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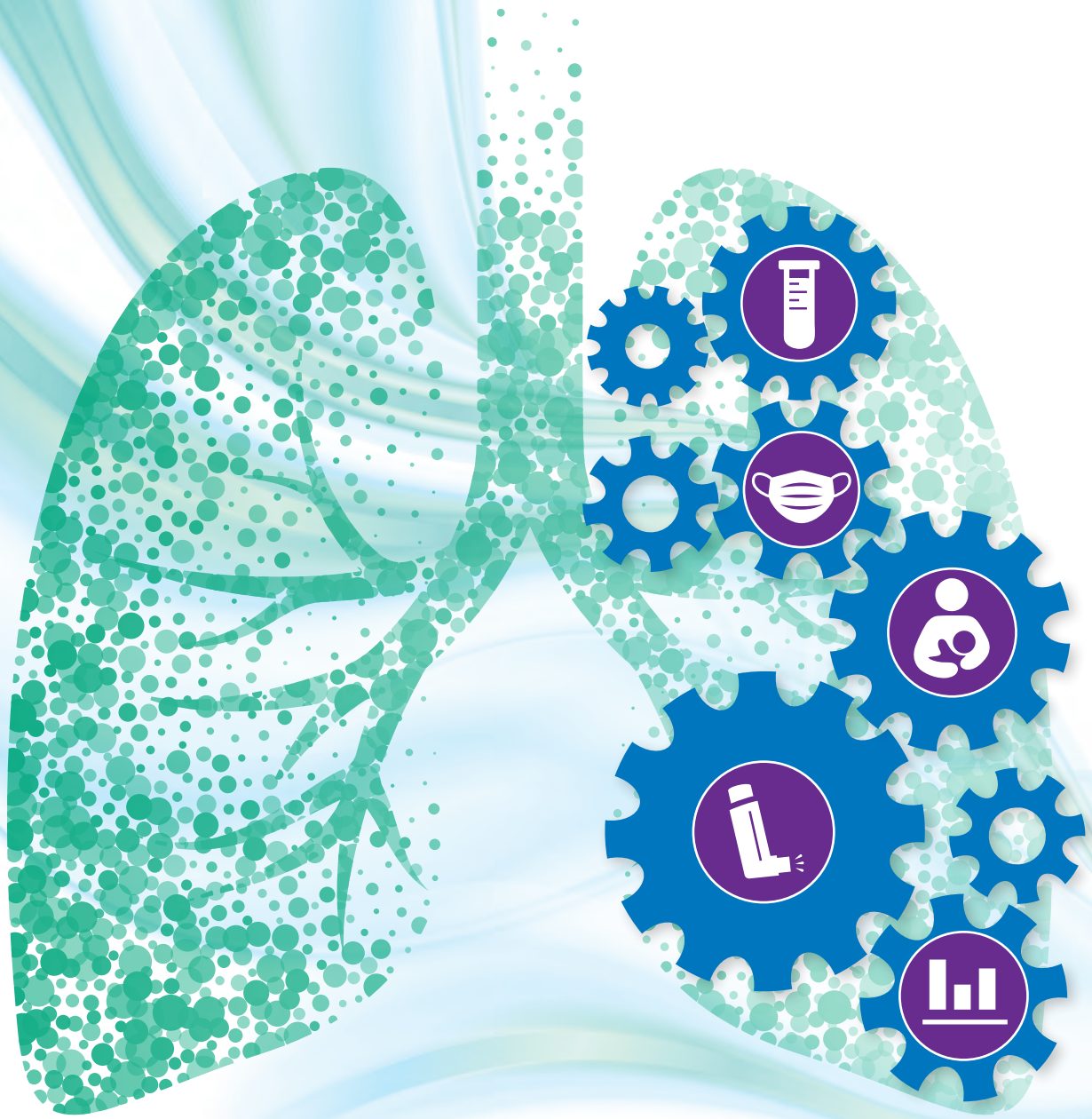
PULMONOLOGY DATA TRENDS 2023



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Long-Awaited RSV Vaccines Now Available for Older Adults and Pediatric Patients

Burton L. Lesnick, MD, FCCP

Respiratory syncytial virus (RSV) is highly contagious and transmitted by large aerosol droplets and fomites, either emitted from an infected person or by making surface-to-eye, -nose, or -mouth contact.[1] Severe RSV can increase the risk of bacterial coinfections, pneumonia, and lower respiratory tract infections (LRTI)—particularly in infants and older adults.[2]

Thankfully, 2023 has been a landmark year for RSV approvals. The FDA approved its first RSV vaccine, called RSV prefusion F protein based (RSVpreF) vaccine, for people aged 60 and over in May 2023.[3] In July 2023, the passive monoclonal antibody injection nirsevimab was approved as a preventative option for infants in their first and second winter seasons.[4] Finally, the FDA approved the RSVpreF vaccine for pregnant individuals in late August 2023, with the goal of protecting infants.[5] However, results from a recent phase 3 trial did not show significance with respect to the primary end point.[6]

Birth through 6 months is the leading timeframe of RSV-related death because of the low natural defenses and small airways of infants. On August 3, 2023, the CDC Advisory Committee on Immunization Practices unanimously recommended use of nirsevimab for all infants up to 8 months of age at the start of the RSV season and for infants at risk for severe RSV infection until 19 months of age.[7] This decision was partly based on the MELODY and MEDLEY trials.[8] In an unprecedented move, this monoclonal antibody will be made available through the Vaccines For Children program, the first monoclonal antibody to receive this designation. It is hoped that uptake of this therapy will result in fewer hospitalizations of infants with RSV bronchiolitis.

Populations at Greatest Risk for Severe Illness From RSV[9,10]

1 Newborns
- Premature infants
- < 6 months of age

2 Children
- < 2 years of age with chronic lung disease or congenital heart disease
- With compromised immune systems
- With neuromuscular disorders, including difficulty swallowing or clearing mucus secretions

3 Adults
- ≥ 65 years of age
- With chronic cardiac or pulmonary disease
- With compromised immune systems

Annual RSV Burden in the United States[11-15]

Among adults aged ≥ 65 years hospitalized with RSV disease[11]:

18% are admitted to an intensive care unit

31% receive home health services at discharge

26% die within 1 year after admission

RSV in children < 5 years of age is associated with[12-15]:

58,000-80,000 hospitalizations

100-300 deaths

520,000 emergency department visits

1.5 million outpatient visits

The Phase 3 RENOIR Study[16]

34,000+ participants aged ≥ 60 years received the RSVpreF vaccine (n=17,215)

or **placebo** (n=17,069)

RSV-associated LRTI with ≥ 2 signs or symptoms occurred in:

11 cases Vaccine vs **33 cases** Placebo

Vaccine efficacy 66.7%

RSV-associated LRTI with ≥ 3 signs or symptoms occurred in:

2 cases Vaccine vs **14 cases** Placebo

Vaccine efficacy 85.7%

RSV-associated acute respiratory illness occurred in:

22 cases Vaccine vs **58 cases** Placebo

Vaccine efficacy 62.1%

Bottom Line:

The vaccine **significantly reduced the risk** of developing RSV-associated LRTI by **82.6%** and severe RSV-associated LRTI by **94.1%**.

Preterm Babies and the Need for Protection[17-20]

Each year in the US,

1 in 10 babies are born at **< 37 weeks**,

Nearly **3%** are born at **< 34 weeks** of gestation.[17]

Preterm babies born at **< 39 weeks** have a greater incidence of respiratory complications and a higher risk of developing diseases over time.[18]

Placenta transfer occurs throughout pregnancy, with the highest levels of antibodies transferred during the third trimester.[19]

Preterm babies receive fewer placental-transfer antibodies, which can compromise immunity.[20]

The Monoclonal Antibody Nirsevimab[8]

The monoclonal antibody nirsevimab is being developed as a long-lasting, single dose for all infants:

- Experiencing their first RSV season
- With specific conditions (i.e., congenital heart disease or chronic lung disease), entering their first and second RSV seasons

Nirsevimab is the first potential immunization to show protection against RSV in the general infant population.

The phase 3 trial, MELODY (NCT03979313), **showed that…**

- A single, fixed dose of nirsevimab provided protection against medically attended RSV-associated LRTI when given to healthy late-preterm and term infants before an RSV season.

