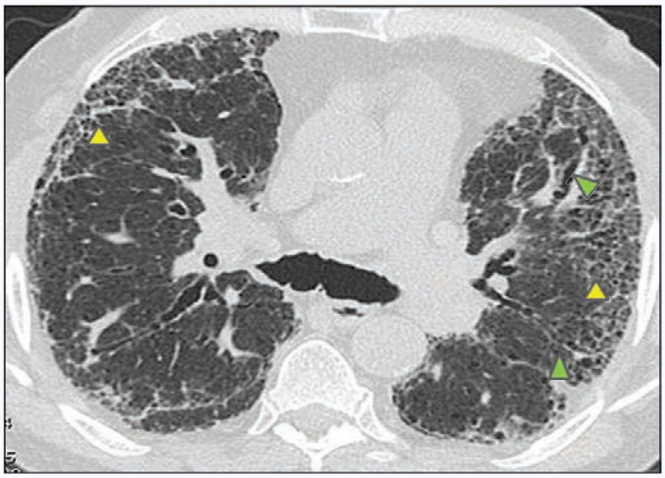


Images courtesy of and used with permission from David Lynch, MD.

HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | HP | OP

Probable UIP



Typical Distribution[1]:
- Subpleural
- Basal predominance
- Occasional upper lobe involvement

HRCT features[1]:
- Traction bronchiectasis ▲
- Reticulation △

• 1. Raghu G et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

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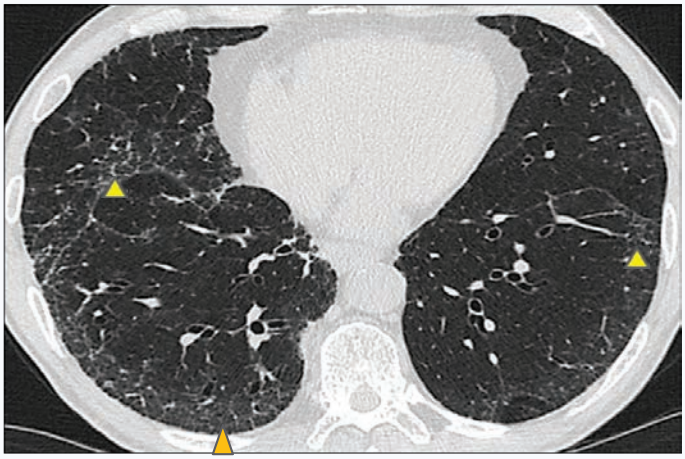
HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | HP | OP



Typical Distribution[1]:
- Subpleural
- Basal predominance

HRCT features[1]:
- Reticulation
- Ground glass opacity

1. Raghu G et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

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INDETERMINATE/ALTERNATIVE[1]

Upper or midlung predominance

Peribronchovascular predominance

Extensive ground glass abnormality

(extent > reticular abnormality)

Profuse micronodules

(bilateral, predominantly upper lobe)

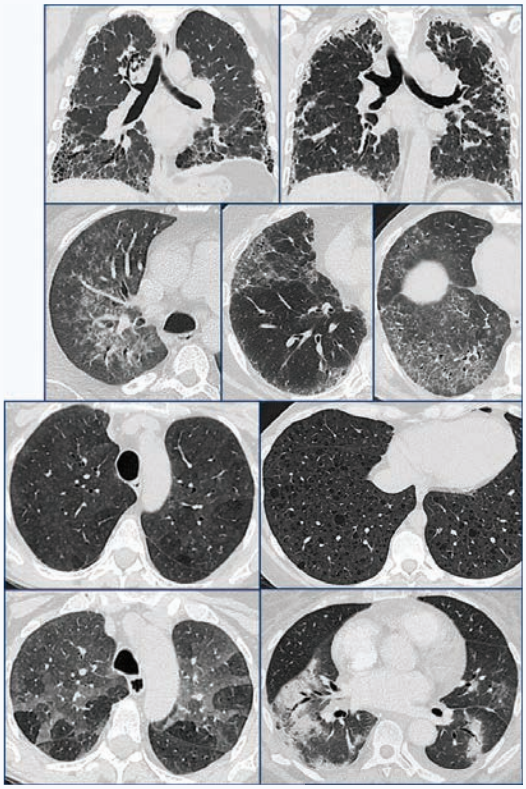
Discrete cysts

(multiple, bilateral, away from honeycombing)

Diffuse mosaic attenuation/air trapping

(bilateral, ≥ 3 lobes)

Consolidation



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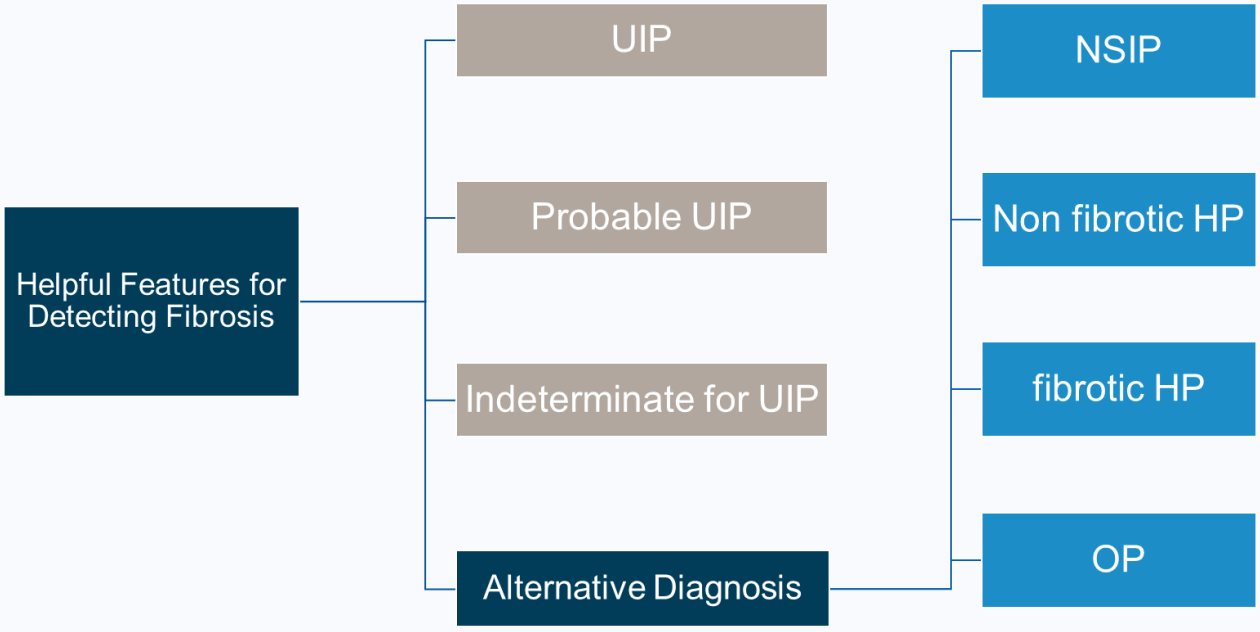
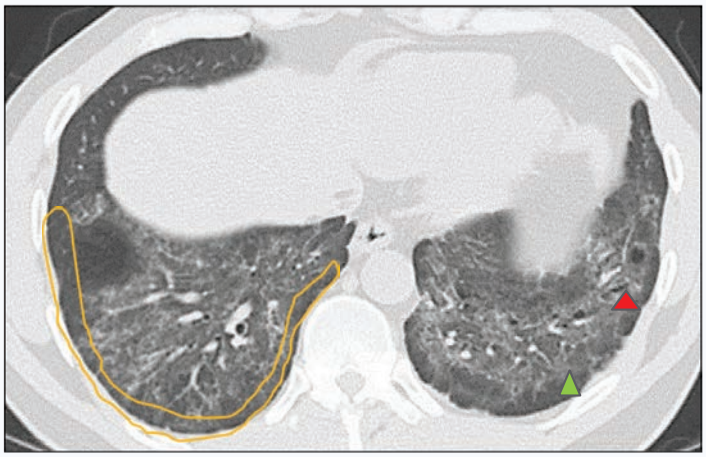
APPROACH FOR EVALUATING HRCT SCANS[1,2]



HRCT PATTERNS: NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

UIP | **NSIP** | HP | OP



Distribution can vary[1]:
- Subpleural (more common)
- Diffuse (less common)
- Subpleural sparing*

HRCT features of NSIP[1]:
- Ground glass opacification
- Traction bronchiectasis
- Reticulation
- Homogenous

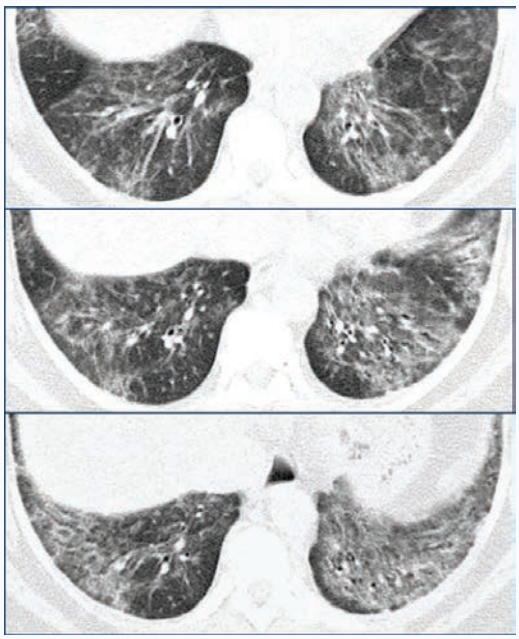
ILDs associated with NSIP[2-4]:
- Connective tissue disease-ILD
- Exposure-related ILDs

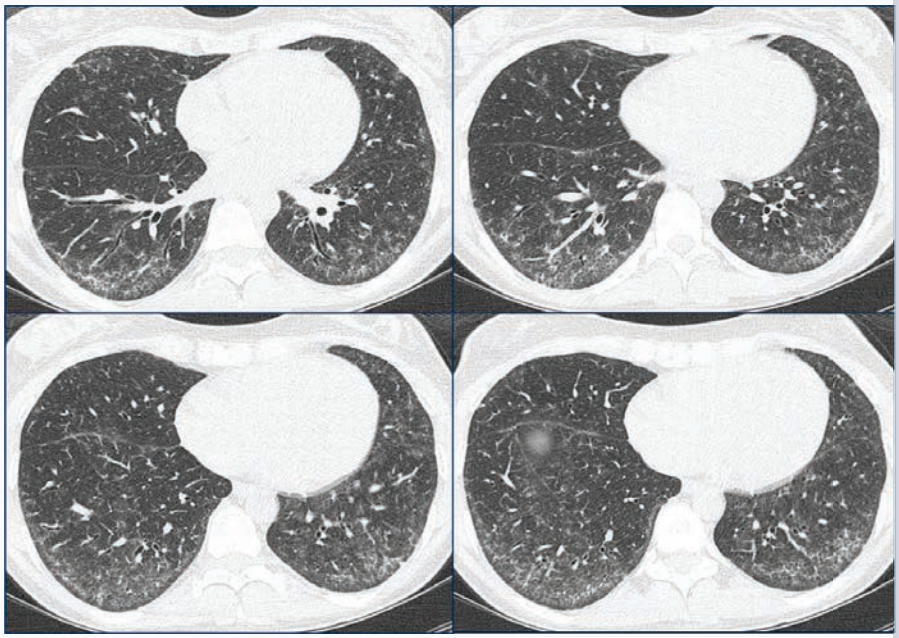
*Not always present but considered specific for NSIP.[1]

Image courtesy of and used with permission from Sudhakar Pipavath, MD.

1. Hansell DM et al. *Radiology*. 2008;246(3):697-722. 2. Travis WD et al. *Am J Respir Crit Care Med*. 2013;188(6):733-748. 3. Schoenfeld SR, Castelino FV. *Ther Adv Respir Dis*. 2017;11(8):327-340. 4. Wallace B et al. *Curr Opin Rheumatol*. 2016;28(3):236-245.

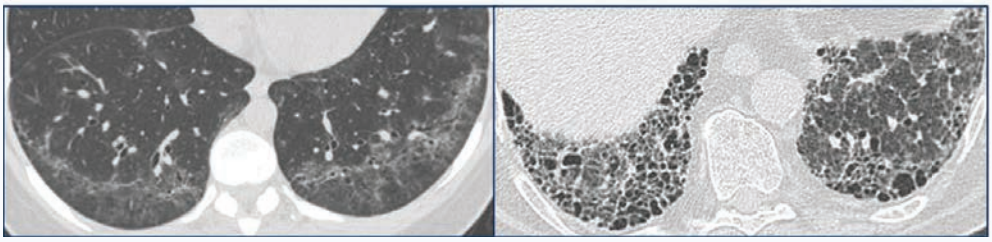
NSIP





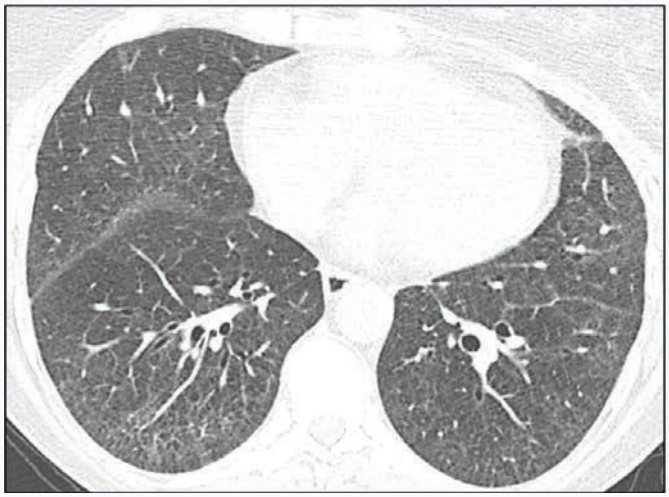
DIFFERENTIATING UIP AND NSIP

NSIP	UIP
Reticulations Traction bronchiectasis	
Ground glass No obvious gradient Homogeneous Subpleural sparing	Honeycombing Apico-basilar gradient Heterogeneous Subpleural involvement

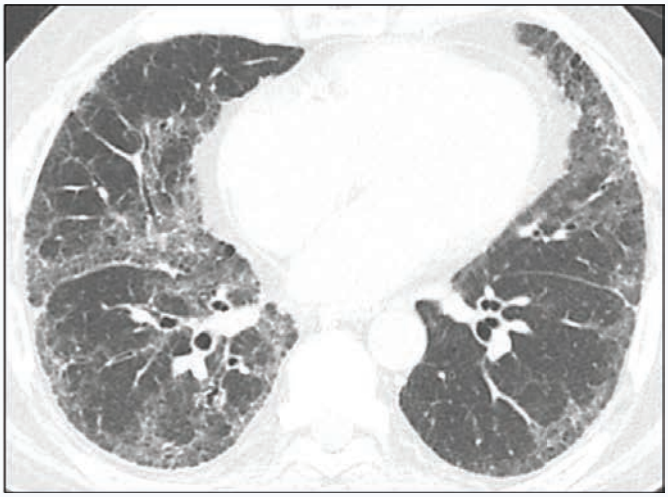


NSIP: PROGRESSION OVER TIME

EARLY



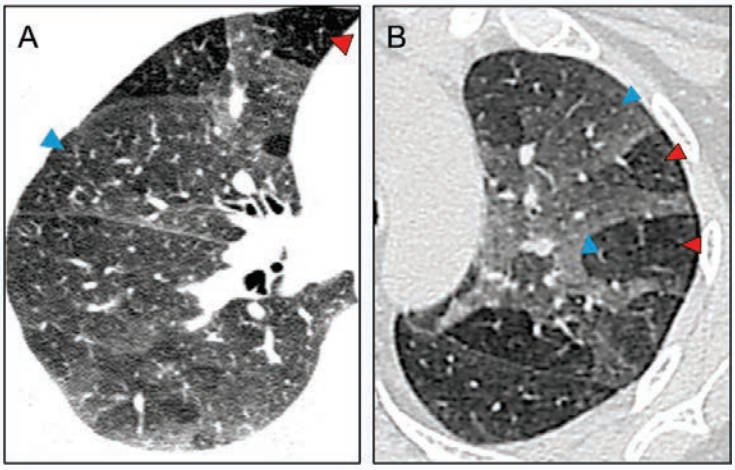
LATE



Images courtesy of and used with permission from Jonathan Chung, MD.

HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | **HP** | OP



HRCT features of non fibrotic HP[1]:

- Mosaic attenuation
- Air trapping ▲
- Ground glass opacification ▲

Although HP is caused by exposure to antigen through occupation or hobby, studies suggest some individuals may have a genetic predisposition to developing HP[2]

• Image A courtesy of and used with permission from Sudhakar Pipavath, MD.1. Selman M et al. *Am J Respir Crit Care Med*. 2012;186(4):314-324. Camarena A et al. *Am J Respir Crit Care Med*. 2001;163(7):1528-1533.

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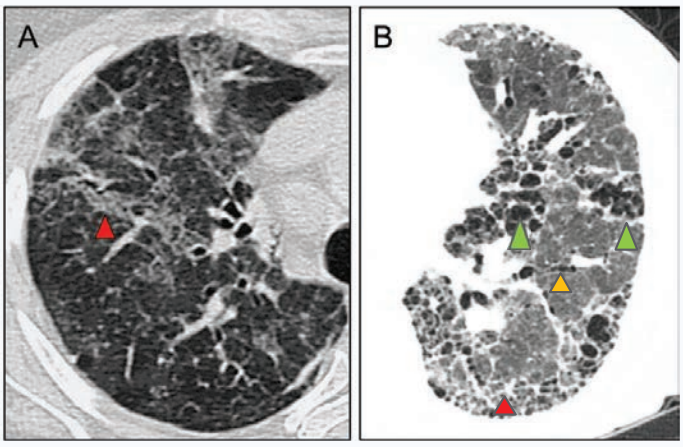
HRCT PATTERNS: HYPERSENSITIVITY PNEUMONITIS (HP)

UIP | NSIP | **HP** | OP



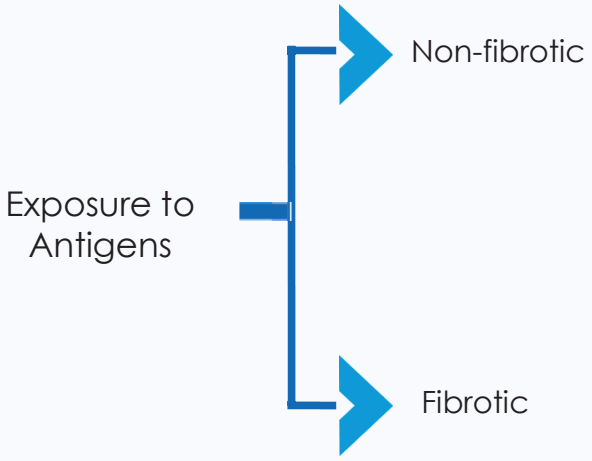
Distribution can vary and features can mimic those seen in UIP and NSIP[1,2]

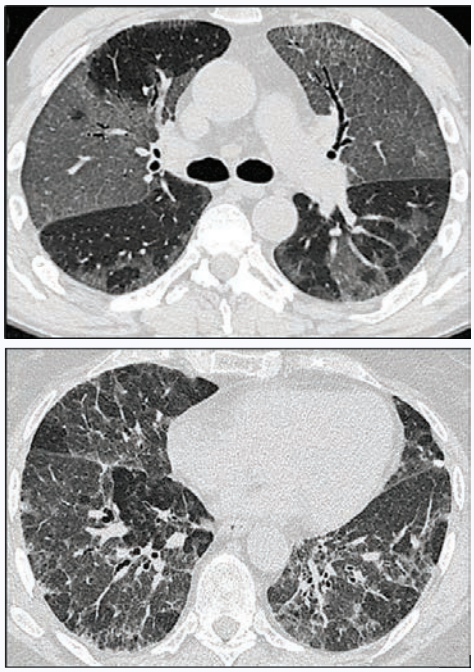
HRCT features of fibrotic HP[1,3]:

- Septal thickening
- Honeycombing* ▲
- Reticulation ▲
- Traction bronchiectasis △

Image A courtesy of and used with permission from Sudhakar Pipavath, MD. Image B courtesy of and used with permission from Jonathan C1. Selman M et al. *Am J Respir Crit Care Med*. 2012;186(4):314-324. 2. Kouranos V et al. *J Clin Med*. 2017;6(6). 3. Magee AL et al. *Radiol Clin North Am*. 2016;54(6):1033-1046. hung, M.D.

HRCT PATTERNS: HYPERSENSITIVITY PNEUMONITIS (HP)





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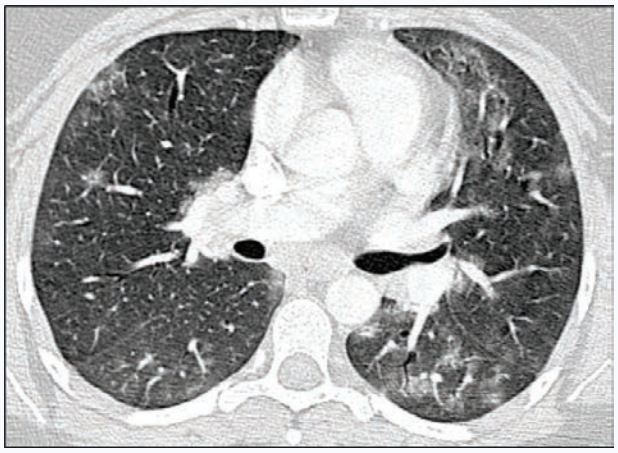
HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | HP | **OP**



Distribution is typically subpleural or peripheral and/or bronchovascular[1,2]

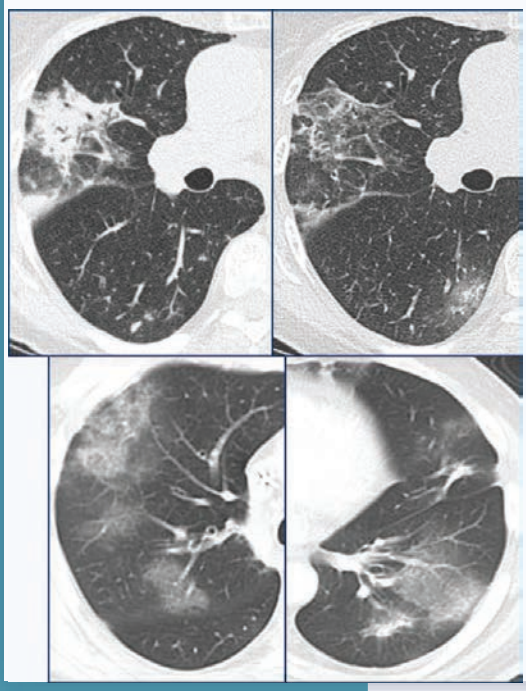
HRCT features of OP[1,2]:

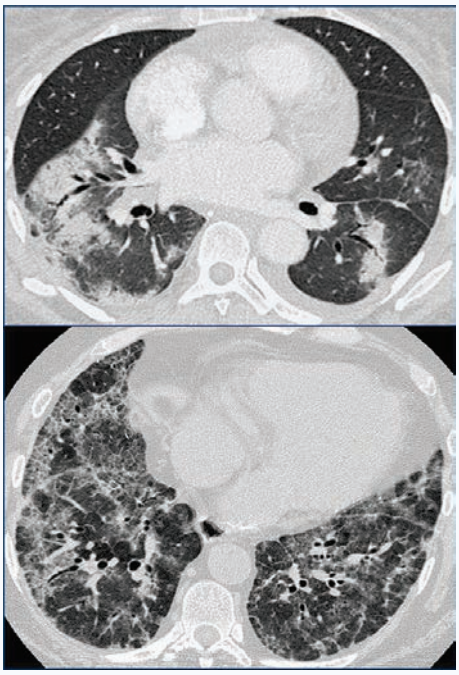
- Atoll signs
- Consolidation
- Ground glass opacification
- Nodular opacities

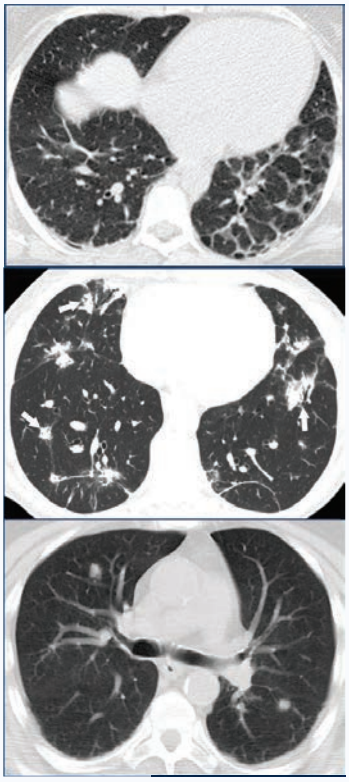
Although OP usually responds well to steroid therapy, a small percentage of patients with OP can develop fibrosis[2]

• Image courtesy of and used with permission from Sudhakar Pipavath, MD. 1. Hansell DM et al. *Radiology*. 2008;246(3):697-7222. 2. Beardsley B, Rassl D. *J Clin Pathol*. 2013;66(10):875-881. 3. Palmucci S et al. *Insights Imaging*. 2014;5(3):347-364.

