

# CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Artificial intelligence techniques and automated language processing may hold the key to early identification of ILD.

geralt/Pixabay/CCO 1.0

## Think it's interstitial lung disease? Tell it to the machines

BY NEIL OSTERWEIL  
*MDedge News*

SAN FRANCISCO – Interstitial lung disease (ILD) is a difficult diagnosis to make, but a combination of artificial intelligence (AI) techniques and automated language processing could help clinicians identify the early signs of ILD and start patients on therapy, investigators say.

For example, applying an AI algorithm to spirometry readings taken from patients whose data were registered in the UK Biobank identified 27% as having ILD, and of this group, 66% had ostensibly normal lung function on spirometry but were later diagnosed with ILD, reported Marko Topalovic, PhD, from the AI company

ArtiQ in Leuven, Belgium, at the American Thoracic Society's international conference.

"A diagnosis of ILD is very challenging, so you have patients who are going to be misdiagnosed or have a very late diagnosis, so we aimed to apply our AI algorithm on spirometry to see whether we could detect ILD much earlier," he said in an interview conducted during a poster discussion session.

AI detected ILD up to 6.8 years before a clinician's diagnosis, Dr. Topalovic said.

### Reading between the lines

In a separate study, investigators at the University of California, Davis, used language analysis

**MACHINES** // continued on page 4

## Can lung cancer ID be as easy as breathing into an analyzer?

BY WALTER ALEXANDER

**B**reathomics testing is one step closer to becoming a reality as a lung cancer screening tool, according to a study published in *The Lancet* journal *eClinicalMedicine* (2022 Apr 26. doi: 10.1016/j.eclinm.2022.101384).

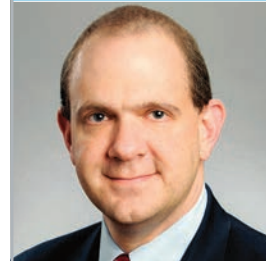
The tool was successfully used to identify, in 84 patients, 16 lung cancer-related carcinogenic volatile compounds (VOCs), such as aldehydes, hydrocarbons, ketones, carboxylic acids, and furan – some of which are compounds used in the production of common household goods, such as furniture, carpeting, and wood floors.

"The test is anticipated to be highlighted for primary screening of lung cancer but not the final diagnosis," according to study authors who were led by Peiyu Wang, MD, PhD, chair of social medicine and health at Peking (China) University.

While early diagnosis and treatment are critical for improving lung cancer survival, early detection of lung cancer is challenging because of the lack of clinical manifestations and specific

**BREATHING** // continued on page 5

### INSIDE HIGHLIGHT



#### NEWS FROM CHEST

**From the President: A day in the life**

Page 19

**Follow CHEST 2022 to Music City**  
*It's time to write a new song*

**NASHVILLE CHEST 2022**  
OCT. 16-19

LEARN MORE AT [chestmeeting.chestnet.org](https://chestmeeting.chestnet.org)

PERMIT 500  
HARRISBURG, PA  
PAID  
U.S. POSTAGE  
PSRST STD

CHANGE SERVICE REQUESTED

CHEST PHYSICIAN  
10255 W Higgins Road,  
Suite 280  
Rosemont, IL 60018

# Knowing eosinophils count is our EOSINOPHILOSOPHY WHAT'S YOURS?

At GSK, we believe eosinophils count for a lot. They play a role not only in disease, but also in health—and we are committed to better understanding their potential impact on patients' lives.



## **In health**

Eosinophils may contribute to overall health and immunoregulation<sup>1-3</sup>



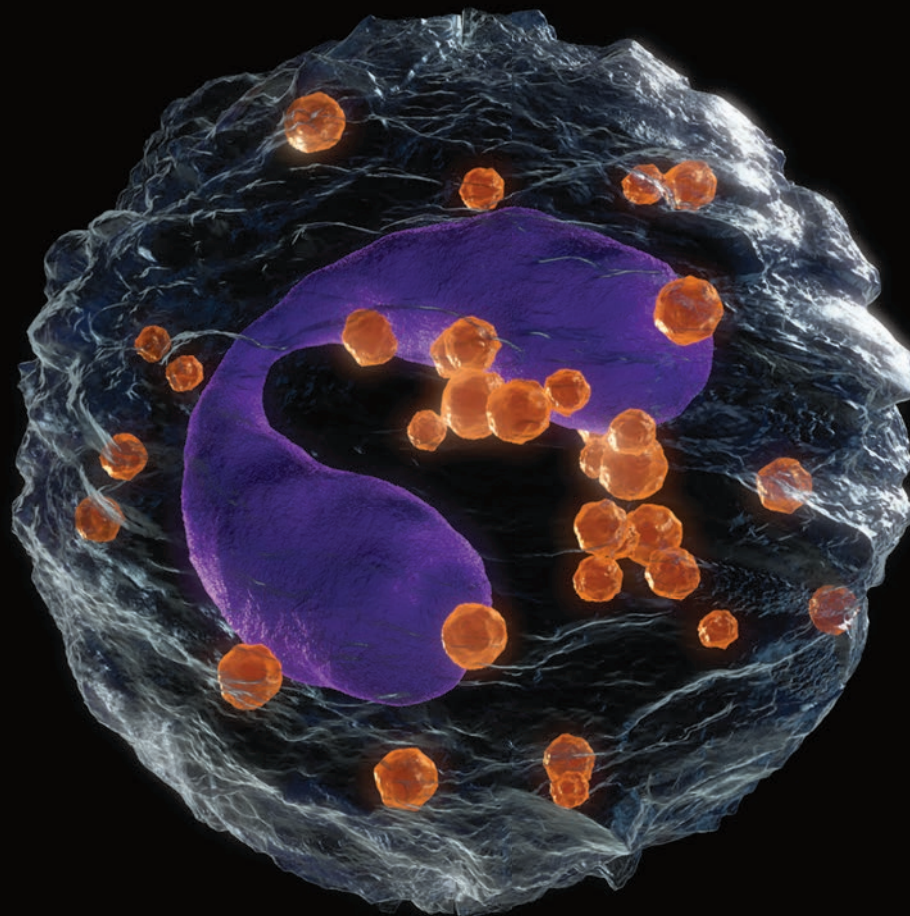
## **In disease**

Eosinophils contribute to inflammation and organ damage or dysfunction<sup>2,3</sup>

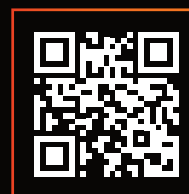


## **In diagnosis and treatment decisions**

Blood and/or tissue eosinophils can serve as an important biomarker in clinical practice<sup>4-11</sup>



Discover more about the important role of eosinophils at [EOCounts.com](https://EOCounts.com)



**References:** **1.** Marichal T, Mesnil C, Bureau F. Homeostatic eosinophils: characteristics and functions. *Front Med (Lausanne)*. 2017;4:101. **2.** Travers J, Rothenberg ME. Eosinophils in mucosal immune responses. *Mucosal Immunol*. 2015;8(3):464-475. **3.** Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. *Annu Rev Pathol*. 2020;15:179-209. **4.** Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2021 main report. <https://ginasthma.org/gina-reports/>. Accessed March 14, 2022. **5.** Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2022 report. <https://goldcopd.org/2022-gold-reports-2/>. Accessed March 14, 2022. **6.** Asano K, Hebisawa A, Ishiguro T, et al. New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. *J Allergy Clin Immunol*. 2021;147(4):1261-1268.e5. **7.** Wechsler ME. Pulmonary eosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27(3):477-492. **8.** Suzuki Y, Suda T. Eosinophilic pneumonia: A review of the previous literature, causes, diagnosis, and management. *Allergol Int*. 2019;68(4):413-419. **9.** Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum*. 1990;33(8):1094-1100. **10.** Reed CC, Dellon ES. Eosinophilic esophagitis. *Med Clin North Am*. 2019;103(1):29-42. **11.** Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*. 2012;130(3):607-612.e9.

Trademarks are owned by or licensed to the GSK group of companies.



©2022 GSK or licensor.  
MPLJRNA220002 March 2022  
Produced in USA.

software to scour electronic health records for words indicative of early ILD, and found that the technique dramatically shortened the median time to a pulmonary referral, compared with historical controls.



**Dr. Marko Topalovic**

help to improve diagnosis of ILD and allow clinicians to prescribe therapy earlier in the disease course.

“What’s going to give you the biggest impact for patients? Everyone working individually is coming up with great advances, and if you put them all together it’s going to provide much greater benefit for our patients,” he said in an interview.

**AI Spirometry details**

In collaboration with colleagues at the Laboratory of Respiratory Disease at University Hospital in Leuven, Dr. Topalovic applied AI to results of spirometry performed prior to diagnosis of ILD among 109 patients registered in the UK Biobank, a repository of information on more than 500,000 volunteers.

The patients selected had ILD listed as their cause of death, had spirometry performed up to 7 years before their deaths, and did not receive a diagnosis of ILD on the day of the index spirometry.

In all 73% of patients were men, 27% women, with an average age of 64.6 years. A large majority of the sample (77.15%) had a history of smoking, and 60 of the patients (55%) died within 1 year of an ILD diagnosis.

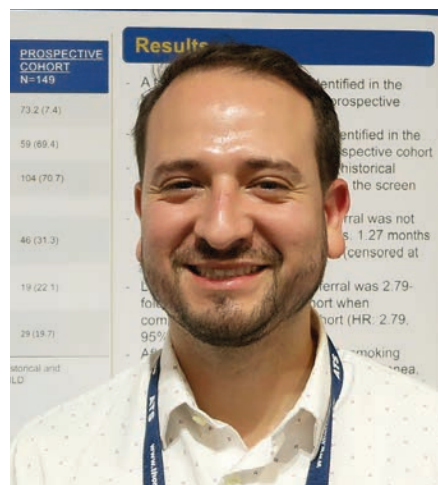
The investigators plugged the spirometry data and each patients demographic information – including gender, age, height, weight, race, and smoking status – into the AI clinical decision support program, which yielded a statistical probability for each subject of having normal lung function, asthma, COPD, ILD, another obstructive disease, or another unidentifiable respiratory disease.

In 29 patients (27%) the software listed ILD as the highest probability, and of this group 19 patients (66%) had normal lung function according to standard interpretation guidelines.

Spirometry parameters among patients identified as having probable ILD were different from those where ILD was not detected. For example, forced vital capacity (FVC) was 76% of predicted among patients with likely ILD versus 87% of predicted in those who had a diagnosis later ( $P = .003$ ). Similar differences were seen in the forced expiratory volume in 1 second to FVC ratio, at 0.82 vs. 0.75, respectively ( $P = .007$ ).

There were no differences in mortality or in median time between spirometry and clinician diagnosis between the groups.

**MACHINES** continued on following page



**Dr. William Leon**

“This is a language processing program that can essentially look through the radiology reports and look for the key words that often describe interstitial lung disease, like traction, honeycomb, fibrotic, etc. With those studies being flagged, an actual pulmonologist will then further review the scan, and see whether it meets criteria for one of the interstitial lung diseases,” lead author William Leon, MD, a resident in the department of internal medicine at the University of California, Davis, said in an interview. “We then sent the primary care doctor a message to say: ‘Hey, this patient has ILD. You need to send them to a pulmonologist,’” he added.

**Putting it together**

Philip L. Molyneaux, MRCP (U.K.), MBBS, BS (Hons), from Imperial College London, who comoderated the session but was not involved in the studies, speculated that combining these and other, nontechnical interventions also discussed could

**NEWS FROM CHEST** // 17

**SLEEP STRATEGIES** // 21

**CHEST PHYSICIAN IS ONLINE**

CHEST Physician is available at [chestphysician.org](http://chestphysician.org).



**Angel Coz, MD, FCCP,** is Editor in Chief of **CHEST Physician**.

**CHEST Physician**  
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

**AMERICAN COLLEGE OF CHEST PHYSICIANS (CHEST)**

- EDITOR IN CHIEF**  
Angel Coz, MD, FCCP
- PRESIDENT**  
David Schulman, MD, MPH, FCCP
- EXECUTIVE VICE PRESIDENT & CEO**  
Robert Musacchio, PhD
- PUBLISHER, CHEST**  
Nicki Augustyn, CAE
- MANAGER, EDITORIAL RESOURCES**  
Pamela L. Goorsky
- MANAGING EDITOR, NEWS CHANNELS**  
Danielle Leber
- SECTION EDITORS**  
Aaron B. Holley, MD, FCCP  
*Pulmonary Perspectives*<sup>®</sup>  
Daniel R. Ouellette, MD, FCCP  
*Critical Care Commentary*  
Michelle Cao, DO, FCCP  
*Sleep Strategies*

**EDITORIAL BOARD**

- Humayun Anjum, MD, FCCP
- A. Christine Argento, MD, FCCP
- Abbie Begnaud, MD, FCCP
- David L. Bowton, MD, FCCP
- Mary Cataletto, MD, FCCP
- Carolyn D'Ambrosio, MD, FCCP
- Mary Jo S. Farmer, MD, PhD, FCCP
- Sachin Gupta, MD, FCCP
- Loren Harris, MD, FCCP
- Jonathan Ludmir, MD
- Diego Maselli, MD, FCCP
- Mangala Narasimhan, DO, FCCP
- Brandon M. Seay, MD
- Shyam Subramanian, MD, FCCP
- Sai Venkateshlah, MD, FCCP
- Corinne Young, MSN, FNP-C, FCCP

**E-mail:** [chestphysiciannews@chestnet.org](mailto:chestphysiciannews@chestnet.org)  
©Copyright 2022, by the American College of Chest Physicians



**FRONTLINE MEDICAL COMMUNICATIONS SOCIETY PARTNERS**

- EXECUTIVE EDITOR** Kathy Scarbeck, MA
- EDITOR** Mark S. Lesney, PhD
- CREATIVE DIRECTOR** Louise A. Koenig
- DIRECTOR, PRODUCTION/MANUFACTURING**  
Rebecca Slebodnik
- DIRECTOR BUSINESS DEVELOPMENT**  
Anne Gilhool,  
914-916-2487  
[agilhool@mdedge.com](mailto:agilhool@mdedge.com)
- DIRECTOR, THE MEDJOBNETWORK**  
Julian Knight  
973-206-2317, cell 201-310-7063  
[jknight@mdedge.com](mailto:jknight@mdedge.com)

**CHEST PHYSICIAN**, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST PHYSICIAN** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

The statements and opinions expressed in **CHEST PHYSICIAN** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Frontline Medical Communications Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

**POSTMASTER:** Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Services, 10255 W Higgins Road, Suite 280, Rosemont, IL 60018-9914.

**RECIPIENT:** To change your address, contact Subscription Services at 1-800-430-5450. For paid subscriptions, single issue purchases, and missing issue claims, call Customer Service at 1-833-836-2705 or e-mail [custsvc.chph@fulcoinc.com](mailto:custsvc.chph@fulcoinc.com)

**CHEST PHYSICIAN** (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Subscription price is \$244.00 per year. Phone 973-206-3434, fax 973-206-9378.

**EDITORIAL OFFICES** 2275 Research Blvd, Suite 400, Rockville, MD 20850, 973-206-3434, fax 240-221-2548

**FRONTLINE MEDICAL COMMUNICATIONS**

- Corporate**
- VP, SALES** Mike Guire
- VP, SALES LEAD** Dino Marsella
- VP, MEMBER MARKETING** Amy Pfeiffer
- VP, SALES, STRATEGY & PARTNERSHIPS**  
JoAnn Wahl
- DIRECTOR, CIRCULATION** Jared Sonners
- EXECUTIVE EDITOR** Patrick Finnegan
- VP, PROPRIETARY CONFERENCES, MEDSCAPELIVE** David J. Small, MBA

# 'Significant' treatment option for incurable NSCLC

BY AMY REYES

MDedge News

The combination of neoadjuvant chemotherapy with immunotherapy led to significant improvements in survival for patients with resectable stage IIIA-B non-small cell lung cancer (NSCLC), according to researchers reporting earlier this month in Chicago at the annual meeting of the American Society of Clinical Oncology.