A total of 1,490 infants underwent randomization:

994 infants Nirsevimab vs **496 infants** Placebo

Through 150 days post-injection the number of infants who were hospitalized for RSV-associated LRTI:

9 (0.6%) Nirsevimab vs **8 (1.6%)** Placebo

Estimated efficacy, 62.1% (95% CI, −8.6 to 86.8; $P = 0.07$ by Poisson regression)

Medically attended RSV-associated LRTI occurred in:

12 infants (1.2%) Nirsevimab vs **25 infants (5.0%)** Placebo

These findings correspond to an efficacy of 74.5%

(95% CI, 49.6 to 87.1; $P < 0.001$)

The current anti-RSV antibody, Synagis, is limited only to high-risk infants, and it provides 1-month of protection–requiring 5 injections for a full RSV season.[21]

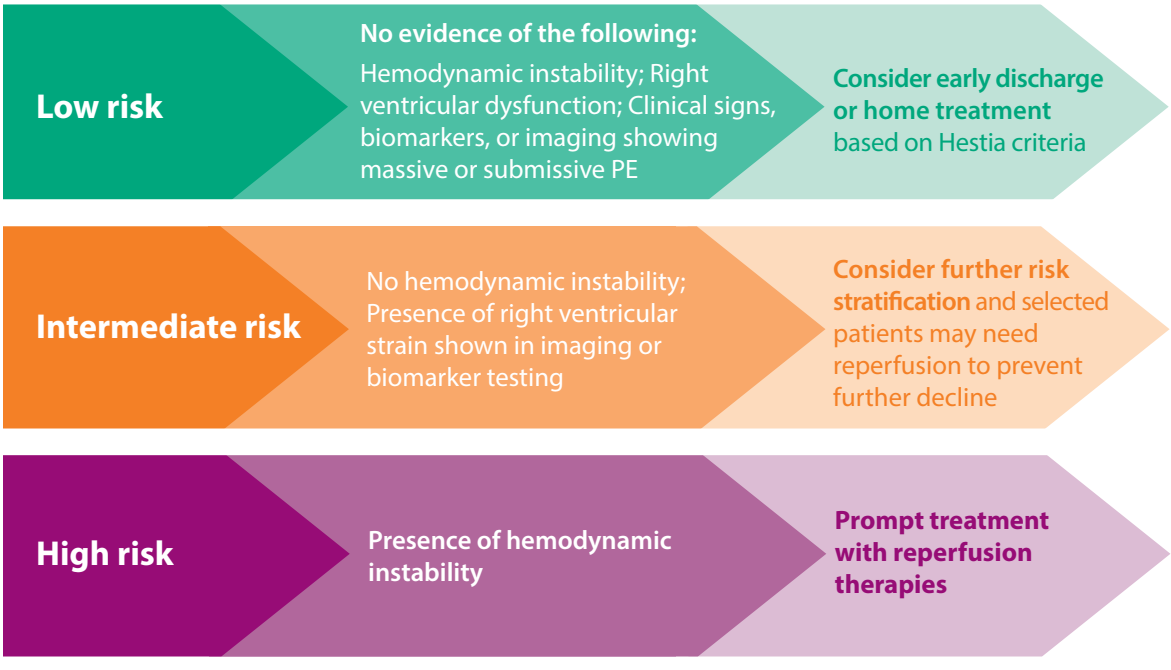
Decreasing Pulmonary Embolism-Related Mortality

Parth Rali, MD

As many as 900,000 patients have deep vein thrombosis (DVT) or pulmonary embolism (PE), also called venous thromboembolism (VTE), each year in the United States, with 100,00 deaths per year.[1] In patients with PE, 56% also have DVT, which can affect 30-day mortality rates.[2] The field of PE is evolving to help decrease mortality from these events. Proper risk stratification is crucial to identify the best approach for each patient, while the presence of comorbidities and unmodifiable risk factors must also be considered when individualizing care and assessing likelihood of mortality.[3,4] As comorbidities increase, mortality increases in PE.[4] As well, racial, ethnic, and socioeconomic demographic differences affect PE, with Black patients having greater PE severity and socioeconomically underserved patients having higher follow-up mortality.[5,6]

Treatments are also advancing, with many upcoming catheter-based treatments in clinical trials, which have demonstrated rapid recovery of right ventricle function—a primary cause of PE-related mortality.[7,8] The effect of catheter-based treatment on long-term functional outcomes is currently being explored in clinical trials. Artificial intelligence is also being used to aid in diagnosis and treatment.[9] As the armamentarium of treatment options diversifies, so must our overall approach to management. The PE response team (PERT) strategy uses a multidisciplinary team of experts to further individualize patient care to help decrease mortality and improve follow-up efforts since the post-PE period is a sensitive time for new morbidity.[10,11] With proven risk stratification and management strategies available and new treatments on the way, the field of PE looks to improve not only in patient acute mortality, but also long-term functional outcomes, and early detection of post-PE comorbid conditions.

PE Risk Stratification Method[3]



Racial, Ethnic, and Socioeconomic Risk Factors in PE[5,6,12,13]

Ethnicity

Hispanic/Latino patients have **lower rates of high-risk PE** vs non-Hispanic patients

Hispanic/Latino patients **19%**

Non-Hispanic/Latino patients **25%**

yet similar rates of inpatient mortality

6.8%

7.5%

Race

Black patients present with PE at **a younger age**

55 years Black patients

63 years White patients

and with higher severity than White patients

Socioeconomic

Nearly 1 in 3 patients from low socioeconomic backgrounds are **readmitted within 90 days of discharge** after a PE hospitalization.

Sex

Female

Women are more likely to have **varicose veins, depression, prolonged immobility, or a history of hormonal therapy...**

Male

While men are more likely to have **atherosclerotic diseases, lung disease, cancer, or unprovoked PE.**

PERT Approach to Decrease Mortality[10,14]

PE Clinical Trials on the Horizon[15-22]

The field of PE is adapting catheter-based treatments in acute PE treatments. These treatments aim to have similar efficacy to systemic thrombolytics with less bleeding risk.[8] The following are selected trials that are ongoing and enrolling patients, and hope to generate more scientific evidence in PE treatment landscape.

Trial	Drug or Catheter Type	Primary Endpoint
PE-TRACT (RCT, *N* = 500)	Anticoagulant therapy vs catheter-directed therapy	3 months: Peak O_2 consumption on CPET 12 months: NYHA classification 7 days: Major bleeding
PEERLESS (RCT, *N* = 550)	Catheter-directed thrombolysis vs FlowTriever System	Composite end point of all-cause mortality, or intracranial hemorrhage, major bleeding, clinical deterioration, or ICU admission
PEERLESS II (RCT, *N* = 1,200)	FlowTriever System vs anticoagulation only	Composite end point of all-cause mortality, or intracranial hemorrhage, major bleeding, clinical deterioration, or ICU admission
HI-PEITHO (RCT, *N* = 406)	Anticoagulation with heparin vs EkoSonic™ Endovascular System	PE-related mortality, PE recurrence, or cardiorespiratory collapse
STORM-PE (RCT, *N* = 600)	Anticoagulation vs mechanical aspiration thrombectomy	Change in right ventricle and left ventricle ratio; Post-PE functional outcomes
PEITHO-3 (RCT, *N* = 650)	Alteplase vs anticoagulation only	Death from any cause, hemodynamic decompensation, recurrent PE
STRIKE-PE (*N* = 600)	Indigo Aspiration System	Change in right ventricle and left ventricle ratio and composite score of major adverse events; Post-PE functional outcomes
RESCUE[a] (*N* = 109)	The Bashir Endovascular Catheter + r-tPA	Change in right ventricle and left ventricle ratio

CPET, cardiopulmonary exercise testing; ICU, intensive care unit; NYHA, New York Heart Association; PE, pulmonary embolism; RCT, randomized clinical trial; r-tPA, recombinant tissue plasminogen activator

[a]Final results from RESCUE (NCT04248868) posted in April 2023.

Neutrophils and neutrophil serine proteases normally help protect the lungs from harm, but in bronchiectasis they can contribute to inflammation and lung destruction.[1-6]

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Visit Insmed's bronchiectasis **Booth #1001** at the CHEST Annual Meeting 2023 in Hawaii

References: 1. Flume PA, et al. *Lancet*. 2018;392(10150):880-890. **2.** Dente FL, et al. *Mediators Inflamm*. 2015;2015:642503. **3.** Effah CY, et al. *Front Immunol*. 2021;12:689866. **4.** Rosales C. *J Leukoc Biol*. 2020;108(1):377-396. **5.** Keir HR, Chalmers JD. *Semin Respir Crit Care Med*. 2021;42(4):499-512. **6.** Chalmers JD, et al. *Am J Respir Crit Care Med*. 2017;195(10):1384-1393.