ORGANIZING PNEUMONIA







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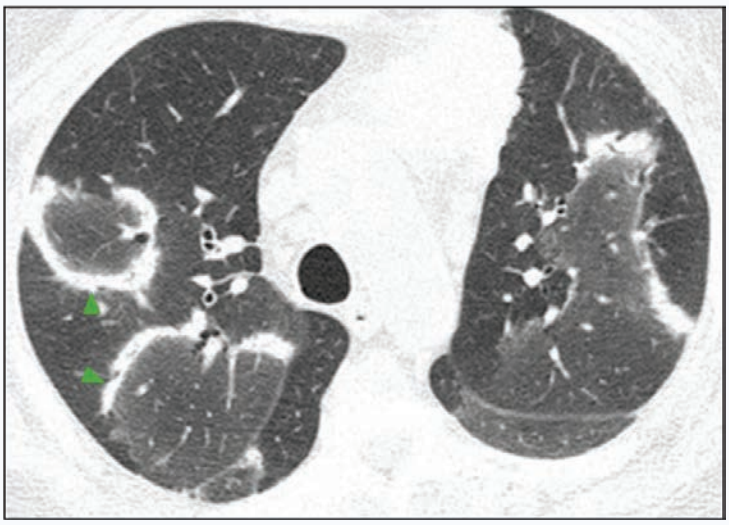
ATOLL SIGN

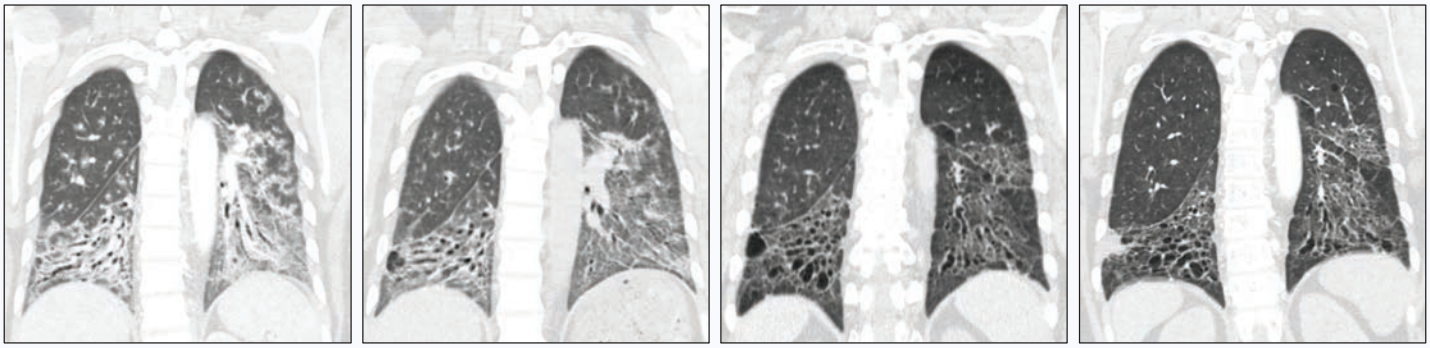


Central ground glass surrounded by peripheral consolidation

HRCT PATTERNS ASSOCIATED WITH FIBROSIS

UIP | NSIP | HP | **OP**

Fibrotic Variant



2010 **2011** **2013** **2014**

Image courtesy of and used with permission from Seth Kligerman, M.D.

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- Thank you!

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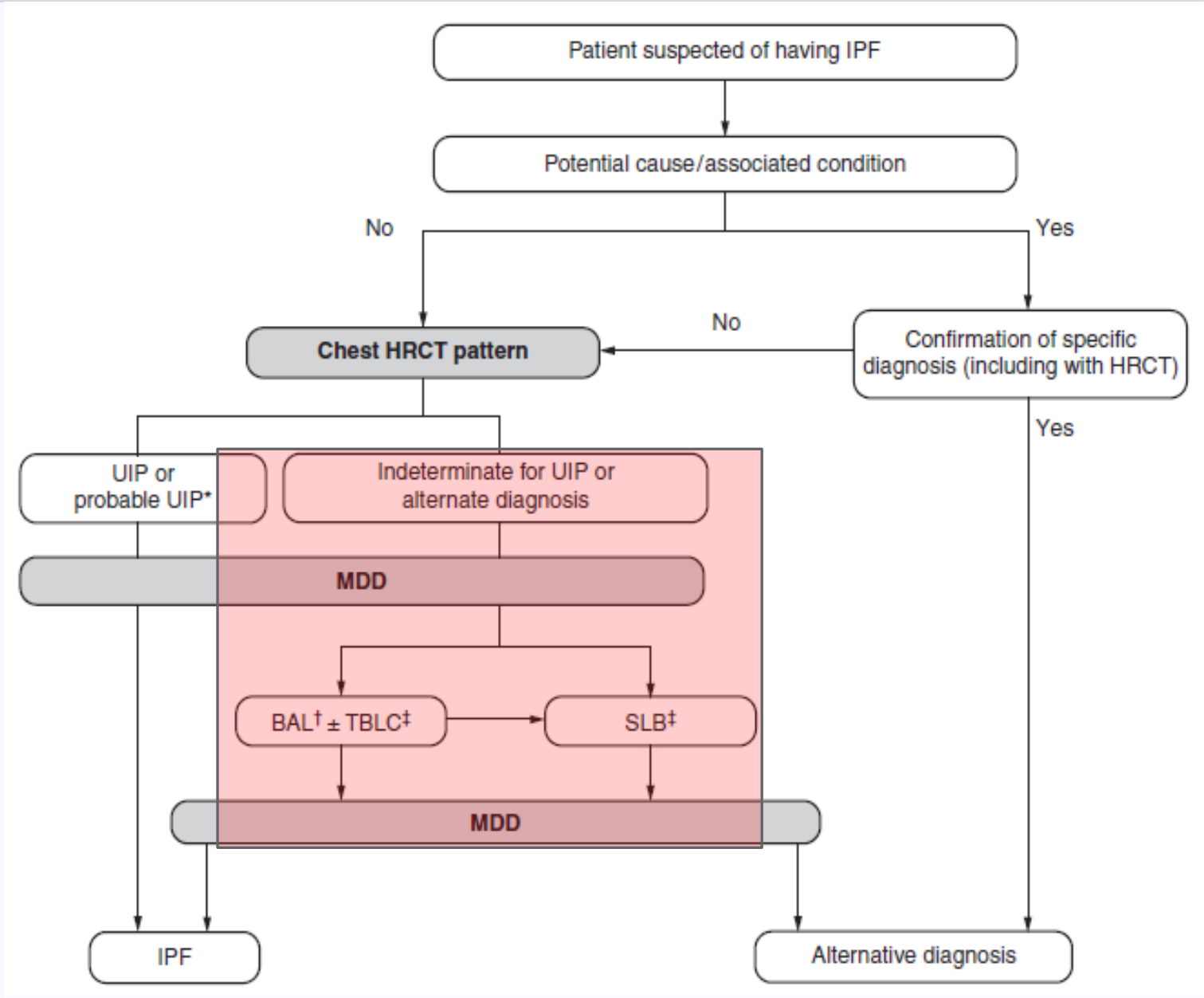
Invasive Diagnostic Approaches in ILD: From BAL to Lung Biopsy

Niranjan Jeganathan, MD, MS, FCCP, ATSF
Associate Professor of Medicine
Division of Pulmonary and Critical Care
Loma Linda University Health

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **NONE**
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Diagnostic Algorithm



• ATS IPF Guidelines, Am J Respir Crit Care Med 2022

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Multi-Disciplinary Discussion "Gold Standard"

- "The process of achieving a multidisciplinary diagnosis in a patient with IIP is dynamic, requiring close communication between clinician, radiologist, and when appropriate, pathologist.
- Clinical data (presentation, exposures, smoking status, associated diseases, lung function, laboratory findings) and radiologic findings are essential for multidisciplinary diagnosis."

• Travis, WD et al. Am J Respir Crit Care Med, 2013.

Bronchoalveolar Lavage

I. Normal Adults (Nonsmokers)	BAL Differential Cell Counts
Alveolar macrophages	>85%
Lymphocytes (CD4+/CD8+ = 0.9–2.5)	10–15%
Neutrophils	≤3%
Eosinophils	≤1%
Squamous epithelial*/ciliated columnar epithelial cells†	≤5%

b. Abnormal BAL differential cell patterns that suggest specific types of ILD

A lymphocyte differential count ≥25% suggests granulomatous disease (sarcoidosis, hypersensitivity pneumonitis, or chronic beryllium disease), cellular nonspecific interstitial pneumonia, drug reaction, lymphoid interstitial pneumonia, cryptogenic organizing pneumonia, or lymphoma.
CD4+/CD8+ >4 is highly specific for sarcoidosis in the absence of an increased proportion of other inflammatory cell types.
A lymphocyte differential count >50% suggests hypersensitivity pneumonitis or cellular nonspecific interstitial pneumonia.
A neutrophil differential count >50% supports acute lung injury, aspiration pneumonia, or suppurative infection.
An eosinophil differential count >25% is virtually diagnostic of acute or chronic eosinophilic pneumonia.
A cell differential count of >1% mast cells, >50% lymphocytes, and >3% neutrophils is suggestive of acute hypersensitivity pneumonitis.

c. Other abnormal BAL findings

Infectious organism	Lower respiratory infection
Malignant cells (light microscopy, flow cytometry)	Cancer
Bloody fluid that increases in successive aliquots	Pulmonary hemorrhage ± diffuse alveolar damage
Milky fluid with positive periodic acid Schiff staining and amorphous debris	Pulmonary alveolar proteinosis
In vitro lymphocyte proliferative response to specific beryllium antigen	Chronic beryllium disease

- Meyer KC et al. Am J Respir Crit Care Med, 2012

Bronchoalveolar Lavage Lymphocytes in the Diagnosis of Hypersensitivity Pneumonitis among Patients with Interstitial Lung Disease

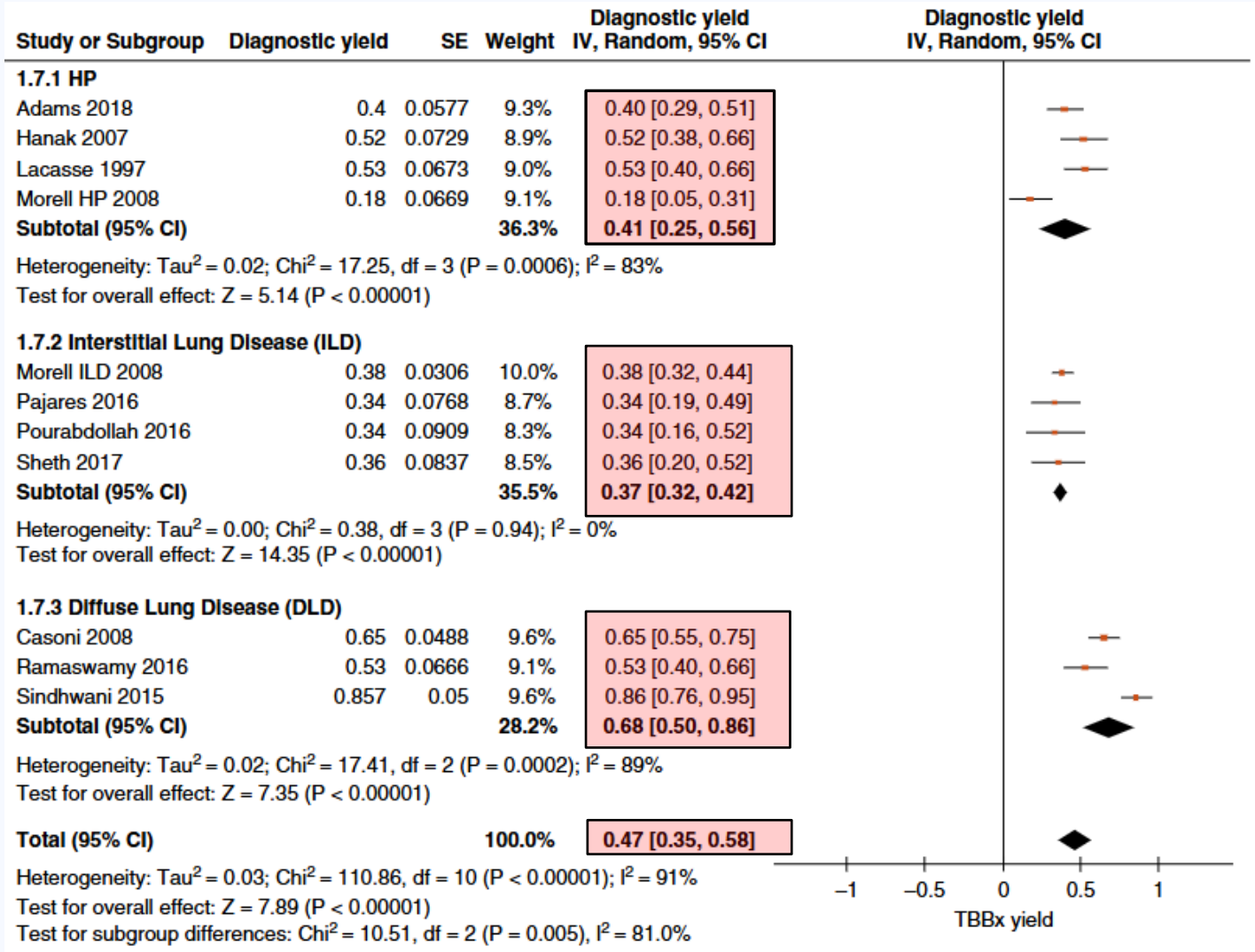
Setu Patolia[1], Maximiliano Tamae Kakazu[2], Hasan A. Chami[3], Abigail Chua[4], Javier Diaz-Mendoza[5], Abhijit Duggal[6], Alex R. Jenkins[7], Shandra L. Knight[8], Ganesh Raghu[9], and Kevin C. Wilson[10]

Table 3. Assessment of various diagnostic thresholds of percentage of BAL fluid lymphocytes

	Fibrotic HP vs. IPF		Nonfibrotic HP vs. IPF		Fibrotic HP vs. Sarcoidosis		Nonfibrotic HP vs. Sarcoidosis	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
20% lymphocytes	69%	61%	95%	61%	69%	26%	95%	26%
30% lymphocytes	55%	80%	88%	80%	55%	43%	88%	43%
40% lymphocytes	41%	93%	76%	93%	41%	61%	76%	61%

- Patolia S et al. Ann Am Thorac Soc, 2020

Transbronchial Biopsy



• Chami HA et al. Ann Am Thorac Soc, 2020

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Transbronchial Cryobiopsy

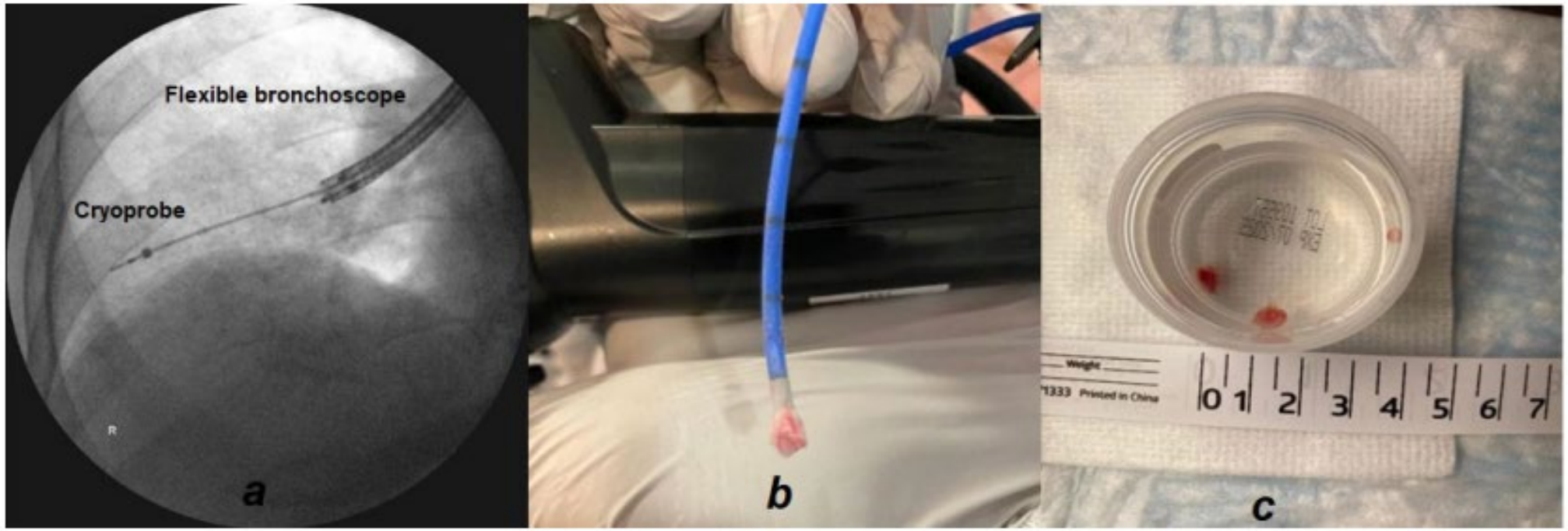


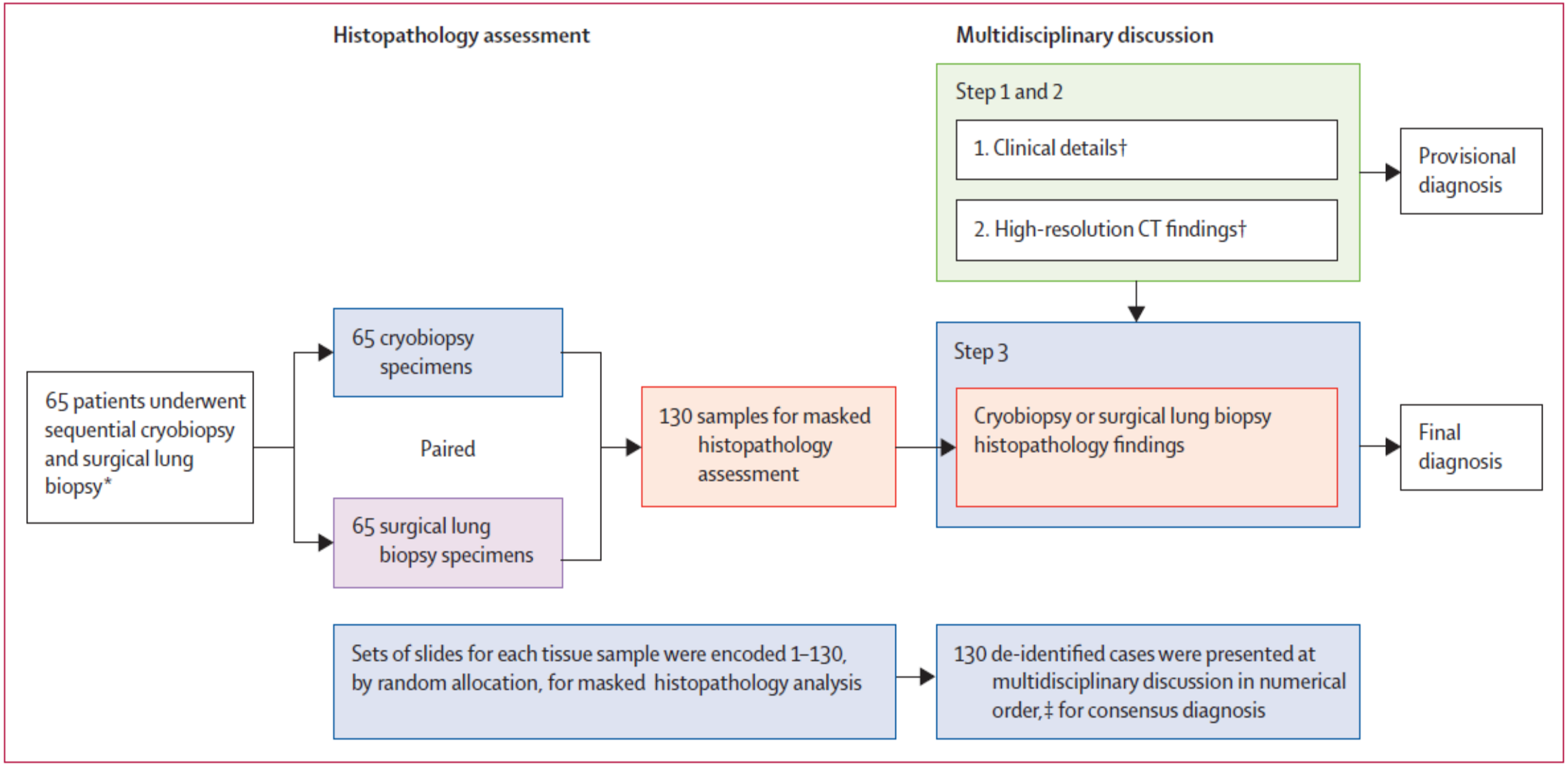
Figure 1. Transbronchial cryobiopsy procedure. (**a**) Fluoroscopic view of transbronchial lung cryobiopsy in the right lower lobe of a patient with intersitial lung disease. (**b**) Bronchoscope and cryoprobe removed en bloc with frozen specimen at the tip of the cryoprobe. (**c**) Cryobiopsy specimens released from the cryoprobe into specimen container.

• Husnain et al. Diagnostics, 2023

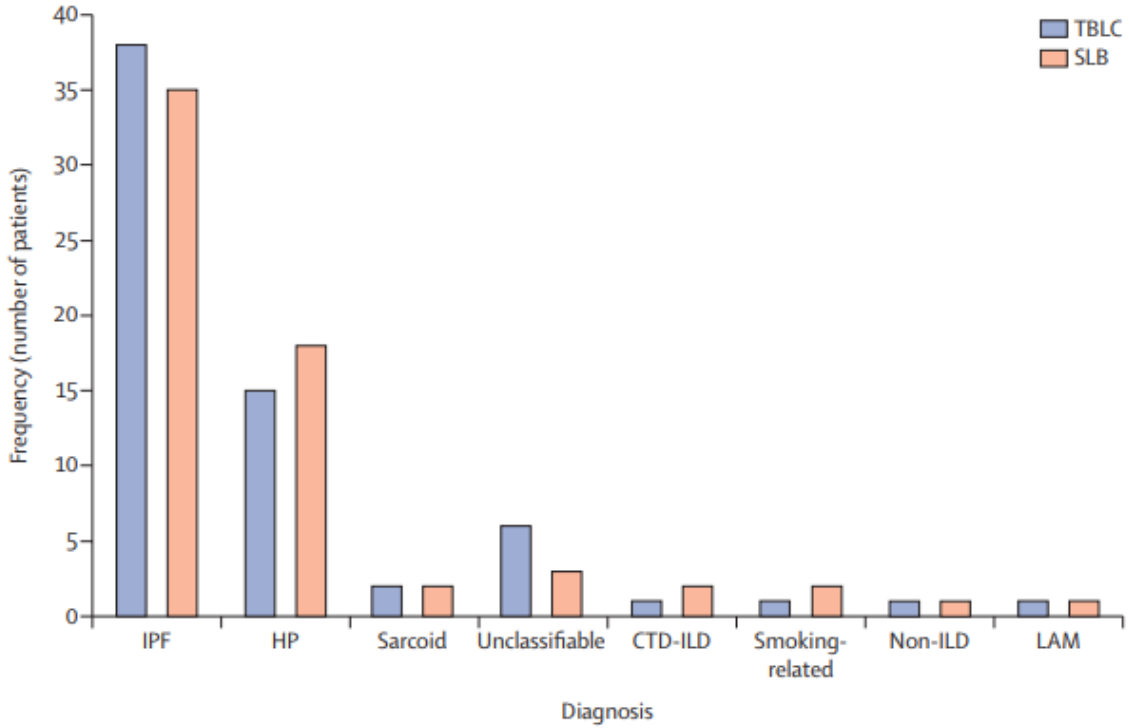
Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study

- Multicenter, prospective study conducted across nine Australian tertiary hospitals with expertise in interventional pulmonology and interstitial lung disease.
- Inclusion Criteria: adults aged 18–80 years requiring lung biopsy for interstitial lung disease diagnosis,
- Exclusion Criteria: Hypoxemia (SpO2 <90%), severe lung impairment (DLCO <40% or TLC <50% predicted), high BMI (>40 kg/m²), pulmonary hypertension (RVSP >40 mm Hg or right ventricular dysfunction), excessive bleeding risk, or advanced comorbidities.
- Screening and Enrollment: Centralized MDD determined biopsy necessity based on baseline assessments and high-resolution CT imaging, along with clinical and serological data.