Advanced stage IIIA NSCLC is incurable in most patients with lung cancer, and with existing treatments only 30% of patients will live up to 5 years. In this study, neoadjuvant chemotherapy with nivolumab significantly increased the pathological complete response rate in 36.2% of patients, compared with 6.8% who received chemo alone, said study author Mariano Provencio-Pulla, MD, PhD, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia, Spain.

The major pathologic response (MPR) – which accounts for residual viable tumor of less than or

equal to 10 – was better in the treatment group as compared with patients who received chemotherapy alone (52% vs 14%). The objective response rate (ORR) – or, the percentage of patients who had a partial or complete response to treatment

*The percentage of patients who had a partial or complete response to the added immunotherapy was 74% in the treatment group, compared with 48% among patients who received chemotherapy alone.*

– was 74% in the treatment group, compared with 48% among patients who received chemotherapy.

“In our opinion this should be the standard of care for patients,” Dr. Provencio-Pulla said during his presentation.

The ASCO treatment guidelines for stage III NSCLC, specify that some patients can receive immunotherapy for up to a year, but for resectable stage III disease, this therapy is still under investigation.

In this study, called NADIM

II (NCT03838159), investigators enrolled 87 patients with resectable clinical stage IIIA disease between February 2019 and November 2021. NADIM II is an open-label, randomized, two-arm, phase 2, multicenter clinical trial. Patients had

ECOG scores of 0-1 and no known EGFR/ALK alterations. Patients received either nivolumab 360 mg with paclitaxel 200 mg/m<sup>2</sup> and carboplatin AUC5 for three cycles every 21 days as treatment before or after surgery. Patients who received a resection that left no microscopic tumor in the primary tumor bed, received adjuvant nivolumab between weeks 3 and 8 after surgery for 6 months.

At 91%, almost all patients who received the immunotherapy and

chemotherapy treatment underwent surgery, compared with 69% of patients in the chemotherapy treatment group. In the treatment group, patients with pathological complete response (pCR) had higher PD-L1 tumor proportion score (TPS) scores (median 70%).

The primary endpoint was pathological complete response of 0% viable tumor cells in resected lung and lymph nodes. The major pathological response was no more than 10% viable tumor remaining. The secondary endpoints included overall response rate, toxicity profile, and potential predictive biomarkers.

The addition of neoadjuvant nivolumab to chemotherapy significantly improved pCR (odds ratio, 7.88). The safety profile was “tolerable” with a moderate increase in grade 3-4 toxicity; plus no surgery was delayed because of problems with the treatment, Dr. Provencio-Pulla said.

This study was funded by Fundación GECP. Dr. Provencio-Pulla has received funding from Bristol-Myers Squibb, the maker of Opdivo (nivolumab). ■

MACHINES *continued from previous page*

## Language processing details

Dr. Leon and colleagues used a language analysis software package to review CT chest reports. Reports were flagged if they contained the words traction, honeycomb, fibrotic, fibrosis, reticular, or reticulation.

The CT scan accompanying each flagged report was reviewed by a pulmonologist for the presence of ILD, and scans with ILD identified were referred to pulmonary specialists. The results of 2,198 prospective scans followed by prospective screening were compared with those of 1,690 historical controls seen in 2015 and 2016.

The investigators found that 85 incident cases of ILD were identified in the historical controls, compared with 143 in the prospective cohort, leading to 38 and 120 pulmonary referrals, respectively.

For the primary outcome of median time from CT to pulmonary referral, the authors found that it was 1.27 months for the prospective cohort, compared with not reached (censored after 18 months) in historical controls.

The hazard ratio for a pulmonary referral in the prospective versus historical cohort was 2.79, an association that was strengthened after adjusting for sex, age, race, smoking pack-years, cough, crackles, and dyspnea (HR, 4.54; both comparisons significant according to confidence intervals).

The studies were internally funded. Dr. Topalovic is CEO and cofounder of ArtiQ. Dr. Leon and Dr. Molyneaux reported no relevant conflicts of interest. ■

## BREATHING // *continued from page 1*

biomarkers. Annual CT scans are costly and include radiation exposure, Dr. Wang and his associates wrote.

Breathomics testing is considered a promising method for detection and screening for lung cancer. It has been under study for years, and in 2014, researchers from Belgium published a review in *Cancer Epidemiology Biomarkers and Prevention* (Jun 2. doi: 10.1158/1055-9965.EPI-13-0737) documenting the use of VOCs as early diagnostic or prognostic biomarkers for mesothelioma.

Lung cancer breath biomarkers identified in various studies have been highly heterogeneous because of differing sample collection methods, and varying patient conditions, testing environments, and analysis methods. As a result, there currently is no breathomics test for lung cancer screening, Dr. Wang said in an interview.

In terms of its potential as a lung cancer screening tool, “Clinicians may introduce this test for people with high risk for lung cancer, such as elderly smokers, or people with suspected symptoms. It may also be introduced for young populations with subjective or objective needs to screen for lung cancer. As the proportion of lung adenocarcinoma in nonsmoking young women is increasing, the test may be a good method for lung cancer screening in this population,” Dr. Wang said.

After adjusting for age, sex, smoking, and comorbidities, researchers found elevated levels for 16 VOCs in patients with lung cancer.

A diagnostic model including the 16 VOCs achieved an area under the curve of 0.952, sensitivity of 89.2%, specificity of 89.1%, and accuracy of 89.1% in lung cancer diagnosis. A model including the top eight VOCs achieved an area under the curve of 0.931, sensitivity of 86.0%, specificity of 87.2%, and accuracy of 86.9%.

After selecting 28 VOCs as candidates through a literature review, Dr. Wang and associates conducted a prospective discovery study from Sept. 1 to Dec. 31, 2020, using high-pressure photon ionization time-of-flight mass spectrometry to evaluate their performance for lung cancer diagnosis. The validation study included 157 lung cancer patients (mean age 57.0 years; 54.1 percent female) and 368 volunteers (mean age 44.5 years; 31.3% female).

“The external validation confirmed good performance of these biomarkers in lung cancer detection,” the researchers stated. It helped, they added, to solve the heterogeneity among published studies, establishing both 16 VOCs and 8 VOCs for lung cancer screening.

The authors stated that a large gap exists between breathomics research and clinical practices in lung cancer detection and screening. While the validated 16 VOCs, mainly aldehydes and hydrocarbon, showed potential for promoting this lung cancer screening strategy, more scientific studies are warranted to investigate the underlying mechanisms of identified lung cancer VOCs.

Dr. Wang declared no competing interests. ■

# Pembro provides DFS benefit in early NSCLC

BY SHARON WORCESTER

MDedge News

**A**djuvant pembrolizumab significantly improves disease-free survival (DFS) compared to placebo in patients with early-stage non-small cell lung cancer (NSCLC) who have undergone complete resection, according to findings from the phase 3 PEARLS/KEYNOTE-091 (PEARLS) study.

Patients in the pembrolizumab arm demonstrated median DFS nearly 12 months longer than those in the placebo arm (53.6 vs. 42.0 months). Investigators observed a DFS benefit for patients with any programmed death-ligand 1 (PD-L1) expression.

“We believe that pembrolizumab has the potential to become a new adjuvant treatment option for patient with [stage IB to IIIA] non-small cell lung cancer following complete resection and adjuvant chemotherapy when recommended,” concluded first author Luis Paz-Ares, MD, chair of the clinical research unit at Hospital Universitario 12 de Octubre, CNIO & Universidad Complutense, Madrid. “Pembrolizumab provided a benefit regardless of pathological stage and PD-L1 progression subgroup.”

The findings were presented by Dr. Paz-Ares at the European Society for Medical Oncology (ESMO) March virtual plenary session and published March 17 in *Annals of Oncology* (doi: 10.1016/j.annonc.2022.02.224).

Pembrolizumab is the standard treatment for patients with advanced NSCLC, but its efficacy in early-stage disease remains unclear. To determine whether patients with early-stage disease benefit from pembrolizumab, Dr. Paz-Ares and colleagues randomized 1,177 adults with stage IB, II, or IIIA NSCLC to 200 mg of pembrolizumab (n = 590) or placebo (n = 587) every 3 weeks.

All patients had Eastern Cooperative Oncology Group performance status of 0-1, and any level of PD-L1 expression. Of the study participants, 168 in the pembrolizumab arm and 165 in the placebo arm had PD-L1 expression and a tumor proportion score (TPS) of at least 50%.

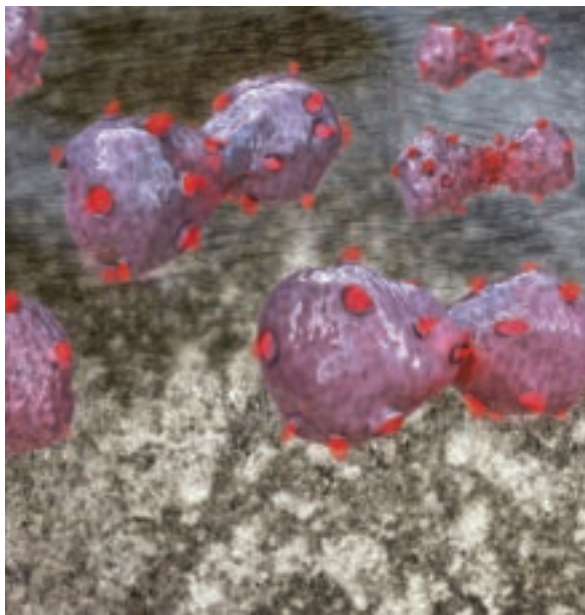
Overall, patients receiving pembrolizumab

had a DFS of 53.6 months compared to 42.0 months in the placebo arm (hazard ratio [HR], 0.76;  $P = .0014$ ). The DFS benefit was generally consistent across patients with PD-L1 TPS <1%, 1%-49%, and  $\geq 50\%$ . In the subset of patients with PD-L1 TPS  $\geq 50\%$ , a slightly higher percentage of patients in the pembrolizumab group demonstrated DFS at 18 months (71.7% vs. 70.2%), but the difference did not reach statistical significance (HR, 0.82;  $P = .14$ ).

Overall survival (OS) at 18 months was 91.7% in the treatment arm and 91.3% in the placebo arm (HR, 0.87;  $P = .17$ ), but the data were immature.

“The disease-free survival benefit was observed across most prespecified subgroups,” Dr. Paz-Ares said.

No new safety concerns were raised. Grade 3 or greater adverse events occurred in 34.1% of patients in the treatment arm and 25.8% in the



placebo arm. Adverse events led to discontinuation in 19.8% of patients receiving pembrolizumab and 5.9% of patients in the placebo group.

Invited discussant Martin Reck, MD, said these findings represent forward progress. “We do see many patients with distant relapse, which

**A. Christine Argento, MD, FCCP, comments:**

The use of adjuvant immune checkpoint inhibitors in patients with early-stage NSCLC who underwent surgical resection to improve disease free survival is an important paradigm shift, especially as it is consistent across all stages of disease. Prolonging the time before distant relapse without increasing adverse events is a huge step forward.



indicates that we have to improve our control of the systemic relapse,” said Dr. Reck, head of the department of thoracic oncology and the clinical trial department at the Lungen Clinic Grosshansdorf, Germany.

Prior data provide a rationale for using immune checkpoint inhibition in early-stage NSCLC, and both the PEARLS study and the IMpower010 trial evaluating atezolizumab in a similar setting have demonstrated relevant improvements in DFS.

“I think we are entering the times of perioperative immunotherapies. We are seeing the first signals of efficacy for adjuvant immunotherapy in two large, randomized trials,” Dr. Reck said.

Based on the PEARLS trial results, Dr. Reck said that PD-L1 appears to have predictive and prognostic value but noted that “several other clinical trials say PD-L1 expression is a poor prognostic marker” for sensitivity to immune checkpoint inhibitor. Given this potential inconsistency, Dr. Reck called for further follow-up in this patient population and for studies in larger groups of patients to further delineate the role of PD-L1 as well as EGFR mutations and adjuvant chemotherapy in patients with early NSCLC.

The PEARLS study was funded by Merck Sharp & Dohme Corp. Dr. Paz-Ares and Dr. Reck disclosed numerous relationships with pharmaceutical companies. ■

# Adagrasib shows durable benefit in KRAS-mutated NSCLC

BY PAM HARRISON

**A**dagrasib, an investigational drug that acts as a KRASG12C inhibitor, has shown durable clinical benefit in patients with previously treated, advanced non-small cell lung cancer (NSCLC) with tumors with KRAS G12C mutations.

“KRAS G12C mutations occur in over 10% of patients with NSCLC [and] remain difficult to target, and outcomes for this patient population have remained poor,” co-investigator Joshua Sabari, MD, assistant professor of medicine, Perlmutter Cancer

Center at NYU Langone, said in a statement.

“Our patients benefited clinically from this agent, and it appears to have improved overall survival (OS), compared with historical outcomes with docetaxel, a standard-of-care chemotherapy regimen, in the second-line setting,” he added.

New data on adagrasib were presented at the annual meeting of the American Society for Clinical Oncology and simultaneously published in the *New England Journal of Medicine* (2022 Jun 3. doi: 10.1056/NEJMoa2204619).

Adagrasib (developed by Mirati) is currently awaiting approval from the U.S. Food and Drug Administration as a treatment for patients with NSCLC harboring the KRAS G12C mutation who have received at least one prior systemic therapy. This would be an accelerated approval based on overall response data from the KRYSTAL-1 study detailed below. The company has an ongoing confirmatory phase 3 trial, KRYSTAL-12, evaluating adagrasib versus docetaxel in patients previously treated for metastatic NSCLC with a KRAS G12C mutation.

If approved, adagrasib would be the second in this class of agents. The first KRASG12C inhibitor for use in lung cancer was sotorasib (Lumakras), approved by the U.S. Food and Drug Administration in May 2021.

Dr. Sabari noted that there are several differences between the two drugs. Adagrasib has CNS penetration and is the first KRASG12C inhibitor to demonstrate clinical activity in patients with KRAS G12C-mutated NSCLC with untreated active CNS metastases.

KRAS continued on following page

# Looking forward to 2030: Expanded genotyping?

BY SHARON WORCESTER

MDedge News

In recent years, patients with advanced lung cancer have benefited from the advent of immune therapies and genotype-directed therapies –both of which have led to improved survival rates. But what will lung cancer look like in 2030?

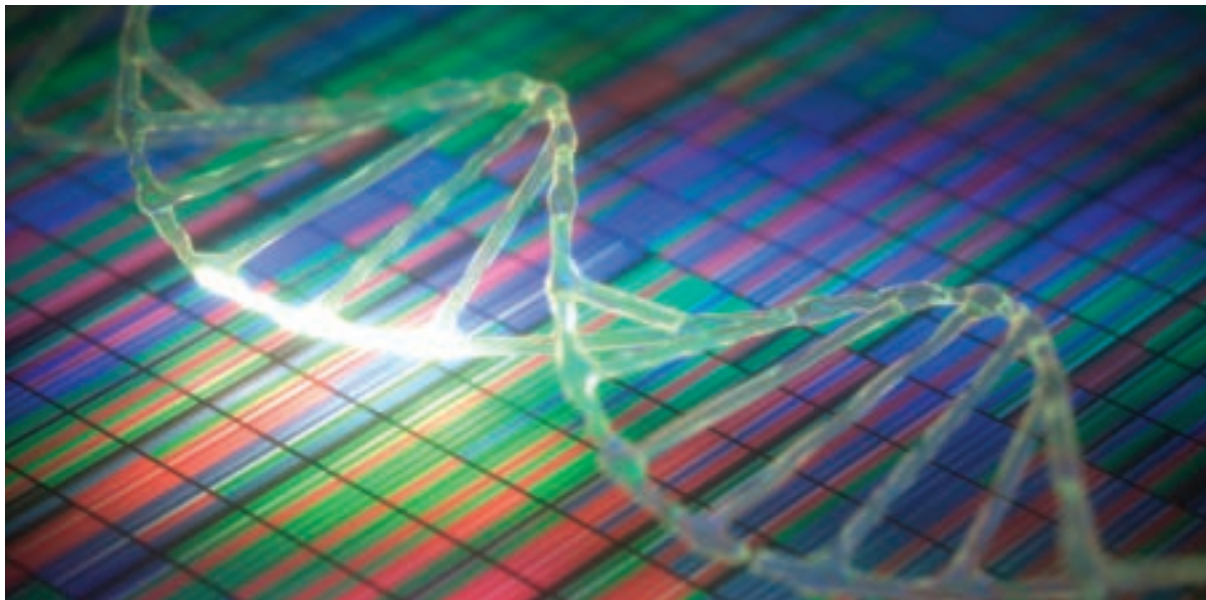
Pasi A. Janne, MD, PhD, of the Dana-Farber Cancer Institute, Boston, hopes to see improved access to tumor and blood-based genotyping.

