

A SUPPLEMENT TO CHEST PHYSICIAN

# PULMONOLOGY

## DATA TRENDS 2024



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### Common abbreviations used throughout this issue:

CDC, Centers for Disease Control and Prevention  
COPD, chronic obstructive pulmonary disease  
FDA, US Food and Drug Administration  
FEV<sub>1</sub>, forced expiratory volume in one second  
FVC, forced vital capacity  
ICU, intensive care unit  
ILD, interstitial lung disease  
IPF, idiopathic pulmonary fibrosis  
MEP, maximum expiratory pressure  
MIP, maximum inspiratory pressure  
OSA, obstructive sleep apnea  
RSV, respiratory syncytial virus  
WHO, World Health Organization



**AMM** Association of Medical Media

# PULMONOLOGY

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# Artificial Intelligence in Sleep Apnea

Ritwick Agrawal, MD, MS, FCCP

OSA disrupts the lives of nearly 1 billion adults globally due to recurrent episodes of upper airway obstruction during sleep.<sup>1</sup> This condition can lead to severe cardiovascular issues, cognitive impairments, and decreased quality of life.<sup>2</sup> Despite the prevalence of OSA, underdiagnosis and undertreatment are significant challenges, exacerbated by the limitations of the current gold-standard diagnostic method, overnight polysomnography. This method is resource-intensive, expensive, and often inaccessible due to high demand in sleep laboratories.<sup>3,4</sup>

Artificial intelligence (AI) has the potential to revolutionize the field of sleep medicine, particularly in the management and diagnosis of sleep disorders such as OSA. AI applications in sleep medicine extend from automating sleep stage scoring with neural networks to enhancing the understanding of sleep disorder pathophysiology through machine learning (ML) models.<sup>5,6</sup> By analyzing patterns in large-scale data, AI has helped identify various OSA endotypes, as well as predict continuous positive airway pressure (CPAP) adherence patterns and surgical success rates, which can influence clinical decision-making.<sup>5,7</sup> Paired with the portability and unobtrusiveness of most AI-based devices, these technologies could offer both effective and convenient treatment alternatives for patients.

However, the integration of AI into clinical practice comes with challenges, including the need for standardized validation of AI algorithms, the creation of representative and comprehensive training datasets, and the security and privacy of health data. Furthermore, addressing disparities in AI application and ensuring equitable health outcomes are crucial steps as this technology becomes more ubiquitous in sleep medicine.<sup>5,6</sup>

While AI presents promising advancements in understanding and managing OSA, careful consideration and implementation are required to realize its full potential in clinical settings, ensuring that all patients benefit from this technological evolution in health care.

## AI in OSA: Benefits and Challenges<sup>5-7</sup>



### Potential Benefits



AI can leverage accessible settings to **measure and analyze** physiological data.



AI can **enhance the ability to identify** phenotypes, biomarkers, disease mechanisms, and CPAP adherence barriers.



AI can **predict treatment success** and guide decision-making.



### Remaining Challenges



Data sets **lack diversity** and are **not generalizable**.



The AI landscape is evolving rapidly. It is **difficult to standardize practices** and **create policies** in this environment.



Gathering data outside of sleep labs raises **privacy and regulation concerns**.



At this stage, many algorithms and devices require **further testing and validation**.

## AI Devices for OSA Monitoring<sup>3,4,7-9</sup>



Pressure-based mattress pads and “smart” bedding can detect respiratory efforts and apnea events.

Some smart pillows and mattresses can adjust positioning automatically to alleviate apneic episodes.

Evidence for detection: **Strong**

Evidence for management: **Further investigation needed**



Smartwatches and body sensors record and analyze electrocardiograms, thoracic movements, positional signals, and snoring. Data can aid in diagnosis and inform treatment.

Current evidence: **Strong**



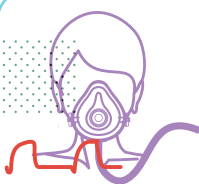
Smartphones easily integrate with wearables and can detect sleep-disordered breathing and classify respiratory movements.

Current evidence: **Moderate to strong**



Under-the-nose pressure sensors and nasal cannulas measure airflow and analyze frequency and duration of apnea events.

Current evidence: **Moderate to strong**



Using data gathered via CPAP, ML algorithms have identified:

- **Biomarkers for OSA severity**
- **Predictors of CPAP adherence**, eg, presence of headaches, psychological symptoms, and arterial hypertension, as well as quality-of-life scores
- **Targeted approaches** to improve patient comfort and compliance

Current evidence: **Strong**



Based on a deep neural network model that predicted adherence at 3-, 6-, and 12-month endpoints



Data gathered through these technologies can provide remote monitoring of patients, enabling clinicians to adjust treatments and provide support without the need for in-person visits.

# RSV Updates: Prophylaxis Approval and Hospitalization for Severe RSV

Riddhi Upadhyay, MD

In 2023, significant progress was made in preventing RSV lower respiratory tract disease (LRTD) with the FDA approval of 3 vaccines and a monoclonal antibody. Published efficacy rates and ongoing trials, like the MONEt (RSV IMMunization Study for AdULts with a Higher Risk of Severe Illness) trial for high-risk 18- to 59-year-olds, continue to advance RSV prophylaxis.<sup>1</sup>

Early 2024 results showed that the RSVpreF vaccine (Abrysvo) effectively protected against RSV A and B, with a 77.8% effectiveness in preventing RSV LRTD in adults aged  $\geq 60$  years in its second season.<sup>2</sup> The CDC reported nirsevimab was 90% effective in preventing RSV hospitalization in infants during their first RSV season.<sup>3,4</sup>

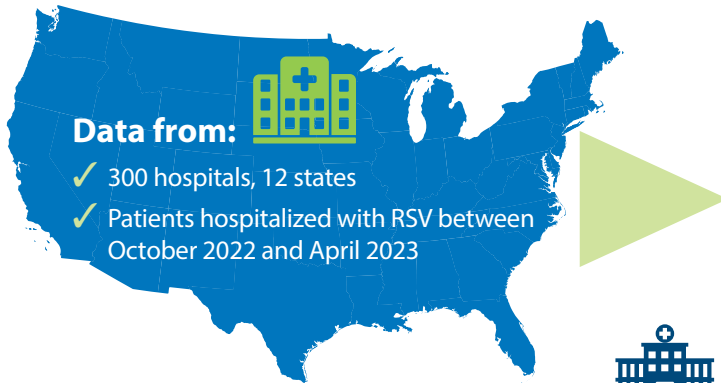
Further, results from a study published in June 2023 identified obesity, COPD, and congestive heart failure (CHF) as common comorbidities in patients who were  $\geq 60$  years and hospitalized with RSV. The study also found that those aged  $\geq 75$  years experienced worse outcomes.<sup>5</sup> This data aids in performing risk assessments for patients with RSV by age and comorbidities.

Ongoing research for preventing RSV in different populations with various risks and comorbidities is imperative. Additional FDA approvals will help protect more individuals from this potentially life-threatening disease.