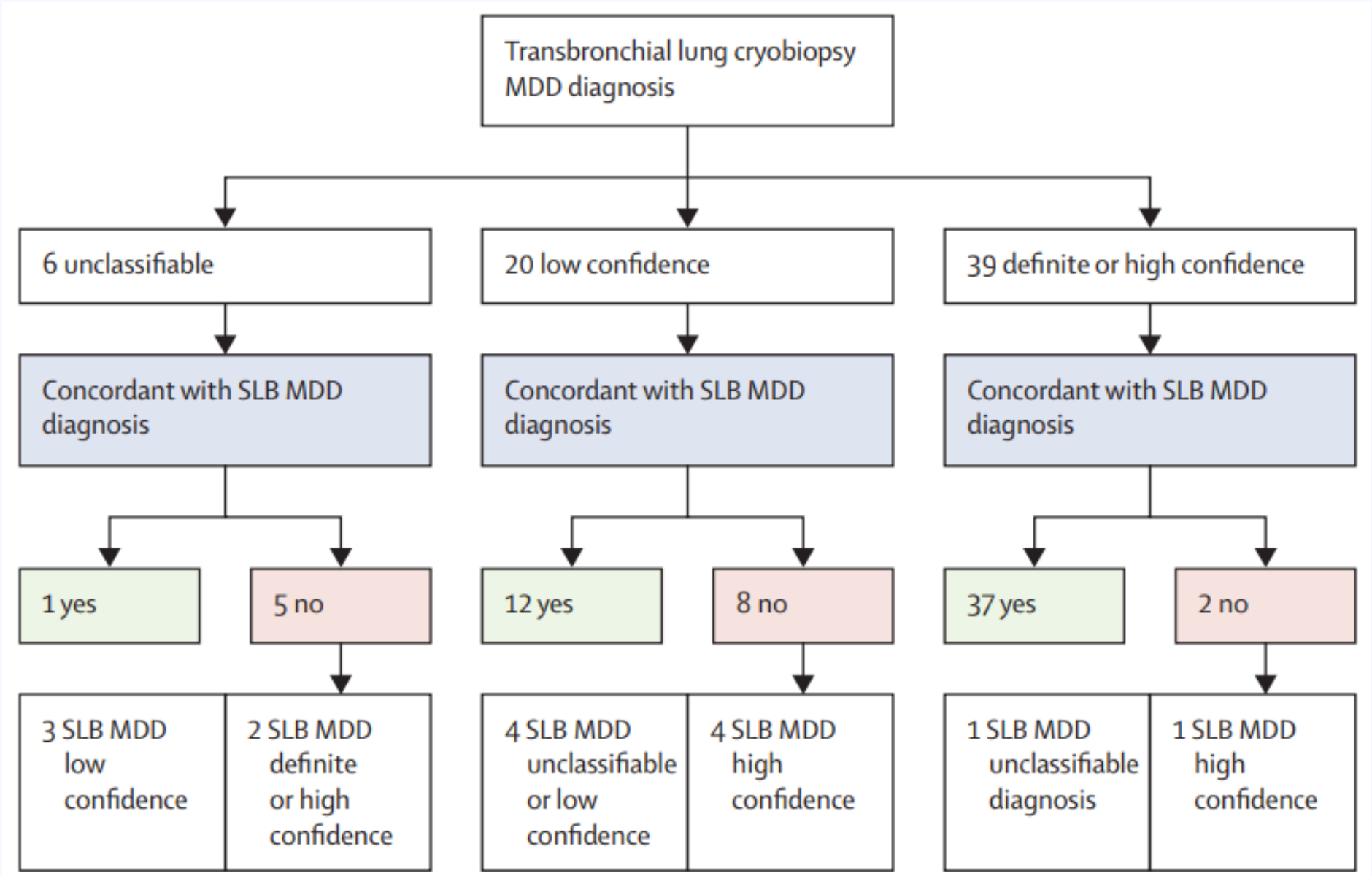
• Troy, L.K., et al. *Lancet Respiratory*, 2020.



	Transbronchial lung cryobiopsy	Surgical lung biopsy
Histopathological patterns		
Usual interstitial pneumonia pattern consistent with idiopathic pulmonary fibrosis	41 (63%)	39 (60%)
Hypersensitivity pneumonitis	10 (15%)	15 (23%)
Sarcoidosis	3 (5%)	2 (3%)
Respiratory bronchiolitis-ILD or desquamative interstitial pneumonia	2 (3%)	2 (3%)
Non-specific interstitial pneumonia overlapping with organising pneumonia pattern	2 (3%)	2 (3%)
Usual interstitial pneumonia pattern consistent with connective tissue disease-ILD	0	2 (3%)
Unclassifiable	3 (5%)	1 (2%)
Non-diagnostic tissue	3 (5%)	1 (2%)
Non-ILD diagnosis*	1 (2%)	1 (2%)
Multidisciplinary discussion diagnoses		
Idiopathic pulmonary fibrosis	38 (58%)	35 (54%)
Hypersensitivity pneumonitis	15 (23%)	18 (28%)
Sarcoidosis	2 (3%)	2 (3%)
Smoking-related ILD†	1 (2%)	2 (3%)
Connective tissue disease-ILD‡	1 (2%)	2 (3%)
Lymphangioleiomyomatosis	1 (2%)	1 (2%)
Unclassifiable ILD	6 (9%)	3 (5%)
Non-ILD diagnosis*	1 (2%)	1 (2%)



- Histopathological agreement 70.8%
- MDD agreement 76.9%



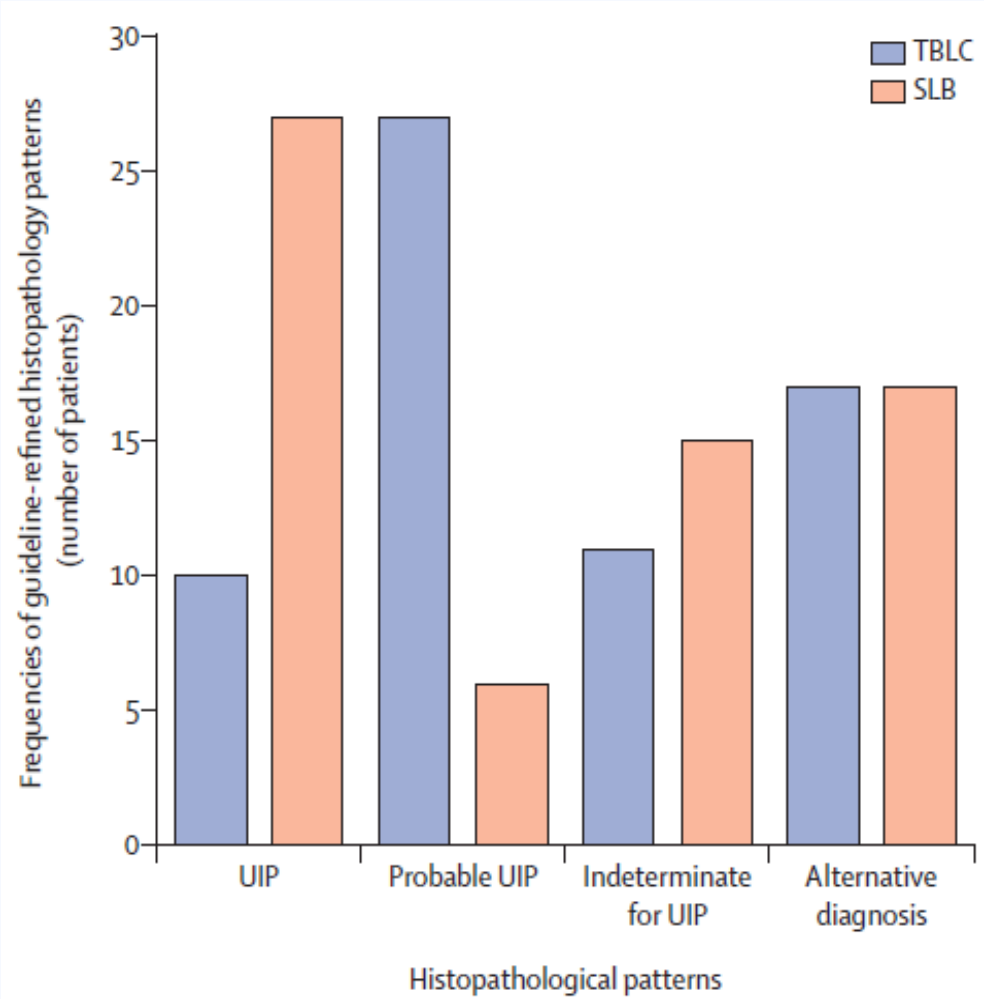


Table 3. Frequencies of Guideline Criteria* for Usual Interstitial Pneumonia in Cryobiopsy Compared with Surgical Biopsy ($n = 33$)

	TBLC	SLB
Pathological features		
Predominantly subpleural† or paraseptal fibrosis/architectural distortion (e.g., honeycomb change)‡	8 (24.2%)	33 (100%)
Patchy fibrosis	33 (100%)	33 (100%)
Fibroblast foci	29 (87.9%)	33 (100%)
Absence of alternative diagnostic features	30 (90.9%)	31 (93.9%)
All four features observed	7 (21.2%)	31 (93.9%)
Three out of four features observed	21 (63.6%)	2 (6.1%)
Two out of four features observed	4 (12.1%)	0
One out of four features observed	1 (3.0%)	0

Usual Interstitial Pneumonia Criteria for Cryobiopsy

Required

- Patchy involvement of lung parenchyma by fibrosis
- Fibroblast foci
- Absence of features to suggest an alternative diagnosis (e.g., granulomas, hyaline membranes, prominent airway-centered changes, organizing pneumonia, marked inflammatory cell infiltrate, prominent lymphoid hyperplasia, vasculitis, eosinophils)

May be present in some, but not all, cases

- Marked fibrosis/architectural distortion (i.e., destructive scarring and/or honeycombing) in a predominantly subpleural or paraseptal distribution

- Troy, L.K., et al. *Lancet Respiratory*, 2020.
  Cooper, W.A. et al. Am J Respir Crit Care Med, 2021

Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases

Micaela Romagnoli[1,2], Thomas V. Colby[3], Jean-Philippe Berthet[4], Anne Sophie Gamez[1], Jean-Pierre Mallet[1], Isabelle Serre[5], Alessandra Cancellieri[6], Alberto Cavazza[7], Laurence Solovei[4], Andrea Dell'Amore[8], Giampiero Dolci[8], Aldo Guerrieri[9], Paul Reynaud[1], Sébastien Bommart[10,11], Maurizio Zompatori[12], Giorgia Dalpiaz[13], Stefano Nava[9], Rocco Trisolini[2], Carey M. Suehs[1], Isabelle Vachier[1], Nicolas Molinari[14], and Arnaud Bourdin[1,11]

Comparison	% Agreement (95% CI)	κ (95% CI)
TBLC vs. SLB	38 (18–62)	0.22 (0.01–0.44)
TBLC vs. MDA2	48 (26–70)	0.31 (0.06–0.56)
SLB vs. MDA2	62 (38–82)	0.51 (0.27–0.75)

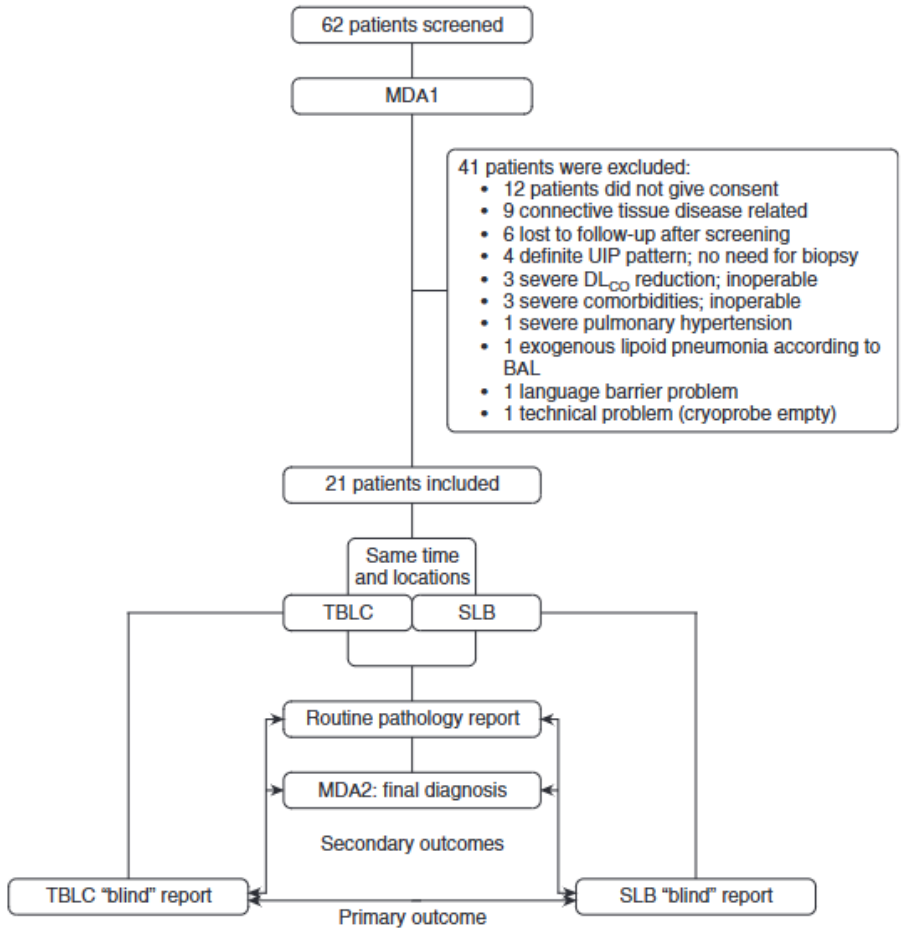
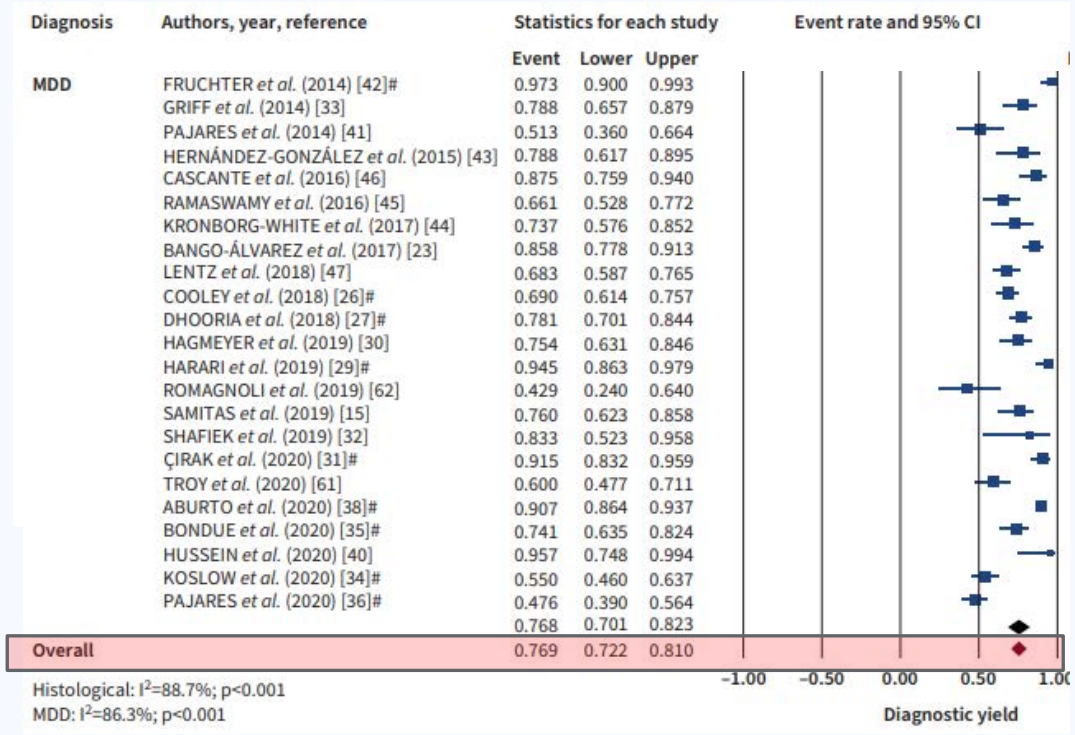


Figure 1. The study flowchart. Among 62 screened patients, 41 were excluded and 21 finally included in the study. After an initial multidisciplinary assessment meeting (MDA1), transbronchial lung cryobiopsies (TBLCs) and surgical lung biopsies (SLBs) were performed on all study participants and their results included in a routine pathology report. A second multidisciplinary assessment meeting (MDA2) was held to determine a final diagnosis. The primary outcome consisted in determining concordance between blinded TBLC and SLB results as well as between each type of biopsy and the MDA2 final diagnosis. UIP = usual interstitial pneumonia.

Diagnostic yield and safety of transbronchial lung cryobiopsy and surgical lung biopsy in interstitial lung diseases: a systematic review and meta-analysis

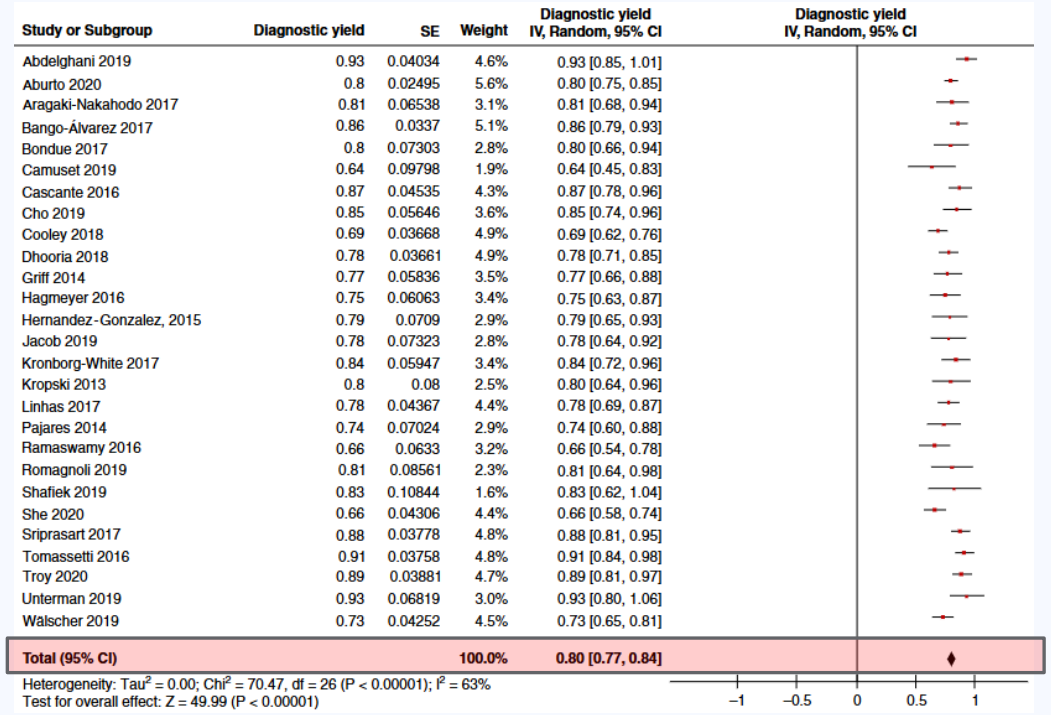
Inês Rodrigues[1,9], Ricardo Estêvão Gomes[2,9], Lígia Maria Coutinho[3], Maria Teresa Rego[3], Firmino Machado[4,5,6], António Morais[6,7] and Helder Novais Bastos[6,7,8]



Transbronchial Lung Cryobiopsy in Patients with Interstitial Lung Disease

A Systematic Review

Fayez Kheir[1], Juan Pablo Uribe Becerra[2], Brittany Bissell[3,4], Marya Ghazipura[5,6,7], Derrick Herman[8], Stephanie M. Hon[9], Tanzib Hossain[6], Yet H. Khor[10,11], Shandra L. Knight[12], Michael Kreuter[13], Madalina Macrea[14], Manoj J. Mammen[15], Fernando J. Martinez[16], Venerino Poletti[17,18], Lauren Troy[19], Ganesh Raghu[20], and Kevin C. Wilson[21]



• Eur Respir Rev, 2022; Ann Am Thorac Soc, 2022

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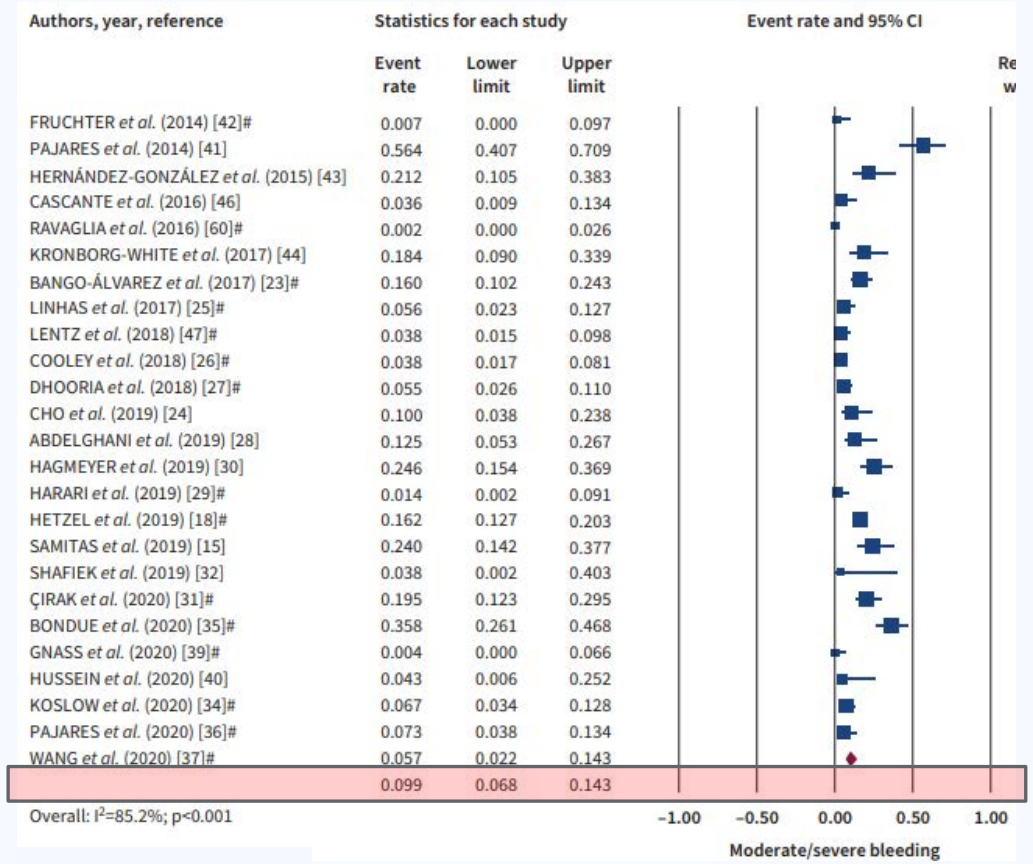
Bleeding Risk with Transbronchial Cryobiopsy

Study or Subgroup	All Type of Bleeding	SE	Weight	All Type of Bleeding IV, Random, 95% CI
Abdelghani 2019	0.28	0.07099	8.1%	0.28 [0.14, 0.42]
Aragaki-Nakahodo 2017	0.67	0.07837	7.9%	0.67 [0.52, 0.82]
Camuset 2019	0.21	0.08314	7.7%	0.21 [0.05, 0.37]
Cirak 2020	0.48	0.05517	8.6%	0.48 [0.37, 0.59]
Hernandez-Gonzalez, 2015	0.31	0.08051	7.8%	0.31 [0.15, 0.47]
Jacob 2019	0.03	0.03016	9.2%	0.03 [–0.03, 0.09]
Kronborg-White 2017	0.16	0.05947	8.5%	0.16 [0.04, 0.28]
Pajares 2014	0.56	0.07949	7.8%	0.56 [0.40, 0.72]
Ravaglia 2017	0.3	0.06831	8.2%	0.30 [0.17, 0.43]
Troy 2020	0.22	0.05138	8.7%	0.22 [0.12, 0.32]
Ussavarungsi 2017	0.22	0.04816	8.8%	0.22 [0.13, 0.31]
Walscher 2019	0.28	0.04301	8.9%	0.28 [0.20, 0.36]
Total (95% CI)			**100.0%**	**0.30 [0.20, 0.41]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 118.58$, df = 11 ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 5.70$ ($P < 0.00001$)