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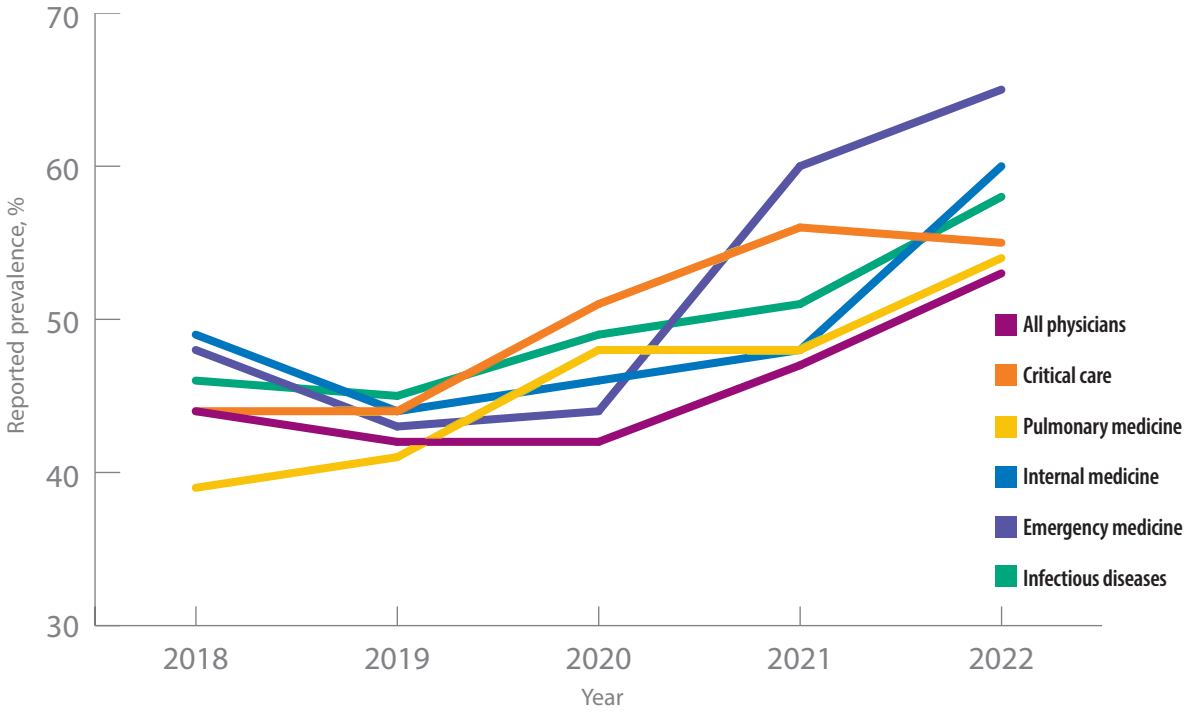
Addressing Physician Burnout in Pulmonology and Critical Care

Kelly Vranas, MD, MCR

Work-related stress has long been a concern for those working in the intensive care unit (ICU); even before the COVID-19 pandemic, it was estimated that up to 45% of critical care physicians had at least one symptom of severe burnout.[1-6] In 2020 and the years following, the combination of significantly increased patient morbidity and mortality rates, excessive workloads, and resource limitations negatively impacted employee morale, decreased feelings of professional fulfillment, increased moral distress, and most importantly, heightened mental health concerns among critical care physicians.[7-10]

While most of the post-pandemic world has returned to "normal," its effect on the health care industry has been slower to wane; in fact, reported rates of physician burnout remain higher today than they were in 2020.[2-6] Almost half of physicians (49%) say their depression affects their patient interactions, while 65% report that their personal relationships are affected.[6] In order to course-correct—not only for the sake of our current workforce and patients, but also to ensure better preparation for future public health crises—we must address the more fundamental burnout contributors that the pandemic only amplified.

Reported Rates of US Physician Burnout[2-6,a]



[a]Based on annual surveys of approximately 9,100 – 15,000 physicians across 29 specialties in total.

Common manifestations of burnout[2]

Combating Physician Burnout and Impending Shortages[11]

Projected physician shortages by 2034

17,800 – 48,000 primary care physicians

21,000 – 77,100 non-primary care specialties

To mitigate the number of health care professionals leaving practice, some changes must be made:

Protect health care workers[7]

8 in 10 report physical or verbal abuse at work

Free up physicians' time[7,12,13]

2 hours vs **1 hour**

> 50% of pulmonologists and intensivists say having **too many administrative tasks** adds to their burnout

Increase mental health care access[12,13]

16% Pulmonologists vs **11%** Intensivists

have sought professional help to reduce their burnout

Improve physician resources[7,8,12,13]

- ✓ **Training**
- ✓ **Equipment access**
- ✓ **Feedback forums**

29% of pulmonologists and intensivists agree that **lack of control/autonomy** contributes to their burnout

Build morale and engagement[6,7,11-13]

37% Pulmonologists vs **58%** Intensivists say that lack of respect from employers, colleagues, and other staff contributes to their burnout

Key components for building a sense of community among clinicians:

- ✓ **Support**
- ✓ **Camaraderie**
- ✓ **Mentorship**
- ✓ **Activism**

Updated Guidelines for COPD Management: 2023 GOLD Strategy Report

Muhammad Adrish, MD, MBA, FCCP, FCCM

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report is an evidence-based strategy document for chronic obstructive pulmonary disease (COPD) diagnosis, treatment, and prevention; the GOLD report is used worldwide as a tool for implementing effective COPD management.[1] The annual report reviews the major research publications published from the previous years and provides important updated recommendations for care providers.

The 2023 GOLD report includes several new updates, such as a new proposed definition[2]; strategies for terminology and taxonomy[2]; etiotypes for COPD[2]; screening and risk factor updates[1]; and vaccination recommendations.[1] The ABCD Assessment Tool has been revised to recognize the clinical relevance of exacerbations,[3] and the section on Interventional and Surgical Therapies for COPD has been expanded.[1] Information on imaging and computed tomography (CT) has been included,[1] and issues related to inhaled delivery[4] and adherence[5] have been addressed. Also included is an expanded role of triple inhaled therapy in select patient populations,[6] and the complexity of COPD is also examined—which involves not only cigarette smoking, but other exposures as well.[7]

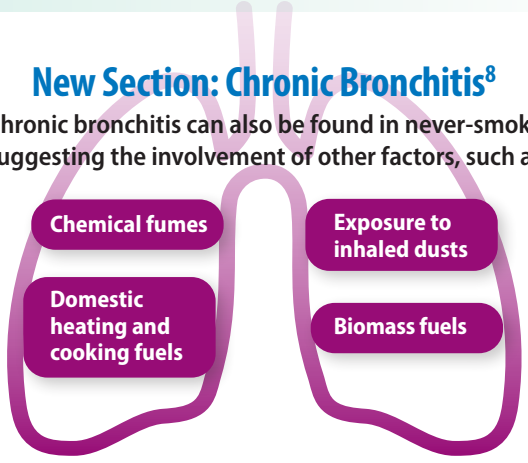
Key Changes in the 2023 GOLD Report [2,3,8-10]

Proposed New Definition of COPD[2]:

"COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration) due to persistent abnormalities of the airways (bronchitis, bronchiolitis), alveoli (emphysema), and/or pulmonary vessels, confirmed by spirometrically determined airflow limitation and/or objective evidence of structural or physiological pulmonary dysfunction."

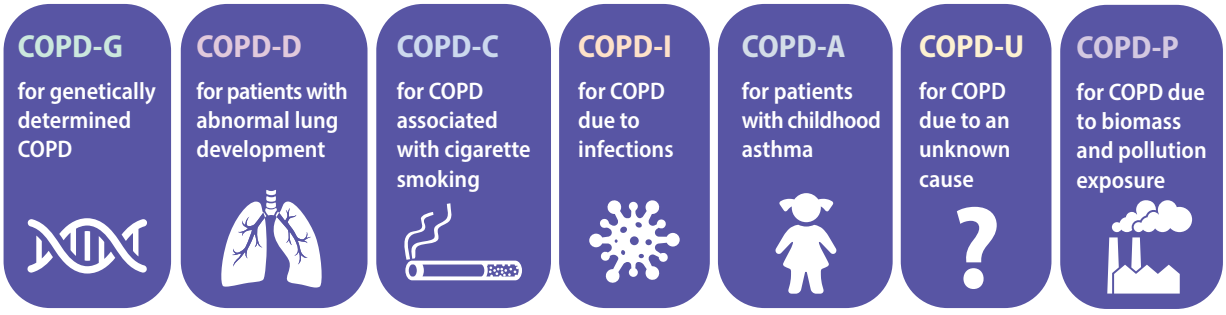
New Section: Chronic Bronchitis[8]

Chronic bronchitis can also be found in never-smokers, suggesting the involvement of other factors, such as:



COPD can be caused by several factors unrelated to smoking. The GOLD report attempts to address this heterogeneity by proposing the following etiotypes for COPD.

New Proposed Taxonomy (etiotypes) for COPD[2]



Updated COPD Assessment Tool[3]

The ABCD patient assessment tool is now called the **ABE Assessment Tool**:

Group A
- ✓ mMRC dyspnea scale score of 0-1
- ✓ CAT score < 10
- ✓ History of 0-1 moderate exacerbation not leading to hospitalization

Group B
- ✓ mMRC score ≥ 2
- ✓ CAT score ≥ 10
- ✓ History of 0-1 moderate exacerbation not leading to hospitalization

Groups C and D

have been merged into a single group E to highlight the clinical relevance of exacerbations. This proposal will need validation in appropriate clinical trials.