## RSV Prophylactics: 2023 – 2024<sup>1,2,4,6-10</sup>

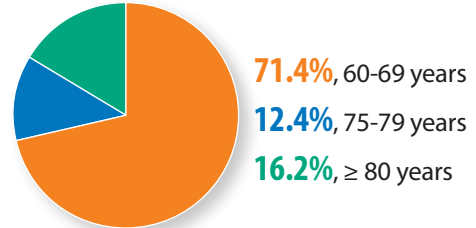
| Therapy                                                                                                                                                                                                        | FDA approval date and indication                                                                                                                                                                 | Efficacy/updates since 2023 approval                                                                                                                                                                                                                                                     | Current investigations                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <br><b>RSVpreF vaccine (Abrysvo)</b><br> | <br><b>May 2023<sup>6</sup></b><br>Preventing LRTD from RSV in adults aged $\geq 60$ years                    | <br><b>March 2024<sup>2</sup></b><br>Efficacy of 77.8% in preventing RSV A & B, LRTD in those aged $\geq 60$ years with 3+ symptoms (per post-2nd-season review)                                      | <br><b>April 2024<sup>1</sup></b><br>MONEt Trial for those aged 18–59 years with increased RSV risk. Met co-primary immunogenicity endpoints and primary safety endpoint<br><br><b>March 2024<sup>8</sup></b><br>Ages 18–49 years with higher risk for RSV |
| <br><b>RSVpreF3 (Arexvy)</b>                                                                                                | <br><b>May 2023<sup>9</sup></b><br>Preventing LRTD from RSV in adults aged $\geq 60$ years                    | <br><b>April 2024<sup>9,10</sup></b><br>NCT05590403, phase 3: Preliminary results show primary endpoints met, with noninferior immune responses observed in those aged 50–59 years vs $\geq 60$ years |                                                                                                                                                                                                                                                            |
| <br><b>Nirsevimab (Beyfortus)</b>                                                                                           | <br><b>July 2023<sup>4</sup></b><br>Preventing LRTD in infants aged $\leq 8$ months; 8–19 months if high risk | <br><b>February 2024<sup>4</sup></b><br>Efficacy of 90% in infants' first season                                                                                                                      | <br>N/A                                                                                                                                                                                                                                                    |

## Severe RSV Requiring Hospitalization<sup>5</sup>



### Cohort:

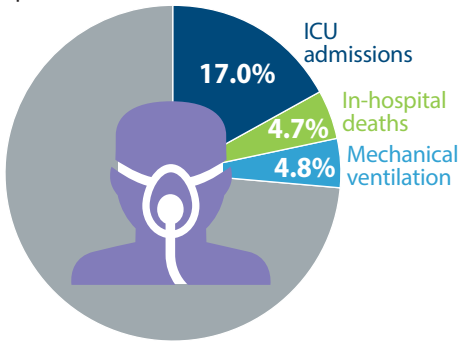
Random sample, n = 1,634, aged  $\geq 60$  years



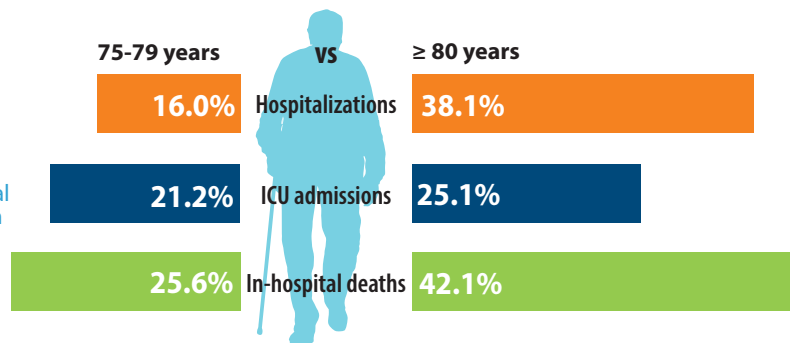
**17.2%**  
resided in long-term care facilities

### Severe Outcomes in All Age Groups

Experienced by 18.5% of all patients; some patients experienced more than one outcome



### Severe Outcomes in Older Age Groups



### Prevalence of Underlying Conditions



**Obesity**  
37.8%



**COPD**  
33.7%



**CHF**  
33.2%



**Diabetes**  
32.6%



**Immunocompromised**  
18.6%

### Underlying Conditions in Patients With Severe Outcomes



<sup>a</sup>Other diseases included ILD, pulmonary fibrosis, restrictive lung disease, sarcoidosis, asbestosis, and chronic respiratory failure, including oxygen dependence



**Shyam Subramanian, MD, FCCP**

Biologics also show enduring efficacy. Of the patients who continued dupilumab for 3 years or benralizumab for 5 years, 89% and 87% experienced zero exacerbations, respectively.<sup>7,8</sup> Biologics have reduced the need for inhaled corticosteroid maintenance therapy, with up to 91% of patients having zero exacerbations after stopping inhaled corticosteroids while on a biologic.<sup>9</sup> This is paving the way for asthma remission. In fact, a recent study found that up to 29% of patients met criteria for remission while on biologic therapy.<sup>10,11</sup>

Biologics represent a breakthrough for severe asthma. Despite their promise, only 25% of eligible patients receive biologics, highlighting the need for increased clinician education.<sup>13</sup> Moreover, disparities in access to these agents remains a concern due to the elevated cost of treatment.<sup>14</sup>

## Type 2 Inflammatory Pathway





## Approved Biologics for Asthma<sup>2,4,7,12,16-20</sup>



### Omalizumab | Anti-IgE

#### Indication

Moderate to severe persistent asthma with positive allergy test, incomplete control with inhaled corticosteroid, IgE level 30-700 IU/mL

Reduction in exacerbations

25%

Age

≥ 6 years

#### Safety profile

Anaphylaxis, risk of cardiovascular and cerebrovascular events, eosinophilic conditions

FEV<sub>1</sub> improvement

N/A

#### Dosing

Based on IgE levels 150-375 mg subcutaneously every 2 or 4 weeks



### Reslizumab | Anti-IL-5

#### Indication

Severe eosinophilic asthma, AEC ≥ 400 cells/μL

Reduction in exacerbations

50%-59%

Age

≥ 18 years

#### Safety profile

Anaphylaxis

FEV<sub>1</sub> improvement

93-160 mL

#### Dosing

3 mg/kg IV every 4 weeks



### Dupilumab | Anti-IL-4/13 receptor

#### Indication

Moderate to severe eosinophilic asthma, nitric oxide ≥ 25 ppb, steroid-dependent asthma

Reduction in exacerbations

46%-70%

Age

≥ 6 years

#### Safety profile

Hypersensitivity reactions, injection-site reactions, hypereosinophilia, keratitis, conjunctivitis, risk of EGPA\*

FEV<sub>1</sub> improvement

130-140 mL

#### Dosing

400-600 mg initially, then 200-300 mg subcutaneously every 2 weeks



### Benralizumab | IL-5α receptor antagonist

#### Indication

Severe eosinophilic asthma, AEC ≥ 300 cells/μL

Reduction in exacerbations

28%-51%

Age

≥ 6 years

#### Safety profile

Hypersensitivity reactions

FEV<sub>1</sub> improvement

116-159 mL

#### Dosing

30 mg subcutaneously every 4 weeks for first 3 doses, then every 8 weeks



### Tezepelumab | Anti-TSLP

#### Indication

Uncontrolled severe asthma, biomarker status not important

Reduction in exacerbations

56%-71%

Age

≥ 12 years

#### Safety profile

Hypersensitivity reactions

FEV<sub>1</sub> improvement

130 mL

#### Dosing

210 mg subcutaneously every 4 weeks



### Mepolizumab | Anti-IL-5

#### Indication

Severe eosinophilic asthma, AEC ≥ 150-300 cells/μL

Reduction in exacerbations

53%

Age

≥ 6 years

#### Safety profile

Hypersensitivity reactions, injection-site reactions, herpes zoster

FEV<sub>1</sub> improvement

98 mL

#### Dosing

100 mg subcutaneously every 4 weeks

\*EGPA, eosinophilic granulomatosis with polyangiitis

### Emerging Biologics

**Itepekimab, Etokimab, Melrilimab:** Currently in clinical trials, targeting IL-33, showing promise for better asthma control



# Updates in COPD Guidelines and Treatment

Dharani K. Narendra, MD, FCCP

COPD is a common and preventable condition characterized by persistent respiratory symptoms and airflow obstruction. Its prevalence ranges from 7.4% to 12.6% among adults aged 40 years and older, with higher rates observed in non-Hispanic White individuals, women, and those aged 65 years and older.<sup>1,2</sup> Despite declining mortality trends, COPD remains the third leading cause of death worldwide and sixth in the United States.<sup>2,3</sup>

Current pharmacological treatments include bronchodilators, inhaled corticosteroids, combination inhalers, azithromycin, and phosphodiesterase-4 (PDE4) inhibitors, the latter two for exacerbation prevention. Each treatment has limitations, such as side effects, disease progression, and pneumonia risks.<sup>4</sup> Ensifentrine, a breakthrough COPD treatment, was recently approved by the FDA and targets both PDE3 and PDE4 enzymes, offering significant benefits in managing moderate to severe COPD.<sup>5</sup> Biologics are also emerging as promising therapies due to their targeted approach against specific inflammatory pathways.<sup>6</sup>

More nonpharmacological approaches are discussed in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, which is updated annually to align with our current understanding of COPD and the available literature. In 2023, GOLD significantly revised its COPD assessment tool, from ABCD to ABE, to simplify classification and focus on effectively treating patients with frequent exacerbations. This new tool helps clinicians identify patients who experience exacerbations and tailor treatments specifically for their needs.<sup>7</sup> The 2024 GOLD report includes updated screening, vaccination, and spirometry guidelines, among many other changes that will be discussed below.<sup>8</sup> These evolving recommendations, combined with the potential introduction of more targeted therapies, offer hope for improved COPD prevention and management in the future.