Dr. Janne, who serves as director of the Lowe Center for Thoracic Oncology at Dana-Farber, gave a keynote presentation at the 2022 European Lung Cancer Congress, where he highlighted the need to broaden the scope of targeted therapies, make “great drugs work even better,” improve the ability to treat patients based on risk level, and expand the use of targeted therapies in the adjuvant and neoadjuvant setting to make significant progress in the treatment of lung cancer in coming years.

Genotyping is underutilized, he said. A 2019 multicenter study reported at the annual meeting

## A. Christine Argento, MD, FCCP, comments:

Despite guidelines and many publications with data showing the importance of biomarkers to direct targeted therapy regimens for patients with advanced lung cancer, it is disheartening to see that, at best, half of patients are even being tested with genotyping. These studies are key to highlighting the importance of testing and utilizing the results of our tests to individualize care for our patients and give them the best prognosis.



KTSDESIGN/SCIENCE PHOTO LIBRARY/Getty Images

of the American Society of Clinical Oncology showed that only 54% of 1,203 patients underwent testing for EGFR mutations, 22% were tested for EGFR, ALK, ROS1, and BRAF mutations, and only 7% were tested for all biomarkers recommended by National Comprehensive Cancer Network guidelines at the time (J Natl Compr Canc Netw. 2021;19[5.5]:610-3).

That study also showed that only 45% of patients received biomarker-driven treatment, even when driver mutations were detected.

“Immunotherapy was often prescribed instead of targeted therapy, even when molecular results were available,” Dr. Janne said.

Another study, reported at the 2021 ASCO annual meeting, showed some improvement in testing rates, but still, only 37% of patients were tested for all biomarkers as recommended.

Racial disparities in testing have also been observed. Bruno and colleagues found that any next-generation sequencing was performed in

50.1% of White patients, compared with 39.8% of Black patients, and NGS prior to first-line therapy was performed in 35.5% and 25.8%, respectively. The study, also reported at ASCO in 2021, showed that trial participation was observed among 3.9% of White patients and 1.9% of Black patients.

“The studies really highlight the need for increased testing rates and appropriate utilization of testing results to deliver optimal care to our patients with advanced lung cancer. We have a long way to go. To live the promise and appreciate the promise of precision therapy ... we need to be able to offer this testing to all of our patients with lung cancer,” he said.

Dr. Janne reported relationships with numerous pharmaceutical companies, including consulting, research support, and stock ownership. He also receives postmarketing royalties from Dana-Farber Cancer Institute–owned intellectual property on EGFR mutations. ■

KRAS continued from previous page

## Published clinical data

The results published in the New England Journal of Medicine are from the company-funded KRYS-TAL-1 clinical trial, which had the primary endpoint of objective response rate.

It was conducted in patients with KRAS G12C-mutated NSCLC who had previously received treatment with at least one platinum-containing chemotherapy regimen and checkpoint inhibitor therapy either sequentially or concurrently.

Patients were treated with oral adagrasib 600 mg twice a day until disease progression, unacceptable toxicity, or death.

On Oct. 15, 2021, the data cutoff date, a total of 116 patients had received at least one dose of adagrasib. At a median follow-up of 12.9 months, the confirmed objective response rate was 42.9% among 112

patients with measurable disease at baseline. One patient achieved a complete response; 42% achieved a partial response, and disease stabilized for a minimum of 6 weeks in over 36% of the group.

*One patient achieved a complete response; 42% achieved a partial response, and disease stabilized for a minimum of 6 weeks in over 36% of the group.*

Only 5.4% of patients had progressive disease as their best overall response, investigators note. Among those patients who responded to twice-daily KRASG12C inhibition, the median time to response was 1.4 months and the median duration of

response was 8.5 months. As of the data cutoff date, one-third of the group were still receiving treatment, the authors note.

Median progression-free survival (PFS) was 6.5 months and median OS was 11.7 months. With a longer median follow-up of 15.6 months, median OS was 12.6 months, and the estimated OS at 1 year was close to 51%.

“The majority of treatment-related adverse events were low-grade, started early in treatment, and quickly resolved after occurrence,” Dr. Sabari noted.

Grade 1-2 treatment-related adverse events occurred in 53% of patients while 45% had grade 3-4 treatment-related adverse events, and there were two fatal grade 5 treatment-related adverse events. The same events led to a dose reduction in 52% of the group overall and dose interruption in

61%, while in 7% of patients, treatment-related adverse events led to discontinuation of the drug.

## CNS metastases

At baseline, some 42 patients had evidence of central nervous system (CNS) metastases. At a median follow-up of 15.4 months, an intracranial-confirmed objective response was achieved in one-third of this subgroup overall while median duration of the intracranial response was 11.2 months. Again, within the same subgroup, the median PFS was 5.4 months.

As Dr. Sabari noted, CNS metastases from KRAS mutant NSCLC are common. “Adagrasib demonstrated encouraging and durable CNS-specific activity in patients with KRAS G12C-mutant NSCLC and active, untreated CNS metastases.”

The study was funded by Mirati Therapeutics. ■

# Vaping safety views shifted following lung injuries

BY KELLY RAGAN

Adults in the United States increasingly perceive electronic cigarettes, or e-cigarettes, as “more harmful” than traditional cigarettes, according to a new study published in the *American Journal of Preventive Medicine* (2022 Jun 8. doi: 10.1016/j.amepre.2022.03.019).

In addition, the percentage of people who exclusively used traditional cigarettes almost doubled between 2019 and 2020 among those who perceived e-cigarettes as more harmful, jumping from 8.4% in 2019 to 16.3% in 2020.

“We were able to show that these changes in perception potentially changed behaviors on a population level,” said Priti Bandi, PhD, principal scientist at the American Cancer Society in Atlanta and lead author of the study.

Since e-cigarettes entered the U.S. market in 2006, public health experts have questioned claims from manufacturers that the products work as a harm-reduction tool to help traditional cigarette smokers to quit. Public perceptions have generally been that e-cigarettes are safer for a person’s health. While the research is still emerging on the long-term health outcomes of users, public opinion has shifted since the introduction of the devices.

The new study showed a sharp change in public perception of e-cigarettes following media coverage of cases of users who presented to emergency rooms with mysterious lung symptoms in 2019. The Centers for Disease Control and Prevention eventually found that what are now called e-cigarette or vaping product use–associated lung injuries were linked to vitamin E acetate, an additive to tetrahydrocannabinol-containing products but not nicotine.

The last update from the CDC came in February 2020, shortly before the COVID-19 pandemic swept through the United States, prompting a sharp shift to investigate the new virus among both health care providers and researchers.

Dr. Bandi and colleagues gathered 2018-2020 data from a National Institutes of Health database called the Health Information National Trends Survey, a mail-based, nationally representative, cross-sectional survey of U.S. adults and their attitudes of cancer and health-related



AndreyPopov/Getty Images

information. More than 3,000 people each year responded to questions about e-cigarettes.

The study found that the percentage of people who believed e-cigarettes to be more harmful than traditional cigarettes more than tripled from 6.8% in 2018 to 28.3% in 2020.

Fewer people also viewed e-cigarettes as less harmful than traditional cigarettes, falling from 17.6% in 2018 to 11.4% in 2020. Fewer people also said they were unsure about which product was more harmful.

Among those who believed e-cigarettes were “relatively” less harmful than traditional cigarettes, use of e-cigarettes jumped from 15.3% in 2019 to 26.7% in 2020.

## The implications

The main finding that people started smoking cigarettes when they thought e-cigarettes were more harmful should be a wake-up to public health officials and doctors who communicate health risks to patients, according to Dr. Bandi and other experts.

Messaging should be more nuanced, Dr. Bandi said. Many adults use e-cigarettes as a cessation tool, and she and other experts point to research that shows the products are, at least in the short-term, less harmful especially as a smoking cessation tool. Vapes are among the most popular tools people use when they want to quit smoking – with the majority of U.S. adults using vapes either partially or

fully to quit, according to the CDC (*Chronic Dis.* 2017;14:160600. doi: 10.5888/pcd14.160600).

Some countries, such as England, are moving to allow doctors to prescribe e-cigarettes to help reduce smoking rates. United Kingdom regulatory authorities in 2021 said

*The main finding that people started smoking cigarettes when they thought e-cigarettes were more harmful should be a wake-up to public health officials and doctors.*

they’re considering allowing licensing of the devices for use in smoking cessation.

“There is an absolute need for ongoing, accurate communication from public health authorities targeted toward the appropriate audiences,” Bandi said.

Ashley Brooks-Russell, PhD, MPH, associate professor at the University of Colorado at Denver, Aurora, said the finding that perceptions can change behavior is good news. However, the bad news is that adults overcorrected and switched to cigarettes, which are proven to cause cancer and other health conditions.

“We’re good in public health about messaging that cigarettes are bad, that tobacco is broadly harmful,” Dr. Brooks-Russell said in an interview. “We’re really bad at talking about

lesser options, like if you’re going to smoke, e-cigarettes are less harmful.”

But other health leaders warn that e-cigarettes might produce the same adverse health outcomes, or worse, as cigarettes.

The only way researchers will gain a conclusive answer is decades into a patient’s life. Until then, it will not be clear if any potential benefit from smoking cessation will outweigh the risks.

“This research should remind healthcare providers to find out what products patients are using, how much, and if those patients experience health issues later on,” said Kevin McQueen, MHA, lead respiratory director at University of Colorado Health System and president of the Colorado Respiratory Care Society.

“My concern is that while people are starting to think e-cigarettes are more dangerous, some people still think they are safe – and we don’t know how much safer they are,” he said. “And we aren’t going to know until 10, 15, 20 years from now.”

All authors were employed by the American Cancer Society at the time of the study, which receives grants from private and corporate foundations, including foundations associated with companies in the health sector for research outside of the submitted work.

The authors are not funded by or key personnel for any of these grants, and their salaries are solely funded through American Cancer Society funds. No other financial disclosures were reported. ■



# Race-based spirometry may miss diagnoses in Black patients

BY NEIL OSTERWEIL

SAN FRANCISCO – It may be time to move beyond relying largely on spirometry to distinguish between healthy and abnormal lung function in diverse populations.

That conclusion comes from investigators who looked at patients with ostensibly normal spirometry values in a large population-based study and found that using standard equations to adjust for racial differences in lung-function measures appeared to miss emphysema in a significant proportion of Black patients.

“Our traditional measures of lung health based on spirometry may be under-recognizing impaired respiratory health in Black adults and particularly Black men,” said lead author Gabrielle Liu, MD, a fellow in the division of pulmonary and critical care medicine at the Northwestern University Feinberg School of Medicine, Chicago.

“CT imaging may be useful in the evaluation of those with suspected impaired respiratory health and normal spirometry,” she said in an oral abstract session at the American Thoracic Society International Conference 2022.

Dr. Liu and colleagues studied the association between self-identified race and visually identified emphysema among 2,674 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The patients had CT scans at a mean age of 50 and spirometry at a mean age of 55.

## Racial differences

The investigators found that, among men with forced expiratory volume in 1 second (FEV<sub>1</sub>) ranging from 100% to 120% of predicted according to race-adjusted formulas, 14.6% of Black men had emphysema, compared with only 1.7% of White men ( $P < .001$ ).

Respective emphysema rates found in Black women and White women were 3.8% and 1.9%; this difference was not statistically significant.

Among patients with FEV<sub>1</sub> from 80% to 99% of predicted according to race-specific measures, 15.5% of Black men had emphysema,

compared with 4% of White men ( $P < .001$ ). Respective rates of emphysema were 6.9% for Black women versus 3.2% for White women ( $P = .025$ ).

When the investigators applied race-neutral spirometry reference equations to the same population, they found that it attenuated but did not completely eliminate the racial disparity in emphysema prevalence among patients with FEV<sub>1</sub>, ranging from 80% to 120% of predicted.

## Relic of the past

The results suggest that race-based adjustments of spirometry measures are a relic of less-enlightened times, said Adam Gaffney, MD, MPH, assistant professor of medicine at Harvard Medical School, Boston, and a pulmonologist and critical care physician at Cambridge Health Alliance, Mass.

“If the average lower lung function of Black people is being driven by adversity, structural racism, and deprivation, that means that race-specific equations are normalizing that adversity,” he said in an interview.

“In my opinion, it is time to move beyond race-based equations in clinical pulmonary medicine, particularly in the context of patients with established lung disease in whom use of race-based equations might actually lead to undertreatment,” said Dr. Gaffney, who was not involved in the study.

Dr. Liu agreed that it’s time to move to race-neutral measures and that the whole concept of race-based differences is flawed.

“The long-standing structural inequities in health likely made the reference populations have lower lung function than among Whites,” she told this news organization.

Dr. Liu said that evaluation of lung function should not rely on spirometry alone, but it should also include – when appropriate – the use of CT scans, as well as improved understanding of how symptoms may be predictive for poor outcomes.

The study was supported by grants from the National Institutes of Health. Dr. Liu and Dr. Gaffney have disclosed no relevant financial relationships. ■



**NASHVILLE CHEST 2022**  
OCTOBER 16-19

## Register today for CHEST 2022

CHEST 2022 is back in person in Nashville, Tennessee, October 16-19. Join your friends and colleagues for the one-of-a-kind experience that is CHEST 2022.

## Music City is waiting for you!

### What can you expect from CHEST 2022?

- More than 300 educational sessions, including simulation and interactive learning opportunities, addressing the challenges you face in clinical practice
- Original investigation presentations with new, unpublished science
- Networking and social opportunities with experts in your field and from around the world
- New diagnostic and treatment solutions showcased in the CHEST Exhibit Hall
- CME/CE credits and MOC points for hundreds of sessions

Register | [chestmeeting.chestnet.org](https://chestmeeting.chestnet.org)

**CHEST**

# NTM lung disease can be challenging to treat

BY JUDY STONE, MD

Living in coastal areas of Florida and California has great appeal for many, with the warm, sunny climate and nearby fresh water and salt water.

But, unknown to many, those balmy coasts also carry the risk of infection from nontuberculous (atypical) mycobacteria (NTM). Unlike its relative, tuberculosis, NTM is not transmitted from person to person, with one exception: patients with cystic fibrosis.

It is estimated that there were 181,000 people with NTM lung disease in the U.S. in 2015, and according to one study, the incidence is increasing by 8.2% annually among those aged 65 years and older. But NTM doesn't only affect the elderly; it's estimated that 31% of all NTM patients are younger than 65 years.

With the warm, moist soil and water, NTM is most commonly found in Florida, California, Hawaii, and the Gulf Coast states. The incidence is somewhat lower in states along the Great Lakes. Other states are not without risk – but NTM is perhaps even more likely to be overlooked in these states by physicians because of a lack of awareness of the disease.