All Type of Bleeding IV, Random, 95% CI

−0.5 −0.25 0 0.25 0.5



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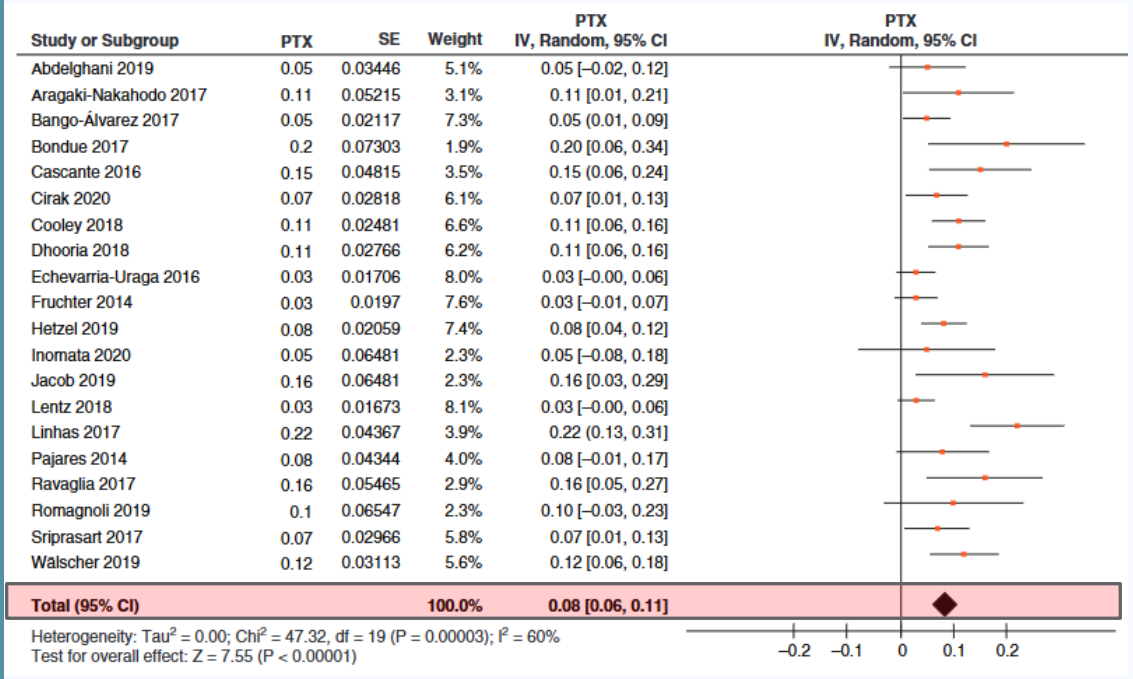
Pneumothorax Risk with Transbronchial Cryobiopsy

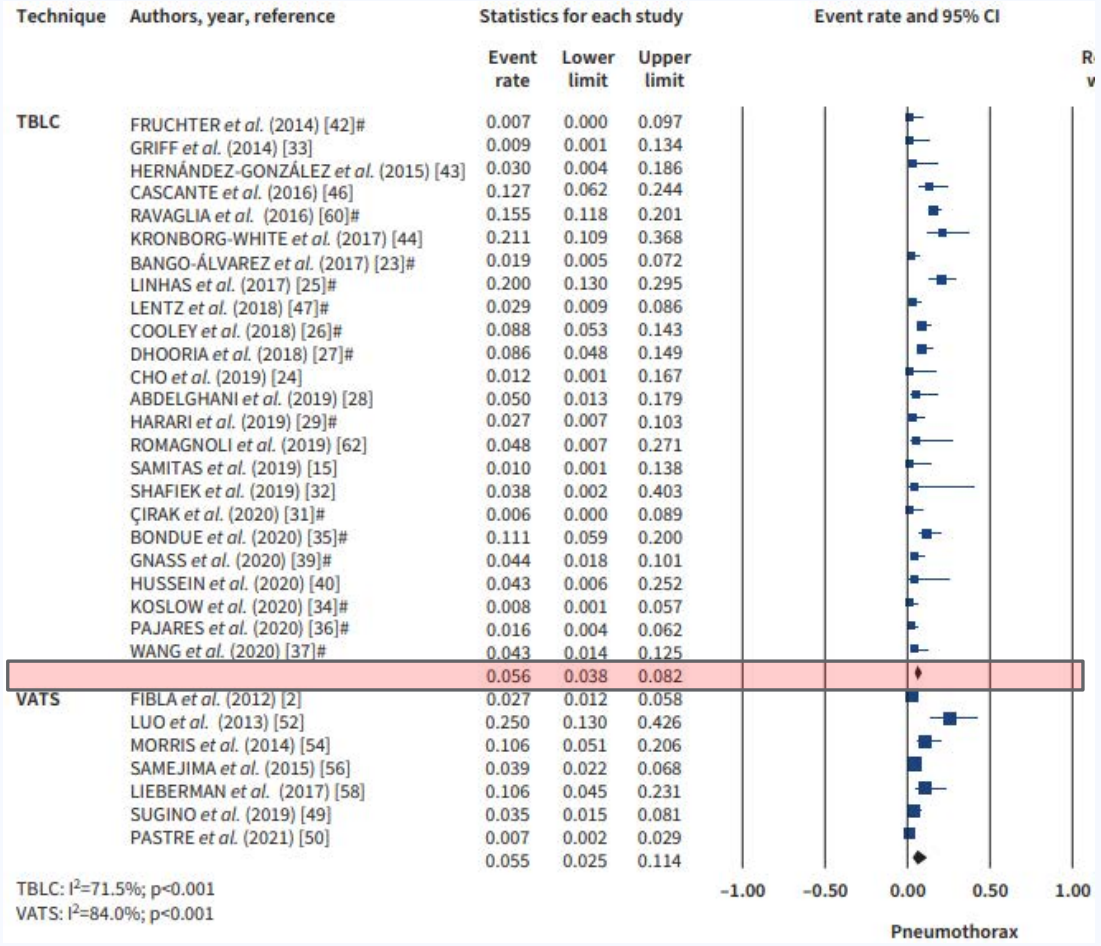


Study or Subgroup	PTX	SE	Weight	PTX IV, Random, 95% CI
Abdelghani 2019	0.05	0.03446	5.1%	0.05 [–0.02, 0.12]
Aragaki-Nakahodo 2017	0.11	0.05215	3.1%	0.11 [0.01, 0.21]
Bango-Álvarez 2017	0.05	0.02117	7.3%	0.05 (0.01, 0.09]
Bondue 2017	0.2	0.07303	1.9%	0.20 [0.06, 0.34]
Cascante 2016	0.15	0.04815	3.5%	0.15 (0.06, 0.24]
Cirak 2020	0.07	0.02818	6.1%	0.07 [0.01, 0.13]
Cooley 2018	0.11	0.02481	6.6%	0.11 [0.06, 0.16]
Dhooria 2018	0.11	0.02766	6.2%	0.11 [0.06, 0.16]
Echevarria-Uraga 2016	0.03	0.01706	8.0%	0.03 [–0.00, 0.06]
Fruchter 2014	0.03	0.0197	7.6%	0.03 [–0.01, 0.07]
Hetzel 2019	0.08	0.02059	7.4%	0.08 [0.04, 0.12]
Inomata 2020	0.05	0.06481	2.3%	0.05 [–0.08, 0.18]
Jacob 2019	0.16	0.06481	2.3%	0.16 [0.03, 0.29]
Lentz 2018	0.03	0.01673	8.1%	0.03 [–0.00, 0.06]
Linhas 2017	0.22	0.04367	3.9%	0.22 (0.13, 0.31]
Pajares 2014	0.08	0.04344	4.0%	0.08 [–0.01, 0.17]
Ravaglia 2017	0.16	0.05465	2.9%	0.16 [0.05, 0.27]
Romagnoli 2019	0.1	0.06547	2.3%	0.10 [–0.03, 0.23]
Sriprasart 2017	0.07	0.02966	5.8%	0.07 [0.01, 0.13]
Walscher 2019	0.12	0.03113	5.6%	0.12 [0.06, 0.18]
Total (95% CI)			**100.0%**	**0.08 [0.06, 0.11]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 47.32$, df = 19 (P = 0.00003); $I^2 = 60\%$
Test for overall effect: Z = 7.55 (P < 0.00001)

PTX IV, Random, 95% CI

–0.2 –0.1 0 0.1 0.2



Technique	Authors, year, reference	Event rate	Lower limit	Upper limit
TBLC	FRUCHTER *et al.* (2014) [42]#	0.007	0.000	0.097
	GRIFF *et al.* (2014) [33]	0.009	0.001	0.134
	HERNÁNDEZ-GONZÁLEZ *et al.* (2015) [43]	0.030	0.004	0.186
	CASCANTE *et al.* (2016) [46]	0.127	0.062	0.244
	RAVAGLIA *et al.* (2016) [60]#	0.155	0.118	0.201
	KRONBORG-WHITE *et al.* (2017) [44]	0.211	0.109	0.368
	BANGO-ÁLVAREZ *et al.* (2017) [23]#	0.019	0.005	0.072
	LINHAS *et al.* (2017) [25]#	0.200	0.130	0.295
	LENTZ *et al.* (2018) [47]#	0.029	0.009	0.086
	COOLEY *et al.* (2018) [26]#	0.088	0.053	0.143
	DHOORIA *et al.* (2018) [27]#	0.086	0.048	0.149
	CHO *et al.* (2019) [24]	0.012	0.001	0.167
	ABDELGHANI *et al.* (2019) [28]	0.050	0.013	0.179
	HARARI *et al.* (2019) [29]#	0.027	0.007	0.103
	ROMAGNOLI *et al.* (2019) [62]	0.048	0.007	0.271
	SAMITAS *et al.* (2019) [15]	0.010	0.001	0.138
	SHAFIEK *et al.* (2019) [32]	0.038	0.002	0.403
	ÇIRAK *et al.* (2020) [31]#	0.006	0.000	0.089
	BONDUE *et al.* (2020) [35]#	0.111	0.059	0.200
	GNASS *et al.* (2020) [39]#	0.044	0.018	0.101
	HUSSEIN *et al.* (2020) [40]	0.043	0.006	0.252
	KOSLOW *et al.* (2020) [34]#	0.008	0.001	0.057
	PAJARES *et al.* (2020) [36]#	0.016	0.004	0.062
	WANG *et al.* (2020) [37]#	0.043	0.014	0.125
		0.056	0.038	0.082
VATS	FIBLA *et al.* (2012) [2]	0.027	0.012	0.058
	LUO *et al.* (2013) [52]	0.250	0.130	0.426
	MORRIS *et al.* (2014) [54]	0.106	0.051	0.206
	SAMEJIMA *et al.* (2015) [56]	0.039	0.022	0.068
	LIEBERMAN *et al.* (2017) [58]	0.106	0.045	0.231
	SUGINO *et al.* (2019) [49]	0.035	0.015	0.081
	PASTRE *et al.* (2021) [50]	0.007	0.002	0.029
		0.055	0.025	0.114

TBLC: I^2=71.5%; p<0.001
VATS: I^2=84.0%; p<0.001

Event rate and 95% CI

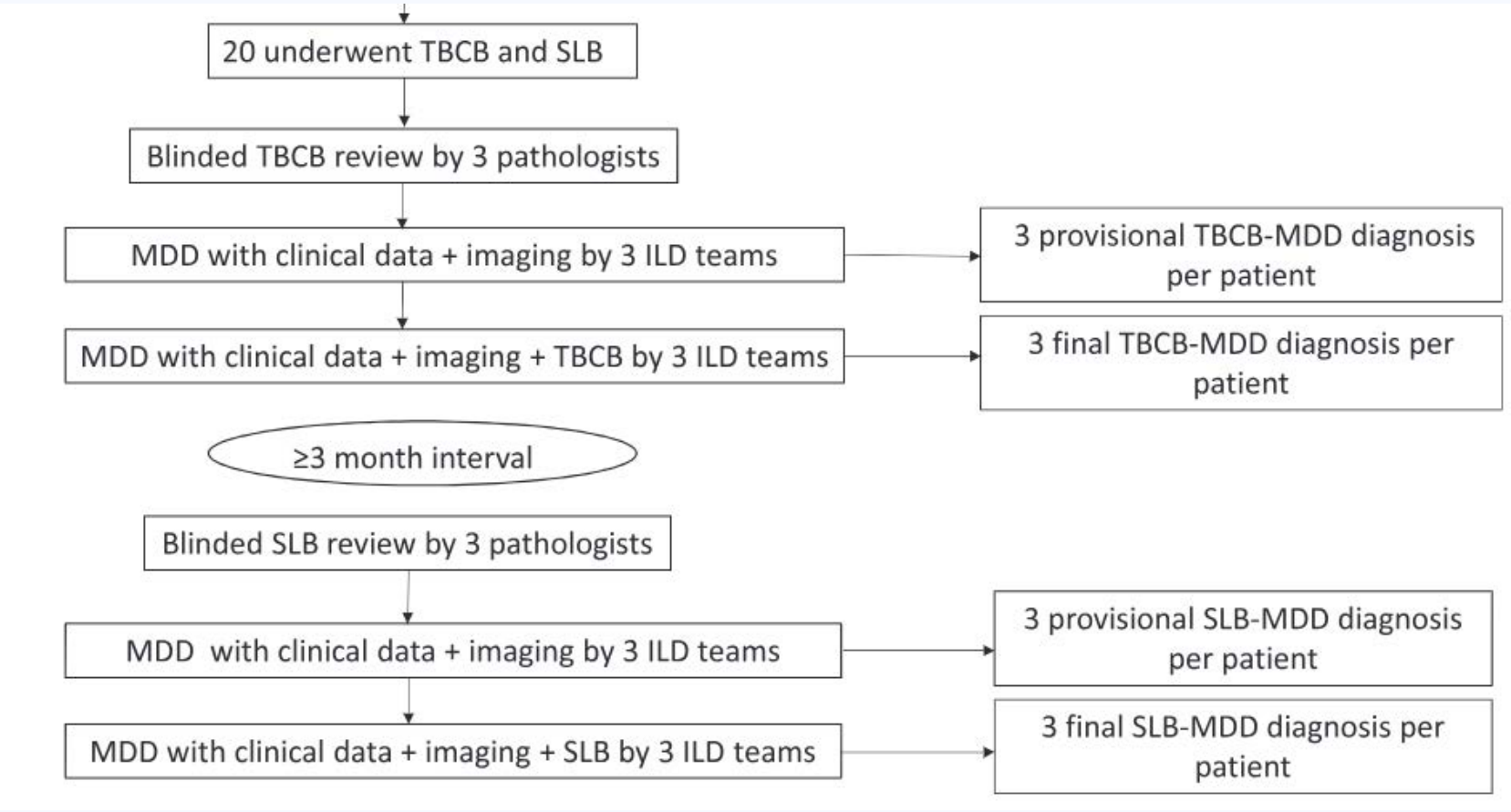
–1.00 –0.50 0.00 0.50 1.00

Pneumothorax

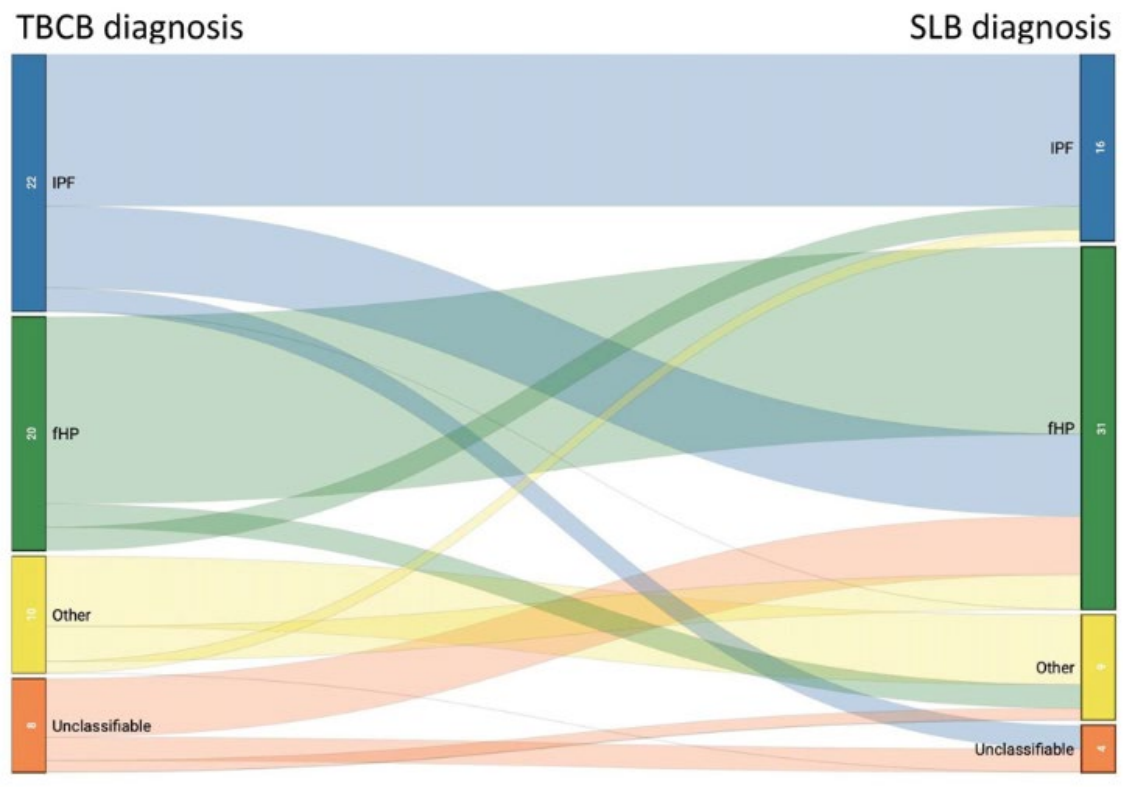
California Thoracic Society
ATS Chapter Serving California and Arizona

Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy: A Prospective Multi-Centre Agreement Clinical Trial (CAN-ICE)

Marc Fortin[1], Moishe Liberman[4], Antoine Delage[8], Geneviève Dion[1], Simon Martel[1], Fabien Rolland[9], Thibaud Soumagne[10], Sylvain Trahan[2], Deborah Assayag[11], Elisabeth Albert[3], Margaret M. Kelly[12], Kerri A. Johannson[13], Zachary Guenther[14], Charles Leduc[5], Helene Manganas[6], Julie Prenovault[7], and Steeve Provencher[1]



• Am J Respir Crit Care Med, 2023

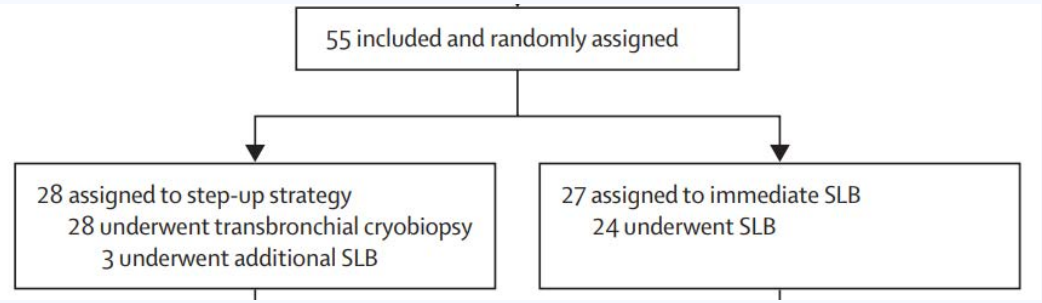


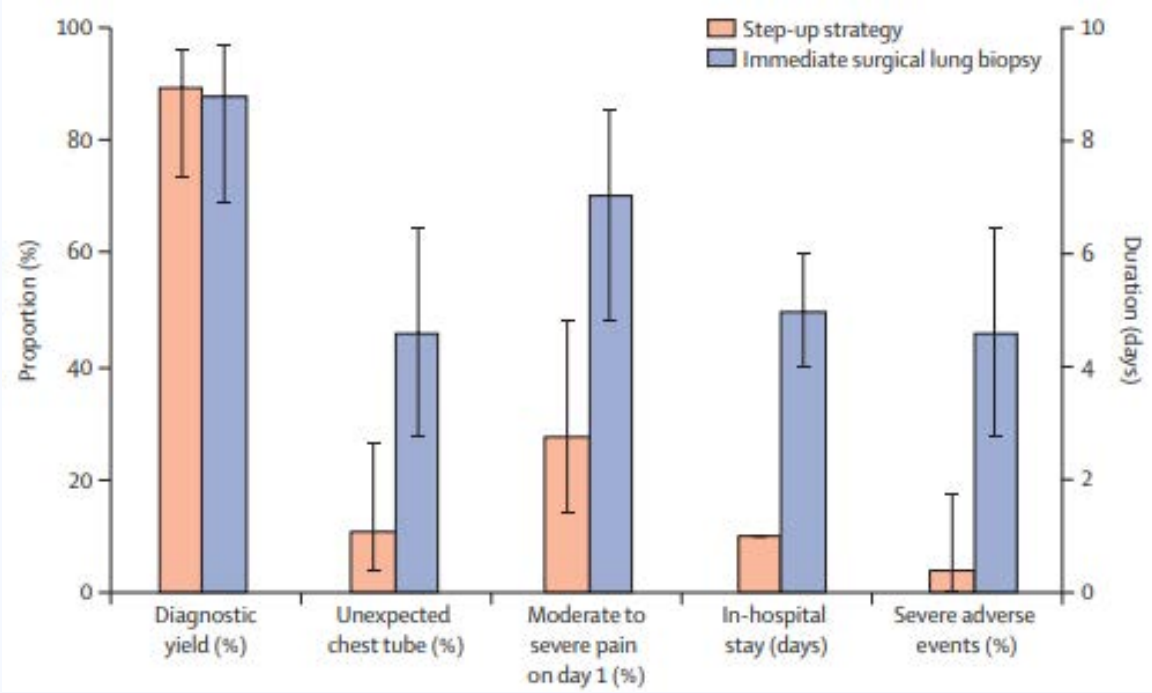
	TBCB-MDD Diagnosis	Sensitivity (%)	Specificity (%)
CAN-ICE	UIP-IPF	81.3	79.6
	fHP	51.6	86.2
COLDICE	UIP-IPF	91.4	83.3
	fHP	61.1	91.5

Transbronchial cryobiopsy followed by as-needed surgical lung biopsy versus immediate surgical lung biopsy for diagnosing interstitial lung disease (the COLD study): a randomised controlled trial

Kirsten A Kalverda, Maarten K Ninaber, Lizzy Wijmans, Jan von der Thüsen, René E Jonkers, Johannes M Daniels, Jelle R Miedema, Chris Dickhoff, Jürgen Hölters, David Heineman, Merijn Kant, Teodora Radonic, Ghada Shahin, Danielle Cohen, Bart Boerrigter, Suzan Nijman, Esther Nossent, Jerry Braun, Bas Mathot, Venerino Poletti, Jürgen Hetzel, Marcel Dijkgraaf, Daniel A Korevaar, Peter I Bonta, Jouke T Annema

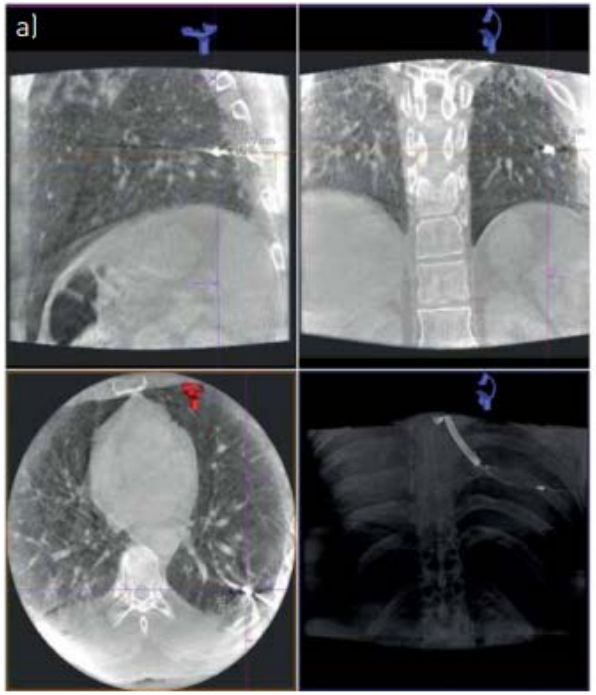
- Multicentre, randomised controlled trial in six hospitals across the Netherlands
- Step-up vs. Immediate SLB strategy





• Lancet Respir Med 2024

Safety and diagnostic efficacy of cone beam computed tomography-guided transbronchial cryobiopsy for interstitial lung disease: a cohort study



c) Outcomes of CBCT-guided TBCB

Patients	155
Complication	
Pneumothorax	3 (1.9%)
Mild bleeding	116 (74.8%)
Moderate bleeding	19 (12.3%)
Acute exacerbation of ILD	1 (0.6%)
Post-bronchoscopy fever	11 (7.1%)
Diagnostic yields	
Pathological diagnosis	134 (86.5%)
MDD diagnosis	140 (90.3%)