## COPD Biologic Pipeline<sup>9-20</sup>

| Biologic                             | Phase III Evidence                                                                                                                                                                                                                                                             | Upcoming Trials: Target Completion Date   |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Dupilumab <sup>a</sup> (IL-4, IL-13) | <b>BOREAS and NOTUS:</b> 30%-34% reduction in annualized moderate or severe acute COPD exacerbations; rapidly and significantly improved lung function; improvements sustained at 52 weeks <sup>9</sup>                                                                        | N/A                                       |
| Mepolizumab (IL-5)                   | <b>METREX and METREO:</b> 18%-20% reduction in annualized rate of moderate or severe exacerbations placebo in patients with highest baseline blood eosinophils; improvement was significant in METREX but not in METREO <sup>10</sup>                                          | <b>MATINEE:</b> August 2024 <sup>11</sup> |
| Benralizumab (IL-5)                  | <b>GALATHEA and TERRANOVA:</b> Original trial results appeared nonsignificant; post hoc analysis showed a 30-day 60% reduction in moderate or severe exacerbations in a small subset of patients with high eosinophil counts and frequent previous exacerbations <sup>12</sup> | <b>RESOLUTE:</b> June 2025 <sup>13</sup>  |

<sup>a</sup>FDA approval of Dupilumab expected October 2024

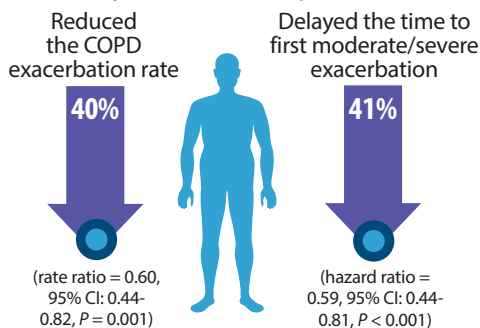
**Other biologics with ongoing COPD trials:**<sup>14-20</sup>  
**tozorakimab** (TITANIA, OBERON, PROSPERO, MIRANDA)  
**itepekimab** (AERIFY-1 and -2)  
**astegolimab** (ARNASA and ALIENTO)



## Now Approved for COPD: Ensifentrine<sup>5,21</sup>

In both the **ENHANCE 1 and ENHANCE 2 trials**, treatment with nebulized ensifentrine 3 mg significantly improved lung function (FEV<sub>1</sub>, AUC 0-12h) at week 12 compared with placebo ( $P < 0.001$ ).

**In a pooled analysis of 1,549 subjects, ensifentrine...**



**Ensifentrine was well tolerated**, with similar rates of adverse events vs placebo.



Back pain | **1.8% vs 1.0%**



High blood pressure | **1.7% vs 0.9%**



Urinary tract infections | **1.3% vs 1.0%**

## 2024 GOLD Report Highlights<sup>8,22</sup>

### Prebronchodilator spirometry



Starting with prebronchodilator spirometry for symptomatic patients is now recommended. Postbronchodilator testing is unnecessary unless initial results are abnormal or suspicious.

### Preserved ratio impaired spirometry (PRISm)



✓ With a predicted postbronchodilator FEV<sub>1</sub> of  $< 80\%$ , over time, patients may shift from normal FEV<sub>1</sub>/FVC ( $> 0.7$ ) to normal or obstructed spirometry.



✓ Patients with PRISm are at a high risk of cardiovascular disease.  
✓ Further research is needed to better understand pathogenesis and management options for PRISm.

### Additional smoking cessation guidance



✓ Tailored counseling optimizes smoking cessation outcomes by considering individual patient factors.  
✓ Many patients with COPD face issues with self-esteem, depression, and nicotine dependence.  
✓ Assess nicotine dependence to tailor effective and appropriate clinical interventions.

### New section: Hyperinflation



✓ Hyperinflation contributes to dyspnea, decreased exercise capacity, hospitalizations, respiratory failure, and mortality.



✓ Lung volume measurements can be assessed via body plethysmography or gas dilution techniques.  
✓ Treatment options include bronchodilators, oxygen, heliox, rehab, pursed lip breathing, or muscle training.

### New screening recommendations



#### Targeted populations

Do not screen asymptomatic adults who are not at an increased risk for COPD and who do not have radiologically identified structural abnormalities.



#### Lung cancer imaging

Spirometry and low-dose CT scans are recommended for lung cancer screening in individuals aged 50-80 with  $\geq 20$  pack-year smoking history.

#### Spirometry during lung cancer screening has found:

Airflow obstruction in **34%-57% of patients**

Emphysema in **68%-73% of patients**

Undiagnosed COPD in **67% of patients**



### RSV vaccination

The recently approved RSV vaccine is now recommended for adults at the highest risk for severe RSV illness, including individuals with chronic lung disease like COPD.

# Targeted Therapies and Surgical Resection for Lung Cancer: Evolving Treatment Options

Saadia A. Faiz, MD, FCCP

Lung cancer, the leading cause of cancer-related deaths in the United States, is expected to have 234,580 new cases and 125,070 deaths in 2024.<sup>1</sup> Targeted therapies directed toward *ROS1*, *ALK*, and *RET*\* have demonstrated clinically significant outcomes for patients with non-small cell lung cancer (NSCLC).<sup>2-5</sup> Further emerging novel drug formulations, including macrophage immune checkpoint inhibitors, inhaled cytokines, and Notch ligands, show promise with targeted delivery and fewer adverse effects with in-vitro and murine models.<sup>6,7</sup>

Lobectomy is currently the gold standard for NSCLC treatment. However, sublobar resection (segmentectomy or wedge) are viable alternatives for early-stage NSCLCs, as shown in the CALGB 140503 and JCOG0802/WJOG4607L112 trials.<sup>8-10</sup> As lung cancer screening with computed tomography increases, detection of early-stage NSCLC, primarily adenocarcinoma, has also grown. Many of these lesions are peripheral and ground-glass opacity-dominant tumors.<sup>9</sup> The CALGB 140503 and JCOG0802/JCOG1211 trials suggest sublobar resection is associated with an even lower risk than lobectomy, thus preserving lung function.<sup>8-10</sup> The JCOG0802/JCOG1211 trials specifically demonstrate segmentectomy does not compromise therapeutic efficacy for tumors  $\leq 3$  cm.<sup>9,10</sup>

Targeted therapies are showing potential for treating NSCLC, and sublobar resection is proving to be a viable alternative to lobectomy for certain NSCLC cases. These developments mark significant strides in lung cancer treatments.

## Targeted and Novel Therapies<sup>2-7,11</sup>

### Targeted Therapies Based on Clinical Trials

#### ***ROS1* target<sup>2</sup>**



**TRIDENT\*-1 trial:** In advanced lung cancer, repotrectinib can shrink tumors that have *ROS1*+ fusions. FDA-approved in 2023 as an initial or second-line treatment for *ROS1*+ NSCLC.

#### ***RET* fusion + NSCLC<sup>4,5</sup>**



**LIBRETTO\*-431 trial:** First-line selpercatinib vs platinum-based chemotherapy with or without pembrolizumab led to significantly longer PFS\* among patients with advanced *RET* fusion+ NSCLC.

#### ***ALK*-positive NSCLC<sup>3</sup>**



**ALINA\* trial:** Adjuvant alectinib significantly improved DFS\* compared with platinum-based chemotherapy among patients with resected *ALK*+ NSCLC (stage IB, II, or IIIA).