Rebecca Prevots, PhD, MPH, chief of the epidemiology and population studies unit of the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases, told this news organization that “why NTM is increasing is one of the most common questions” she gets, followed by whether it is due to climate change. “The short answer is, we don't know.”

She suggests that the increase in diagnoses is due to a combination of increased awareness, host susceptibility, and perhaps environmental changes. One problem is that NTM is not a reportable disease. Also, public health resources have been decimated, both through funding cuts and loss of personnel. Dr. Prevots said, “It's not just NTM surveillance that is important, but you can't just make a certain condition reportable and expect to have good data without putting resources to it. ... Diseases are made reportable at the state level. There's no mandated reporting up to CDC. So CDC is piloting reporting events through their emerging infectious program.”

Anthony Cannella, MD, assistant professor of infectious diseases at the University of South Florida (USF), is in the midst of NTM. He told this news organization that “there's a huge circle with big old dots right over the center of the state.” He is adamant that “a soil-water survey has to occur. We need to know what the devil is happening.”

## Who gets NTM?

*Mycobacterium avium* complex primarily causes lung disease, which presents as two clinical syndromes.

“These infections don't affect everyone,” Kenneth Olivier, MD, MPH, chief of pulmonary clinical medicine, Cardiovascular Pulmonary Branch of the National Heart, Lung, and Blood Institute, said in an interview. They affect “patients that have underlying genetic conditions

that cause abnormalities in the airway clearance mechanisms, particularly cystic fibrosis and primary ciliary dyskinesia [and], to some extent, patients with COPD.”

The second group is “comprised mainly of postmenopausal women, many of whom have had no predisposing medical problems prior to onset of generally frequent throat clearing or chronic cough, which is what brings them to medical attention.” Dr. Olivier added that “many of these patients have a fairly unique appearance. They tend to have a high prevalence of curvature of the spine, scoliosis, indentation of the chest wall (pectus excavatum), and physical characteristics that overlap heritable connective tissue disorders like Marfan syndrome or Ehlers-Danlos syndrome.”

Dr. Olivier pointed out a major problem in NTM diagnosis and treatment: “The guidelines-based approach to chronic cough generally calls for treating postnasal drip, airway reactivity, asthma-type symptoms first empirically, before doing different diagnostic studies. That generally causes a delay in obtaining things like CT scan, where you can see the characteristic changes.”

Dr. Cannella added, “People are starting to become more aware of it. It's kind of like pneumocystis back in the 80s. ... We've had patients who have had long periods of febrile neutropenia, and NTM wasn't on the radar. Now we've picked up at least seven or eight.”

In addition to pulmonary infections, nosocomial outbreaks have occurred, owing to contaminated heater-cooler units, catheter infections, nail salons, or medical tourism. These more commonly involve rapidly growing species, such as *M. abscessus*, *M. chelonae*, and *M. fortuitum*. Clinicians should also be aware of skin infections from *M. marinum*, which come from wounds from aquariums, fish, or shellfish. Incubation can occur over months, highlighting the importance of a detailed history and special cultures.

## Diagnostics

The diagnosis of NTM is delayed for several reasons. One is the lack of awareness among clinicians about NTM and its risk factors, including hobbies such as gardening or working in places where dirt is aerosolized, such as on road crews, or even from hot tubs. A thorough history is critical.

Another is not recognizing the need for an acid-fast bacilli (AFB) culture, which requires specialized media. Fortunately, NTM can be picked up on fungal cultures, Dr. Cannella noted. Clinicians are sometimes discouraged from culturing AFB because doing so may not be cost effective. And many hospital laboratories are increasingly sending cultures to outside labs, and it can take days – sometimes even more than a week – to receive a report of results.

Charles Daley, MD, chief of the Division of Mycobacterial and Respiratory Infections at National Jewish Health, expressed his frustration about labs in an interview, saying diagnostics is “an important hole in the U.S., as our laboratories do not provide clinicians with the results that they need to make good decisions.

## Sachin Gupta, MD, FCCP, comments:

NTM is challenging to diagnose and manage, like many of the less common conditions in pulmonology we manage. Our residents, and sometimes fellows, frequently lack the preparedness to diagnose and manage the disease, much less tackle the systems issues (lab collection, processing, lengthy follow-up, etc.) once they are in practice. This article is a nice, brief, summary of the “state of NTM” by experts in the field.



Most laboratories in the U.S. just don't speciate the organisms or subspeciate in the setting of abscesses. They don't tell the clinician enough about the susceptibility, particularly whether there's inducible resistance. As a clinician, you just don't have the information to make the right decisions. ... We need to improve diagnostics in NTM. Everything is there and available. They just don't want to do it because it increases the costs.”

Men tend to have fibrocavitary disease, which shows on ordinary chest x-rays, but CT scans are essential for women because women tend to have either nodular disease or bronchiectasis, which does not show on a plain film.

## Treatment

A standard treatment for NTM lung disease includes three or four medications – clarithromycin or azithromycin, rifampin or rifabutin, ethambutol, and streptomycin or amikacin. In vitro resistance is important in predicting the clinical response to a macrolide or amikacin.

For bronchiectatic disease, National Jewish Hospital recommends treatment three times per week rather than daily therapy, as it is better tolerated. Azithromycin is preferred over clarithromycin. Amikacin should be added if there is cavitary or severe disease, and the macrolide is then given daily.

Dr. Olivier suggested that physicians stagger the initiation of those drugs to improve the tolerability of the difficult regimen. Generally, treatment is for 18 months – a year after sputum cultures become negative.

If therapy fails – that is, sputum is persistently positive at 6 months – amikacin liposomal inhalation solution (Arikayce) is likely to be added. Patients should be monitored with monthly safety labs, sputum cultures, and an audiogram (if receiving amikacin). Every 3 months, vestibular tests, eye exams, and spirometry should be conducted, and every 6 months, physicians should order a CT, an audiogram, and an electrocardiogram.

Despite completing such a rigorous regimen, about half of patients experience reinfection because of their underlying host susceptibility.

NTM continued on following page

# NAVIGATOR steers severe asthma toward safe harbor

BY NEIL OSTERWEIL

SAN FRANCISCO – Nearly half of all patients with severe, uncontrolled asthma who received a full course of the biologic agent tezepelumab (Tezspire) in the NAVIGATOR trial had a complete response to treatment at 1 year, results of a prespecified exploratory analysis indicated.

Among 471 patients assigned to tezepelumab who completed the on-treatment period of the phase 3 randomized trial, 46% had a complete response at 52 weeks, compared with 24% of patients assigned to placebo.

Complete response was defined as reduction in exacerbations of at least 50% over the previous year, improvement from baseline in Asthma Control Questionnaire 6 (ACQ-6) total score of at least 0.5 points, improvement in prebronchodilator forced expiratory volume in 1 second (pre-BD FEV<sub>1</sub>), and physician-assessed Clinical Global Impression measure of clinical change (CGI-C) score.

“These data further support the efficacy of tezepelumab in a broad population of patients with severe, uncontrolled asthma,” said Njira Lugogo, MD, of the division of pulmonary and critical care medicine at the University of Michigan, Ann Arbor.

Dr. Lugogo presented results of the exploratory analysis at the American Thoracic Society’s international conference.

## Exacerbations reduced, lung function improved

Primary results from NAVIGATOR, published in *The New England Journal of Medicine* (2021 May 13, doi: 10.1056/NEJMoa2034975),

showed that patients with severe, uncontrolled asthma randomly assigned to tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life compared with patients assigned to placebo.

The investigators noted that approximately 10% of patients with asthma have symptoms and exacerbations despite maximal standard-of-care controller therapy.

Tezepelumab is a human monoclonal antibody that inhibits action of thymic stromal lymphopoeitin (TSLP), an epithelial cytokine that is released in response to airborne triggers of asthma. TSLP is a major contributor to initiation and persistence of airway inflammation, Dr. Lugogo said.

The on-treatment analysis looked at all patients in the trial who completed 52 weeks of treatment and had complete data for all criteria studied.

The odds ratios (OR) for patients on tezepelumab achieving each of the response criteria are shown in the table.

## Exacerbations explored

In a separate presentation, Christopher S. Ambrose, MD, MBA, of AstraZeneca in Gaithersburg, Md., presented information from investigator-narrative descriptions of all hospitalization events related to asthma exacerbations (mild, moderate, or severe) that occurred while the investigator was blinded to each patient’s treatment assignment in NAVIGATOR.

In all, 39 of 531 patients (7.3%) assigned to placebo had a total of 78 exacerbations requiring hospitalization, compared with 13 of 528 patients (2.5%) assigned to tezepelumab. The latter group had a total of 14 exacerbations requiring

TEZPELUMAB VS. PLACEBO

## Likelihood of patients achieving response criteria

Response criterion	Odds ratio	95% confidence interval
Asthma Control Questionnaire 6 total score	1.99	1.38-2.87
Prebronchodilator FEV <sub>1</sub>	1.52	1.15-2.01
Reduced exacerbations	2.73	1.98-3.77
Improvement in Clinical Global Impression measure of clinical change score	2.25	1.61-3.14
Complete response	2.83	2.10-3.82

Note: Based on data for 471 patients assigned to tezepelumab who completed the on-treatment period of the phase 3 randomized trial.

Source: Dr. Lugogo

hospitalization during the study.

Among hospitalized patients, 32 of the 39 assigned to placebo had severe, incapacitating exacerbations, compared with 5 of 13 assigned to tezepelumab.

Reported symptoms were generally similar between hospitalized patients in the two treatment groups, although there appeared to be trends toward lower incidence of dyspnea, fever, and tachycardia with tezepelumab.

Health care resource utilization, a surrogate marker for disease burden, was substantially lower for patients assigned to tezepelumab.

Infections were the most common triggers of exacerbations in both groups.

“These data provide further evidence that tezepelumab can reduce the burden of disease of severe uncontrolled asthma, both to patients and to health care systems,” Dr. Ambrose said.

## Head-to-head studies needed

Although there have been no head-to-head comparisons of biologic agents for asthma to date, results of these studies suggest that

tezepelumab has efficacy similar to that of other agents for reducing exacerbation, said Fernando Holguin, MD, MPH, from the University of Colorado at Denver, Aurora, who comoderated the oral session but was not involved in the study.

Biologic agents appear to be slightly more effective against type 2 inflammation in asthma, “but in general I think we give it to a broader severe population, so that’s exciting,” he told this news organization.

Comoderator Amisha Barochia, MBBS, MHS, of the National Institutes of Health, Bethesda, Md., told this news organization that head-to-head trials of biologic agents would provide important clinical information going forward.

“Should we switch to a different biologic or add a second biologic? Those are questions we need answers for,” she said.

The NAVIGATOR trial is funded by AstraZeneca and Amgen. Dr. Lugogo disclosed financial relationships with both companies. Dr. Holguin and Dr. Barochia disclosed no relevant financial relationships ■

NTM continued from previous page

Genomic sequencing shows that these are new infections, not relapses, Dr. Prevots also noted that gastroesophageal reflux disease is a significant risk factor because of chronic aspiration.

Dr. Daley outlined the newer treatments being studied, including Arikayce, omadocycline, and bedaquiline. He added, “There’s a neutrophil elastase-inhibitor trial that’s ongoing, a huge trial. There’s another one looking at basically eosinophilic inflammation.” Other trials are in the offing, he said, all focusing on the inflammatory response – a development he described as exciting, because for the longest time, there were few if any NTM trials.

Dr. Cannella is also buoyed by the potential synergy of dual beta-lactam therapy with

ceftriaxone and a carbapenem for *M. abscessus* infections, which are notoriously difficult to treat.

## Tips for patients and physicians

The experts interviewed gave recommendations:

- NTM is resistant to chlorine and bromine, so tap water is a major source of infection. Patients should consider increasing the hot water temperature to greater than 130° F and using metal showerheads or bathing rather than showering.
- Good bathroom ventilation helps.
- Patients should consider using a water filter that filters entities less than 5 micrometers in size – but not carbon filters, which concentrate the organisms.
- Humidifiers and hot tubs should be avoided.
- A good face mask, such as an N95, should be

worn when gardening or repotting plants.

Dr. Olivier stressed that clinicians should familiarize themselves with the guidelines for diagnosing and treating NTM. And clinicians should be aware that using azithromycin for bronchitis might cause resistance in NTM. “Macrolide resistance turns what may be a slowly progressive or bothersome infection into a lethal infection with a 1-year mortality of 35%. ... I would just urge that, if the patient’s on their second or third Z-Pak within a year, it’s probably time to look for other causes of what might be happening.”

Dr. Cannella, Dr. Prevots, and Dr. Olivier reported no relevant financial relationships. Dr. Cannella added, “My views are not those of my employers.” Dr. Daley reported relationships with a variety of companies. ■

# GOLD report: Tips for diagnosing, evaluating patients

BY LINDA GIRGIS, MD

For many years, COPD has remained one of the top four leading causes of death in the United States according to CDC data. Around the world, it is responsible for about 3 million deaths annually. It is estimated that 16 million Americans are now diagnosed with COPD. However, it is commonly agreed by experts that it is widely underdiagnosed and there may be millions more suffering from this disease.

The costs of COPD are around \$49 billion a year in direct costs, with billions more in indirect costs. Around the globe, COPD is one of the top three causes of death, with 90% of deaths happening in low- and middle-income countries. The burden of COPD is expected to grow over time because of the aging population and continued exposure to COPD risk factors.

The Global Initiative for Chronic Obstructive Lung Disease report (or GOLD) is revised every year, translated into many languages, and used by health care workers globally. It was started in 1998, and its aim was

to produce guidelines based on the best scientific evidence available that was nonbiased to be used for assessment, diagnosis, and treatment of patients with COPD. The first report was issued in 2001. The method of producing the GOLD report was to do a search of PubMed for evidence-based, peer-reviewed studies. Those not captured by this method could be submitted for review. The science committee then meets twice a year and reviews each publication, eventually agreeing on a set of guidelines/updates.

## 2022 GOLD report

For the 2022 GOLD report, 160 new references were added. Overall, the GOLD report is five chapters (more than 150 pages) giving in-depth guidance for the diagnosis, prevention, management, and treatment of patients with stable COPD, COPD exacerbations, and hospitalized patients.

The report suggests that COPD is being underdiagnosed. It's important for primary care doctors to understand the new guidelines, because they are the clinicians who are most likely to be diagnosing and

treating patients with COPD.

Family physicians and internists will be seeing more and more cases as the population ages, and we need to do a better job of recognizing patients who have COPD. If possible, we should try to have spirometry available in our practices. Like any other disease, we know prevention works best so primary care physicians also need to be looking for risk factors, such as smoking history, and help patients try to reduce them if possible. Below is more explanation of the latest guidelines.

For most of us, when we learned about COPD as a disease, the terms "chronic bronchitis" and "emphysema" were emphasized. These words are no longer used as synonymous for COPD.

The disease is now described as involving chronic limitation in airflow that results from a combination of small airway disease and parenchymal destruction (emphysema). The rates of each vary from person to person and progress at different rates. Key factors that contribute to COPD disease burden include chronic inflammation, narrowing of small airways, loss of alveolar attachments, loss of elastic recoil, and mucociliary dysfunction, according to the 2022 GOLD report.

Respiratory symptoms may precede the onset of airflow limitation. COPD should be considered in any patient with dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections, and risk factors for the disease.

The biggest risk factor for COPD is smoking. Other risk factors include occupational exposure, e-cigarette use, pollution, genetic factors, and comorbid conditions. Symptoms of the disease can include chest tightness, wheezing, and fatigue.