Group E

History of ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization, irrespective of mMRC or CAT scores

CAT, COPD Assessment Test; mMRC, modified Medical Research Council

Updated COPD Assessment Tool[3]

When initiating treatment with long-acting bronchodilators, the preferred choice is a combination of a LAMA and a LABA.

The use of a LABA-ICS combination should not be encouraged in patients with COPD. When ICS use is indicated, the recommendation is to use LABA + LAMA + ICS combination because of its superiority over LABA + ICS.

ICS should be used in patients with COPD who have features of asthma.

The algorithm also recommends considering LABA + LAMA + ICS for patients in group E if blood eosinophil counts are ≥ 300 cells per µL.

ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic agent

COPD Exacerbation Definition Update[9]

"An event characterized by increased dyspnea and/or cough and sputum that worsen over ≤ 14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways."

COPD and Comorbidities[1,10]

COPD often coexists with other diseases that may have a clinically significant impact on prognosis:

- Cardiovascular disease
- Obstructive sleep apnea
- Periodontitis
- Metabolic syndrome, diabetes
- Gastroesophageal reflux disease
- Osteoporosis or frailty
- Anemia
- Polycythemia
- Anxiety, depression
- Lung cancer
- Bronchiectasis
- Cognitive impairment

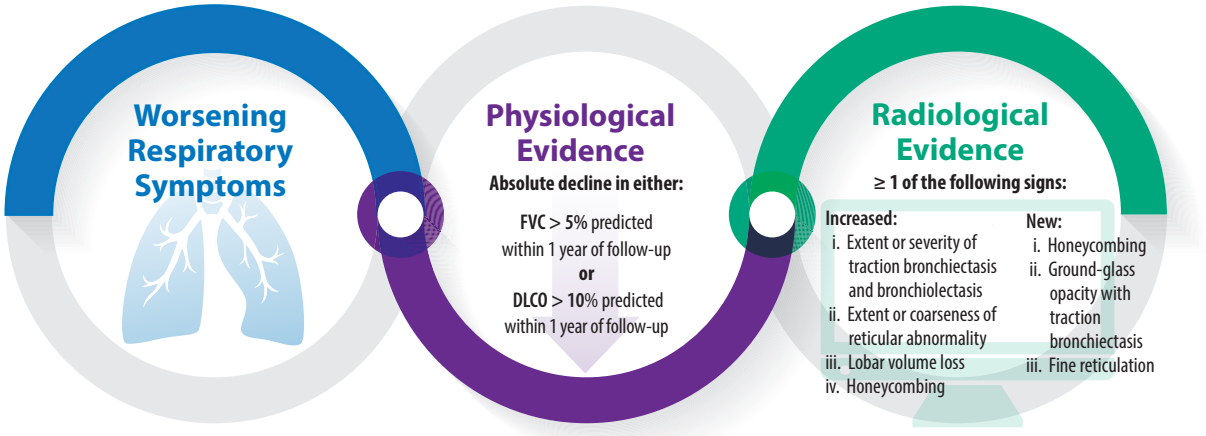
Progressive Pulmonary Fibrosis: Understanding Its Many Forms

Tejaswini Kulkarni, MD, MPH, FCCP

The updated idiopathic pulmonary fibrosis guideline from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax was based on multiple clinical trials and includes many different disease manifestations. The intention of the update is to more accurately monitor disease progression to help inform therapeutic decisions for our patients.[1] Interstitial lung diseases (ILD) most likely to develop a progressive phenotype include idiopathic, nonspecific interstitial pneumonia; unclassifiable ILD; fibrotic hypersensitivity pneumonitis; and ILDs associated with autoimmune disorders.[2] Management of progressive pulmonary fibrosis (PPF) is far from a "one size fits all" approach. Many variables need to be better understood, such as how different disease etiologies progress, the role of comorbidities, and the best timing and sequence of therapy including escalation in immunosuppression and/or antifibrotic agents for different patient profiles.[1,3]

New Definition for PPF[1]

In 2022, the American Thoracic Society established a new definition for PPF, formerly referred to as progressive fibrosing interstitial lung disease.[1,4] Patients with ILD with radiological evidence of pulmonary fibrosis meet the criteria for PPF if they have at least 2 of the following findings with no alternative known cause:



DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity

Pathophysiology of Pulmonary Fibrosis[5]

Early Phase

Disease-specific triggers

- Lymphocyte activation/ differentiation
- Autoimmunity
- Exaggerated immune response
- Chronic granulomatous inflammation (often from an inhaled antigen or other exposure)

Environmental triggers

- Tobacco smoking
- Occupational exposures
- Air pollution
- Microaspiration
- Viral infection

Uncontrollable variables

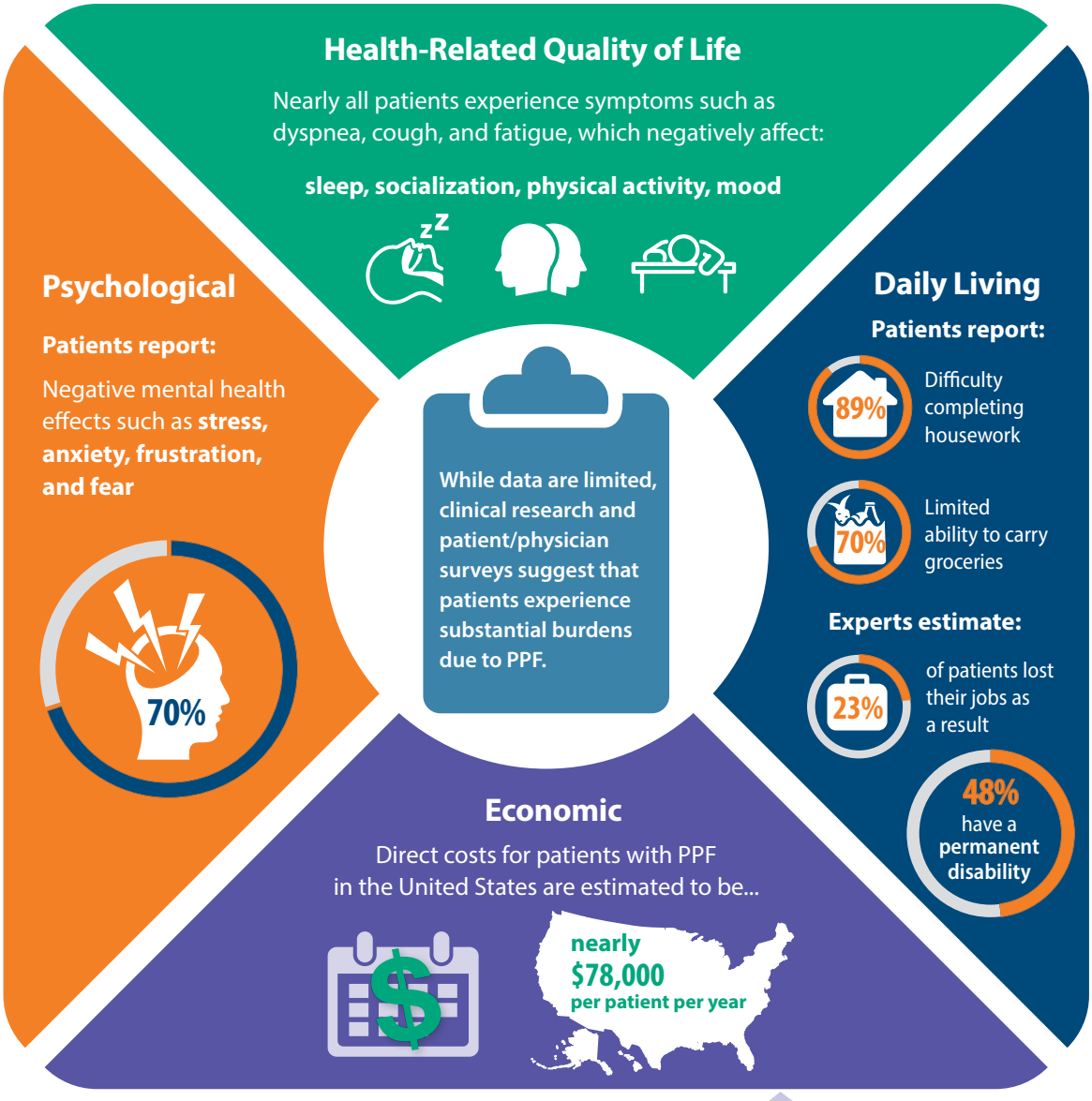
- Aging
- Genetic background
- Epigenetic modifications