### Novel Therapies in the Pipeline

#### **Inhalable therapy<sup>7</sup>**



Using nanobubbles/exosomes through inhalation treatment can directly deliver anti-lung cancer cargo, IL\*-12 mRNA, to the lungs. (This is still in murine models.)

#### **Novel drug screen<sup>6</sup>**



This is an unbiased screening platform that identifies existing cancer therapies capable of rendering lung cancer cells more vulnerable to attack by macrophages (ie, priming cells).

#### **NSCLC target<sup>11</sup>**

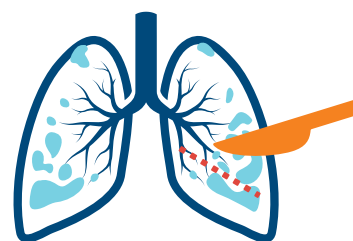


The Jagged2 molecule plays a primary role in fueling the aggressiveness and immune-evasion capacity of lung cancer.

\*ALINA, Adjuvant Alectinib in *ALK*+ Non-small Cell Lung Cancer; *ALK*+, anaplastic lymphoma kinase; DFS, disease-free survival; IL, interleukin; LIBRETTO, Lilly's RET Inhibitor Efficacy and Safety Trials in Tumors With RET Alterations; mRNA, messenger ribonucleic acid; PFS, progression-free survival; RET, rearranged during transfection; TRIDENT, Treatment with Retevmo in Non-Small Cell Lung Cancer with RET Alterations

# Sublobar Resection: Challenging the NSCLC Standard<sup>8-10</sup>

| Parameter                | CALGB 140503 <sup>8</sup>                                                                                                                                                                           | JCOG0802/JCOG1211 <sup>9,10</sup>                                                                                                                              |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Trial</b>             | Lobar vs sublobar resection for peripheral stage IA NSCLC (T1aN0, tumor size < 2 cm)                                                                                                                | Segmentectomy with hilar, interlobar, and intrapulmonary lymph node dissection for tumors up to 3 cm, including ground-glass opacity (GGO) and predominant GGO |
| <b>Design</b>            | Phase 3 multicenter, international, randomized, noninferiority trial (United States, Canada, Australia)                                                                                             | Multicenter, single-arm, confirmatory phase 3 trial (Japan)                                                                                                    |
| <b>Primary end point</b> | Primary: disease-free survival                                                                                                                                                                      | Primary: 5-year relapse-free survival                                                                                                                          |
| <b>Other end points</b>  | Locoregional and systemic recurrence<br>Pulmonary function                                                                                                                                          | N/A                                                                                                                                                            |
| <b>Total</b>             | N = 697<br>Lobar (n = 357) vs sublobar (n = 340)                                                                                                                                                    | N = 396, all segmentectomy                                                                                                                                     |
| <b>Conclusion</b>        | Median follow-up of 7 years; sublobar resection was noninferior to lobar resection for disease-free survival<br>Overall survival after sublobar resection was similar to that after lobar resection | Median follow-up of 5.4 years; 5-year relapse-free survival was 98% (95% CI, 95.9-99.1)                                                                        |



These trials have significantly contributed to the era of precision lung cancer surgery.

This treatment modality could ensure sufficient surgical margins and preserve more lung function, which is preferential in patients with comorbidities contraindicating lobectomy.



**Segmentectomy may be a viable alternative to lobectomy** for small-sized peripheral NSCLC, but further evaluations are necessary to clarify the clinical significance of segmentectomy for pure-solid NSCLC.

# Closing the GAP in Idiopathic Pulmonary Fibrosis

Humayun Anjum, MD, FCCP

IPF, the most prevalent ILD and one of unknown etiology, affects up to 207,000 Americans and up to 58,000 new patients each year.<sup>1</sup> Prognosis is poor; median survival estimates have ranged between 2 and 5 years for the last decade.<sup>2,3</sup> Although IPF is not curable, initiating a treatment plan as early as possible is critical to managing symptoms and slowing disease progression.<sup>4</sup>

Introduced in 2012, the GAP (gender, age, physiology) prognostic model offers clinicians a framework for assessing mortality risk, with the goal of improving IPF outcomes.<sup>5</sup> The GAP model uses a standardized approach to staging patients while also aiding clinicians in tailoring each patient's treatment approach.<sup>5-8</sup> The "physiology" component evaluates forced vital capacity (FVC) to assess lung function and diffusing capacity of the lungs for carbon monoxide (DLCO) to measure gas exchange efficiency.

While the integration of FVC and DLCO into the GAP model provided a more comprehensive assessment at the time of its introduction, our understanding of IPF has evolved over the last decade. There has been a recent surge in proposed modifications to the original GAP model. Studies have examined the integration of additional criteria, such as comorbidities, body mass index (BMI), exercise capacity, and other factors, into the GAP model to help to improve predictive precision.<sup>9-15</sup> The incorporation of additional parameters and biological markers offers promising prospects for more accurate prognostications and personalized treatment strategies. Although these proposed enhancements to the GAP model require further validation, their potential to refine treatment personalization makes them worthy of careful consideration.

## GAP Scoring: Initial Impact on IPF<sup>5-8</sup>

### Improves Prognostic Accuracy

Assessment of gender, age, FVC, and DLCO provides an **accurate estimation of disease progression and mortality**, helping clinicians stratify patients into appropriate risk categories.



### Standardizes Clinician Assessment

Following the GAP framework helps foster **consistency in the evaluation, diagnosis, and management** of patients, both at the day-to-day practice level and within IPF clinical trials.



### Aids in Treatment Planning and Counseling

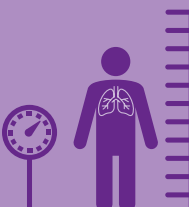
- Patients classified as **low risk may be candidates for less aggressive treatment** such as antifibrotic therapy, oxygen therapy, pulmonary rehabilitation, and symptom management, while **higher risk patients may need lung transplantation**.

- Clinicians can provide patients with **more details** about their mortality risk and potential disease course to **help them make informed decisions**.