To make a diagnosis of COPD, spirometry is required, the latest GOLD report says. A postbronchodilator  $FEV_1/FVC$  less than 0.70 confirms persistent airflow limitation and hence COPD. This value is used in clinical trials and forms the basis of what most treatment guidelines are derived from. It would be beneficial for any physician treating COPD patients to have easy access to spirometry. It provides the most reproducible and objective measurement of airflow limitation. Also, it was found that assessing the degree of reversibility of airflow limitation to decide therapeutic decisions is no



Dr. Girgis practices family medicine in South River, N.J., and is a clinical assistant professor of family medicine at Robert Wood Johnson Medical School, New Brunswick, N.J.

longer recommended and thus, asking the patient to stop inhaled medications beforehand is unnecessary. To access the impact COPD has on a patient's life beyond dyspnea, the guidelines recommend doing a disease-specific health questionnaire, such as the COPD Assessment Test (CAT).

Along with patient symptoms and history of exacerbations, spirometry is crucial for the diagnosis, prognosis, and therapeutic decisions in COPD patients, according to the GOLD guidance. The best predictor of frequent exacerbations, however, is a history of previous exacerbations. In cases where there is a discrepancy between airflow limitation and symptoms, additional testing should be considered. Alpha-1 antitrypsin deficiency (AATD) screening should be considered in younger patients (under 45 years) with perilobular emphysema, and those in areas of high AATD prevalence. Chest x-rays are not recommended in diagnosing COPD but can be helpful if other comorbidities are present. CT scan is not routinely recommended but should be used only for the detection of bronchiectasis, if the patient meets the criteria for lung cancer screening, if surgery is necessary, or if other diseases may need to be evaluated.

Pulse oximetry can be helpful in accessing degree of severity, respiratory failure, and right heart failure. Walking tests can be helpful for evaluating disability and mortality risk. Other tests that have been used but are not routinely recommended include plethysmography and diffusing capacity of the lungs for carbon monoxide.

Composite scores can identify patients who are at increased risk of mortality. One such score is the BODE (Body mass, Obstruction, Dyspnea, and Exercise) method. Biomarkers are being investigated, but data are still not available to recommend their routine use. ■





**Join CHEST for online live sessions in August**

<b>PEDIATRIC PULMONARY MEDICINE</b> AUGUST 12-15	<b>CRITICAL CARE MEDICINE</b> AUGUST 12-15	<b>PULMONARY MEDICINE</b> AUGUST 17-20
---------------------------------------------------------	---------------------------------------------------	-----------------------------------------------

Prep for your board certification exam with the experts in chest medicine board review. Leading chest medicine experts show you how to solve case-based problems during live sessions and give in-depth answers to your questions.

**12 months of unlimited access** to course materials with online live sessions in August

Course content follows the **ABIM certification exam blueprint**

**Earn CME/MOC** for completing the course

**More than 89% of attendees** would recommend CHEST Board Review courses to colleagues

Register at [boardreview.chestnet.org](http://boardreview.chestnet.org)

# Is sleep an important key to exacerbations?

BY MARK S. LESNEY, PHD

MDEdge News

**P**oor sleep quality was linked to an increased risk of life-threatening exacerbations in people with chronic obstructive pulmonary disease (COPD), according to a study reported online in the journal *Sleep* (2022 Jun 6. doi: 10.1093/sleep/zsac107).

Researchers followed 1,647 patients with confirmed COPD who were enrolled in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS). SPIROMICS is a multicenter study funded by the National Heart, Lung, and Blood Institute and the COPD Foundation and is designed to evaluate COPD subpopulations, outcomes, and biomarkers. All participants in the study were current or former smokers with confirmed COPD.

COPD exacerbations over a 3-year follow-up period were compared against reported sleep quality. The researchers used the Pittsburgh Sleep Quality Index (PSQI), a combination of seven sleep measures, including sleep duration, timing of sleep, and frequency of disturbances. The higher the score, the worse the quality of sleep.

Individuals who self-reported having poor-quality sleep had a 25%-95% higher risk of COPD exacerbations, compared with those who reported good-quality sleep, according to the results.

There was a significant association between PSQI score and total and mean exacerbations in the unadjusted analysis (incidence rate ratios, 1.09; 95% confidence interval, 1.05-1.13) and the analysis adjusted for demographics, medical comorbidities, disease severity, medication usage, and socioeconomic environmental exposure (IRR, 1.08; 95% CI, 1.03-1.13).

In addition, the PSQI score was independently associated with an increased risk of hospitalization, with a 7% increase in risk of hospitalization with each 1-point increase in PSQI, according to the researchers.

## Surprising findings

These findings suggest that sleep quality may be a better predictor of flare-ups than the patient's



Tuttye/Thinkstock

history of smoking, according to the researchers.

“Among those who already have COPD, knowing how they sleep at night will tell me much more about their risk of a flare-up than knowing whether they smoked for 40 versus 60 years. ... That is very surprising and is not necessarily what I expected going into this study. Smoking is such a central process to COPD that I would have predicted it would be the more important predictor in the case of exacerbations,” said lead study author Aaron Baugh, MD, a practicing pulmonologist, and a clinical fellow at the University of California, San Francisco, in a National Institutes of Health press release on the study.

The study findings were applicable to all races and ethnicities studied; however, the results may be particularly relevant to Black Americans, Dr. Baugh indicated, because past studies have shown that Black Americans tend to have poorer sleep quality than other races and ethnicities. With poorer sleep linked to worse COPD outcomes, the current study may help explain why Black Americans as a group tend to do worse when they have COPD, compared with other racial and ethnic groups, the researchers suggested.

The study was supported by the National Institutes of Health and the COPD Foundation. SPIROMICS was supported by NIH and the COPD Foundation as well as numerous pharmaceutical and biotechnology companies. The authors reported no other financial disclosures. ■

9<sup>TH</sup> ANNUAL

Irving Feldman  
TEXAS  
HOLD 'EM  
ANNUAL TOURNAMENT & CASINO NIGHT

IN PERSON | SATURDAY, AUGUST 27, 2022  
DOORS OPEN: 5:30 PM | CARDS FLY: 7 PM

## FIRST PRIZE

**\$10,000 seat to the 2023 World Series of Poker  
Main Event in Las Vegas**

The CHEST Foundation invites you to a lively Texas Hold 'Em tournament, plus dining and more:

- ♠ Casino gaming
- ♠ Silent auction
- ♠ Raffle prizes
- ♠ Steak and seafood dinner
- ♠ Specialty cocktails by Tito's Vodka

Supporting improved patient access and better quality of life for those battling pulmonary fibrosis.

Get tickets or donate to the cause at  
[one.bidpal.net/irv](http://one.bidpal.net/irv)

**GIBSONS**  
BAR • STEAKHOUSE

GIBSONS BAR & STEAKHOUSE  
2105 SOUTH SPRING ROAD | OAK BROOK, IL 60523

**FFF** | FELDMAN  
FAMILY  
FOUNDATION

**CHEST**<sup>®</sup>  
FOUNDATION

PRESENTED BY



Poker partner organizations:  
Poker League of Nations, Poker Power, Chicagoland Poker Players

# Can eosinophils predict acute exacerbation outcomes?

BY HEIDI SPLETE

MDedge News

**H**igh levels of eosinophils had a protective effect for individuals who experienced acute exacerbations of chronic obstructive pulmonary disease, based on data from nearly 1,000 patients.

Several blood biomarkers are under investigation for links to acute exacerbation of chronic obstructive pulmonary disease (AECOPD), which remains one of the top three causes of death worldwide, wrote Riuying Wang, MD, of Third Hospital of Shanxi Medical University, Taiyuan, China, and colleagues.

“Numerous studies have shown the relationship between eosinophilia and clinical outcomes of patients with AECOPD. However, the evidence lacks consensus, and the research thresholds are controversial,” they said.

In a study published in *Heart & Lung*, the researchers reviewed data from 984 adults with AECOPD over a 3-year follow-up period. The mean

age of the patients was 71 years, and 78% were men. The patients’ blood eosinophil levels were grouped into three categories: EOS < 2%, EOS from 2% to < 3%, and EOS 3% or higher. The researchers examined the association between eosinophilia and various comorbidities, treatment, and mortality.

*Significantly fewer deaths occurred among patients with EOS of 2% or higher, compared with the lower EOS group, suggesting that “Eosinophils can be used as a prognostic indicator of mortality in AECOPD.”*

Eosinophilia occurred in 477 cases. The prevalence of eosinophilia in the three groups was 36.48%, 22.87%, and 48.48% respectively, with eosinophilia defined as eosinophil counts of at least 100 cells per microliter, according to the report in *Heart & Lung* (2022 Jun 7.

doi: 10.1016/j.hrtlng.2022.05.012).

An EOS of 2% or higher was associated with significantly fewer cases of complicated pulmonary heart disease and atrial fibrillation than the lower EOS group. Similarly, patients in the EOS group of 2% or higher were less likely to use ventilators and systemic glucocorticoids and those in the EOS less than 2% group had significantly heavier airflow limitation, higher D-dimer, higher burden of infectious inflammation, and higher prevalence of respiratory failure than the other groups.

In addition, significantly fewer deaths occurred during the study period among patients with EOS of 2% or higher, compared with the lower EOS group ( $P < .01$ ). The findings suggest that “Eosinophils can be used as a prognostic indicator of mortality in AECOPD,” the researchers said.

The researchers also used the area under the curve to examine the predictive value of EOS. The ROC curve showed that the indicators of AUC 0.5 included chest CT imaging, osteoporosis, mental illness,

dust exposure, and being a former smoker; however, “the predictive value of EOS by the ROC curve was unstable. Further validation in large samples is needed,” the researchers wrote in their discussion.

The study findings were limited by several factors including the retrospective design and use of data from a single center, the researchers noted. Other limitations included the relatively small sample size and a lack of data on some clinical features and performance metrics, as well as lack of evaluation of chest CT subtypes.

However, the results are consistent with previous studies on infection and antibiotics and reviewed the optimal threshold of AECOPD, the researchers wrote. Based on their findings, “Eosinophils can not only guide clinical treatment but also be used as an index to predict the clinical outcome and prognosis of AECOPD patients,” they concluded.

The study received no outside funding. The researchers had no financial conflicts to disclose. ■

## New target found for mitigating mucus hypersecretion

BY HEIDI SPLETE

MDedge News

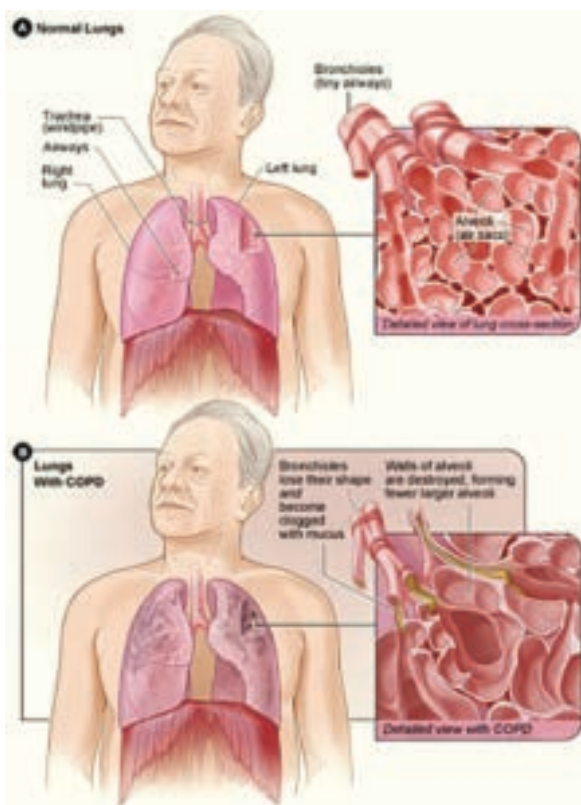
**T**reatment with an interleukin-6 neutralizing antibody significantly reduced airway mucus hypersecretion (AMH) in chronic obstructive pulmonary disease (COPD), based on data from human and mouse cells in a human organoid model.

AMH plays a large part in aggravating airway obstruction in patients with COPD, Yuan-Yuan Wei, MD, of First Affiliated Hospital of Anhui Medical University, Hefei, China, and colleagues wrote.

Current pharmacotherapies relieve COPD symptoms and improve exercise tolerance, but have not proven effective for relieving the airflow limitations caused by mucus accumulation that “leads to irreversible structural damage and an unfavorable prognosis,” the researchers said. Although reducing AMH could help manage COPD, the molecular mechanisms of action have not been fully explored.

In a study published in *Biomedicine & Pharmacotherapy* (2022 Jun 7. doi: 10.1016/j.biopha.2022.113244), the researchers examined the relationship between IL-6 and AMH. Since IL-6 has been shown to cause overexpression of the mucin-type protein known as Muc5ac, they hypothesized that IL-6 antibodies (IL-6Ab) might block this protein elevation.

The researchers recruited 30 adults with COPD and 30 controls from a single center. Bronchial



epithelial cells were isolated from the participants and measured the levels of Muc5ac protein and mRNA in the lung tissue. Compared with controls, COPD patients had elevated Muc5ac positively correlated with IL-6.

The researchers then created an organoid model of a trachea for COPD patients and

controls. In the model, Muc5ac was similarly elevated in COPD patients, compared with controls. “Furthermore, IL-6 significantly induced excessive secretion of mucus in the organoid model of trachea in COPD patients as observed under electron microscope, and IL-6Ab attenuated these effects,” they noted.

IL-6 significantly increased both Muc5ac mRNA and protein expression in the organoid model of trachea ( $P < .0001$  and  $P < .005$ , respectively), but both of these significantly decreased when treated with IL-6Ab ( $P < .0001$  and  $P < .05$ , respectively).

The researchers also examined human and mouse cells to explore the mechanism of action of IL-6Ab. Using high-throughput sequencing, they found that the IL-6Ab induced nuclear translocation of the Nrt2 gene in COPD patients, and that this action promoted the effect of IL-6Ab on excessive mucus secretion.

The study findings were limited by the relatively small study population from a single center, the researchers noted.

However, the results support the potential of IL-6Ab as “a novel therapeutic strategy in the treatment of IL-6-induced hypersecretion of airway mucus so as to improve airflow limitations in COPD,” they concluded.

The study was supported by the National Natural Science Foundation of China and the Scientific Research Project of Education Department of Anhui Province. The researchers had no financial conflicts to disclose. ■

# Childhood melatonin poisonings skyrocket in the past 10 years

BY PAM HARRISON

MDedge News

The number of children in the United States who unintentionally ingested melatonin supplements over the past 10 years has skyrocketed to the point where, as of 2021, melatonin ingestions by children accounted for almost 5% of all poisonings reported to poison control centers in the United States, data from the National Poison Data System (NPDS) indicate.

This compared with only 0.6% of melatonin ingestions reported to poison control centers in 2012, the authors added.

Basically, the number of pediatric melatonin ingestions increased from 8,337 in 2012 to 52,563 in 2021, from the beginning of the study until the end, Michael Toce, MD, one of the study authors and attending, pediatric emergency medicine/medical toxicology, Boston Children's Hospital, said in an interview.

“And I think the biggest driver of this increase is simply that sales of melatonin have increased astronomically so there is just more melatonin at home and studies have shown there is a correlation between the amount of an individual medication in the home and the risk of pediatric exposure – so simply put: The more of a single substance in a home, the greater the chance that a child is going to get into it,” he underscored.

The study was published in the *Morbidity and Mortality Weekly Report* (2022 Jun 3. doi: 10.15585/mmwr.mm7122a1).

## Melatonin ingestions

All cases of single substance melatonin ingestions involving children and adolescents between Jan. 1, 2012, and Dec. 31, 2021, were included in the analysis. During the 10-year study interval, 260,435 pediatric melatonin ingestions were reported to the NPDS. Over 94% of the reported ingestions were unintentional and 99% occurred in the home.

Over 88% of them were managed on-site; most involved young male children aged 5 years and under, and almost 83% of children who ingested melatonin supplements remained asymptomatic. On the other hand, 27,795 patients sought care at a health care facility and

close to 15% of them were hospitalized. Among all melatonin ingestions, 1.6% resulted in more serious outcomes; more serious outcomes being defined as a moderate or major effects or death. Five children required mechanical ventilation in order to treat their symptoms and 2 patients died.