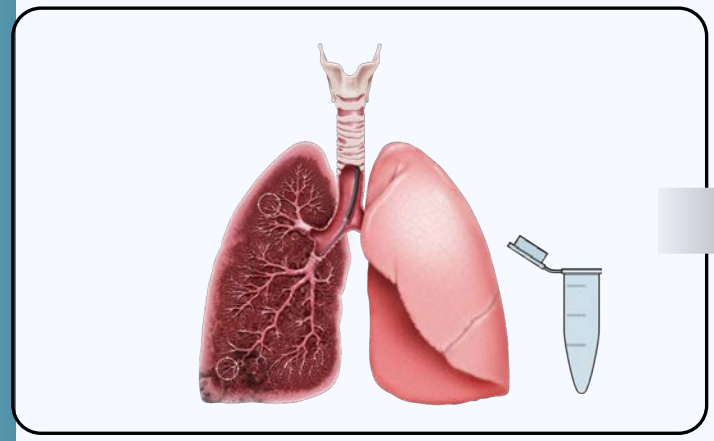
b) Patient characteristics

Patients	155
Median age years	55.2±12.1
Male-to-female (ratio)	90/65 (1.4)
Smokers	73 (47.1%)
Environmental or occupational history	55 (34.5%)
Mean FVC % predicted	88.6±20.5
Mean D_{LCO} % predicted	68.0±19.5
HRCT pattern	
Fibrotic	67 (43.2%)
Non-fibrotic	88 (56.8%)
Cryoprobe	
1.9 mm	48 (31.0%)
2.4 mm	107 (69.0%)
Biopsy site	
Single segment	72 (46.5%)
Multiple segments	83 (53.5%)
Mean sample number	3.39±0.96
Mean sample size	
Surface area mm^2	24.5±11.1
Long axis diameter mm	5.4±1.4
Short axis diameter mm	4.3±1.1
Mean CBCT scanning times	2.1±0.7
Cryoprobe re-position after CBCT	66 (42.6%)
Radiation exposure mSv	17.0±7.0
Procedure duration min	38.5±15.3

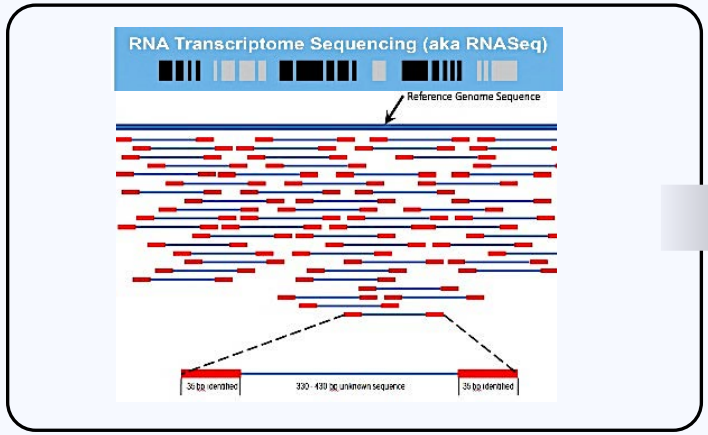
• Zhou, G., et al. Eur Respir J 2020

UIP Genomic Classifier

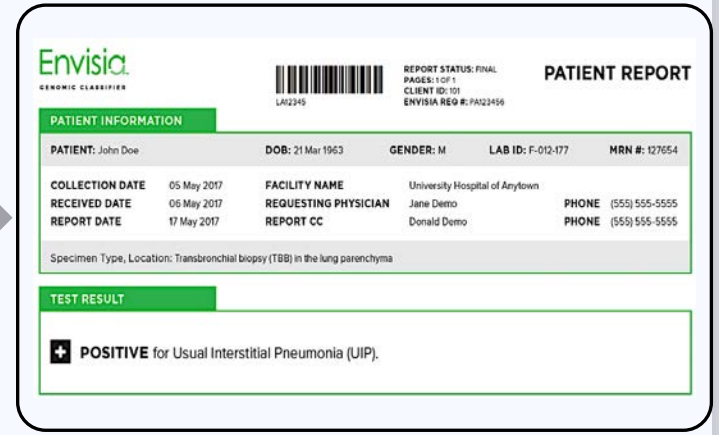
How Envisia Works:



3-5 transbronchial biopsy ***(TBFB)*** samples are collected during a routine bronchoscopy



Epithelial DNA is analyzed for UIP signature



Locked Envisia classifier is used to designate either ***positive*** or ***negative*** molecular UIP

The Envisia Genomic Classifier test is available as part of Veracyte's CLIA-validated laboratory-developed test (LDT) service. This test has not been cleared or approved by the FDA.

Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study

Ganesh Raghu, Kevin R Flaherty, David J Lederer, David A Lynch, Thomas V Colby, Jeffrey L Myers, Steve D Groshong, Brandon T Larsen, Jonathan H Chung, Mark P Steele, Sadia Benzaquen, Karel Calero, Amy H Case, Gerard J Criner, Steven D Nathan, Navdeep S Rai, Murali Ramaswamy, Lars Hagmeyer, J Russell Davis, Umair A Gauhar, Daniel G Pankratz, Yoonha Choi, Jing Huang, P Sean Walsh, Hannah Neville, Lori R Lofaro, Neil M Barth, Giulia C Kennedy, Kevin K Brown, Fernando J Martinez

- 237 patients recruited from the BRAVE study, a prospective, noninterventional study at 29 sites (US & Europe) with patients undergoing biopsy for ILD.
- 3–5 transbronchial lung biopsy samples per patient were collected, pooled, and analyzed using machine learning and whole-transcriptome RNA sequencing.
- After exclusions, 90 patients were used to train the Envisia Genomic Classifier to identify a 190-gene signature to differentiate UIP pattern.
- The classifier was validated in 49 patients by comparing results with diagnostic histopathology, and its clinical utility was assessed by multidisciplinary teams.

• *Lancet Respir Med , 2019*

Envisia Validation Performance

	UIP reference standard (n=23)	Non-UIP reference standard (n=26)
Classifier results		
UIP	16	3
Non-UIP	7	23
Sensitivity	70% (95% CI 47–87)	
Specificity	88% (95% CI 70–98)	
NPV	77% (95% CI 58–90)	
PPV	84% (95% CI 60–97)	
UIP frequency in study	47%	

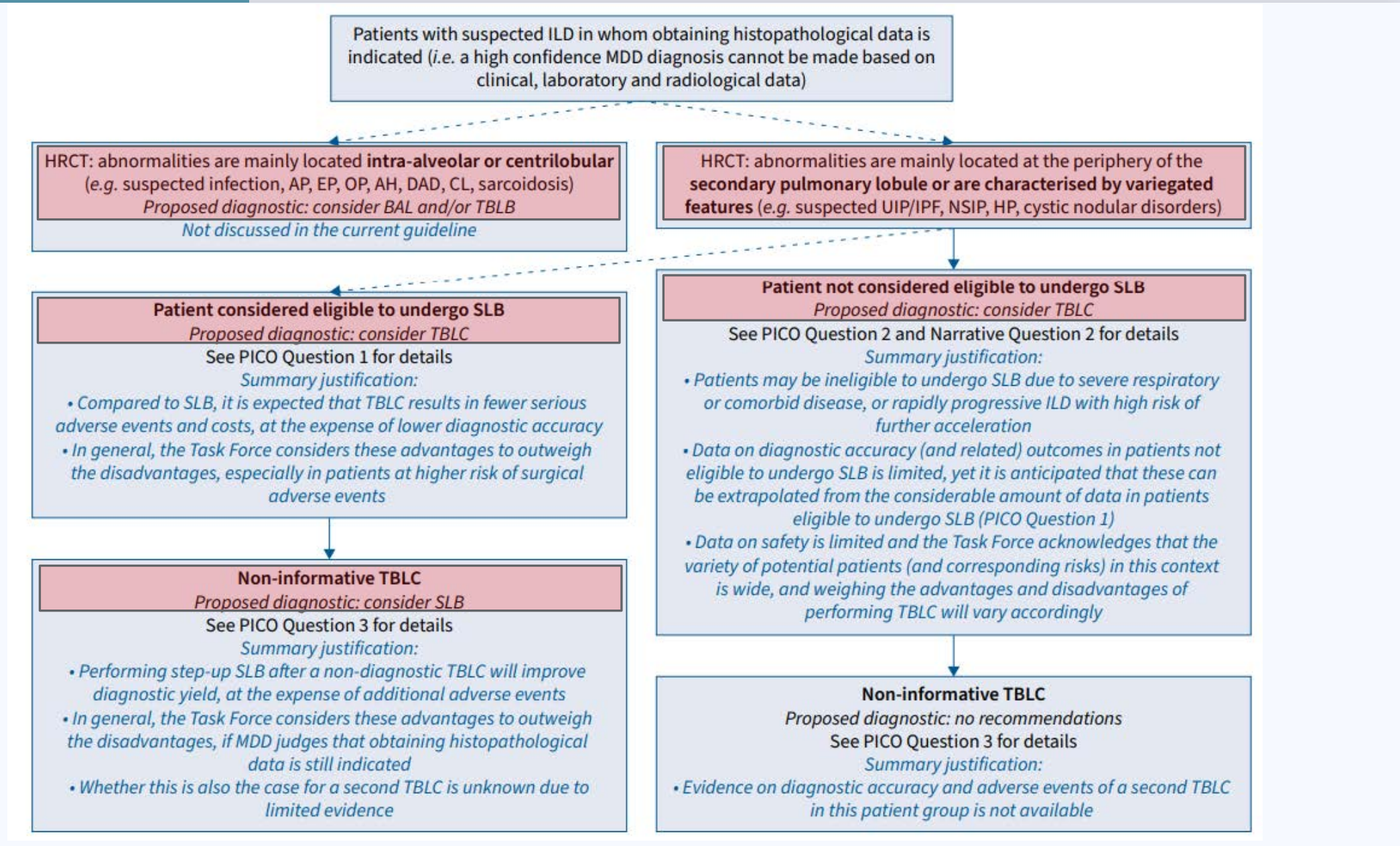
Utility of a Molecular Classifier as a Complement to High-Resolution Computed Tomography to Identify Usual Interstitial Pneumonia

Luca Richeldi[1], Mary Beth Scholand[2], David A. Lynch[3], Thomas V. Colby[4], Jeffrey L. Myers[5], Steve D. Groshong[6], Jonathan H. Chung[7], Sadia Benzaquen[8], Steven D. Nathan[9], J. Russell Davis[10], Shelley L. Schmidt[11], Lars Hagmeyer[12], David Sonetti[13], Jurgen Hetzel[14], Gerard J. Criner[15*], Amy H. Case[16], Murali Ramaswamy[17], Karel Calero[18], Umair A. Gauhar[19], Nina M. Patel[20], Lisa Lancaster[21], Yoonha Choi[22], Daniel G. Pankratz[22], P. Sean Walsh[22], Lori R. Lofaro[22], Jing Huang[22], Sangeeta M. Bhorade[22], Giulia C. Kennedy[22], Fernando J. Martinez[23*], and Ganesh Raghu[24]

		Reference label	
		Non-UIP	UIP
Envisia Genomic Classifier	Non-UIP	35	23
	UIP	3	35
Sensitivity		60.3% [46.6 – 73.0]	
Specificity		92.1% [78.6 – 98.3]	
NPV		60.3% [46.6 – 73.0]	
PPV		92.1% [78.6 – 98.3]	
UIP prevalence		60.4%	

Local Radiology Result	Pathology Reference Standard	
	UIP ($n=53$)	Non-UIP ($n=32$)
Definite/probable UIP, *n*	18	1
Indeterminate for UIP/consistent with non-IPF, *n*	35	31
Sensitivity, % (95% CI)	34.0 (21.5–48.3)	
Specificity, % (95% CI)	96.9 (83.8–100)	
NPV, % (95% CI)	47.0 (34.6–59.7)	
PPV, % (95% CI)	94.7 (74.0–99.9)	
UIP prevalence, %	62.4	

Local Radiology + Envisia Classifier	Pathology Reference Standard	
	UIP ($n=53$)	Non-UIP ($n=32$)
Definite/probable UIP or Envisia Classifier UIP, *n*	42	3
Indeterminate for UIP/consistent with non-IPF and Envisia Classifier non-UIP, *n*	11	29
Sensitivity, % (95% CI)	79.2 (65.9–89.2)	
Specificity, % (95% CI)	90.6 (75.0–98.0)	
NPV, % (95% CI)	72.5 (56.1–85.4)	
PPV, % (95% CI)	93.3 (81.7–98.6)	
UIP prevalence, %	62.4	



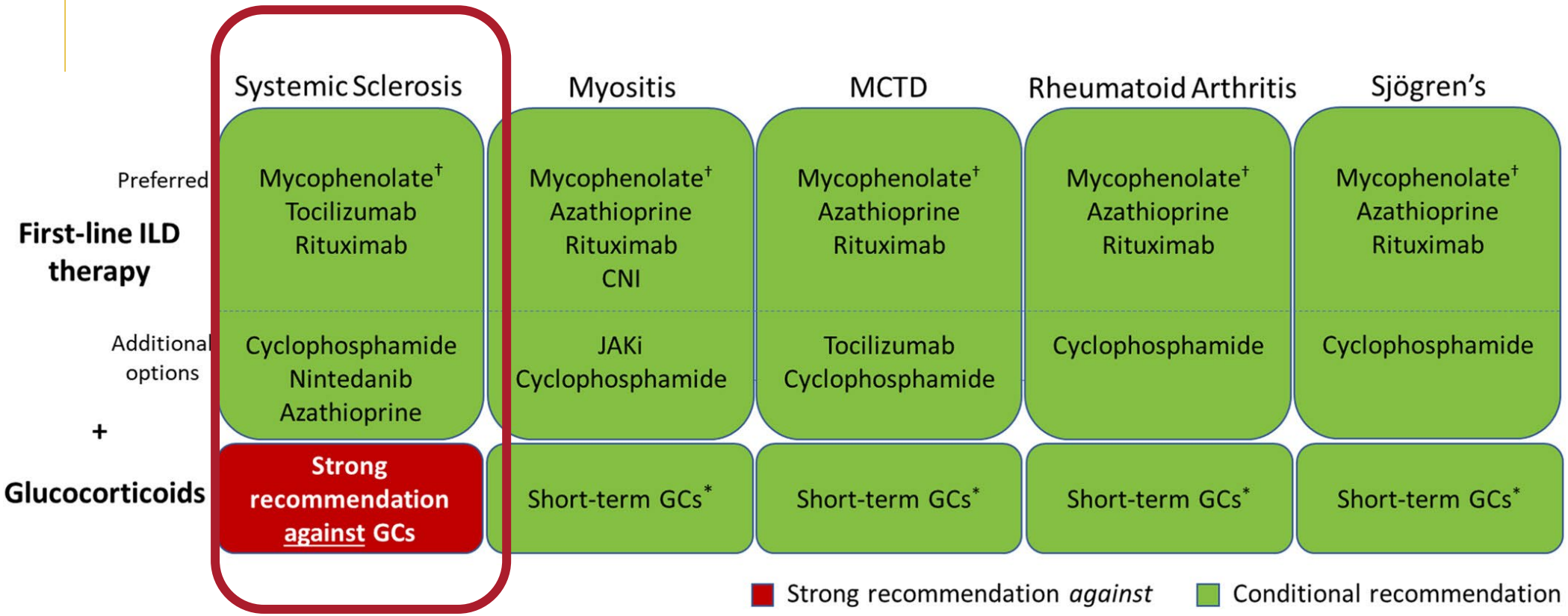
• ERS TBLC Guidelines. Eur Respir J 2022

- Thank you for your time
- and attention!

When to use immunosuppressants and antifibrotics in non-IPF ILD

Gabrielle Liu, MD, MS
Assistant Professor of Medicine
Associate Director, UC Davis ILD Program
UC Davis PCCSM
March 22, 2025

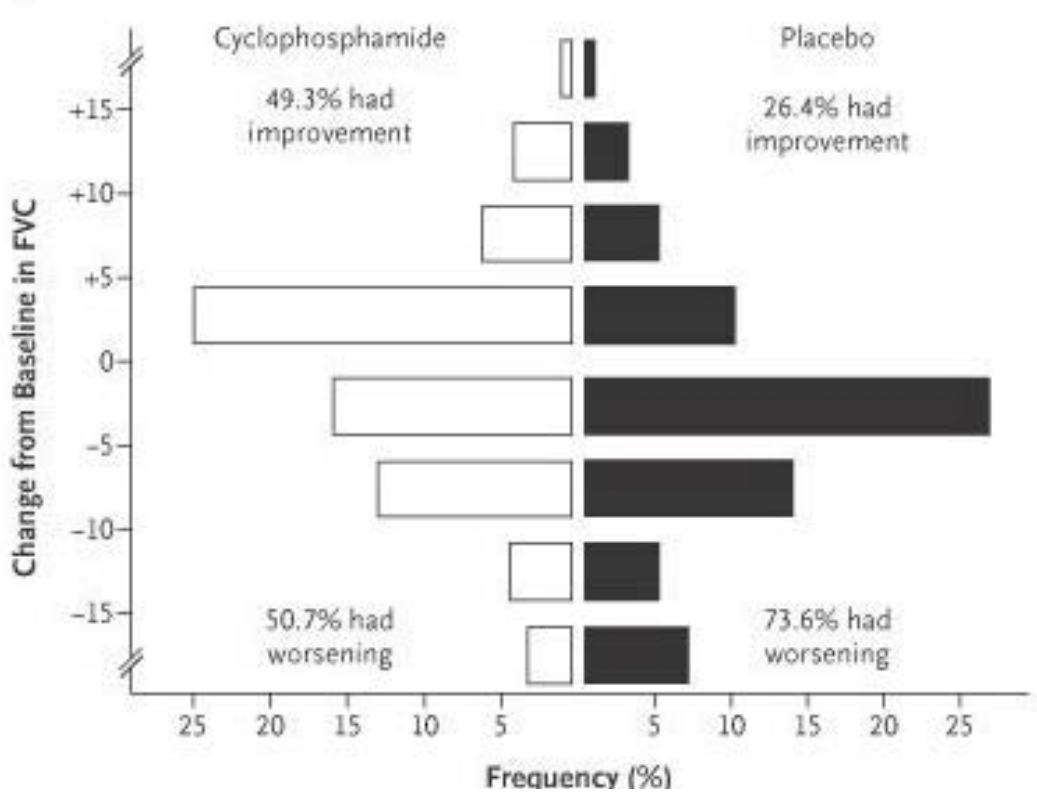
ACR/CHEST guidelines for initial treatment of CTD-ILD



Johnson et al. Arthritis Care Res 2024

Systemic sclerosis-ILD: cyclophosphamide

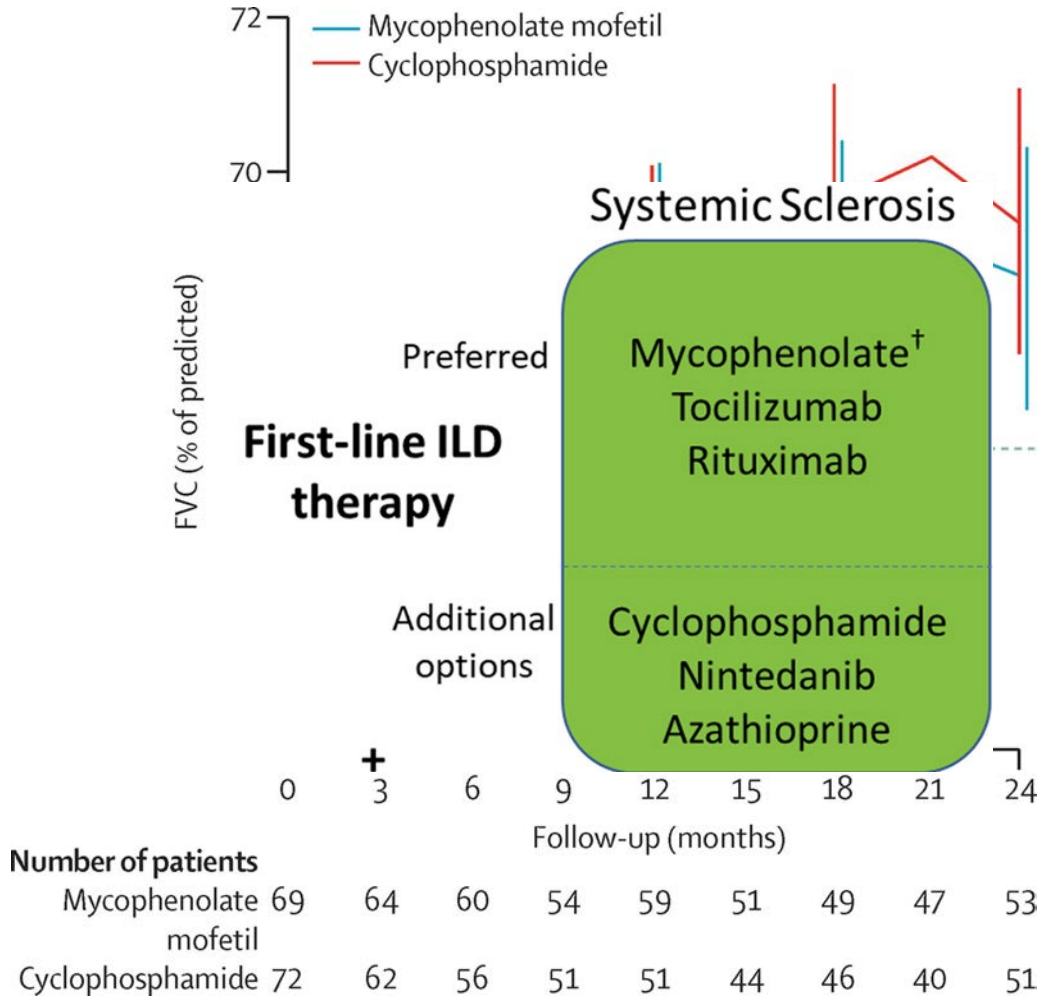
- **Cyclophosphamide (CYC) :** alkylating agent that impairs DNA replication and transcription → cytotoxicity or altered function of affected cells
  - Associated with hemorrhagic cystitis, bladder cancer, gonadal dysfunction/infertility
- **Scleroderma Lung Study I**
  - Double-blind RCT of CYC vs placebo for 12 months
  - 158 patients with SSc-ILD
  - Primary outcome: Mean diff in FVC at 12 months was 2.53% (CI 0.28 – 4.29%), favoring CYC
  - Improved dyspnea, skin thickening (mRSS), functional ability
  - Hematuria, cytopenia, and pneumonia were more common among patients in the CYC group
  - Post-hoc analysis: Waning effects after treatment
    - No difference in FVC compared to placebo group at 24 months



Tashkin et al. NEJM 2006; Tashkin et al. AJRCCM 2007

Systemic sclerosis-ILD: mycophenolate mofetil

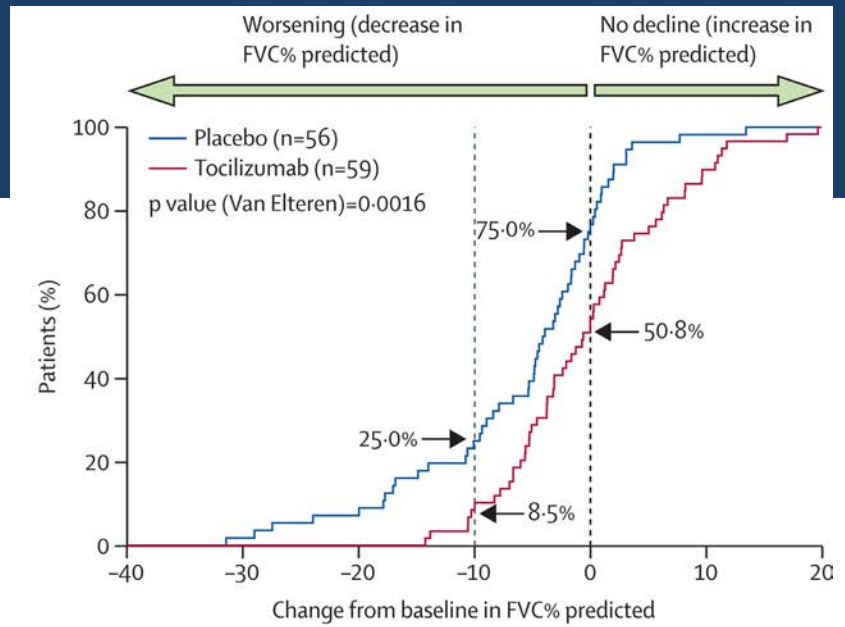
- **Mycophenolate mofetil (MMF):** Inhibits purine nucleotide synthesis -- particularly in lymphocytes, leading to decreased B-cell and T-cell proliferation
- **Scleroderma Lung Study II**
  - Double-blind RCT of MMF (up to 3g/day) for 2 years vs cyclophosphamide (CYC) for 1 year
  - 142 patients with SSc-ILD
  - Primary outcome: no significant difference in FVC % predicted change over 24 months
    - Improved in both groups
  - Improved skin thickening in both groups equally
  - Better tolerability and toxicity profile with MMF:
    - Leukopenia and anemia less common
    - Fewer treatment-related SAEs and greater time to withdrawal from study