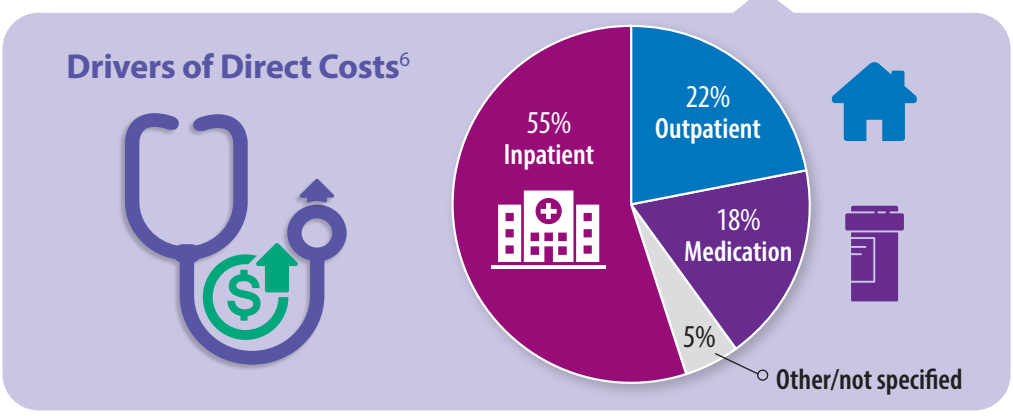
Later Phase

Impact of extracellular matrix production by fibroblasts

- Lung tissue remodeling and honeycombing
- Tissue stiffness and hypoxia upregulate profibrotic cytokine pathways and myofibroblast activation
- Perpetuating fibrogenesis

Burdens of PPF[2]





In general, the overall prognosis and implication of PPF offer insight into early phase and later phase variables that are critical when defining the comprehensive burdens, which impact not only direct costs but also the specific approach clinicians take in treating this disease.

Sleep Apnea: Comorbidities, Racial Disparities, Weight Guidelines, and Alternatives to CPAP

Lauren Tobias, MD, FCCP

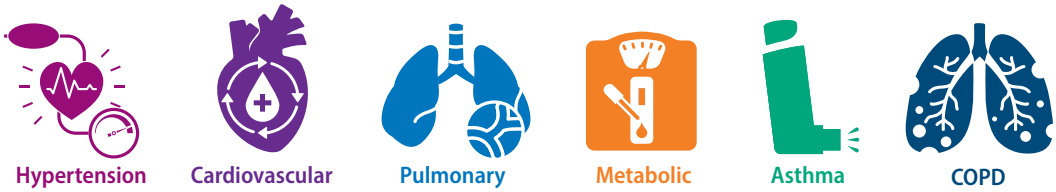
Obstructive sleep apnea (OSA) is a disorder in which the upper airway repeatedly collapses during sleep, resulting in hypoxemia and sleep disruption. Approximately 9-17% of women and 25-30% of men in the United States are diagnosed with OSA.[1,2] Patients may present with a range of symptoms, including daytime sleepiness, snoring, breathing pauses, or unexplained awakenings from sleep.[1] OSA severity is classified according to the apnea-hypopnea index (AHI), and defined by the presence of either ≥ 15 events per hour or 5-14 events per hour with symptoms such as excessive daytime sleepiness, insomnia, or impaired sleep-related quality of life.[1] OSA has been associated with stroke, hypertension, atrial fibrillation, coronary artery disease, heart failure, and mood disorders.[3] Continuous positive airway pressure (CPAP) is the standard of care for treating OSA in most patients and is highly cost-effective.[4]

Unfortunately, racial disparities exist in sleep apnea, as with sleep health generally. Black individuals have disproportionately high rates of OSA and higher OSA severity in comparison with White patients.[5] Racial inequity also exists in disease outcomes and sleep apnea-related mortality.[5,6] CPAP adherence may be lower in marginalized racial groups, with Black patients demonstrating lower nightly CPAP usage.[4] Initiatives are needed to improve sleep health equity, such as through increased access to sleep care through telehealth, lessening barriers to sleep apnea diagnostics, and reducing structural inequities associated with CPAP treatment including cost.

Obesity is a well-established risk factor for sleep apnea, and all patients whose body mass index (BMI) is elevated should be counseled on weight loss.[7,8] For patients unable to acclimate to CPAP, alternatives are available; there was increased reliance upon these during the recent major CPAP recall.[9] Some alternatives include mandibular advancement devices, positional therapy, and hypoglossal nerve stimulation therapy.[9] Emerging research is exploring the possibility of drug therapy to manage sleep apnea in the future.[9]

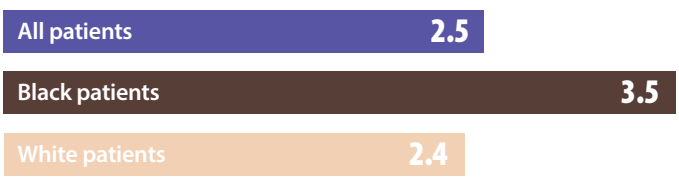
Comorbidities in Sleep Apnea[3,10]

80% of those diagnosed with OSA have comorbidities.



Racial Disparities in Sleep Apnea–Related Mortality[6]

Age-adjusted mortality (per 1,000,000 population)



Black male patients' OSA-related mortality has increased by 2.7% from 1999-2019.[6]

ATS Clinical Practice Guidelines for Weight Management in Sleep Apnea[7]

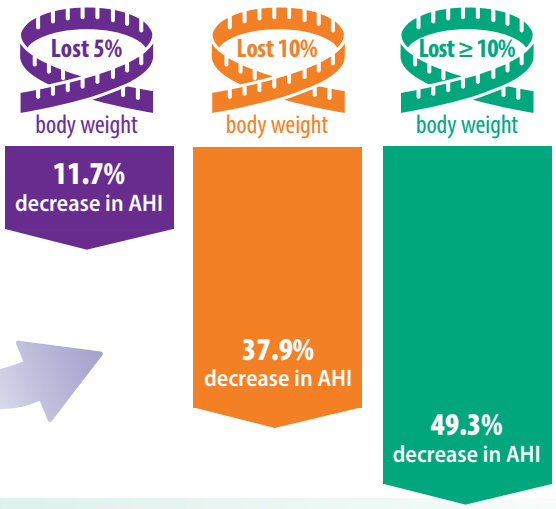
Patients with **OSA who are overweight or obese** should be treated with lifestyle interventions, including:

1. Reduced-calorie diet
2. Exercise/ physical activity
3. Behavioral counseling

For patients who need further assistance, anti-obesity **pharmacotherapy and/or bariatric surgery*** should be considered.

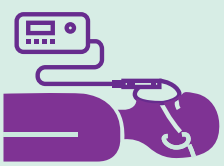
*Anti-obesity pharmacotherapy for BMI ≥ 27 and consider bariatric surgery referral for BMI ≥ 35.
ATS, American Thoracic Society

Effect of Weight Loss on Apnea Hypopnea Index (AHI)[11]



Alternative Treatments to CPAP[9,11-16]

Treatment	Description	Comments
Behavioral modification	Weight management, minimizing alcohol and sedatives before bedtime, and positional therapy (avoiding supine sleep)	Greater weight loss leads to more reduction in respiratory events; weight loss rarely leads to full resolution of OSA.
Mandibular advancement device	Plastic mouthpiece that moves the lower jaw forward, opening the airway	Candidates must have sufficient dentition in upper and lower jaws; the device is custom-fit by a dentist.
Hypoglossal nerve stimulator	Implantable device that stimulates the tongue to protrude in sync with a patient's respirations	Candidates must have BMI ≤ 32-35 and favorable soft palate collapse during sleep.
Other upper airway surgeries	Uvulopalatopharyngoplasty (UPPP) and variants that aim to reduce pharyngeal collapse and/or adenotonsillar enlargement	Patient selection is based on presence of a surgically correctable problem. Often guided by craniofacial imaging with a ~50% success rate.



CPAP is the most effective treatment for OSA. Efficacy varies across studies, from ~20% to 80%.