The largest number of patients who were hospitalized were adolescents who took melatonin intentionally but the largest increase in the rate of exposure was in young, unintentional patients, as Dr. Toce observed. Interestingly, the largest yearly increase in pediatric melatonin ingestions – almost 38% – coincided with the onset of the COVID-19 pandemic.

“This might be related to increased accessibility of melatonin during the pandemic, as children spent more time at home because of stay-at-home orders and school closures,” the authors speculate. Moreover, sleep disturbances were common during the pandemic, leading to a greater likelihood that parents were buying melatonin and thus exposing children to more melatonin at home.

Taken appropriately and at normal doses, melatonin in itself is quite safe, as Dr. Toce stressed. However, “for any substance, the dose makes the poison, so taken in any significant quantity, anything is going to be dangerous.” Moreover, it's important to appreciate that melatonin, at least in the United States, is regulated as a dietary supplement, not as a pharmaceutical.

“Thus, it doesn't get the same rigorous testing that something like acetaminophen does by the FDA and that means two things,” Dr. Toce noted. First, if the product says that each gummy contains 3 mg of melatonin, no independent body is verifying whether or not that statement is true so there could be 3 mg of melatonin in each gummy or there could be 10 mg.

Secondly, because there is no impartial oversight for dietary supplements, there may in fact be no melatonin at all in the product or something else may be added to it that might be harmful.

“Just because something is sold over-the-counter does not necessarily mean that it's safe,” Dr. Toce stressed. To keep children safe from pharmaceuticals and supplements,



Marjia Stepanovic/Getty Images

he recommended several generic poison prevention tips. This advice could be passed on to patients who are parents.

- Keep all pharmaceuticals and supplements preferably locked away so there is less risk of children and adolescents taking products either unintentionally or intentionally
- If parents have no place to lock their products up, put them out of reach, high-up so children cannot easily access them
- Keep the product in the original child-resistant packaging as opposed to taking the pills out of the packaging and putting it in a plastic bag. “Certainly we've seen that, when medications are moved into a non-child-resistant container, ingestions go up,” Dr. Toce warned
- Don't refer to any medicine or supplement a child might take as “candy.” “A lot of children have difficulty taking medications so some families will say: ‘It's time for your candy,’” Dr. Toce explained. They will not recognize it as medication and they're likely to pop it into their mouth, thinking it is candy.

Lastly, and most importantly, parents who are considering trying a melatonin supplement to help a child sleep better should first establish a stable sleep routine for their child. “They also need to limit caffeinated beverages before bed as well as screen time,” Dr. Toce added.

And they should talk with their primary care provider as to whether or not initiation of a melatonin supplement is appropriate for their child.

## Remarkable rise

In a comment on his own experience with melatonin poisoning over recent years, toxicology expert Kevin Osterhoudt, MD, of the University of Pennsylvania, Philadelphia and the Children's Hospital of Philadelphia, noted that it has been their experience that there has been a remarkable rise in poison center reports of children ingesting melatonin in the recent past. For example, the Poison Control Center at CHOP received nearly 4,000 calls involving melatonin ingestion by children 5 years old or younger in the 5 years between 2017 and 2021 with increasing numbers every year.

“The [current study] supports that our regional observation that this has been a national trend,” Dr. Osterhoudt said. Dr. Osterhoudt agreed with Dr. Toce that good sleep is healthy, and it is very important to develop good sleep habits and a regular bedtime routine in order to do so. “In some situations, melatonin may be useful as a short-term sleep aid and that's a good discussion to have with your child's health care provider.”

If parents do decide to give their child a melatonin supplement, they need to keep in mind that melatonin may alter how the body handles other drugs such as those used to treat epilepsy or blood clotting. They also need to know that experts are still uncertain about how melatonin affects the body over the long term.

The study authors and neither Dr. Toce nor Dr. Osterhoudt had any relevant conflicts of interest to declare. ■

# RSV kills 100,000 kids under age 5 a year worldwide

BY MARCIA FRELICK

**R**espiratory syncytial virus (RSV) caused more than 100,000 deaths in children under age 5 years globally in 2019, according to an analysis published online in *The Lancet* (2022 May 19. doi: 10.1016/S0140-6736[22]00478-0).

Researchers, led by You Li, PhD, of Nanjing (China) Medical University, found that nearly half of those (more than 45,000) occurred in children younger than 6 months old.

They estimated that RSV causes 1 in 50 deaths among children under 5 years old, and 1 in 28 deaths in children under 6 months old.

Additionally, RSV is responsible for an estimated 3.6 million hospital admissions globally each year, according to the report.

This analysis is the first to sift RSV disease burden into narrow age brackets, the authors said.

The numbers highlight that almost all of the deaths (97%) were in low- and middle-income countries.

## Messages for prevention

Tina Hartert, MD, MPH, a professor in the division of allergy, pulmonary, and critical care medicine at Vanderbilt University, Nashville, Tenn., who was not part of the study, wrote in an invited commentary that these findings will be important in RSV prevention (*Lancet*. 2022 May 19. doi: 10.1016/S0140-6736[22]00623-7).

Among the most notable findings, she wrote, is the heavy mortality in the 0- to 6-month age group, which she notes is “the age group targeted by vaccination during pregnancy and birth-dose immunoprophylaxis.”

Dr. Hartert, who coauthored the commentary with Justin R. Ortiz, MD, MS, with the Center for Vaccine Development and Global Health, University of Maryland, Baltimore, told this news organization, “RSV is a respiratory virus that infects nearly every child by the time they are 2-3 years of age, with severe infection and death most common in the youngest infants. Vaccines that prevent the most severe infections in these young infants will likely be one of the best

ways to prevent these severe infections and death.”

Though the authors found most deaths occur in low- and middle-income countries, RSV is one of the most common reasons for infant hospitalization in the US and affects 1%-3% of infants, half of whom are full term and otherwise healthy, Dr. Hartert said.

*“As people return to normal activities and the public health measures put in place to stop the spread of COVID are eased, we are likely to see increases in circulation of RSV and return to its circulation during the winter months – typically similar to circulation of flu.”*

It is also one of the most common causes of infant lower-respiratory tract infection in young children in the United States, she said, and it causes the most severe disease at the age extremes, with older adults experiencing significant morbidity with RSV.

Dr. Li said in an interview that, although the team did not focus on reporting country-specific estimates in this work, their previous work resulted in estimates of 98,000-155,000 RSV-related hospitalizations in children under 5 years old in the United States in 2019 (*Lancet Respir Med*. 2021 Feb;9[2]:175-85). Between 65,000 and 86,000 were in infants less than 1 year old.

Currently, he said, the only available RSV prophylaxis is palivizumab (Synagis), which is expensive and given only to high-risk infants in high-income countries, including the United States.

“There have been a number of promising RSV prophylactic products including maternal vaccine and monoclonal antibodies that have the potential for targeting the general infant population – not just high-risk infants – in late-phase clinical trials,” he said. “Our estimates of RSV-related disease burden will help anticipate the impact of future RSV immunization programs.”

## Pandemic changed patterns

This research was completed before the COVID-19 pandemic, and it is not yet known how that could affect RSV disease burden long term.

However, Dr. Hartert said, RSV

circulation has been significantly changed during the pandemic, both in intensity and timing, likely because of a combination of COVID and the public health preventive measures.

“As people return to normal activities and the public health measures put in place to stop the spread of COVID are eased, we are likely to see increases in circulation of RSV and return to its circulation during the winter months – typically similar to circulation of flu – from November through March in temperate climates in the northern hemisphere,” she said.

A coauthor of the paper, Harish Nair, PhD, with the Centre for Global Health, Usher Institute, University of Edinburgh, said in a press release that their findings have particular significance as COVID restrictions ease around the globe.

“The majority of the young children born in the last 2 years have never been exposed to RSV (and therefore have no immunity against this virus),” Dr. Nair wrote.

## Most deaths occurring outside hospitals

A challenge in reducing the deaths in those 5 years old and younger is that most (76%) of deaths are happening in the community outside hospitals.

The authors wrote: “For every RSV-associated acute lower respiratory infection in-hospital death, we estimate approximately three more deaths attributable to RSV in the community.”

The percentage dying outside hospitals is even larger (81%) in low- to middle-income countries.

This work built on a previous review by the team that analyzed 317 studies. They updated their search with 113 new eligible studies and unpublished data from 51 papers published between Jan. 1, 2017, and Dec. 31, 2020.

The authors acknowledged some limitations, including variations in study settings and in definitions for acute lower respiratory infection, health care access, and eligibility for RSV testing.

The study was funded by EU Innovative Medicines Initiative Respiratory Syncytial Virus Consortium in Europe. Dr. Li reported grants from Wellcome Trust and the World Health Organization outside the submitted work. Dr. Hartert, Dr. Ortiz, and Dr. Nair disclosed no relevant financial relationships. ■



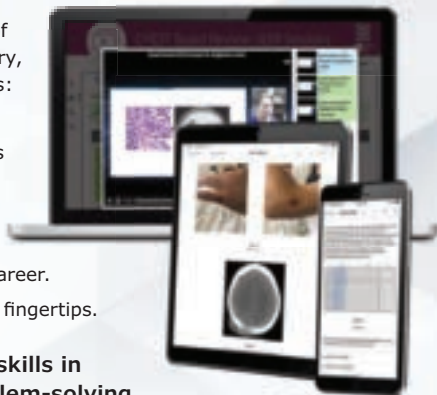
## Challenge Yourself With CHEST SEEK™ Education

Offering a comprehensive collection of case-based questions in the pulmonary, critical care, and sleep medicine fields:

- Prepare for your ABIM exams.
- Learn more with detailed rationales written by top experts in the field.
- Earn all the CME credit and MOC points you need.
- Stay up-to-date throughout your career.
- Achieve bite-sized learning at your fingertips.

Test and improve your clinical skills in recall, interpretation, and problem-solving.

**PRINT** [chestnet.org/store](http://chestnet.org/store)  
**DIGITAL** [seeklibrary.chestnet.org](http://seeklibrary.chestnet.org)



 CHEST®



## NETWORKS

# Responding to Ukraine, EBUS for lung cancer, RSV protection, and more ...

## CHEST INFECTIONS & DISASTER RESPONSE NETWORK

### Disaster Response and Global Health Section

#### Physician response to Ukraine and beyond

Displaced persons, international refugee crises, gun violence, and other disasters remain prevalent in current news. Recent events highlight the need for continued civilian physician leadership and response to disasters.

Before the Ukraine crisis, the



Dr. Miller

United Nations Refugee Agency estimated displaced persons more than doubled to > 82 million persons over the last decade (uncr.org, accessed 5/20/2022). Since that analysis, there have been over 6.5 million externally displaced persons, 7.5 million internally displaced persons, and significant numbers of injured patients from the Ukraine crisis alone. The Ukraine Ministry of Health has shown preparedness in its ability to handle significant patient surges with minimal assistance.

However, organizations like the Ukraine Medical Association of North America, Razom for Ukraine, Doctors Without Borders (MSF), MedGlobal, Samaritan's Purse, Global Response Management, and many more have deployed to assist in Ukraine. These NGOs continue to help with medical care, fulfill critical supply needs, and provide training in cutting-edge medicine (POCUS, trauma updates).

Challenges posed by unstable environments, from wars to active shooter situations, further underscore the need for continued education, advances in technology, and preparedness. Providers responding to these events often treat vulnerable populations suffering from physical and mental violence, requiring physicians to step out of their comfort zone.

Opportunities remain plentiful to affect many lives as physicians respond through well-established and coordinated efforts with NGOs

across the world. Physicians should continue to be leaders in the care of vulnerable displaced persons.

Christopher Miller, DO, MPH  
Fellow-in-Training Member  
Thomas Marston, MD  
Member-at-Large

## THORACIC ONCOLOGY & CHEST PROCEDURES NETWORK

### Interventional Procedures Section

#### Role of EBUS for staging and prognostication in patients with lung cancer

Lung cancer is the leading cause of cancer-related deaths worldwide and forms of a large burden of cancer-related mortality in the United States.

With the rapid advent of new disease-directed therapy, including molecular and targeted therapies, the outlook for management of lung cancer has changed dramatically over the last decade.

The choice of therapy, as well as prognosis, is dependent on the stage at diagnosis. It is thus imperative that we accurately differentiate between stages I, II, and III disease by assessment of hilar and mediastinal lymph nodes. Traditionally, CT and PET/CT scans have been the mainstay to assess stage, with patients with abnormal lymph nodes or high risk of nodal metastasis ( $\geq$  T2 disease or "central" location) undergoing invasive mediastinal evaluation (Silvestri, et al. *Chest*. 2013 May;143(5 Suppl):e211S).

The decision to perform invasive mediastinal staging for T1 tumors remains a matter of discussion. DuComb and colleagues, in their study demonstrated a high rate of N2 metastasis (8.1%) even amongst those with T1 tumors, which was independent of tumor location (DuComb, et al. *Chest*. 2020 Nov;158[5]:2192). This rate is consistent with previous reported rates ranging from 6.9% to 13% of N2 disease in patients with no radiographic evidence of lymph node metastasis (Gonzalez-Stawinski, et al. *J Thorac Cardiovasc Surg*. 2003



Dr. Agrawal

Dec;126[6]:1900; Bao, et al. *J Thorac Dis*. 2014;6[12]:1697; Shin, et al. *Eur Respir J*. 2019;53[3]:1801508). The above indicates a possible role of invasive mediastinal staging using EBUS-TBNA in patients with T1 disease to accurately stage the disease prior to curative intent treatment.

While the role of EBUS-TBNA in diagnosis and staging has been a role of ongoing research, data are limited on prognostic implications of EBUS-guided staging in patients with NSCLC. In a recently published paper in *Chest*, Hwangbo and colleagues assessed the prognostic impact of staging via EBUS in these patients (Hwangbo et al. *Chest* 2022 May;161[5]:1382). In the 1,089 patients who underwent EBUS-TBNA, they observed a significant difference in survival based on the staging established via EBUS-TBNA, highlighting the importance of EBUS-TBNA in staging for NSCLC. Also of note, patients with false-negative EBUS results had favorable survival that was similar to patients with pathologic N1 disease. While the exact reason for this is unclear and may be related to disease burden, the authors postulated that this may provide a rationale to performing surgery after negative EBUS-TBNA results.

Abhinav Agrawal, MD, FCCP,  
Member-at-Large

Ellen Volker, MD, MSPH, FCCP,  
Member-at-Large

## AIRWAYS DISORDERS NETWORK

### Pediatric Chest Medicine Section

#### Hope is on the horizon—new RSV protection for all infants

There is a dire unmet need for RSV protection in healthy term infants as available preventive therapies are limited and currently reserved for former preterm infants and those with certain underlying medical conditions (Brady MT, et al. *Pediatrics*. 2014;134[2]:415). Globally, RSV is a significant cause of lower respiratory tract infection impacting all age groups, yet, in infants and young children, the first infection may cause severe bronchiolitis that can be fatal (Li Y, et al. *Lancet*. 2022;399:2047).

There are currently three approaches for protection at various



Dr. Coates



Dr. Cataletto

stages of clinical development. The first is direct administration of antibodies to the infant. Two potent, longer-lasting, single-dose monoclonal antibody products, including nirsevimab which is a monoclonal antibody to the RSV fusion protein that has an extended half-life, for the general infant population are in phase 3 trials (Hammit LL, et al. *N Engl J Med*. 2022;386:837; Griffin PM, et al. *N Engl J Med*. 2020;384:415).

Passive antibody acquired from maternal vaccination in pregnancy is a second approach. Notably, a recent phase 3 trial that evaluated maternal vaccination did not show significance with respect to the primary end point of medically significant RSV-associated lower respiratory tract infection in infants up to 90 days of life (Madhi SA. *N Engl J Med*. 2020;383:426).