## Evolving GAP to Improve Outcomes<sup>9-15</sup>

| Variation                                                                                                                  | Studies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <br><b>GAP + exercise capacity</b>        | Lee et al (2023) <sup>9</sup> proposed the <b>GAP6</b> model, which adds points for <b>nadir SpO<sub>2</sub></b> during the 6MWT.*                                                                                                                                                                                                                                                                                                                                                                           | <p>The addition of nadir SpO<sub>2</sub> resulted in a statistically significant reclassification of patients diagnosed with stage II and III IPF, compared with their original standard GAP staging.</p> <p><b>Predictive accuracy (IPF-related mortality):</b><br/>           GAP: <b>67.4%</b><br/>           GAP6: <b>69.1%</b><br/>           Based on C-index values</p>                                                                                                                                                                                                       |
|                                                                                                                            | Chandel et al (2023) <sup>10,11</sup> proposed the <b>DO-GAP</b> model, which adds points for distance ambulated during the 6MWT and <b>exertional hypoxia</b> .                                                                                                                                                                                                                                                                                                                                             | <p>In the original DO-GAP analysis, GAP consistently overestimated mortality, while the additional exercise parameters were associated with mortality.</p> <p><b>Predictive accuracy (IPF-related mortality):</b><br/>           GAP: <b>67.6%</b><br/>           DO-GAP: <b>75.6%</b></p> <p>An external validation analysis also demonstrated improvement in prediction of transplant-free survival.</p> <p><b>Predictive accuracy (transplant-free survival):</b><br/>           GAP: <b>67.0%</b><br/>           DO-GAP: <b>73.0%</b><br/>           Based on C-index values</p> |
| <br><b>GAP + BMI</b>                     | Suzuki et al (2021) <sup>12</sup> evaluated GAP staging and BMI in patients who had initiated <b>treatment with antifibrotic therapy</b> .                                                                                                                                                                                                                                                                                                                                                                   | <p>Lower BMI (<math>\leq 24</math>) demonstrated a strong prognostic value independent of GAP staging. Combining GAP with BMI at treatment initiation <b>improved the discriminative performance to predict 3-year survival by 21%</b> compared with the original GAP model (although this difference was not statistically significant).</p>                                                                                                                                                                                                                                        |
|                                                                                                                            | Lacedonia et al (2023) <sup>13</sup> <b>used machine learning</b> to validate the addition of BMI as a parameter in the GAP model.                                                                                                                                                                                                                                                                                                                                                                           | <p>While the original GAP model successfully predicted mortality, the addition of BMI further improved predictive accuracy.</p> <p><b>Classification accuracy:</b><br/>           GAP: <b>71.0%</b><br/>           GAP + BMI: <b>70.0%-72.0%</b></p>                                                                                                                                                                                                                                                                                                                                 |
| <br><b>GAP + comorbidities</b>          | Fujii et al (2023) <sup>14</sup> proposed <b>ILD-GAPC</b> —which <b>assigns points for Charlson Comorbidity Index score</b> to the GAP model—to account for presence and severity of comorbidities when evaluating patient prognosis.                                                                                                                                                                                                                                                                        | <p>Comorbidity scores were the most influential factor in prognosing patients with ILD. Based on these results, the authors speculated that individual comorbidities could directly affect the progression of ILD.</p> <p><b>Predictive accuracy (3-year ILD-related events):</b><br/>           GAP: <b>72.1%</b><br/>           ILD-GAPC: <b>75.8%</b><br/>           Based on area under curve</p>                                                                                                                                                                                |
| <br><b>GAP + longitudinal variables</b> | <p>Ley et al (2015)<sup>15</sup> examined several novel predictor variables along with the original GAP model. These variables included:</p> <ul style="list-style-type: none"> <li>• Baseline 6MWD* and dyspnea score</li> <li>• Lowest oxygen saturation level during 6MWT</li> <li>• Use of long-term oxygen therapy</li> <li>• Respiratory hospitalization in the last 24 weeks</li> <li>• 24-week relative change in FVC or DLCO</li> <li>• 24-week absolute change in 6MWD or dyspnea score</li> </ul> | <p>The longitudinal GAP model improved predictive accuracy compared with the original model, with a reclassification improvement of 8.5%.</p> <p><b>Predictive accuracy:</b><br/>           GAP: <b>75.7%</b><br/>           Longitudinal GAP: <b>78.5%</b><br/>           Based on C-index values</p>                                                                                                                                                                                                                                                                               |

\*6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; SpO<sub>2</sub>, saturation of peripheral oxygen



# Severe Community-Acquired Pneumonia: Diagnostic Criteria, Treatment, and COVID-19

Sujith V. Cherian, MD, FCCP

Pneumonia, a common respiratory infection, can be categorized as community-acquired or hospital-acquired pneumonia, which includes ventilator-associated pneumonia.<sup>1</sup> Severe community-acquired pneumonia (CAP) poses unique challenges for clinicians, with high mortality and risk for long-term complications.<sup>1,2</sup> Severe CAP is defined by the American Thoracic Society (ATS) guidelines as having 1 major criterion of septic shock needing vasopressors or the requirement of mechanical ventilation, or meeting 3 or more minor criteria based on respiration, hemodynamics, and other clinical characteristics.<sup>3</sup> Another well-known tool for defining severe CAP is SMART-COP, which includes measures of systolic blood pressure, multilobar infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygen, and pH for determining severity.<sup>4</sup>

Mortality for severe CAP can be as high as 23%, with 24% of patients requiring invasive mechanical ventilation and 20% requiring noninvasive ventilation.<sup>2,5</sup> Advances in treatment, along with antibiotics as the current standard of care, are helping to decrease mortality. Corticosteroids, such as hydrocortisone, have also been shown to decrease mortality in bacterial severe CAP when combined with antibiotics.<sup>6</sup>

The COVID-19 pandemic complicated the field of severe pneumonia.<sup>7</sup> COVID-19-related severe pneumonia has been linked to long-term lung abnormalities, such as decreased lung function, and symptoms such as dyspnea, with other implications still being investigated.<sup>7</sup> Severe pneumonia poses a burden to the health care community, but new treatments are helping to combat high mortality and prevent worsening long-term outcomes. Research is needed into other corticosteroids that could help lessen this burden.

## CAP Epidemiology and Hospitalization<sup>5,8-10</sup>

**Worldwide incidence  
of CAP**  
per 1,000 person-years



**US hospitalizations  
per year**

**1.5 million**



**ICU admission  
1.2%-10.0%**

**Of those hospitalized in the US...<sup>a</sup>**



**5.0%-6.5%**

Died during  
hospitalization



**13.0%**

Died within 30 days  
posthospitalization



**30.6%**

Died within 1 year  
posthospitalization

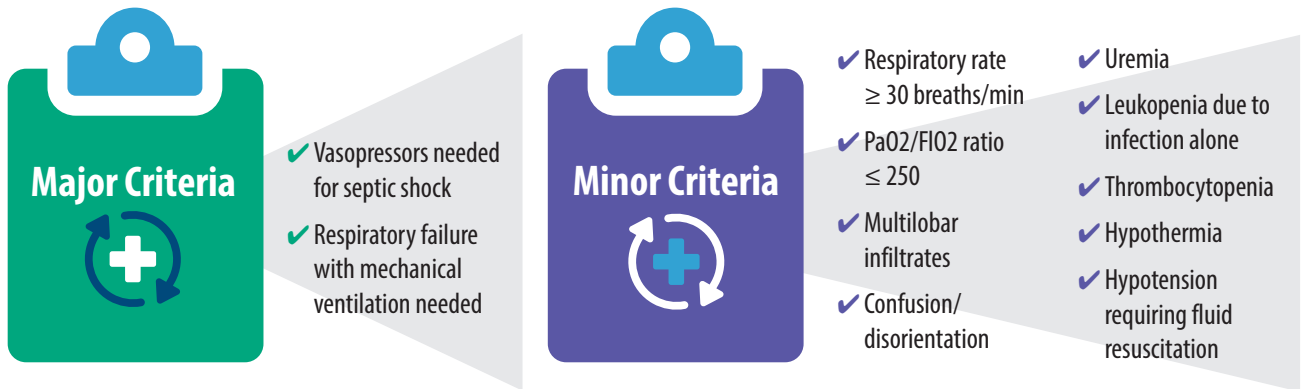


**90% of deaths related to severe pneumonia  
are in patients > 70 years of age.**

<sup>a</sup>Data are from a 2-year population-based study of patients hospitalized for CAP.<sup>8</sup>

## ATS Definition for Severe CAP<sup>3</sup>

Patients must meet **1 major or ≥ 3 minor criteria**:

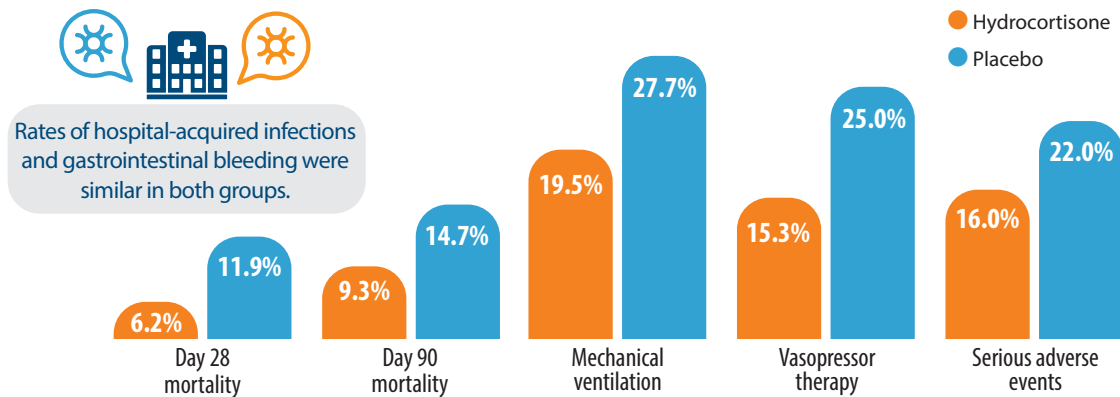


### Value for predicting ICU admission

1 major or 3 minor criteria: **84% sensitivity, 78% specificity**

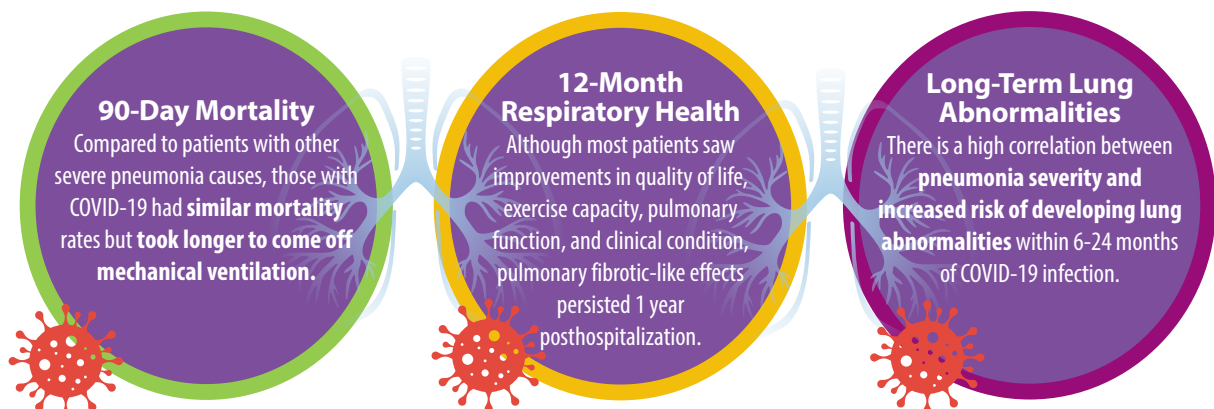
No major, ≥ 3 minor criteria: **56% sensitivity, 91% specificity**

## Hydrocortisone for Bacterial Severe CAP<sup>6</sup>



## Severe Pneumonia and COVID-19: Lasting Impact<sup>7,11,12</sup>

Recent studies have sought to understand the long-term implications of COVID-19-associated severe pneumonia.



# Pulmonary Hypertension: Comorbidities and Novel Therapeutics

Mary Jo S. Farmer, MD, PhD, FCCP

Pulmonary hypertension (PH), a disease of the pulmonary vasculature characterized by mean arterial pressure of > 20 mmHg, has high mortality and morbidity and encompasses a series of conditions.<sup>1,2</sup> The 5 groups of PH as defined by the WHO include pulmonary arterial hypertension (PAH; group 1), pulmonary hypertension with left-sided heart disease (PH-LHD; group 2), PH with chronic lung disease (group 3), PH associated with blood clots and scarring as a complication of long-term pulmonary embolism or thromboembolic disease (CTEPH; group 4), and multifactorial or unclear mechanism PH (group 5).<sup>2</sup> Many comorbidities predispose patients to PH and interact with disease features, such as congenital heart disease, chronic lung disease, interstitial lung disease, COPD, endemic infections, systemic hypertension, diabetes, coronary artery disease, and sleep apnea.<sup>2,3</sup> For example, features of sleep apnea interact with PH, changing clinical sleep breathing measures.<sup>4</sup>

Efforts in recent years have focused on improving disease management and developing treatment options that target novel pathways, especially so in PAH.<sup>1,5,6</sup> A recently approved treatment, sotatercept, is a novel fusion protein that attempts to restore balance between growth-promoting and growth-inhibiting signaling pathways in PAH. Sotatercept has been shown to improve 6-minute walk distance, a measure of aerobic capacity.<sup>5</sup> Established PAH oral therapies are now available in single-tablet combinations (macitentan/tadalafil), which have demonstrated improvements in pulmonary vascular resistance compared with either medicine alone.<sup>6</sup> For chronic thromboembolic disease, treatment approaches such as balloon pulmonary angioplasty are being used to improve cardiopulmonary outcomes and are constantly advancing.<sup>7</sup> These new treatments provide additional options in management of the various manifestations of this chronic disease.

## PH and OSA Clinical Characteristics<sup>4</sup>



**25% of patients (N=35/140) with PH (any type) in a recent study had OSA**

**0.0%**  
Idiopathic PAH

**76.0%**  
Pulmonary disease or low oxygen

### OSA in PH Types

**15.4%**  
PAH associated with connective tissue disease

**8.0%**  
PAH associated with congenital heart disease

**50.0%**  
Chronic thromboembolic

**11.8%**  
Unknown mechanisms

### Clinical Characteristics (with vs without OSA)



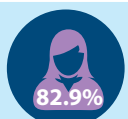
**Mean age (years)**



**46.7** vs **37.1**



**Sex (number of females)**



**57.1%** vs **82.9%**



**Mean blood pressure (SBP/DBP mmHg)**



**119/77 mmHg** vs **111/72 mmHg**

### Sleep Breathing Measures (with vs without OSA)



**Apnea hypopnea index (mean)**  
**16.2 vs 1.6**



**Obstructive apnea index (mean)**  
**3.3 vs 0.3**



**Oxygen saturation < 90% (minutes)**  
**166.30 vs 74.97**

## New Treatments in PAH<sup>5,6</sup>

### Sotatercept<sup>5,a</sup> Activin signaling inhibitor

- Sotatercept
- Placebo

#### Median Change Estimate in 6-Minute Walk Distance

(from baseline at week 24)



### Secondary Endpoints

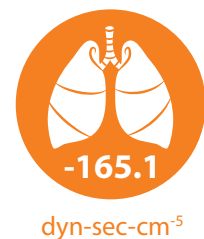
#### Multicomponent Improvement

(met all 3 criteria for 6-minute walk distance, NT-pro-BNP\* level, and WHO functional class)



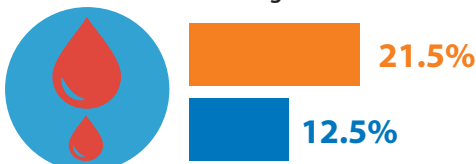
#### Pulmonary Vascular Resistance

(median change estimate from baseline at week 24)



### Adverse Events

#### Bleeding



#### Headache

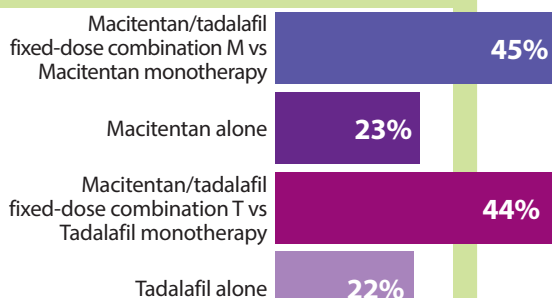


<sup>a</sup>All patients received stable background therapy before and during treatment.

<sup>\*</sup>NT-pro-BNP, N-terminal pro b-type natriuretic peptide

#### Pulmonary Vascular Resistance

(reduction from baseline to week 16)



### Macitentan/Tadalafil Combination Therapy<sup>6,b</sup>

Endothelin receptor antagonist (ERA)/  
phosphodiesterase 5 inhibitor (PDE5i)

Changes in baseline exercise capacity and improvements in cardiopulmonary and cardiovascular symptoms were similar in each group.

#### Adverse Events

- ✓ Macitentan/tadalafil fixed-dose combination was well tolerated.
- ✓ The safety profile of the fixed-dose combination was consistent with macitentan and tadalafil given individually.

<sup>b</sup>Macitentan/tadalafil M fixed-dose combination refers to patients who were treatment-naïve or on prior ERA at baseline. Macitentan/tadalafil T fixed-dose combination refers to patients who were treatment-naïve or on prior PDE5i at baseline.