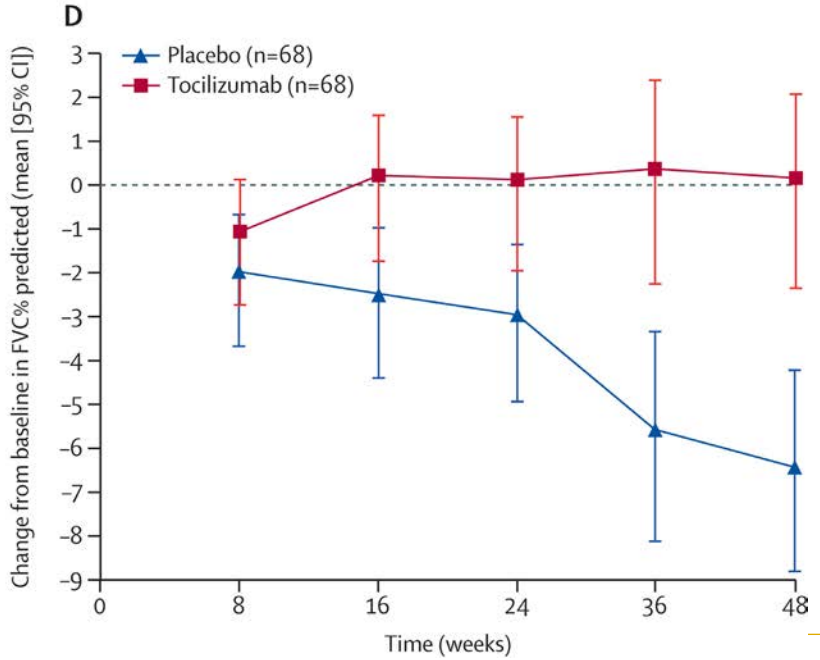


Allison and Eugui, Immunopharmacology 2000; Tashkin et al. Lancet Resp Med 2016

Systemic sclerosis-ILD: tocilizumab

- **Tocilizumab:** Inhibits IL-6, a proinflammatory cytokine that regulates the immune response and is implicated in pathogenesis of autoimmune disease
- **faSScinate**: Phase 2 RCT in 87 patients with SSc (irrespective of ILD)
- **focuSSced**: Phase 3 RCT in 210 patients with SSc (65 – 67% with ILD)
  - Primary skin fibrosis endpoint not met
  - Secondary endpoint: Stabilization of FVC with tocilizumab
  - Week 48: LSM change in FVC % predicted
    - -4.6 in placebo group vs. -0.4 in tocilixumab group
  - More SAEs in placebo group
- <u>One of 2 FDA-approved meds for SSc-ILD</u>

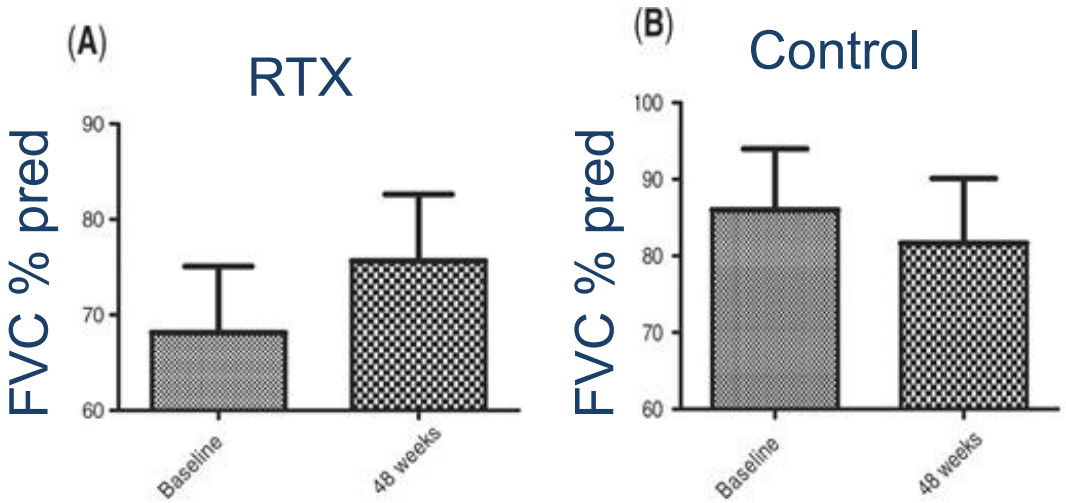


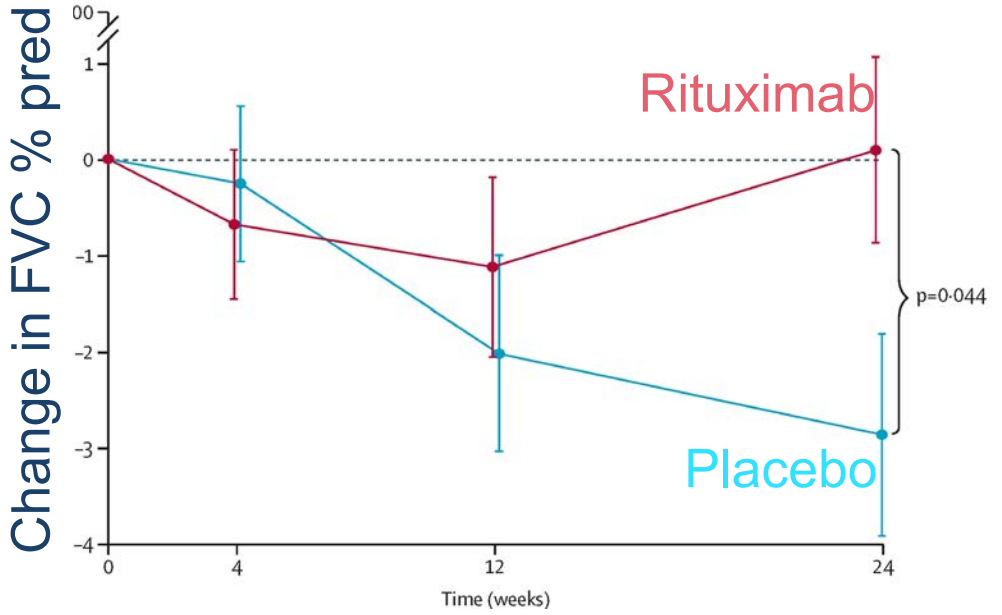


Choy et al. Nat Rev Rheumatol 2020; Khanna et al. Lancet 2016; Khanna et al. Lancet Resp Med 2020

Systemic sclerosis-ILD: Rituximab

- **Rituxmab:** anti-CD20 antibody that depletes peripheral B cells
- 2 small RCTs in SSc
- 14 pts with SSc-ILD: Rituximab add-on vs standard treatment
- DESIRES: 56 patients with SSc (88% with ILD): Rituximab monotherapy vs placebo
- <u>Stabilization/improvement in FVC with RTX</u>
- Improvement in skin thickening
- DESIRES: Adverse drug reactions higher w/ rituximab
  - Mucositis, decreased PMN, decreased WBC more common

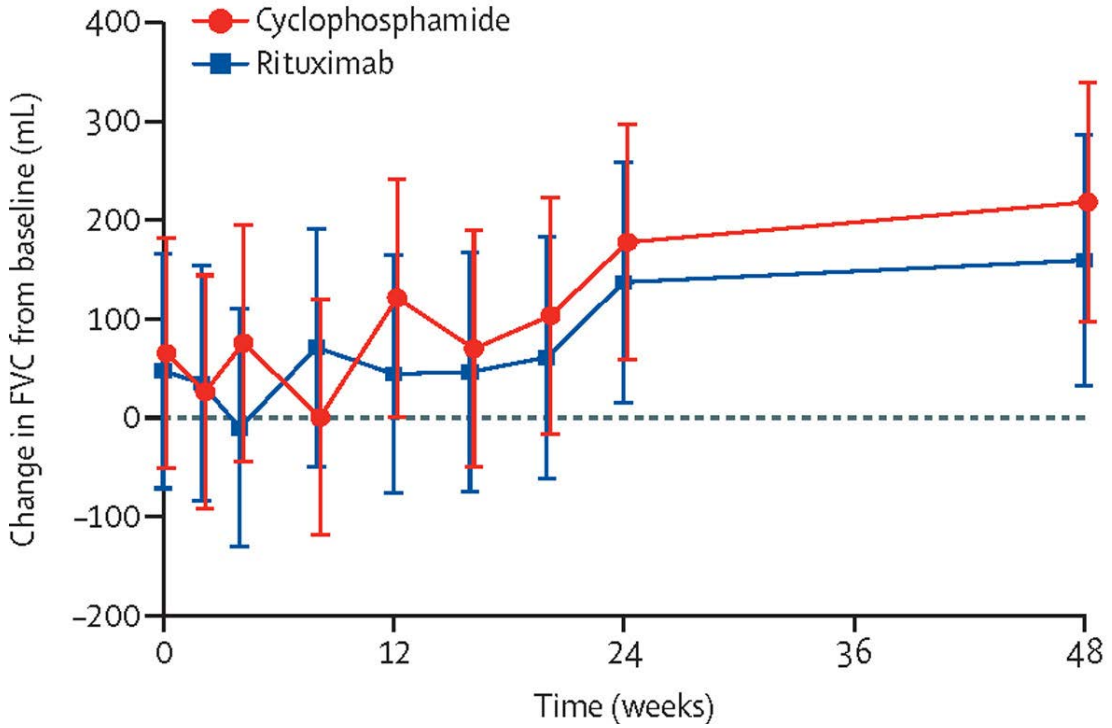




Daoussis et al. Rheumatology 2010; Ebata et al. Lancet Rheumatology 2021

Scleroderma-, myositis-, MCTD-ILD: Rituximab

- **Rituximab**:
  - **RECTIAL** trial:
  - Phase 2b RCT of rituximab vs cyclophosphamide for 6 months
  - 101 patients with severe or progressive ILD due to scleroderma, idiopathic myositis, MCTD
  - Primary end point:
    - CYC and RTX had similar improvement in FVC at week 24
    - Effects consistent across CTD subgroup
  - Quality of life scores improved similarly in both groups
  - Fewer adverse events with RTX



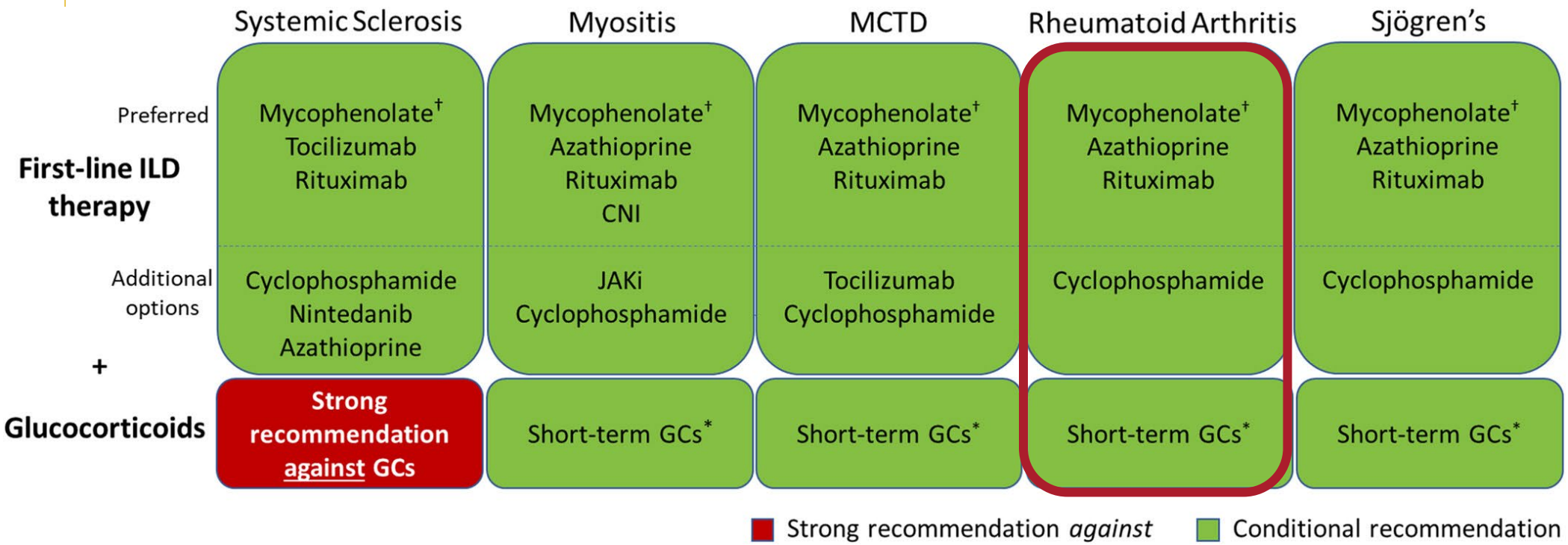
Goldblum et al, Clin Exp Rheumatol 1993; Edwards et al. NEJM 2004; Maher et al, Lancet Respir Med 2023;

SSc-ILD recap

Mycophenolate	Rituximab	CYC	Tocilizumab
Improves skin thickening	Improves skin thickening	Improves skin thickening	No change in skin thickening
Impairs humoral response to vaccination	Severely impairs humoral response to vaccination	Major toxicities	
	Risk of severe infections with long half-life; risk of hypo-IgG		

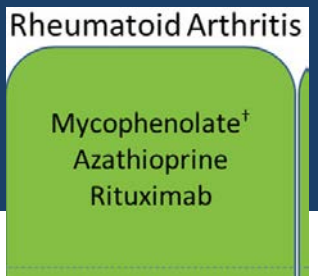
Calderon et al. Rheum Dis Clin North Am. 2024

ACR/CHEST guidelines for initial treatment of CTD-ILD



Johnson et al. Arthritis Care Res 2024

RA-ILD: immunosuppression



- No RCT data on efficacy of immunosuppression in RA-ILD population
  - Recommendations based on RCTs from SSc-ILD or observational data
- **Azathioprine (AZA):** Thiopurine analog that inhibits leukocyte DNA synthesis and T-cell proliferation
- Conflicting data on efficacy of azathioprine
- One unblinded RCT: prednisone + either cyclophosphamide or AZA for 1 year, among 60 patients with SSc
  - FVC pp and DLCO pp worsened with AZA but stable with cyclophosphamide
- Single-center retrospective study: Compared patients with fibrotic CTD-ILD on AZA (n=54) vs mycophenolate (n=43)
  - Improved yearly change in FVC pp with AZA:
    - 1.46% (CI 0.1 – 2.8%) with AZA vs -0.52% (-1.5 – 0.5%) with MMF
    - Differences in CTD diagnosis and concurrent prednisone dose
  - No significant difference in adverse outcomes (death, transplant, respiratory hospitalization) with AZA in those with UIP pattern

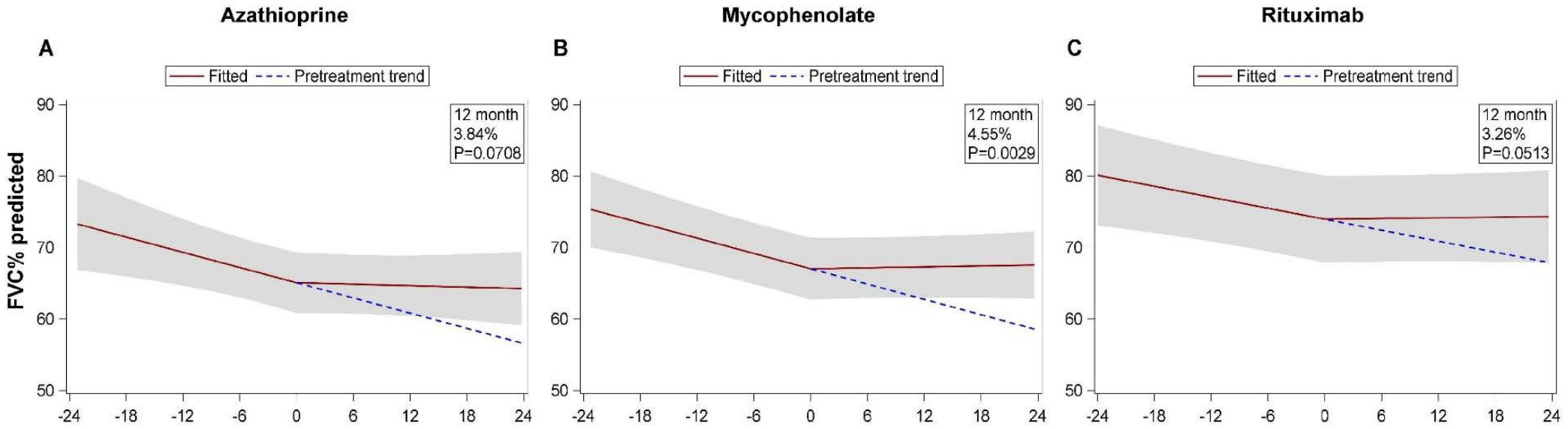
Nadashkevic et al. Clin Rheumatol 2006; Oldham et al. Respir Med 2016

RA-ILD: immunosuppression

Rheumatoid Arthritis

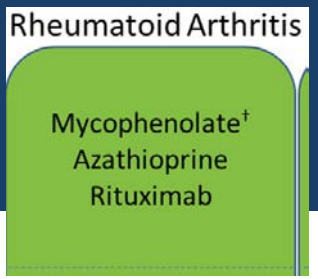
Mycophenolate†
Azathioprine
Rituximab

- Multicenter observational study of 212 pts with RA-ILD treated with mycophenolate (36%), azathioprine (43%), rituximab (20%)
  - FVC and DLCO improved after 12 months of treatment, no difference by HRCT pattern or choice of agent
  - More treatment discontined due to adverse events with AZA (13%) vs MMF (3.9%) or RTX (2.3%)
    - Elevated transaminases, recurrent infections more common with AZA

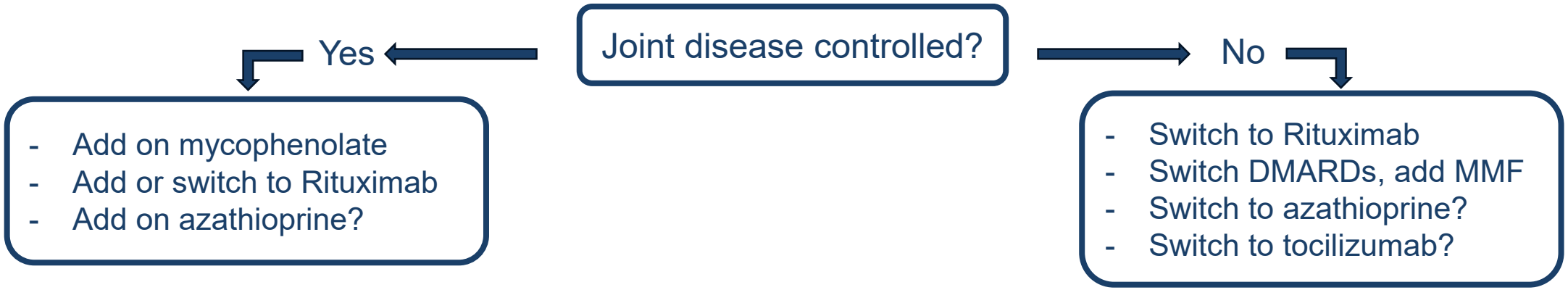


Nadashkevic et al. Clin Rheumatol 2006; Matson et al. Chest 2023

RA-ILD: first line treatment



- Significant uncertainty as to which drugs are most effective
- Consider controlling joint disease
  - High RA disease activity is associated with risk of disease progression and mortality in RA-ILD
  - Rituximab: FDA-approved to treat RA, significantly improves RA disease activity
  - Tocilizumab: FDA-approved to treat RA, improves RA disease activity
  - Mycophenolate: Poor efficacy in controlling RA joint disease
  - Azathioprine: Not one of recommend DMARDs in ACR or EULAR RA practice guidelines
    - Generally felt to be less effective



UCDAVIS HEALTH

Brooks et al. Rheumatology 2022; Chai et al. Front Med 2023; Liu et al. Int J Rheum Dis 2022 ; Edwards et al NEJM 2004;

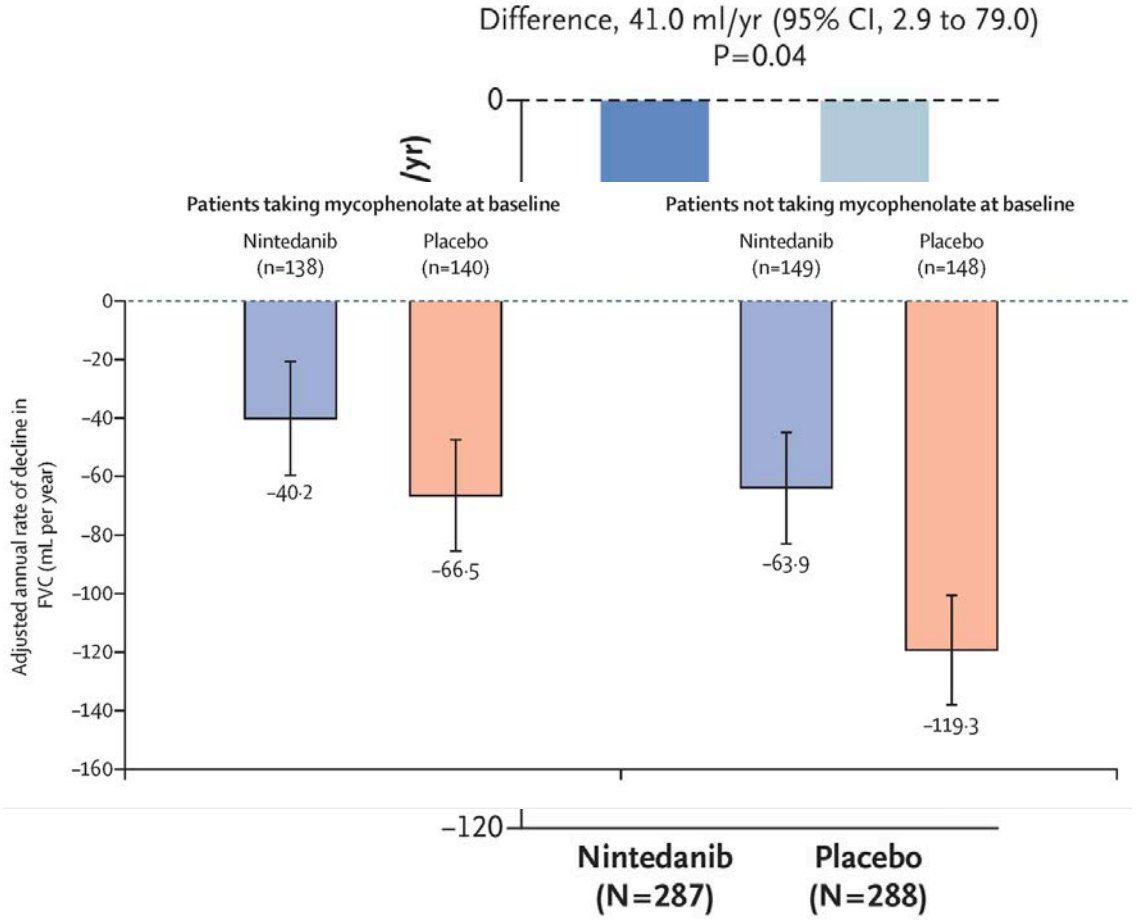
Progressive pulmonary fibrosis: Nintedanib

- **Nintedanib**: Tyrosine kinase inhibitor, inhibits growth factor signaling reducing proliferation of lung fibroblasts, differentiation to myofibroblasts, and ECM deposition
- **INBUILD**:
  - Phase 3 RCT of Nintedanib vs placebo for 1 year
  - 663 patients with PPF
    - 26% HP, 26% CTD-ILD, 19% iNSIP, 17% Unclassifiable, 12% other fibrosing ILD
    - Could not be on immunosuppression
  - Primary outcome: 1 year decline in FVC:
    - Nintedanib: -81 ml/yr, Placebo: -188 ml/yr
    - Consistent between imaging pattern (UIP vs other)
  - Post-hoc subgroup analyses: effect consistent cross ILD diagnosis subgroup
  - Death or acute ILD exacerbation: HR 0.68 (CI 0.46 – 1.01)
  - Diarrhea, nausea common with nintedanib
    - 20% discontinued nintedanib due to AE (vs 10% with placebo)