The third type of protection is active vaccination. Increased understanding of the biology of RSV and related technological advances have resulted in the entry of multiple vaccines into clinical development for pediatrics and adults, some of which may receive regulatory approval in the near future (Munoz FM, et al. *Vaccine*. 2021;39[22]:3053).

The burden of RSV is tremendous, yet the future of RSV protection looks promising.

Anne Coates, MD, FCCP,  
Member-at-Large

Mary Cataletto, MD, FCCP,  
Member-at-Large

## DIFFUSE LUNG DISEASE & LUNG TRANSPLANT NETWORK

### Pulmonary Physiology & Rehabilitation Section

#### Interpretive strategies for routine lung function tests

In December 2021, the *European Respiratory Journal* published the, ERS/ATS technical standard on

NETWORKS continued on following page

NETWORKS *continued from previous page*

interpretive strategies for routine lung function tests (Stanojevic S, et al. *Eur Respir J*. 2021 Dec 23;2101499). Briefly, a few of the updated recommendations are discussed here.

First, the task force recommends the use of Global Lung Initiative (GLI) reference values for spirometry, lung volumes, and diffusing capacity of carbon monoxide. GLI equations were derived from the largest sample of healthy individuals to date and provide an internal consistency across all ages.

Second, it is now recommended that z-scores are used as opposed to percent predicted in grading severity of impairment.

Z-scores, which refer to the number of standard deviations a measurement is positioned from the predicted value, centered at zero, account better for age, sex, and height biases compared with percent predicted, and is simplified into mild (z-score -1.65 to -2.5), moderate (-2.51 to -4), and severe (< -4) categories.

Finally, there are new and possibly controversial recommendations in defining a bronchodilator response and interpretation of change over time. A bronchodilator response is now defined as a > 10% change from the predicted value in FEV<sub>1</sub> or FVC while the concept of a conditional change score in children and FEV<sub>1</sub>Q in adults has been introduced to describe lung function change.

The recommendations reflect and reiterate a shift in reporting a range of values, rather than using absolute threshold values, with an emphasis on the classification of physiologic impairments. The uncertainty present as lung function approaches the lower limit of normal is acknowledged, emphasizing the importance of pretest probability in making a clinical diagnosis and/or clinical decision. We encourage all pulmonary clinicians to review this important paper for more detailed information on these changes.

Tom DeCato, MD, Vice-Chair  
Gina Lee, MD, Member-at-Large



Dr. DeCato



Dr. Lee

## PULMONARY VASCULAR & CARDIOVASCULAR NETWORK

### Pulmonary Vascular Disease Section

#### Restoration of RV function in PAH: Is it the holy grail to improve mortality and long-term outcomes?

Pulmonary arterial hypertension (PAH) remains an incurable disease, and clinical progression is inevitable. Despite several therapeutic advances, PAH continues to be associated with high mortality. Even mild increases in mean pulmonary arterial pressure (mPAP) have been shown to directly impact outcomes (Maron BA, et al. *Circulation*. 2016 Mar 29;133[13]:1240), leading to a change in the hemodynamic definition of PAH (mPAP > 20 mm Hg) at the 2018 World Symposium on Pulmonary Hypertension (WSPH) (Galie N, et al. *Eur Respir J*. 2019;53[1]:1801889). The WSPH also recommended a more aggressive and proactive approach to move patients to “low-risk” status.

Elevated mPAP results in increased RV afterload with subsequent RV dysfunction and consequent abnormal remodeling, which is associated with poor outcomes. Reversal of RV remodeling has been demonstrated in patients after PEA for CTEPH and/or lung transplantation for PAH (D’Armini AM, et al. *J Thorac Cardiovasc Surg*. 2007;133:162).

Aggressive mPAP reduction facilitates RV recovery, which may alter the course of PAH in the form of improved survival. RV dysfunction is mainly attributed to afterload mismatch and uncoupling of the RV. Although oral therapies have shown significant improvements in symptoms, functional class, and delaying clinical worsening, normalization of RV size and function is often not achieved. More aggressive reduction of mPAP with a combination of parenteral and oral therapies has been shown to be more effective in restoring RV function (Vizza CD, et al. *Am J Respir Crit Care Med*. 2022;205)



Dr. Balasubramanian



Dr. Elwing

with the ultimate goal of improving quality and quantity of life in those affected by PAH.

Vijay Balasubramanian, MD, FCCP,  
Chair  
Jean M. Elwing, MD, FCCP,  
Ex-Officio

## SLEEP MEDICINE NETWORK

### Respiratory-Related Sleep Disorders Section

#### Reducing racial disparities in sleep apnea

Health inequity pervades many aspects of medicine, including the care of patients with obstructive sleep apnea. For example, a grow-



Dr. Gogineni



Dr. Tobias

ing body of research has shown that black race is associated with underdiagnosis of OSA, greater disease severity at time of diagnosis and reduced PAP adherence (Hsu N, et al. *J Clin Sleep Med*. 2020;16[8]:1249; Thornton JD, et al. *Ann Am Thorac Soc*. 2022;19[2]:272).

A recent article (Billings ME, et al. *Chest*. 2021;159[3]:1232) offered potential strategies to mitigate racial disparities in sleep apnea management. To expand access to care, they advocate embracing telemedicine for those who may have difficulty coming to clinic – due to transportation issues, arranging sufficient time off work, or residing in remote locations. On the other hand, an over-reliance on telemedicine has the potential to worsen disparities in populations whose access to technology is limited.

The authors also recommend inpatient screening of high-risk patient populations to detect disease earlier and to help facilitate referrals to a sleep center. They propose the idea of “peer buddies” of similar racial and socioeconomic backgrounds to provide support and counseling, while cautioning against overburden these populations. Finally, they propose broadening the sleep provider workforce by training primary care providers to manage OSA.

The higher proportion of non-white providers in these groups as compared with sleep specialists may

improve care, since concordant race provision has been associated with better communication. Underlying these interventions is the need to diversify representation within the medical field at large.

Swetha Gogineni, MD, Vice-Chair  
Lauren Tobias, MD,  
Member-at-Large

## CRITICAL CARE NETWORK

### Sepsis and Shock Section

#### SEP-1 measure saves lives, let’s not debate!

On December 21, 2021, the National Quality Form (NQF) re-endorsed Measure 0500 Severe Sepsis and Septic Shock: Management Bundle, which CMS adopts as the SEP-1 core measure. The decision was initially met by a request for appeal. On April 29, 2022, the appeals board met to adjudicate the appeal and voted unanimously to uphold the Standards Approval Committee (CSAC) decision to endorse the measure once again (<https://tinyurl.com/yc4tjxbz> - Accessed June 9, 2022).

The appeals board voted 5-0 on whether procedural errors reasonably affected the outcome of the original endorsement and whether there was new information or evidence unavailable at the time of the CSAC endorsement decision that would reasonably affect the outcome of the original endorsement decision.

The implementation of NQF 0500 and SEP-1 continues to spark controversy in the medical community even though the results of this bundled approach support an opportunity to save lives. SEP-1 compliance is associated with a lower 30-day mortality, and rendering this care saves lives.

In the Townsend, et al cohort study (*Chest*. 2022 Feb;161[2]:392) examining patient level Medicare data from October 2015 – March 2017, there was an absolute risk reduction of 5.67% in a standard propensity matched comparison of SEP-1 compliant vs noncompliant care. With a more stringent match, the absolute risk reduction was 4.06%. That’s an outcome that our patients likely appreciate the most... lives saved.

As former CHEST President, Dr. Steven Simpson highlighted in his April 2022 commentary (*CHEST Physician*. 2022 April;17[4]:392), “Success is not dependent only on what we do but on when we do it.” Let’s not debate any further.

Namita Jayaprakash, MBBCh  
Member-at-Large

# From the President: A day in the life

BY DAVID SCHULMAN, MD, MPH, FCCP

For those of you in the Northern Hemisphere, like me, spring has transitioned into summer, allowing us all to spend more time outdoors, gathering again with family, friends, and colleagues. As in-person gatherings resume, albeit cautiously, it has been wonderful to have the chance to catch up with folks in-person once again. And, while people are always happy to hear about what's going on with the family, or how things are going at Emory, the most common question I get is "So what's it like to be President of CHEST?" Now that I've been on the job for 6 months, I thought it was well enough time to pull back the curtain on the role for all of you out in CHEST-land who might be interested, as well. For the purposes of this column, I'll be incorporating things that occurred over the past week.

As I've previously reported, the most important decisions that relate to CHEST strategy are made by the Board of Regents. While I do have the privilege of organizing and running Board meetings, most presidential duties between these meetings focus on communication: with our members, our leaders, and other organizations. One of the best parts of the job is the opportunity to interact with our members; between the [president@chestnet.org](mailto:president@chestnet.org) account and my own, I receive a couple of emails each day with questions about navigating CHEST, or ideas about ways that things might be better accomplished. With our recent Network and section reorganization, many of those questions have focused on leadership opportunities, inquiring about whether the writer should apply, or asking for information about the qualities that might increase the odds of earning a position. My answer is almost always the same: go ahead and throw your name in the hat; for most members, the sections are the first place to start the journey in CHEST leadership. And I'm pleased to say that I've had the chance to see some of the members who've reached out to me in the past selected for the positions to which they'd applied (in full disclosure, I have little role in selecting leadership positions; Network and section positions are chosen by current members of those Networks and sections). I look forward to

watching their progress in our organizational leadership.

While CHEST CEO Robert Musacchio and I communicate almost every day, Wednesday is our weekly meeting during which we



Dr. Schulman

review progress on our organizational goals, the status of ongoing projects, and concerns from our membership and leadership. I also have the pleasure of meeting with my co-Presidents every other week; though Jack, Doreen, and Steve have always been happy to offer their counsel on very short notice, this semimonthly meeting helps to provide continuity in leadership, as well as a more formal opportunity for me to meet with trusted advisors to get a sounding board on active issues that affect CHEST. And, this gets to the other main job of CHEST President, which is to facilitate the making of important decisions on behalf of the College. I receive sporadic emails from CHEST staff as we are approached by other organizations or international partners for input on or approval for statements that they wish to make. In the case where the topic is clearly in the CHEST wheelhouse and the statement is consistent with our organizational goals, I can unilaterally sign off; a common example of something that fits in this category is content related to tobacco cessation. In the more frequent situation where the statement for approval is a bit more complex, I will usually refer the request to one of our committee, Network, or section chairs for consideration. Since the turnaround time on these requests is usually pretty short, I may ask them to advise me on their own, although they sometimes opt to run things by their own membership for further input or to achieve consensus.

The CHEST President also serves as ambassador to other organizations; this week, I had the pleasure of participating in a meeting with the American Board of Internal Medicine and a number of medical

to see how CHEST can contribute to the success of those endeavors by contributing content, speakers, or both. At the time of this writing, the CHEST Congress in Bologna, Italy, is right around the corner, and so I also spent time working with our Italian partners and program co-chair William Kelly, MD, FCCP, to finalize the meeting's opening session. Though our own international meeting is still months away, work continues with the annual meeting innovations group, and I've been working with my own small team on some special surprises that you'll hear more about in the coming months! The other CHEST meeting-related item on the front burner is the selection of the keynote speaker. The way this works is that I outline in broad strokes a sense of the flavor I'm targeting, and the CHEST staff work with a consulting group to propose some options. They provide me with a brief biography in clips, and we narrow the list down. As I write, we are finalizing our invitation, and I look forward to formally announcing

PRESIDENT *continued on following page*

*"So what's it like to be President of CHEST?"*

*Now that I've been on the job for 6 months, I thought it was well enough time to pull back the curtain on the role for all of you out in CHEST-land who might be interested."*

specialty leaders focused on how professional societies can help to mitigate the spread of medical misinformation. I also interfaced with several of our international partners in the pulmonary space, as they plan their own international meetings,



#### Ready to Go Hands-on?

Keep your knowledge and skill set up to date with our expert-led continuing medical education courses. Get all the relevant updates plus the irreplaceable benefits of hands-on instruction and practice. Measures designed to ensure your safety against COVID-19 will be enforced.

 CHEST<sup>®</sup>

## 2022 COURSES

CHEST Global Headquarters | Glenview, IL

- AUG 5-6 | Cardiopulmonary Exercise Testing
- AUG 26-27 | **NEW!** Advanced Diagnostic Bronchoscopy for Peripheral Nodules
- SEP 8-10 | Difficult Airway Management
- SEP 15-16 | Ultrasonography: Essentials in Critical Care
- SEP 22-24 | Comprehensive Bronchoscopy With Endobronchial Ultrasound
- NOV 10-11 | Critical Care Ultrasound: Integration Into Clinical Practice
- NOV 18 | Comprehensive Pleural Procedures With Cadavers
- NOV 19 | Advanced Airway Management With Cadavers
- DEC 1-2 | Ultrasonography: Essentials in Critical Care
- DEC 9-10 | Extracorporeal Support for Respiratory and Cardiac Failure in Adults
- DEC 6, 13, 15 | Virtual Advanced Critical Care Echocardiography Board Review Course

LEARN MORE AND REGISTER  
[chestnet.org/simulation](https://chestnet.org/simulation)

# And, they're off! Belmont Stakes Dinner and Auction fundraises for patient education

BY LAURA DIMASI

CHEST PR and Communications Specialist

For a night of fun and philanthropy, CHEST leadership and supporters of the CHEST Foundation came together in New York City to watch the Belmont Stakes race and raise money to support patient education.

What started 8 years ago as a brunch in the living room of Doreen Addrizzo-Harris, MD, FCCP, the 2022 Belmont Stakes Dinner and Auction has grown into an event that welcomed 250 guests to the Manhattan waterfront and raised over \$290,000 to support the initiatives of the CHEST Foundation.

Spearheaded by Dr. Addrizzo-Harris, President-Elect of the American College of Chest Physicians, this year's event was focused entirely on patient education and advocacy.

The attendees heard the moving stories of Betsy Glaeser and Fred Schick who are both patients living with lung disease and advocates for others living with like afflictions. Betsy is living with nontuberculous mycobacteria (NTM) disease and Fred with idiopathic pulmonary fibrosis (IPF). Betsy and Fred have used their experiences to serve as support for others in similar positions.

Betsy Glaeser, a longtime patient of Dr. Addrizzo-Harris, shared a story about the struggle of being one of the first cases of NTM bronchiectasis and helping to define the course of action. She shared that her original doctors gave her 5 years to live. The room erupted in applause when she shared that with the exceptional treatment she's received, over 20 years later, she is standing in front of the supporters of the CHEST Foundation to share her story.

Because of the rarity of her disease, she was hospitalized multiple times with pneumonia before finally reaching her diagnosis of NTM disease. She channeled the accompanying frustrations into helping others who were recently diagnosed with the NTM disorder by sharing her experiences. "I would give them guidance on treatment options because in my years of living with the disease, I'd been there and tried almost everything," said Betsy. "I would get calls from my doctor all of the time



CHEST member Bravein Amalakuhan, MD, FCCP, and his wife, Megan Cool Amalakuhan, show off their winning raffle number.

to speak with someone who just received an NTM disease diagnosis. I was happy to do so – at the time, the Internet didn't exist, and firsthand experiences were all we had. Since forming our physical support group, the most memorable experience I can recall is when a woman, newly diagnosed with NTM, walked into the room and immediately burst into tears. She shared that she expected to see all of us on oxygen and wheelchair-bound, but that wasn't the case at all. That day, we were able to give her hope. That's why I do what I do, and I'm proud to do it."

Fred Schick shared with the attendees his story of struggling to find his IPF diagnosis and how incredibly frustrating it was to be so short of breath that he needed to be rescued from the water while on vacation. With a history of cardiac complications, Fred's doctors were looking at his heart.

For Fred to get to his IPF diagnosis, it took the careful ear of a primary care doctor Fred started to see when his previous doctor retired.

"It was almost like she was listening with different ears and was hearing what others didn't. Once she recommended speaking with a pulmonologist, everything fell into place," said Fred. "From my experience, IPF is best treated by a lot of pieces coming together and working together.