# The Genetic Side of Interstitial Lung Disease

Priya Balakrishnan, MD, MS, FCCP

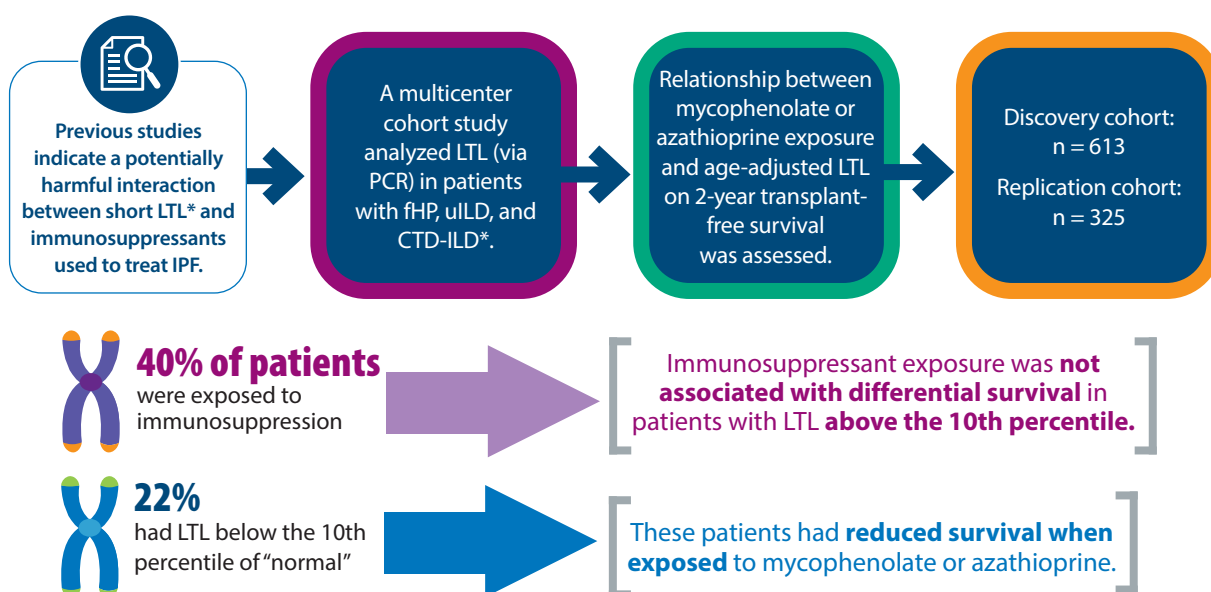
ILDs often require pharmacological therapy to prevent progressive loss of lung function. The initial treatment choice is determined by the ILD subtype.<sup>1</sup>

Telomeres shorten with cellular replication and the natural aging process, and telomere dysfunction has been linked with ILD development and disease progression.<sup>1</sup> A pharmacogenomic relationship may exist between immunosuppressive treatment and shorter leukocyte telomeres. Historical use of immunosuppression is associated with worse survival for patients with IPF with short age-adjusted telomere length.<sup>1</sup>

Genetic factors may contribute to ILD development, as seen in familial interstitial pneumonia (FIP).<sup>2</sup> More than 10 gene mutations are associated with FIP.<sup>2</sup> When FIP is suspected, next-generation sequencing (NGS) helps facilitate a targeted gene panel with a known familial ILD association. Initial studies of familial clustering of ILD led to the discovery of gene mutations implicated in telomere homeostasis (telomere-related genes) and surfactant homeostasis (surfactant-related genes).<sup>2</sup> The disease phenotype in families was not limited to IPF, but included various fibrosing diseases, all of which have the potential for progressive pulmonary fibrosis.

Genetic and epigenetic (eg, viral, exposure) underpinnings highlight the complexity of ILD etiology, with mutations in telomere-related and surfactant-related genes contributing to pulmonary fibrosis phenotypes.<sup>3</sup> As research advances, understanding these genetic, environmental, and molecular mechanisms holds promise for tailored therapeutic strategies for ILD management.

## Telomere Dysfunction: ILD Development and Trajectory<sup>1</sup>



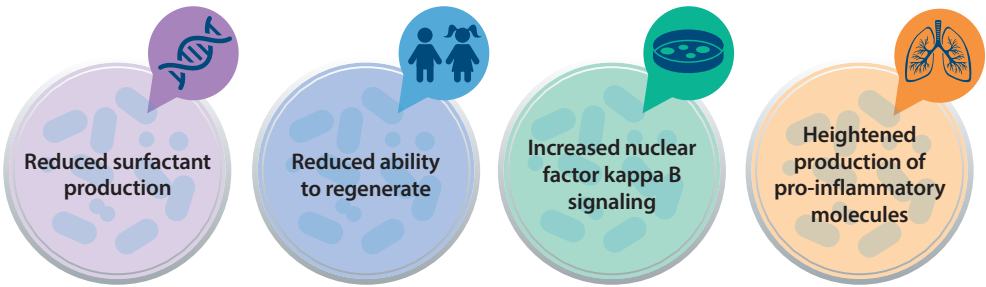
**Conclusion:** LTL may be a clinically viable genomic marker to aid treatment decisions for patients with fHP and uILD.

\*CTD, connective tissue disease; fHP, fibrotic hypersensitivity pneumonitis; LTL, leukocyte telomere length; PCR, polymerase chain reaction; uILD, unclassifiable interstitial lung disease

## Understanding the Pathogenesis of Childhood ILD<sup>4,5</sup>

- ▶ Researchers recently created a model using CRISPR/Cas9 gene editing to study the effects of *ABCA3* mutations.
- ▶ **AEC2s were generated from the induced pluripotent stem cells (iPSCs)** of children carrying *ABCA3* mutations. Both corrected and uncorrected cells were engineered for comparison.

**When grown in the culture dish, the researchers saw several quantifiable differences between the corrected and uncorrected cells. Mutated cells had:**



*ABCA3* gene mutations are the leading genetic contributors to childhood interstitial lung disease (chILD). **Limited treatment options are available for patients with *ABCA3* mutations because the disease pathogenesis is not well understood**, partially due to an inability to obtain AEC2 cells from children with ILD.

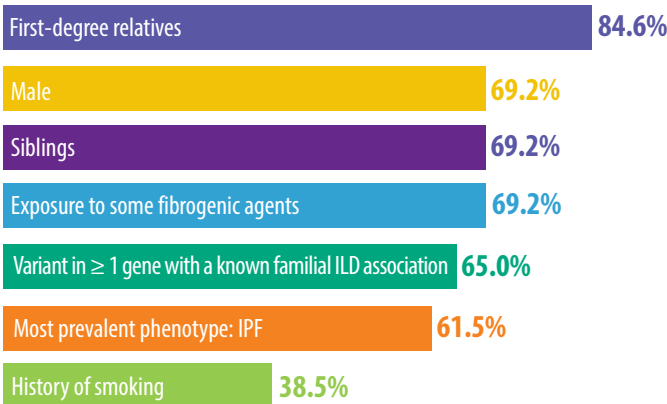
These results allowed the researchers to better understand the mechanisms of chILD, opening the door for targeted therapies in the future.

## NGS in Diagnosing Familial Interstitial Pneumonia<sup>2</sup>

**A 10-fold increase in the prevalence of ILD among families of patients** diagnosed with IPF suggests a genetic predisposition to ILD. Investigations into familial ILD have uncovered variants in genes associated with the maintenance of telomeres and surfactant homeostasis. These genetic variations, along with several genetic polymorphisms, have been implicated in the disease.

**Genetic testing was performed on 20 patients with ILD.**

Variants in genes implicated in telomere and surfactant homeostasis and *MUC5B* variants were detected.



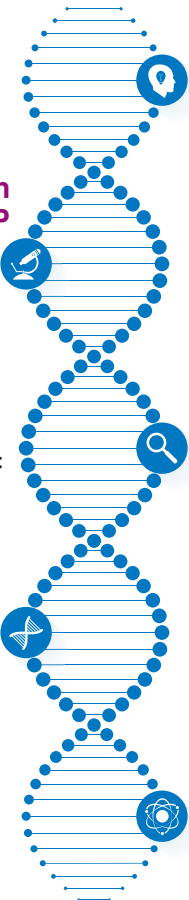
### Genetic Variants Detected in Patients With Suspected FIP

- **61.5%** had variants detected in genes implicated in telomere homeostasis (*TERT*, *RTEL1*, *PARN*, and *TINF2*).
- **30.8%** presented variants in genes implicated in surfactant homeostasis: *SFTPA2*, *ABCA3*, and *DMBT1*.
- **15.4%** had a *MUC5B* variant.
- Most variants were classified with uncertain clinical significance.