Flaherty et al. NEJM 2019; Wells et al. Lancet Respir Med 2020

Systemic sclerosis-ILD: Nintedanib

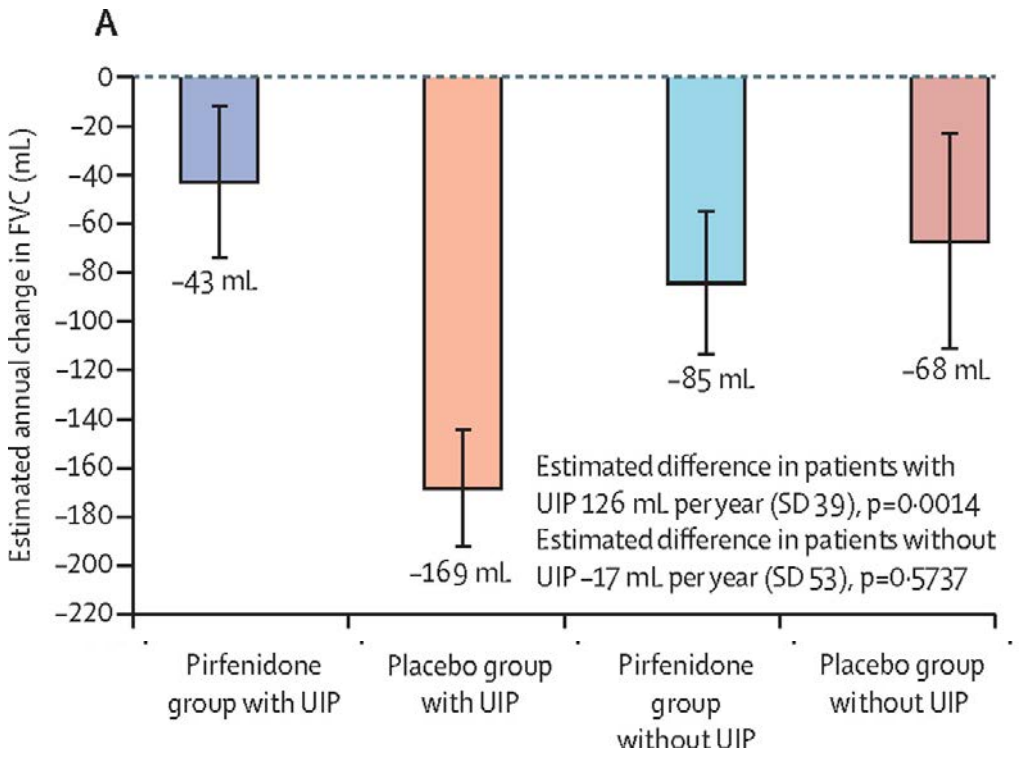
- **Nintedanib**: Tyrosine kinase inhibitor, inhibits growth factor signaling reducing proliferation of lung fibroblasts, differentiation to myofibroblasts, and ECM deposition
- **SENSCIS**:
  - RCT of Nintedanib add-on vs placebo (could receive MMF or MTX or pred <10 mg/day)
  - 576 SSc-ILD patients (no requirement for PPF)
  - Primary outcome: lower annual rate of FVC change with Nintedanib
    - MMF + Nintedanib = least decline
  - No change in skin thickening
  - Higher discontinuation due to adverse event with Nintedanib (16% vs 8.7% placebo)



Distler et al. NEJM 2019; Highland et al. Lancet Respir Med 2021

Pirfenidone: Progressive pulmonary fibrosis and RA-ILD

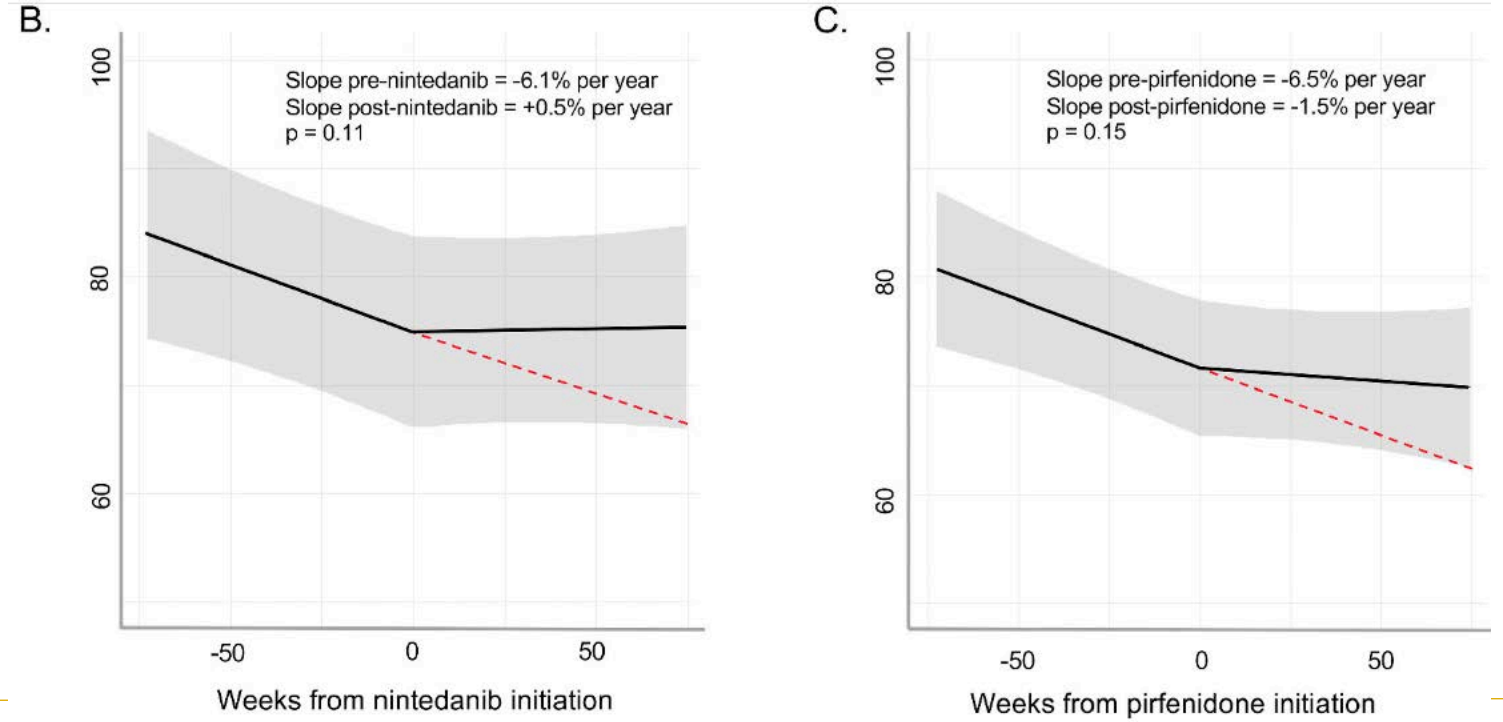
- **Pirfenidone:** Unclear mechanism of action but has anti-inflammatory and antifibrotic properties
- **RELIEF**: Phase 2 trial of pirfenidone vs placebo for 48 weeks
  - 127 patients with PPF randomized
    - 45% HP, CTD-ILD 29%, iNSIP 21%
  - Stopped early for futility due to slow recruitment
  - Primary outcomes: Slower decline in FVC pp with pirfenidone
- **TRAIL1:** Phase 2 trial of pirfenidone vs placebo for 52w
  - 123 RA-ILD pts
  - Stopped early due to slow recruitment
  - Primary endpoint (FVC pp decline >10% or death) was not significant (11% pirfenidone vs 15% placebo)
  - Slower rate of FVC decline (-66 ml/yr vs -146 ml/yr)
    - Most pronounced with UIP pattern
- GI side effects more common with pirfenidone



Behr et al. Lancet Respir Med 2021; Solomon et al. Lancet Respir Med 2023

Real world use of antifibrotics in RA-ILD

- Single center retrospective cohort of 74 patients with RA-ILD on nintedanib (n=50) or pirfenidone (n=34)
  - Slower decline in FVCpp trajectory after initiation of both antifibrotics
  - Initial antifibrotic discontinued in 46% of patients, no difference between nintedanib and pirfenidone



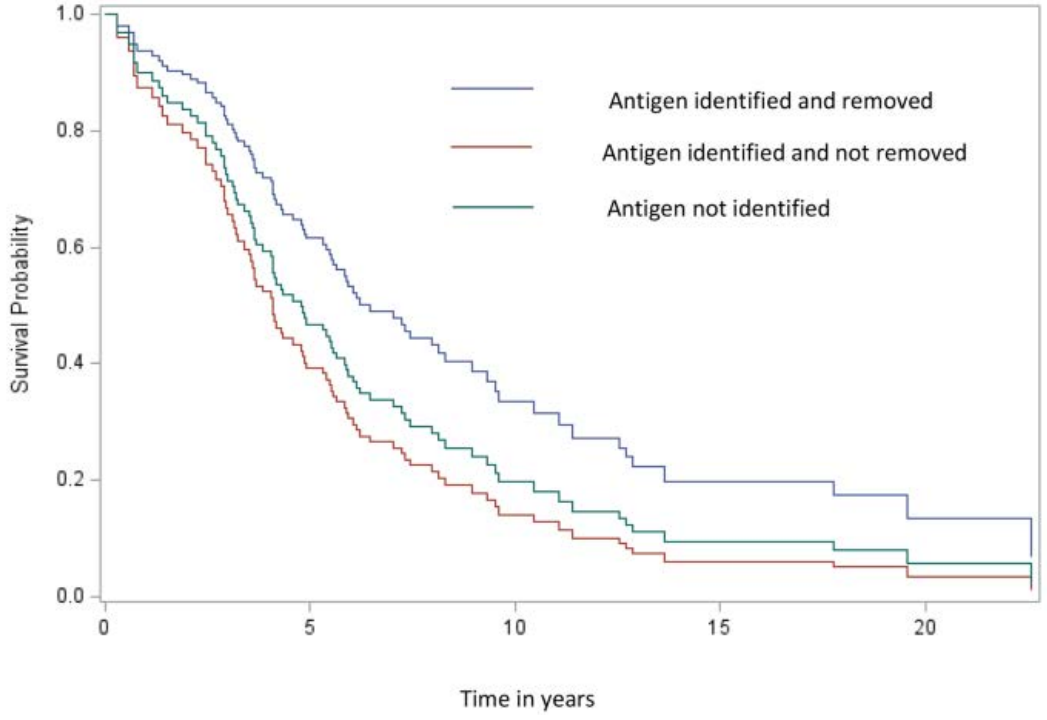
Juge et al. Semin Arthritis Rheum 2024

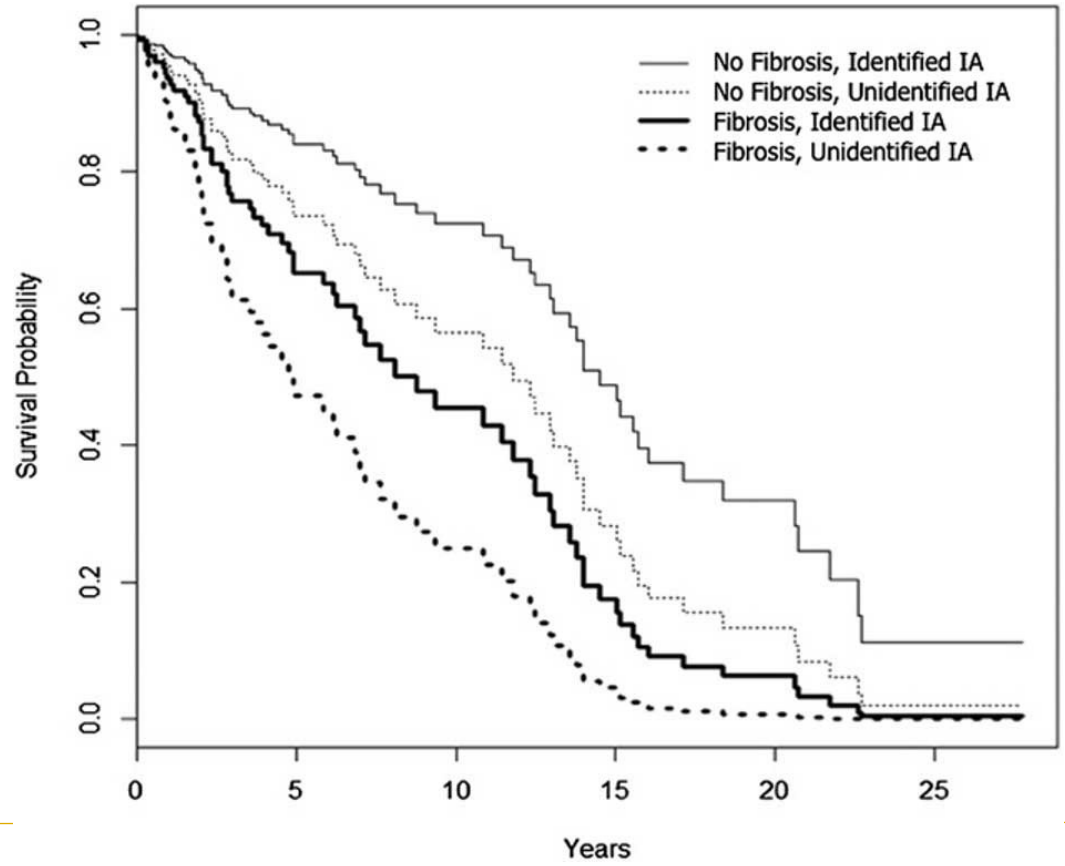
Antifibrotics Recap

- **When to initiate antifibrotics in CTD-ILD?**
  - Scleroderma-ILD:
    - With evidence of progressive fibrosis: Nintedanib
    - Can also consider Nintedanib as first line treatment in conjunction with immunosuppression, particularly in severe disease
  - RA-ILD:
    - With evidence of progressive fibrosis: Nintedanib, pirfenidone
  - Other CTD-ILD
    - With evidence of progressive fibrosis: Nintedenib

Hypersensitivity pneumonitis

- Identification and removal of inciting antigen is critical
  - Associated with improved survival and improved lung function in multiple retrospective cohort studies



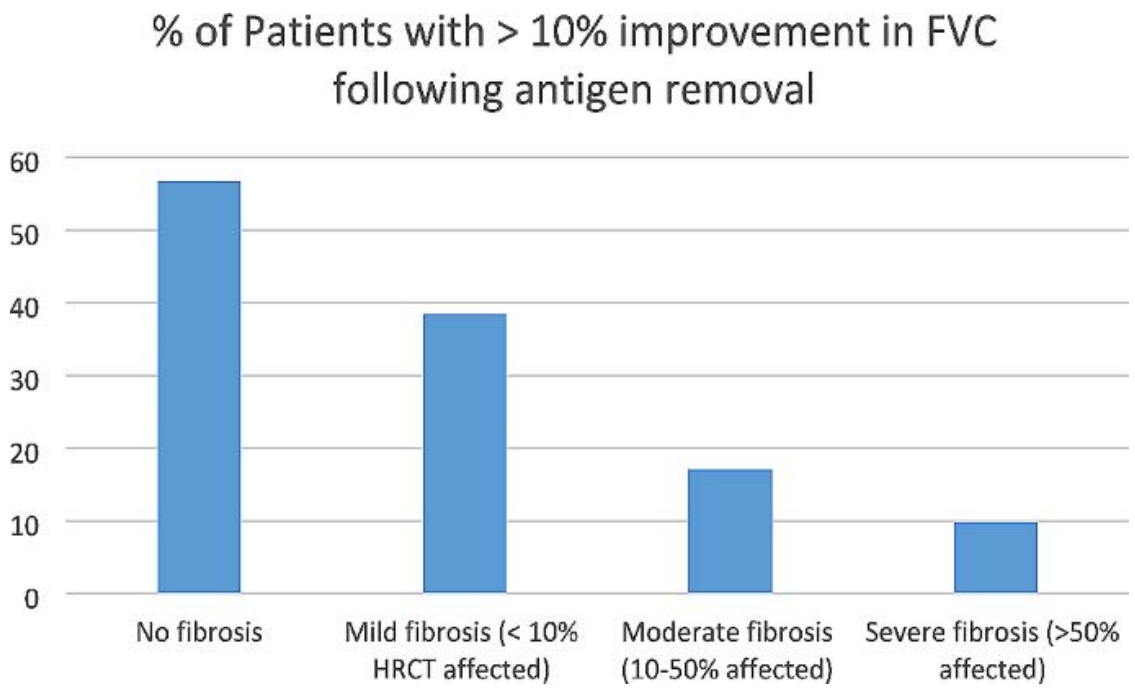


UCDAVIS HEALTH

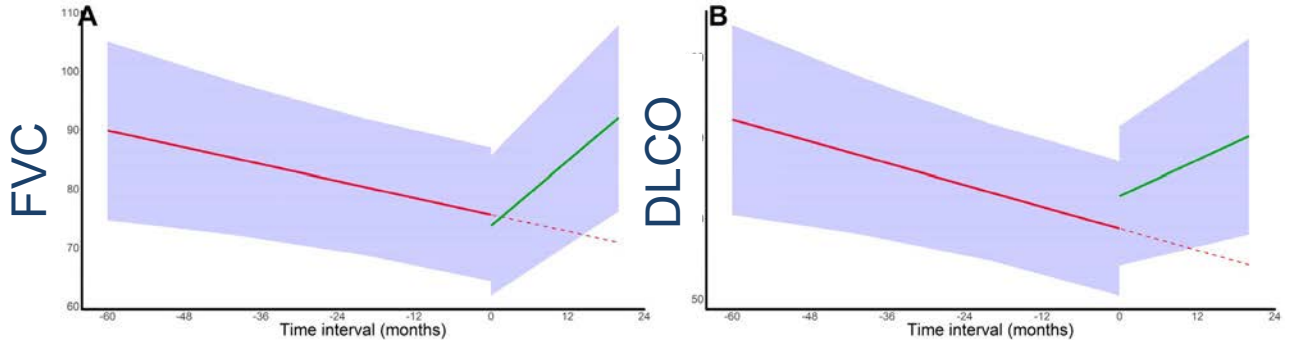
Robertshaw et al. BMC Pulmonary Med 2024; Fernandez-Perez et al. Chest 2013

Hypersensitivity pneumonitis

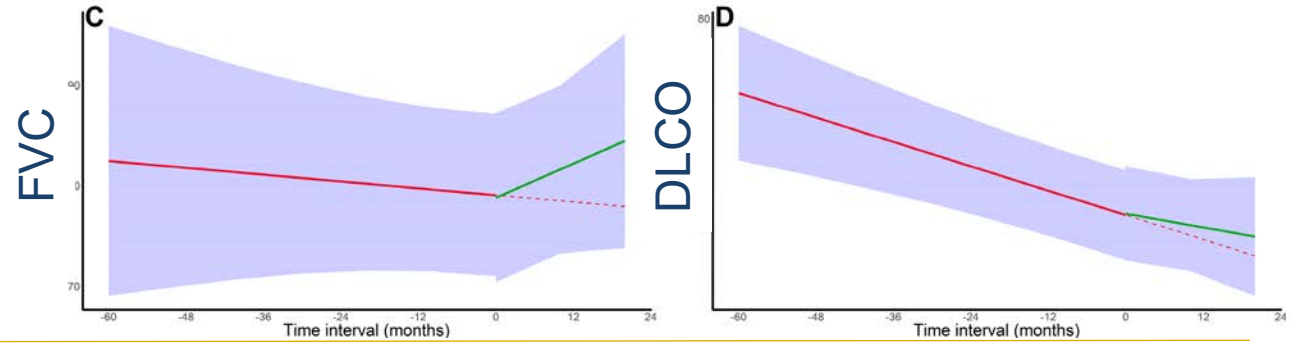
- Identification and removal of inciting antigen is key
  - Associated with improved survival and improved lung function in multiple retrospective cohort studies



Non-fibrotic HP



Fibrotic HP



UCDAVIS HEALTH

Robertshaw et al. BMC Pulmonary Med 2024; De Sadeleer et al, J Clin Med 2019

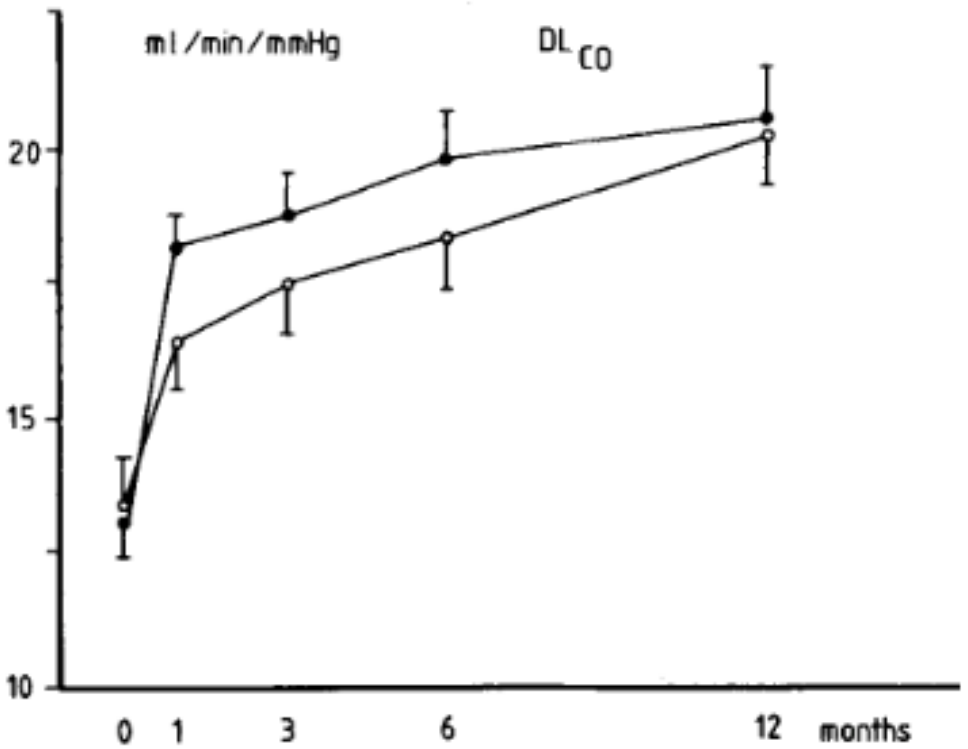
Hypersensitivity pneumonitis

Treatment of hypersensitivity pneumonitis often involves immunosuppression

What is the evidence for this?