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Lung Cancer Screening: A Need for Adjunctive Testing

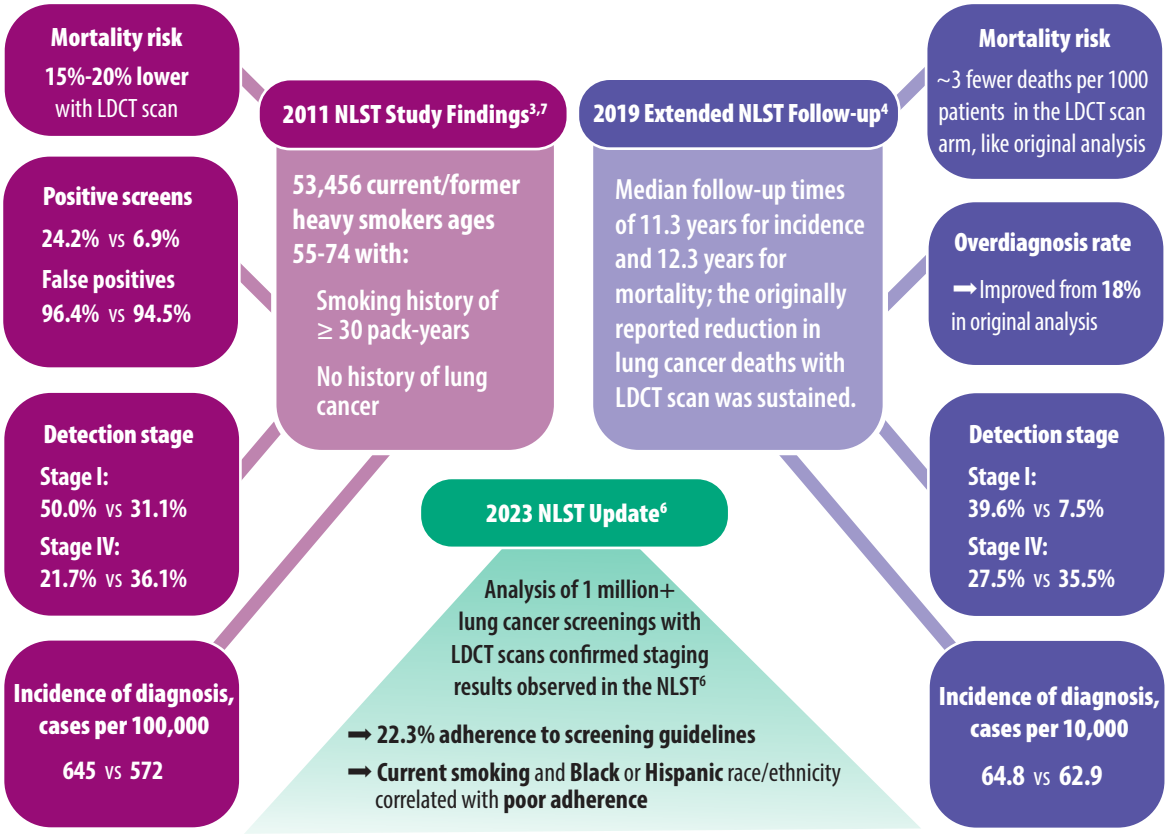
Eric S. Edell, MD, FCCP

Early detection of lung cancer by screening with low dose computed tomography (LDCT) scanning has long been investigated as a potential means of reducing related deaths.[1,2] The 2011 National Lung Screening Trial (NLST) compared LDCT scanning with standard chest radiograph (CXR). Results showed a significant reduction in mortality in high-risk current and former smokers who were screened annually (3×) with LDCT scan vs CXR.[3]

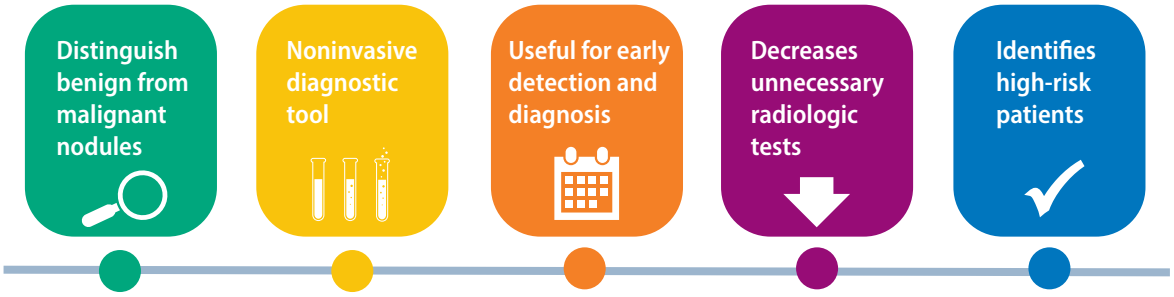
LDCT scanning for lung cancer is currently a standard of care, partially due to the results of the NLST.[4,5] In 2013, LDCT scanning was recommended by the US Preventive Services Task Force (USPSTF), making about 8 million Americans eligible for screening.[6] In 2019, an extended NLST cohort follow-up study showed that earlier detection with LDCT scanning not only delayed lung cancer death, but also prevented it—or at least delayed it by a decade or more.[4,7] This sparked another change in eligibility criteria in the 2021 USPSTF guidelines, allowing an additional 6.5 million people to be eligible for screening.[6]

Unfortunately, LDCT scanning has some negative aspects to its use, such as high false-positive rates, repeated radiation exposure, and the lack of ability to distinguish between nodules that are benign or malignant.[8] There is a need for adjunctive testing for screening. Some current research is focusing on the development of liquid biomarkers intended to be complementary to imaging as a method of using noninvasive lung cancer diagnostics.

LDCT Scan vs CXR[3,4,6,7]



Potential Benefits of Biomarkers for Detecting Lung Cancer[8]



Review of Lung Cancer Biomarkers[8]

Autoantibodies

Blood-based biomarker showing promise in early detection and diagnosis; limited ability to identify high-risk populations for screening

The EarlyCDT 7-autoantibody panel measures p53, NY-ESO1, CAGE, GBU4–5, HuD, MAGE A4, and SOX

Sensitivity 37%-41%
Specificity 91%

microRNA

Small, noncoding, single-stranded RNA molecules linked to the pathogenesis of most cancers; excellent biomarkers due to stability and resistance to degradation

Sensitivity 78%-87%
Specificity 75%-81%

Complement fragments

Higher concentrations of C4d have been detected in patients with lung cancer (especially higher stages), and are associated with shorter overall survival

Sensitivity 44%
Specificity 89%

Blood proteins

Multiple studies have supported use to aid in early detection and accurate diagnosis; challenges such as low concentration and sample variability remain

Various tests have shown wide ranges:

Sensitivity 49%-97%
Specificity 44%-96%

DNA methylation

An epigenetic modification that has demonstrated potential for early detection of lung cancer

One study noted *SOX17*, *TAC1*, and *HOXA7* as the best performing markers

Using sputum:	**Using plasma:**
Sensitivity 98%	Sensitivity 93%
Specificity 71%	Specificity 62%

Circulating tumor DNA (ctDNA)

Demonstrated value in detecting advanced-stage cancer; little evidence exists regarding early detection

One new test, CancerSEEK, uses 8 protein biomarkers + ctDNA to detect early-stage cancers

Sensitivity 59%
Specificity 99%

Asthma Across a Woman's Lifespan

Navitha Ramesh, MD, FCCP

The severity and symptoms of asthma vary greatly across a woman's lifespan. Gender-based variances start early, with boys having a higher asthma prevalence than girls in childhood, and women having a higher prevalence than men starting around puberty and through adulthood, related to changes in sex hormones.[1] In the pediatric age group, questions arise about both the necessity and choice of biologic therapies and how best to transition patients from pediatric to adult care.[2,3] During this transition, patients often have worsening symptoms mainly due to decreased adherence to medications, lack of insurance, or lack of parental and social support.[3]

In adulthood, around 13% of women have asthma symptoms during pregnancy, necessitating maintenance treatment with inhalers.[4] In some women, asthma symptoms tend to worsen during pregnancy due to some of the natural changes in lung function and breathing patterns during pregnancy.[4,5] Uncontrolled asthma in pregnancy can lead to adverse effects for both mother and fetus. Maternal adverse outcomes include preeclampsia, placental abruption, increased risk of Caesarean sections, increased risk of gestational diabetes mellitus, and pulmonary embolism.[4-6] Child adverse outcomes include low birth weight, increased risk of minor congenital malformations, and asthma.[4,5] Aging in women also affects lung function, including reducing the forced expiratory volume in 1 second (FEV_1).[7] Menopause specifically is related to decreased lung function due to changes in sex hormones, and this effect is seen even more in women with asthma.[7,8] It is important for providers to be aware of asthma manifestations throughout a woman's lifespan and personalize care accordingly.

FDA-Approved Biologics for Pediatric Asthma[2,9]

Biologics	Approved Age	Mechanism
Omalizumab	6 years	Inhibits IgE, preventing activation of TH2
Mepolizumab	6 years	Binds to IL-5, reducing eosinophil levels
Benralizumab	12 years	Binds to IL-5, causing apoptosis of eosinophils
Dupilumab	6 years	Binds to IL-4, downregulating TH2 inflammatory pathways
Tezepelumab	12 years	Binds to TSLP, inhibiting upstream action in the inflammatory cascade

Ig, immunoglobin; IL, interleukin; TH2, T helper 2; TSLP, thymic stromal lymphopoietin

As children grow, their lungs develop more alveoli and increase in capacity, which impacts asthma symptoms.[10,11] These changes, combined with the hormonal shifts associated with puberty, can worsen asthma symptoms in women.[1]

Challenges in Transitioning from Pediatric to Adult Asthma Care[3,12]

A survey of HCPs treating adolescent and young adult patients with allergy and asthma revealed…

86% feel they lack transitional guidance

87% agree training is needed

48% acknowledge the lack of an established feedback system between pediatric and adult medical services

< 5% report using a transition readiness questionnaire with adolescents

Decline in Adherence

Another study reported an asthma treatment **adherence rate of 77% in adolescents, vs 92% in children.**

Pregnancy and **menopause** are also important times for asthma care during a woman's life, due to the physical changes that take place during these transitions.