Mean age at symptom onset **60.5 years**

Mean age at diagnosis **64.4 years**





# Noninvasive Ventilation in Neuromuscular Disease

Sreelatha Naik, MD, FCCP, and Kelly Lobritto, CRNP

Noninvasive ventilation (NIV) delivers oxygen into the lungs via positive pressure without the need for endotracheal intubation and is typically used in COPD, obesity hypoventilation syndrome, and neuromuscular disease (NMD).<sup>1</sup> Clinicians are used to recognizing pulmonary diseases that require ventilation, but NMDs—in which early intervention is critical due to its effect on respiration—are often overlooked. Emerging data show that patients with lung function even at 80% may benefit from early NIV in the long term.<sup>2</sup> NMDs that benefit from NIV include amyotrophic lateral sclerosis (ALS), myasthenia gravis, and muscular dystrophies.<sup>2-4</sup>

New CHEST guidelines for NMD respiratory management provide guidance on the timing of pulmonary function testing, when to initiate NIV, and how to manage sleep-disordered breathing.<sup>2</sup> Clinicians should be aware of inconsistencies between CHEST and Medicare/insurance reimbursement guidelines.<sup>5</sup> For example, current Medicare/insurance guidelines require vital capacity to be < 50% to treat with NIV, whereas CHEST guidelines recommend a threshold of 80% if a patient is symptomatic based on more recent evidence.<sup>5</sup>

Due largely to increased respiratory fragility during the COVID-19 pandemic, there has been an increased need for NIV and home ventilation (HMV) devices, and the number of available devices has also expanded due to the NIV recall.<sup>6,7</sup> These new ventilators each have their own unique features that can optimize to certain conditions and populations and more data is now available to address previously unanswered treatment questions.<sup>6</sup> Data on measures, such as mode, observed overall usage, respiratory rates, tidal volumes, and pressures, can now help determine optimal ventilator use and long-term outcomes in NMDs.<sup>6</sup>

## CHEST Respiratory Guidelines for NMDs<sup>2,8</sup>

### Pulmonary Function Testing

1. Pulmonary function testing should guide management decisions for patients with pulmonary features.
2. Patients at risk of respiratory failure should be tested every ≤ 6 months.
3. In patients with normal pulmonary function testing and overnight oximetry results, polysomnography should guide whether NIV is indicated.

### Use of NIV

1. **Respiratory failure** | The initiation threshold varies by disease, age, and rate of progress. FVC < 80% with symptoms, FVC < 50% without symptoms, MIP to < -40 cm H<sub>2</sub>O, or hypercapnia would call for the initiation of NIV.
2. **Sleep-related breathing disorders** | NIV is suggested. More specific guidelines for adults are outlined by the American Academy of Sleep Medicine.

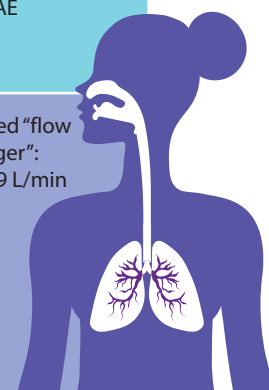
### Respiratory Parameters for NIV Initiation

1. Diagnostic tests (FVC, MIP/MEP, ONO\*), or evidence of sleep-disordered breathing or hypoventilation on polysomnography can guide initiation timing.
2. NIV should be tailored based on treatment goals. Parameters (eg, mode of ventilation, inspiratory time, and pressures) can be optimized.
3. With preserved bulbar function, MPV\* is suggested for daytime ventilatory support.

\*MPV, mouthpiece ventilation; ONO, overnight oximetry

## Ventilators Used in NMD<sup>9-13</sup>

| Ventilator Feature      | Philips Trilogy Evo                                                                                                    | ResMed Astral 150                                                                                                                  | Breas 65/45 LS                                                                                                             | Lowenstein Luisa                                                                                                                                                                    | Ventec VOCSN                                                                                          |
|-------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Battery (hours)         | 7.5                                                                                                                    | 8                                                                                                                                  | 7.5                                                                                                                        | 6                                                                                                                                                                                   | 9                                                                                                     |
| Cloud System            | CareOrchestrator                                                                                                       | AirView                                                                                                                            | EveryWare                                                                                                                  | Prisma CLOUD                                                                                                                                                                        | Multi-View                                                                                            |
| AHI Detection           | No                                                                                                                     | Yes                                                                                                                                | Yes                                                                                                                        | No                                                                                                                                                                                  | No                                                                                                    |
| Differentiating Feature | Discontinued in US in 2024; support available until 2029<br>Potential CO <sub>2</sub> monitoring<br>AutoPEEP reporting | iVAPS™ mode targets alveolar minute ventilation instead of Vt                                                                      | Both can monitor CO <sub>2</sub><br>Itime for timed breaths (vs spontaneous breaths in PS mode)                            | High flow oxygen<br>Expiratory pressure reduction ranging from 1-4 (4 being slowest)<br>Itime for timed breaths (vs spontaneous breaths)                                            | Can have a cough assist, oxygen concentrator, suction, and nebulizer in 1 device                      |
| Modes                   | CPAP<br>BPAP ST<br>AC (PC and VC)<br>SIMV (PC and VC)<br>AVAPS-AE<br>MPV (PC and VC)                                   | CPAP<br>BPAP ST<br>AC (PC and VC)<br>SIMV (PC and VC)<br>iVAPS-AE                                                                  | CPAP<br>PS<br>AC (PC and VC)<br>SIMV (PC and VC)<br>MPV (PC and VC)<br>45 LS has AE-modes, with TTV;<br>65 LS does not HFT | CPAP<br>BPAP ST, S, T<br>AC (PC and VC)<br>SIMV (PC and VC)<br>TTV-VAPS-AE<br>MPV (pressure and volume)<br>HFT                                                                      | BPAP ST<br>AC (PC and VC)<br>SIMV (PC and VC)<br>Volume-targeted<br>PS-AE<br>Volume-targeted<br>PC-AE |
| Inspiratory Trigger     | AutoTrack and AutoTrack sensitive<br>Can be changed to a flow trigger: 0.5-9 L/min                                     | Can be set to low, medium, high, and very high (most sensitive) when set to pressure<br><br>When set to flow trigger: 0.5-15 L/min | Can be set to 1-9 (9 being hardest to trigger)                                                                             | Called “inspiratory sensitivity”<br>Can be auto or set to 1-10 (1 being easiest to trigger)<br><br>Has inspiratory lockout time to prevent excessive triggering, from 0.2-5 seconds | Called “flow trigger”:<br>0.5-9 L/min                                                                 |
| Cycle Sensitivity       | “Flow cycle sensitivity”:<br>10-90% of peak flow                                                                       | “Cycle sensitivity”:<br>5-90%                                                                                                      | “Expiratory sensitivity”:<br>1-9 (9 being hardest to cycle off)                                                            | “Expiratory sensitivity”:<br>5-95%                                                                                                                                                  | “Flow cycle sensitivity”:<br>10-85%; allows “flow termination” in pressure control mode               |
| Rise Time               | 0-6 (6 being slowest)                                                                                                  | 150-900 ms                                                                                                                         | 1-9 (9 being slowest)                                                                                                      | 1-4 (4 being slowest)<br>Called “pressure increase”                                                                                                                                 | 1-6 (6 being slowest)                                                                                 |



\*AC, assist control; AE, automatically adjusting expiratory positive airway pressure; AHI, Apnea-Hypopnea Index; AVAPS, automatic volume assured pressure support; BPAP, bilevel positive airway pressure; CO<sub>2</sub>, carbon dioxide; CPAP, continuous positive airway pressure; HFT, high-flow therapy; Itime, inspiratory time; iBR, intelligent backup rate; iVAPS, intelligent volume assured pressure support; PC, pressure control; PEEP, positive end expiratory pressure; PS, pressure support; RR, respiratory rate; S, spontaneous triggering for breaths; SIMV, synchronized intermittent mandatory ventilation; ST, spontaneous triggering, but timed breaths are given if no spontaneous breaths; T, timed breaths only; TTV, targeted tidal volume; VAPS, volume-assured pressure support; VC, volume control; Vt, tidal volume

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