Hypersensitivity pneumonitis: immunosuppression

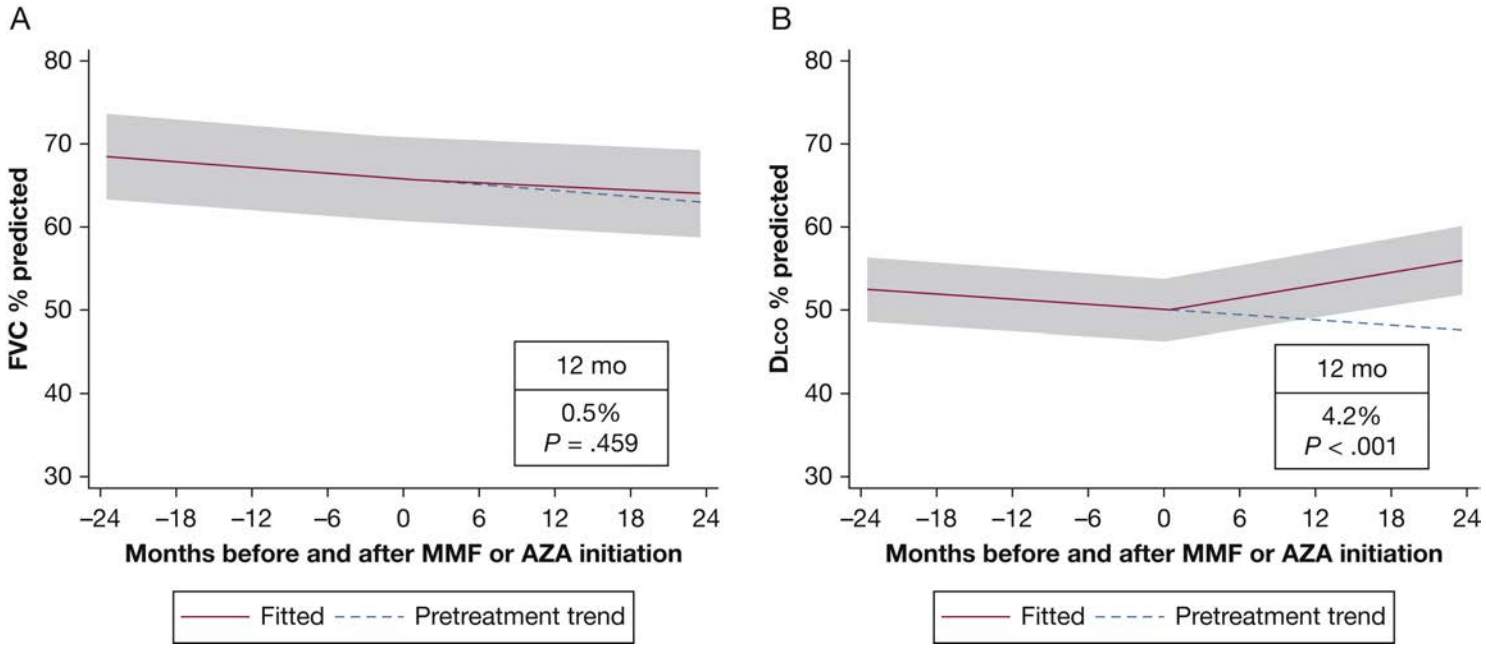
- Unclear impact of immunosuppression on lung function in HP
- Only 1 RCT, which was in acute farmer's lung:
- Double-blind RCT of 36 patients with farmer's lung (unknown if fibrotic or non-fibrotic):
  - Prednisolone (40 mg daily follow by taper) vs placebo for 8 weeks
  - Significant improvement in DLCO (but not FVC, FEV1, or PaO2) with prednisolone
  - No difference in lung function 5 years later



Kokkarinen, Tukiainen, Terho et al. Am Rev Respir Dis 1992

Hypersensitivity pneumonitis: Immunosuppression

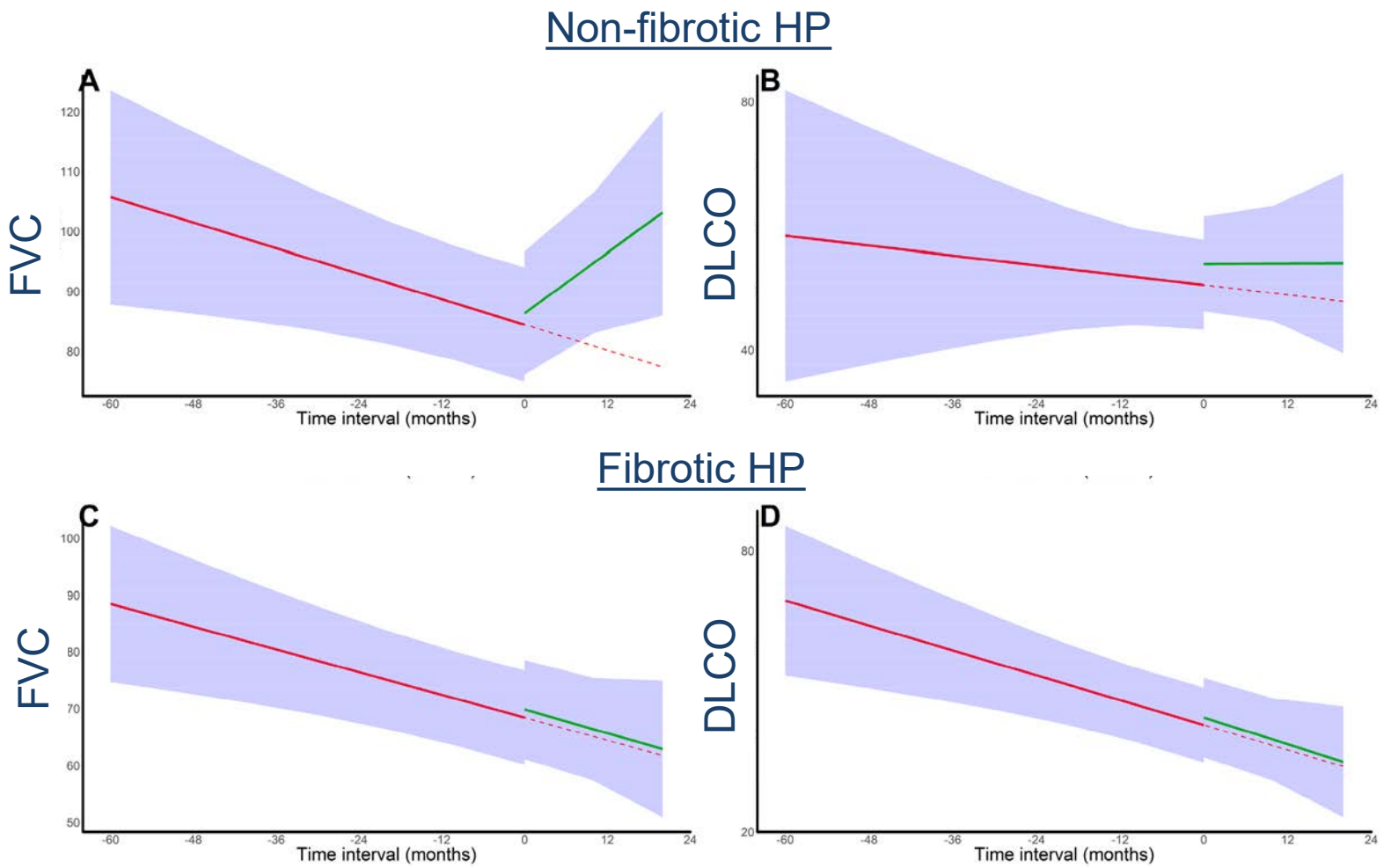
- Several retrospective cohort studies with some conflicting results as to impact of immunosuppression on HP outcomes
- Several have shown treatment with prednisone or MMF or AZA is associated with improvement in DLCO but not FVC



Morisset et al. Chest 2017; Fiddler et al. Clin Respir J 2019, De Sadeleer et al, J Clin Med 2019

Hypersensitivity pneumonitis: Corticosteroids

- Single-center retrospective study of 202 patients with HP
- Improvements in FVC and DLCO seen after steroid initiation in non-fibrotic HP, but not fibrotic HP

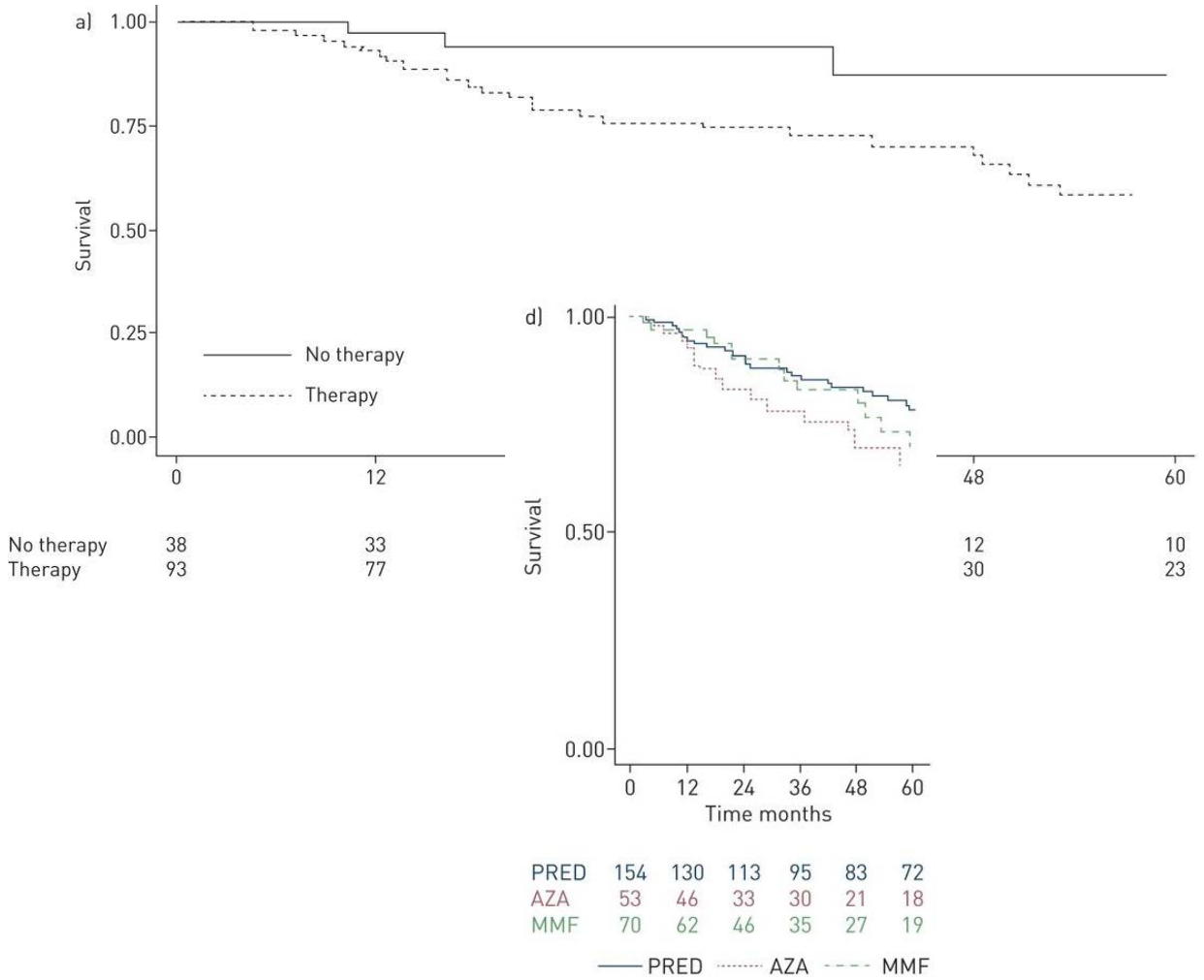


UCDAVIS HEALTH

De Sadeleer et al, J Clin Med 2019

Hypersensitivity pneumonitis: Immunosuppression

- Immunosuppression is associated with increased mortality risk: HR 5.37 (CI 1.08 – 26.67)
  - After adjusting for age, sex, race FVC % predicted, DLCO % predicted, and identified antigen
  - No significant differences between treatment with prednisone, MMF, or AZA
- Treatment with MMF or AZA associated with fewer adverse effects than prednisone

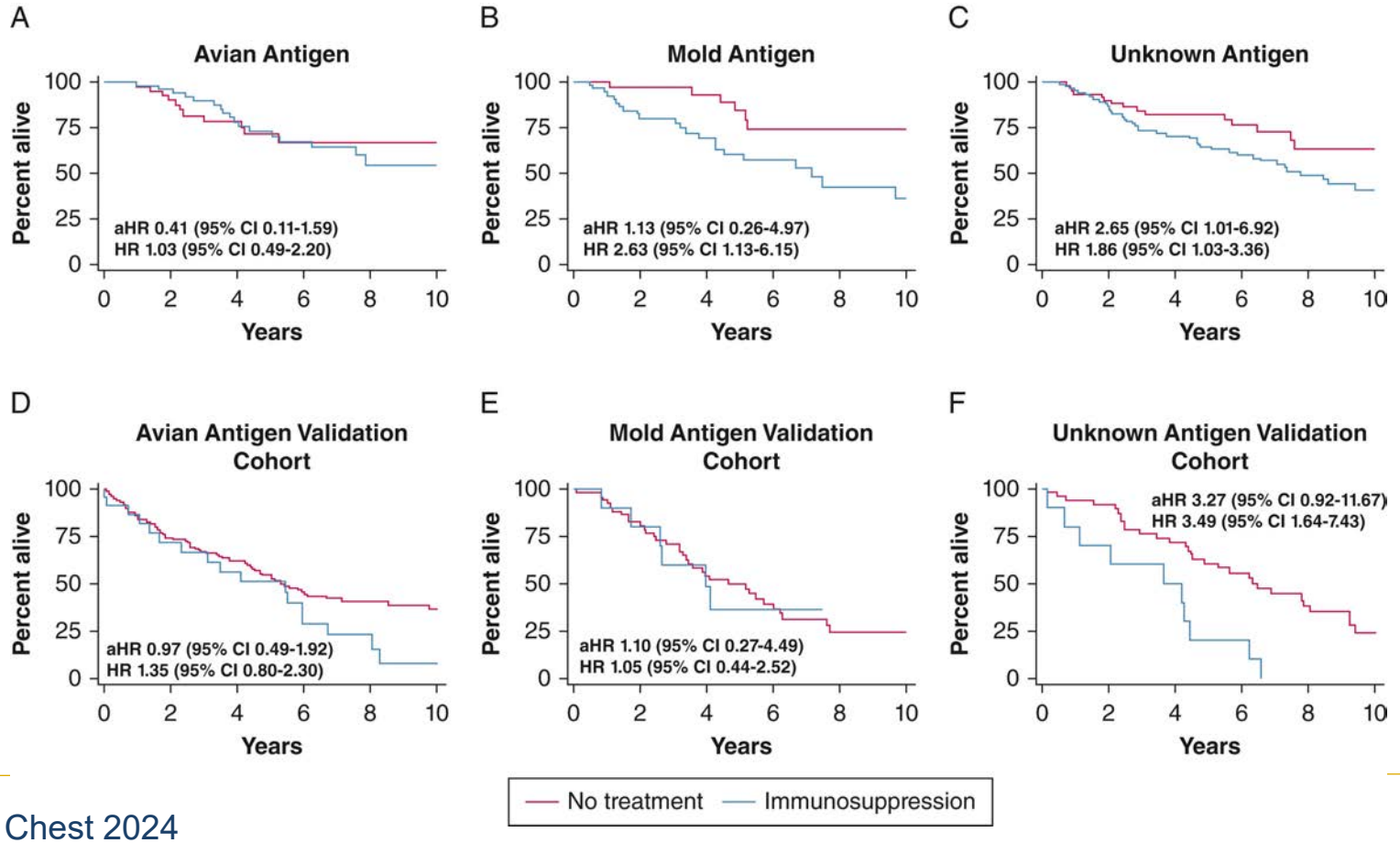


Adegunsoye et al. ERJ Open Res 2017

Hypersensitivity pneumonitis: Immunosuppression response

Interaction with HP antigen:

- Patients with HP and unknown antigen have worse survival with immunosuppression vs no treatment in primary cohort and validation cohort

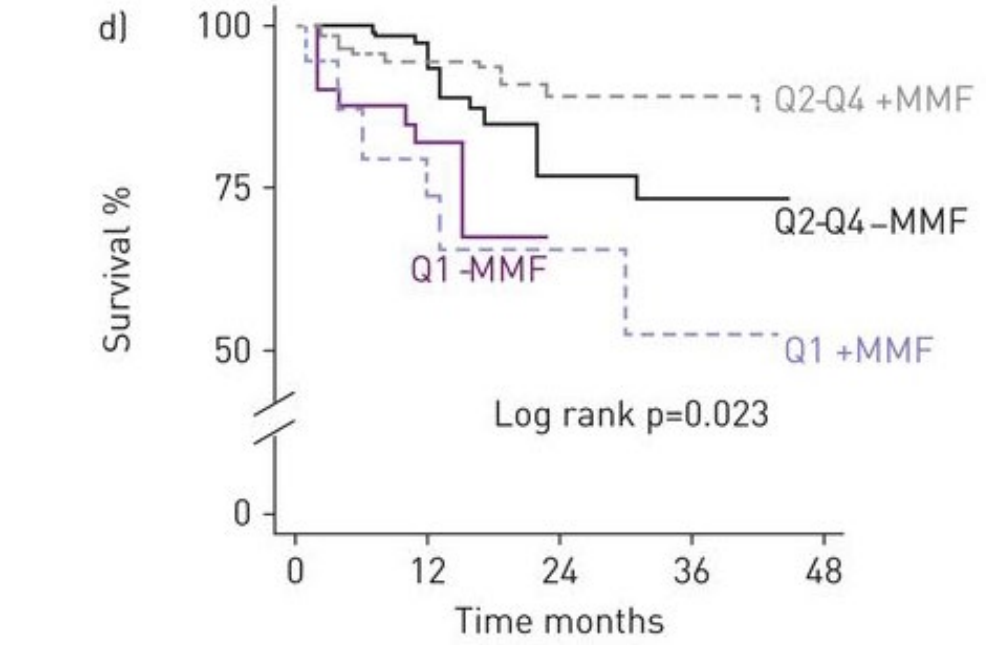


Mullin et al. Chest 2024

Hypersensitivity pneumonitis: Immunosuppression response

Interaction with short telomeres:

- Mycophenolate associated with <u>improved survival among patients with chronic HP without short telomeres</u>
- Among chronic HP patients with short telomeres, MMF therapy is not associated with improved survival or lung function



Adegunsoye et al. Eur Repsir J 2021

Hypersensitivity pneumonitis recap

- Very little evidence to support using immunosuppression, particularly in fibrotic/chronic hypersensitivity pneumonitis
- Good evidence for using Nintedanib for progressive pulmonary fibrosis associated with HP
- Antigen removal is associated with less decline in lung function and improved survival
- When to consider immunosuppression and antifibrotics in HP?
  - Antigen removed and mild disease → consider just close monitoring
  - Antigen removed and moderate/severe non-fibrotic HP → corticosteroids + monitoring
    - If disease not completely resolved, consider adding MMF or AZA to wean steroids
  - Fibrotic HP → consider corticosteroids with short follow-up to evaluate response
    - Switch to Nintedanib if there is evidence of progression (especially if no antigen identified)
    - ?Nintedanib up front rather than corticosteroids
  - Progressive fibrosis despite antigen removal or immunosuppression→ add Nintedanib

Multidisciplinary Fellows Case Conference

Stephanie Chen

Stanford

Disclosures

- I have the following relationships with ACCME defined ineligible companies:
- **None**
- I **WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.

Patient 1

- 74F w/ PMH OSA on CPAP, osteoporosis referred to pulmonology for dyspnea on exertion

Brief HPI:

- Developed dyspnea after viral illness in 2019; worsening in the past year
- Only able to walk 1 block before needing to rest
- Requiring 2-4L NC with exertion
- No fevers, chills, night sweats, weight gain, leg swelling

Social/exposure history:

- Works as a high school teacher
- Uses swim spa 1-2x/day for past 6 years
- Minimal smoking history (1p/week x6 yrs, quit >40y ago)
- No birds or down products

Family history:

- No family history of ILD, premature graying, cirrhosis, bone marrow dysfunction

Patient 1

- 74F w/ PMH OSA on CPAP, osteoporosis referred to pulmonology for dyspnea on exertion

Exam:
- Unremarkable, occasional inspiratory squeaks

PFTs:
- FEV1/FVC 0.79
- FEV1 1.81, z-score -1.09
- FVC 2.30, z-score -1.2
- DLCO 18.7, z-score 0.24
- TLC 5.52L, z-score 0.45
- RV 3.04, z-score 1.87
- No BDR

Notable labs:
- Anti-Ro: 40 (elevated)
- Anti-RNA-pol III: 20.5 (barely elevated)
- All else negative

Patient 1

video placeholder

• 2/2024 CTA chest

Patient 1

video placeholder

- 12/2024 CT chest wo contrast, inspiratory

Patient 1

video placeholder

- 12/2024 CT chest wo contrast, inspiratory

Patient 1

video placeholder

- 12/2024 CT chest wo contrast, expiratory

Patient 2

- 57F w/ PMH ?pulm cocci s/p fluconazole x3mo referred for ILD

Brief HPI:

- Developed dyspnea, dry cough in 3/2024; treated for CAP x2 without improvement
- Cocci Ab screen (+), but CF (-); treated with fluconazole x3mo
- CT PE with findings of diffuse ILD
- Since 4/2024 requiring 4-6L NC with exertion
- Reports puffy/tight fingers >20y, Raynaud's, difficulty swallowing, photosensitivity

Social/exposure history:

- Works as merchandise manager at grocery store; significant dust exposure
- Field/farm exposure near living area

Family history:

- Mother -- Raynaud's
- Father -- Raynaud's, +premature graying (started at 18yo)
- +premature graying in multiple siblings (started in their 20s)
- No ILD, CTD, cirrhosis, or bone marrow dysfunction

Patient 2

- 57F w/ PMH ?pulm cocci s/p fluconazole x3mo referred for ILD

Exam:
- CTAB, clubbing
- Puffy and tight skin with minimal skin folds on digits of bilateral hands

PFTs:
- FEV1/FVC 0.92
- FEV1 1.90, 91% pred
- FVC 2.07, 81% pred
- DLCO 11.19, 62% pred

Ex ox:
- 98 --> 94% on RA with exertion

Notable labs:
- 6/2024
  - ANA + 1:1280, speckled
  - Anti-DS Ab 14 (positive)

- 3/2024
  - ANA + 1:1280, speckled
  - DS-DNA 9 (neg)
  - Anti-ENAs (SSA/SSB) negative
  - Anti-SCL-70 negative
  - Mayo myositis panel negative
  - Anti-Jo-1 negative
  - Anti centromere negative
  - CCP negative
  - Anti-RP negative

Patient 2

video placeholder

- 5/2024 CT chest wo contrast, inspiratory

Patient 2

video placeholder

- 5/2024 CT chest wo contrast, expiratory

Patient 2

video placeholder

- 5/2024 CT chest wo contrast, expiratory

Patient 2

video placeholder

• 3/2024 CTA chest

Patient 2

video placeholder

Patient 3

- 71M w/ PMH migraines, OSA, and hypothyroidism referred for ILD

Brief HPI:
- Incidentally noted ILD on work-up for kidney stones
- Asymptomatic

Social/exposure history:
- Retired, worked as a management consultant
- Has down pillows
- No hot tubs, asbestos, pets

Family history:
- Mother – NHL
- Father – "crystalline quality to lungs", worked with fumes and had asbestos exposure without PPE
- No ILD, CTD, cirrhosis, or premature graying

Patient 3

- 71M w/ PMH migraines, OSA, and hypothyroidism referred for ILD

Exam:
- Fine bibasilar crackles, no clubbing

PFTs:
- 3/2023
  - FVC 5.51, 127% pred
  - FEV1 4.09, 141% pred
  - TLC 10.73, 165% pred
  - DLCO 24, 104% pred
- 6/2023
  - FVC 5.28, 121% pred
  - DLCO 20.39
- 9/2023
  - FVC 5.18, 119% pred
  - TLC 7.77, 119% pred
  - DLCO 20.68, 90% pred

Notable labs:
- 2/2023
  - RF, ANCA, SSA, SSB, Scl70, HP panel negative

Patient 3

video placeholder

- 3/2023 CT chest wo contrast

Patient 3

video placeholder

- 3/2023 CT chest wo contrast prone

Patient 3

video placeholder

Patient 3

video placeholder

Patient 4

- 50M w/ PMH COVID x3 referred for fibrotic lung disease

Brief HPI:

- First developed COVID 2021, had mild dyspnea on exertion
- Developed 3rd COVID infection in 2023 and has had progressive dyspnea with oxygen requirement
- Now requiring 3L at rest, 8L with exertion
- Started on OFEV by local pulmonologist
- No fevers, chills, autoimmune symptoms

Social/exposure history:

- Poured asphalt x1 year, worked as delivery driver for many years
- Never smoker
- Mother had birds

Family history:

- Mother – ILD after COVID, cirrhosis (thought secondary to NASH)
- GM – COPD
- No CTD or premature graying

Patient 4

- 50M w/ PMH COVID x3 referred for fibrotic lung disease

Exam:
- On 3L NC satting 97%
- Bibasilar crackles, no clubbing

PFTs:
- 7/2024
  - Spirometry shows normal FEV1/FVC ratio
  - FVC is decreased and there is no reversibility with bronchodilator
  - Lung volumes show severe restriction
  - DLCO is severely reduced

Ex ox:
- Desaturation to 81% on 3L, required 10L to improve saturation >88%

Notable labs:
- 8/2024:
  - ANA: positive, speckled, 1:80
  - Anti Ro: >100
  - SSA 52 IgG: >200
  - Anti La: negative
  - Anti-Scl70: negative
  - Anti-RNP: negative
  - Anti Jo1: <20
  - Mayo myositis panel: negative
  - RNA pol III: negative
  - MPO Ab: negative

Patient 4

- 50M w/ PMH COVID x3 referred for fibrotic lung disease

Telomere testing:

Lymphocytes			Granulocytes		
MTL	MTLN	INT	MTL	MTLN	INT
(kb)	(kb)		(kb)	(kb)	
4.8	6.4	L	6.6	8.0	L

VH = Very High (≥ 95th percentile)
H = High (≥ 90th and < 99th percentile)
N = Normal (≥ 10th and < 90th percentile)
L = Low (≥ 1st and < 10th percentile)
VL = Very Low (<1st percentile)

Genetic testing:

SUMMARY OF RESULTS: Indeterminate

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
CFTR, NM_000492.3	AD ,AR, 602421	c.1727G>C, p.Gly576Ala, Heterozygous	7165	0.77%, European (Non-Finnish)	Conflicting	UNCERTAIN
CFTR, NM_000492.3	AD ,AR, 602421	c.2002C>T, p.Arg668Cys, Heterozygous	35835	0.93%, European (Non-Finnish)	Damaging	UNCERTAIN
CFTR, NM_000492.3	AD, AR, 602421	c.1210-34TG[11]T[5] (5T/11TG allele), Intronic, Heterozygous	242535	Not Applicable	Not Applicable	LIKELY BENIGN

Patient 4

video placeholder

- 3/2024 CT chest wo contrast

Patient 4

video placeholder

- 3/2022 CT chest wo contrast

Patient 4

video placeholder

- 7/2021 CT chest wo contrast