Effects of Asthma During Pregnancy[5]

Respiratory:

Progesterone induces hyperventilation and dyspnea; as fetus grows, diaphragm is displaced, and functional residual capacity decreases by 20%

Immune:

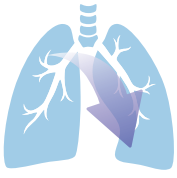
Proinflammatory chemokine release at beginning, then anti-inflammatory environment later in pregnancy; pregnant women with asthma have higher levels of proinflammatory chemokines and oxidative stress

Cardiovascular:

Cardiac output increases, blood pressure decreases, plasma volume decreases

Asthma negatively affects the fetus if exacerbations continue, so treatment with inhaled corticosteroids, short-acting beta-agonists, or bronchodilators is recommended. More studies are needed to determine if biologic medications should be continued or prescribed during pregnancy.

Airway Remodeling and Lung Function Decline During Menopause[8,a]



Mean FVC decline:

-10.2 mL/y

-12.5 mL/y

Mean FEV_1 decline:

-3.8 mL/y

-5.2 mL/y

Transitional women

Postmenopausal women

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

[a]All data compared to regularly menstruating women.

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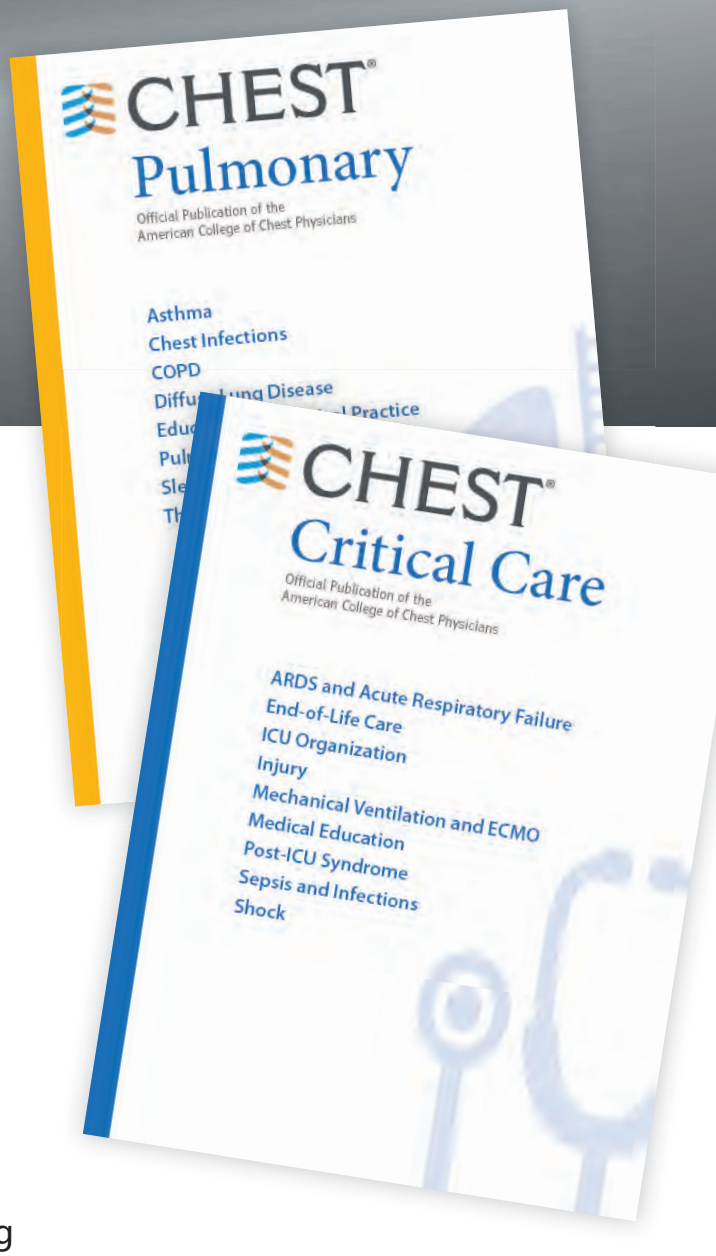

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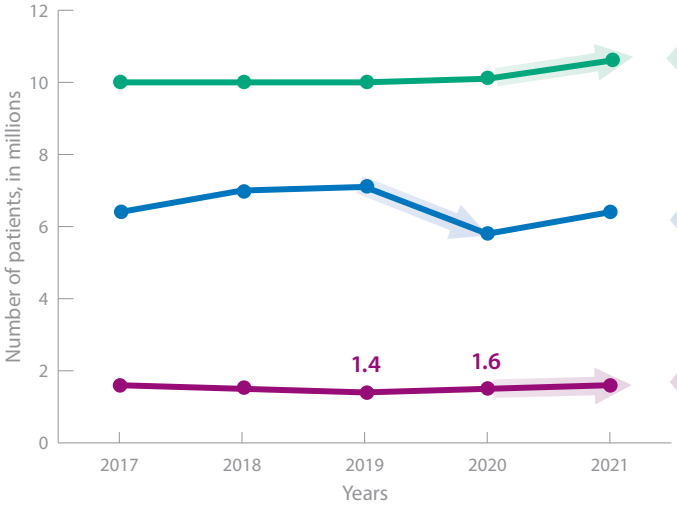
Tuberculosis Management: Returning to Pre-Pandemic Priorities

Patricio Escalante, MD, MSc, FCCP, and Paige K. Marty, MD

Although we are officially living in a "post-pandemic" world, some long-term global impacts of COVID-19 are still being addressed. We remain off track on global tuberculosis (TB) milestone targets due to halted progress over the last 3 years, with more people going undiagnosed and untreated for TB compared with pre-pandemic years.[1] Drug-resistant TB (DR-TB) and multidrug-resistant TB (MDR-TB) continue to represent a major burden, and global spending on TB efforts remains significantly lower than what is needed to reach goals set forth by World Health Organization (WHO).[1]

Despite these challenges, there are also some exciting updates. We now know that TB treatment success rates remained steady during the pandemic (86%), and strong efforts have been made to address DR-TB and MDR-TB via improved treatment options with highly effective, all-oral, shortened treatment regimens, as well as new and promising testing modalities.[1-3]

Global Burden of TB[1]



4.5% increase from 2020 to 2021

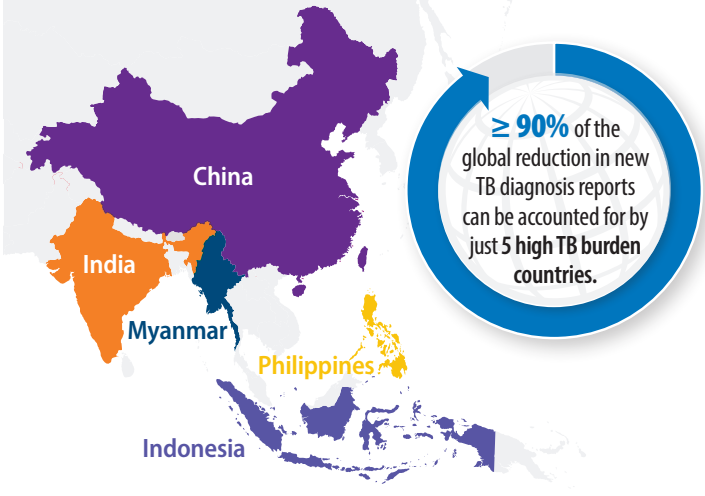
Estimated TB cases

While the number of diagnosed cases increased from 2020 to 2021, the decrease compared with 2019 indicates a probable growing number of undiagnosed and untreated cases (about 40% globally).

Newly diagnosed TB cases

Since the pandemic, the global declining trend in the number of deaths has been reversed, unfortunately.

Deaths from TB



Reasons for varying regional trends from 2019–2021 include:

- When each country was initially affected by the pandemic (including subsequent waves)
- Severity of COVID-19 impact
- Extent of local restrictions and adherence
- Local health care system capacity and resilience

Tackling Drug-Resistant TB Globally[1,3,4]

Each year, about **500,000 new cases** of DR-TB or MDR-TB emerge, yet **only 1 in 3** of these patients **receive treatment.**[1,3]

This represents a **17% decrease** compared with pre-pandemic treatment rates.[1]

The number of patients with DR-TB or MDR-TB has increased by **20% annually over the last decade.**[4]

Treatment of Drug-Resistant TB[2,3,5-7]

Regimen	Duration (months)	Evidence	Guidance
BPaLM/BPaL	6	**~90% cure rate** Patients are **2.2× more likely to experience favorable 24-month outcomes** vs standard of care.	In 2023, WHO recommended accelerated implementation of this regimen due to its high efficacy and lower costs.
All-oral, BDQ-based treatment for MDR-TB and XDR-TB	9	**Studies have shown success rates similar to 6-month BDQ regimens.**	Use in patients with MDR/DR-TB without previous second-line treatment, FQ resistance, or extensive pulmonary or severe extrapulmonary TB disease.
Individualized longer regimens	18+	**Varies based on drug grouping**	Although new, shorter regimens are preferred, longer regimens are still necessary for patients with extensive forms of DR-TB or who are ineligible for shorter regimens.

BDQ, bedaquiline; BPaLM, bedaquiline, pretomanid, linezolid, moxifloxacin; FQ, fluoroquinolone; XDR, extensively drug-resistant.

Notable Molecular Drug Resistance Testing Tools[8,9]

By laboratory network level

Level 1

Rapid diagnostics for TB and initial drug resistance detection

- Xpert MTB/RIF
- Xpert Ultra
- Xpert MTB/XDR
- Truenat MTB
- TB-LAMP
- AFB smear microscopy
- LF-LAM
- Low complexity automated NAAT
- Specimen referral

Level 2

May require more expertise or biosafety precautions

- FL-LPA
- SL-LPA
- Moderate complexity automated NAAT
- High complexity reverse hybridisation NAAT

Level 3

Requires highly advanced skills and infrastructure; focus on troubleshooting and surveillance

- Culture using liquid media
- Phenotypic DST
- Genome sequencing

AFB, acid-fast bacilli; DST, drug susceptibility testing; FL, first-line; LAMP, loop-mediated isothermal amplification; LF-LAM, lateral flow lipoarabinomannan assay; LPA, line-probe assay; NAAT, nucleic acid amplification test; SL, second-line; TB, tuberculosis.

Long COVID: Advocating for Patients and Implementing Effective Techniques

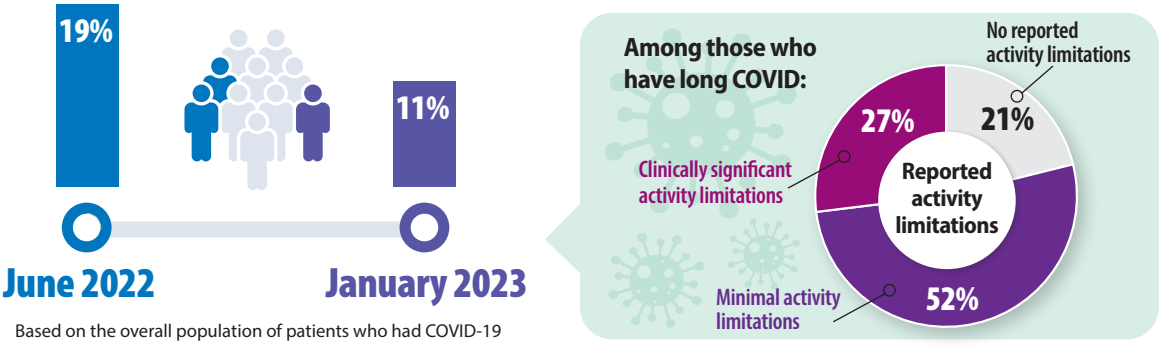
Kyle B. Enfield, MD, MS, FSHEA, FCCM

While definitions of postacute sequelae of SARS-CoV-2 (PASC), commonly referred to as long COVID, are heterogeneous, it is internationally recognized that some patients have symptoms that persist after recovery from their acute illness.[1,2] Most clinicians agree that this disease manifestation begins at around 60 to 90 days after original COVID-19 infection, based on the World Health Organization (WHO) definition.[1] Long COVID has similarities to postviral infections seen in SARS, MERS, Ebola, and West Nile virus.[1,3] Theories on its potential cause include ongoing inflammation and autoimmunity, among other theories.[1,2]

Currently, no FDA-approved treatments are available for long COVID and most patients are receiving variable care with off-label use of drugs.[1] Multiple clinical trials are in early stages. Certain nonpharmacological approaches have been effective for 2 common lingering long COVID symptoms: exercise intolerance and fatigue.[4] These techniques provide patients with tips to help manage decreased energy levels and provide breathing exercises for patients experiencing exercise intolerance.[4]

Long COVID is a challenge for the medical community, but progress is being made in pinpointing causes, effective treatments, and techniques to help people who continue to have symptoms after having had COVID-19.[1,4]

Long COVID Prevalence in the United States[5]



Proposed Mechanism and Causes of Long COVID[1,2,6,7]

Immune dysregulation:
chronic stimulation of T cells and B cells from viral reservoir, persistence of pro-inflammatory cells, altered cytokine production, altered immunometabolism pathways

Dysfunctional neurological signaling and neuroinflammation:
dysfunctional signaling in brainstem and vagus nerve, neuroinflammation and microglia activation, oxidative stress

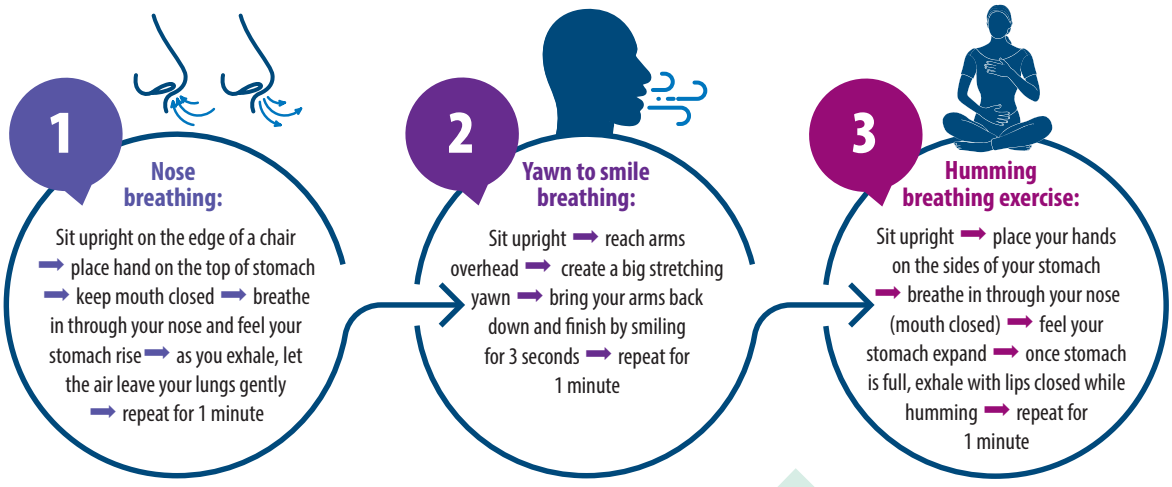
Persistent endothelial injury:
microvascular blood clotting with endothelial injury

Microbiome dysbiosis:
SARS-CoV-2 adversely affects the microbiome, causing reduced microbial diversity

Autoimmunity and immune priming:
molecular mimicry, autoimmune antibodies, microbial breakdown of tolerance

Nonpharmacological Approaches for Long COVID Symptoms[4]

Breathing Techniques for Exercise Intolerance and Fatigue



The UK's National Institute for Health and Care Excellence (NICE) recommends against a graded exercise program for people recovering from COVID-19. Graded exercise programs are structured exercise programs that gradually increase the amount of physical activity.

Tips for Dealing with Fatigue

Clinical Trials for Long COVID Treatments[1,8,9]

Treatments	Class of Drug	Clinical Trial Phase
Paxlovid	Protease inhibitor	Phase 2
Sodium pyruvate nasal spray	Pyruvic acid	Phase 2/3
Nirmatrelvir/ritonavir	Protease inhibitor	Phase 2
Prednisolone	Corticosteroids	N/A
Hyperbaric oxygen chamber	N/A	Phase 2
Naltrexone and NAD+	Opiate antagonist, and involved in glycolysis	Phase 2

The RECOVER Initiative is also working to collect data on long COVID to discover the long-term effects and improve current treatment options.[9] Learn more at www.recovercovid.org.

Based on a ClinicalTrials.gov search of treatment: recruiting, active, not recruiting, completed, enrolling by invitation studies; Long+COVID. Results as of August 2, 2023.

N/A, not available; NAD+, nicotinamide adenine dinucleotide.

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Long-Awaited RSV Vaccines Now Available for Older Adults and Pediatric Patients

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Decreasing Pulmonary Embolism-Related Mortality

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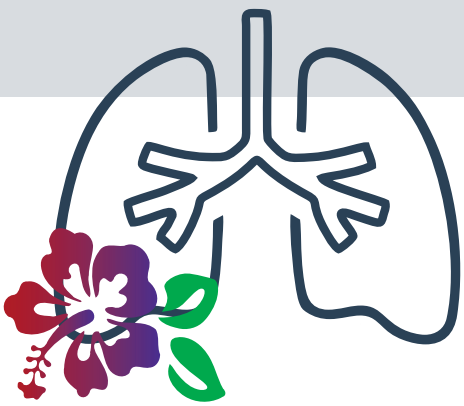

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