It takes the dedication of a care team in the hospital, proper diet and exercise and, just as importantly, it takes a support group to guide you through the process. I'm grateful to my care team, but I'm equally thankful for the work I get to do as an advocate for others living with IPF."

When she spoke to the attendees, Lisa Moores, MD, FCCP, reflected on what the patients shared. "We saw great examples of why we're here tonight," said Dr. Moores. "One of the things CHEST and the Foundation are focusing on is earlier diagnosis for interstitial lung diseases like pulmonary fibrosis and, with voices like Fred Schick, we'll get there. The patients remind us why we're here. We're here for our patients; we're here for Fred; and we're here for Betsy."

Laurence Feldman, Vice President of the Feldman Family Foundation that partners with the CHEST Foundation for their annual casino fundraiser benefiting pulmonary fibrosis, was able to participate in the dinner and the auction.

He shared, "Tonight, I was so impressed with the generosity of the attendees and the organization of this event. It reminded me that if you ask your supporters to give, they'll be there for you. Almost like the 'Field of Dreams' quote of 'if you build it, they will come.' Being at the Belmont Stakes Dinner and Auction makes me that much more excited for our upcoming Irv Feldman Casino Night and Texas Hold 'Em Tournament coming up in late August. Thanks to our corporate partners and the support of the CHEST Foundation, we're able to produce an excellent event like the Belmont Stakes fundraiser that helps bring in donations that can make a difference in the lives of patients."

At the end of the day, medicine is all about the patients and, by dedicating the night to patient education and patient advocates, the Belmont Stakes event brought the focus to where it should always be – improving care and helping patients.

To learn more and to support the various initiatives of the CHEST Foundation, visit [foundation.chestnet.org/donate](http://foundation.chestnet.org/donate). ■

PRESIDENT *continued from previous page*

the CHEST 2022 keynote speaker shortly!

After I explain the breadth of duties involved in my role, the most common follow-up question asked of me is whether I am enjoying the position. I'll concede that it's not for everyone. There's a lot less independent decision-making than people

assume. But, if you like getting to meet and interact with people from around the globe, helping them to see how CHEST can help them in their pursuits or career goals (and how they can help CHEST in our mission), it's a super fun job. And I'll most definitely miss it when I'm done.

So that, in brief, is an overview

of what the CHEST President does. But each week is different. And, I get better at the job each day, as I learn something new about the position, the organization, and our outstanding members, leaders, and staff. I look forward to continuing to represent each of you in making decisions and communicating on behalf of CHEST. As always,

I remain interested in your input as to how things are going; please consider reaching out to me at [president@chestnet.org](mailto:president@chestnet.org) at your convenience. ... I expect to have a few minutes to write back sometime next Thursday.

Until next time,  
David

## SLEEP STRATEGIES

# Beyond CPAP: Looking to alternative treatments for obstructive sleep apnea

BY BRANDON NOKES, MD;  
CHRISTOPHER N. SCHMICKL,  
MD; ANDREW VAHABZADEH-  
HAGH, MD; AND ATUL  
MALHOTRA, MD

## Overview of the problem

Obstructive sleep apnea (OSA) is an extraordinarily common condition impacting nearly 1 billion individuals globally (Benjafield AV, et al. *Lancet Respir Med.* 2019;7[8]:687). For the past 40 years, the mainstay of treatment has been continuous positive airway pressure (CPAP). However, CPAP usage is highly variable, and not all sleep apnea is created the same with respect to underlying mechanism or patient symptoms. Currently, there is a global CPAP shortage, which has expedited the need for alternative therapies in OSA

(Owens RL, et al. *Am J Respir Crit Care Med.* 2021;204[8]:887). Here, we will provide a broad overview of how individual sleep apnea therapies may be implemented in the sleep clinic and beyond.

## Characterizing OSA

First, it is important to understand that sleep apnea emerges for multiple reasons. Some examples include: an excessively collapsible airway, insufficient upper airway reflexes, low arousal threshold (awakening easily to ventilatory disturbance), as well as an unstable chemoreflex system. This list is not comprehensive. However, we believe that the future of OSA management will be targeted therapy for individual OSA traits.

Notably, the patient experience of OSA is also highly variable. Some

individuals are excessively sleepy. Some individuals experience OSA as insomnia. Other patients are asymptomatic, but present to the sleep clinic at the behest of a disgruntled bed partner. These individual factors should all be kept in mind when deciding when and how to treat sleep apnea.

## OSA scoring – past, present, and future

The traditional method for scoring sleep apnea severity is the apnea-hypopnea index (AHI), with mild, moderate, and severe OSA being stratified by the number of events per hour. This metric has shaped many of the modern sleep practices and consensus recommendations but is simply not sophisticated enough to capture the nuance of

how or why an individual's sleep is disrupted from flow-limited breathing. As such, there has been a push in recent times to tailor treatment for OSA to an individual's physiology. Examples of alternative metrics which quantify sleep apnea traits include the apnea-hypopnea event duration, the sleep apnea-specific hypoxic burden (area under the SpO<sub>2</sub> curve for flow-limited events), as well as the arousal intensity from sleep in the setting of flow-limited breathing. There are numerous other metrics that have been proposed but are beyond the scope of this review (Malhotra A, et al. *Sleep.* 2021;44[7]:zsab030).

What therapies are available and how can we individualize them to our patients?


CPAP continued on following page

## CLASSIFIEDS

Also available at [MedJobNetwork.com](https://www.MedJobNetwork.com)

### PROFESSIONAL OPPORTUNITIES

**FIND YOUR NEXT JOB AT**




Physician • NP/PA Career Center


**The first mobile job board for Physicians, NPs, and PAs**

**Mobile Job Searches**—access MedJobNetwork.com on the go from your smartphone or tablet

**Advanced Search Capabilities**—search for jobs by specialty, job title, geographic location, employers, and more




Scan this QR code to access the mobile version of MedJobNetwork.com

CLASSIFIEDS

**For Deadlines and More Information,**

Contact: Julian Knight  
Tel: (973) 290-2317  
Email: [jknight@mdedge.com](mailto:jknight@mdedge.com)




**Holzer Health System**, located along the banks of the Ohio River, is looking for an additional Pulmonologist to join our team. ICU, call, and clinic schedule flexibility to match your practice style.

In addition to a great practice environment, Holzer proudly offers these additional benefits:

- Sign-on bonus of \$25,000
- Competitive guaranteed salary plus production incentive (based on AMGA)
  - Additional salary for Critical Care and or Sleep Medicine trained providers
- Educational loan repayment- Up to \$100,000
- Stipend- \$2,000 per month for 18 months
- Relocation expense reimbursement- Up to \$10,000
- Work life balance & accommodating schedule
- Minimal call
- Malpractice insurance
- Generous vacation package
- 5 days off for Category 1 CME
- Physician leadership options
- Teaching Opportunities (medical students and residents)

Come practice in state-of-the-art facilities while living in a region known for friendly people, strong values, and beautiful scenery. With all our employees, physicians and high-level services working as one, Holzer provides patient-centered medical excellence every day.

If you are looking for a great town to live in and a supportive health care system to practice medicine, look no further than Gallipolis, Ohio and Holzer Health System.

**Please contact Ginger anytime for details!**  
Ginger Thompson  
(740) 645-7596  
[gthompson@holzer.org](mailto:gthompson@holzer.org)

357542

CPAP continued from previous page

As noted, CPAP has been the gold-standard for OSA treatment for 40 years but is not always accepted or tolerated (Malhotra A, et al. *Chest*. 2018;153[4]:843). Broad categories of OSA management are presented as follows.

### Surgery for OSA

Upper airway surgery is effective for pediatric OSA treatment, where enlarged tonsils are often the culprit for flow-limited breathing in sleep. For adults, however, there is no one best surgery or surgical candidate. For instance, surgery can be used to improve CPAP tolerance or as a primary OSA treatment. Many individuals with sinus disease may require sinus surgery or septoplasty to improve CPAP tolerability by creating more space for airflow through the nasopharynx. Retrognathic individuals, on the other hand, may benefit from maxillomandibular advancement. Others may benefit from genioglossus advancement or hyoid suspension. The characteristics of the soft palate can be predictive of surgical success with respect to uvulopalatopharyngoplasty (UPPP), with longer uvulas and redundant soft palate tissue being attractive surgical targets. Obviously, this list is far from comprehensive, but Friedman tongue position, tonsil size, and body mass index also appear to be important in predicting surgical success (MacKay S, et al. *JAMA*. 2020;324[12]:1168).

Hypoglossal nerve stimulation is one surgical treatment option for patients with moderate-severe OSA who are unable or unwilling to use CPAP therapy, have a BMI <32-35 kg/m<sup>2</sup> (center-dependent), no concentric velopharyngeal collapse on drug-induced sleep endoscopy, and fewer than 25% central/mixed apneas on their sleep study. Areas for further study are whether unilateral or bilateral stimulation are most effective, as well as which of the sleep apnea traits are most predictive of a treatment response (Strohl MM, et al. *Curr Sleep Med Rep*. 2017;3[3]:133).

Notably, surgical techniques are highly variable, and there are individual patient characteristics, such as lower loop gain (more stable ventilatory control), which may have a greater likelihood of successful upper airway surgery. This is likely because making the upper airway more patent allows for ventilatory overshoots and thereby airway collapse and cyclic, unstable breathing in those with an unstable ventilatory



From surgery to appliances to training and pharmacotherapy, new approaches are being used or investigated to replace or augment traditional CPAP use.

control system. Trials with prespecified surgical techniques based on individual traits are welcome. Additionally, the metrics of a successful surgical treatment for OSA, much like the AHI, are in need of evolution. The Sher criteria, for instance (50% AHI reduction to an AHI < 20/h), are arbitrary, and their clinical utility is unclear.

### Oral appliances

Oral appliances fall into two broad categories – tongue-retaining devices and mandibular advancement splints (MAS). Of the two, MAS are much more commonly prescribed. Of the MAS devices, custom made devices by an American Academy of Dental Sleep Medicine (AADSM)–trained dentist are recommended over noncustom MAS in the treatment of primary snoring or OSA for those unwilling or unable to wear CPAP. Notably, the 2015 American Academy of Sleep Medicine (AASM) and AADSM shared guidelines were unable to make OSA treatment recommendations based on severity of disease as stratified by the AHI due to the limited quality of evidence. These devices are broadly thought to work by protruding the mandible/tongue and, in-turn, advancing multiple soft tissue components of the velopharynx. Relatively recent work suggests that the following OSA traits are associated with MAS efficacy: lower loop gain, higher arousal threshold, lower ventilatory response to arousal, moderate pharyngeal collapsibility, and weaker upper airway dilator muscle

compensation. However, in order for these devices to be successful, close follow-up for titration with a AADSM-certified dentist, as well as a follow-up efficacy sleep study, are recommended. Adherence for custom device use appears to be about 70% use greater than 4 hours per night, with 35% to 40% of those prescribed a device achieving an AHI less than 5/h. Over the counter devices are not routinely recommended, though some practices do use these devices as a trial to see if patients may tolerate custom made devices (Ramar K, et al. *J Clin Sleep Med*. 2015;11[7]:773).

### Upper airway training

Upper airway training has been shown possibly to be effective in treating OSA, though the ideal endotype is still being established. Upper airway training has taken many forms, from woodwind instrument playing, to nocturnal electrical stimulation of the tongue, and, more recently, daytime awake transoral neuromuscular stimulation. These interventions appear to be effective for mild sleep apnea and snoring, but the best training regimen has yet to be established. Equally, as with other routine exercise, there appears to be a “use it or lose it” component, and the ideal maintenance regimen for each of these therapies is yet to be determined.

### Weight loss and bariatric surgery

Obesity is a common, reversible risk factor for OSA. However, not

all obese individuals develop OSA (typically those with robust upper airway reflexes). Improvements in weight appear to correlate with reductions in tongue fat, which correlate to AHI reduction. Weight loss also creates lower CPAP requirements for many individuals, conceivably improving tolerability. Ongoing work is seeking to understand whether there are changes in upper airway muscle recruitability as well as other change in endotype traits following weight loss surgery.

### Pharmacotherapy for OSA

There is a great deal of promise in tailoring pharmacotherapy to individual sleep traits. Acetazolamide, for instance, results in improvements an AHI for both obstructive and central sleep apnea through changes in chemosensitivity and is generally well-tolerated (Schmickl CN, et al. *Physiol Rep*. 2021;9[20]:e15071). Eszopiclone has been used to raise the arousal threshold for those who awaken from breathing events too easily. With added time, individuals with a low arousal threshold can more effectively recruit upper airway dilator muscles without waking up. Pharmacotherapy to improve upper airway recruitability with combination noradrenergic stimulation and antimuscarinic activity has limited data thus far but may be a useful part of the sleep armamentarium moving forward.

### Summary

OSA is a public health priority, and the current global CPAP shortage emphasizes the need for alternative OSA therapies. The ideal therapy for a given patient requires a careful consideration of their individual traits and will be much more refined when endotyping is available in a routine clinical setting. Individualized sleep apnea treatment is the future of sleep medicine and a one-size fits all approach no longer meets the needs of our patients given the current state of sleep medicine knowledge. ■

Dr. Nokes, Dr. Schmickl, and Dr. Malhotra are with the University of California, San Diego, Division of Pulmonary, Critical Care, and Sleep Medicine, La Jolla, CA. Dr. Nokes also is with the Veterans Affairs San Diego Healthcare System, sleep section, San Diego, CA. Dr. Vahabzadeh-Hagh is with the University of California, San Diego, Department of Otolaryngology, San Diego, CA.

# Starting CHEST 2022 off with a step kick

After years of remote learning from behind computer screens, we're kicking off the in-person CHEST 2022 meeting in Nashville, Tennessee, with a bang—or, more accurately, with a step kick, swivel, and stomp—at the Wildhorse Saloon.

The Wildhorse is famous for hosting daily line dancing lessons on the largest dance floor in the downtown area and for having a menu full of Nashville favorites, including Nashville hot chicken and a hearty selection of entrees (as well as a decadent bananas foster) with a “Jack Daniels” single barrel whiskey glaze.

The opening reception offers attendees the opportunity to relax and reconnect with their peers from across the fields of pulmonary, critical care, and sleep medicine before the jam-packed schedule of more than 300 educational sessions starts the following day.

But the fun doesn't stop there. Attendees interested in exploring the city after hours have a host of options, from world-class music venues to iconic distilleries and restaurants. The Music City Center, where CHEST 2022 will be held, is located in the SoBro neighborhood of Nashville, not far from the Arts District, Downtown, and Music Row.

According to Nashville local and CHEST member Meredith Pugh, MD, MSCI, “it goes without saying that we have the best music scene in the country, but it's a great place for outdoor activities and food.”

For those who don't get their fill at the Wildhorse, Dr. Pugh recommends attendees check out the Assembly Food Hall (.3 miles from the convention center) to try the city's famous Nashville Hot Chicken and a variety of other local options. And, don't miss the many excellent options for BBQ. Fellow Nashville

transplant and CHEST member Todd Rice, MD, FCCP, suggests Martin's Bar-B-Que Joint and Jack's Bar-B-Que—both within walking distance of the Music City Center—as well as other local options.

To learn more about everything Nashville has to offer, and get more recommendations from Drs. Rice and Pugh, check out the latest CHEST 2022 blog on [chestnet.org](https://chestnet.org) (<https://tinyurl.com/y6vt3kar>). ■



## This month in the journal CHEST®

### Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

**Dupilumab Reduces Oral Corticosteroid Use in Patients With Corticosteroid-Dependent Severe Asthma.**

By Lawrence D. Sher, MD, et al.

**Carriage and Transmission of Macrolide Resistance Genes in Patients With Chronic Respiratory Conditions and Their Close Contacts.**

By Yiming Wang, MSc, et al.

**An Evaluation of Factors That Influence Referral to Pulmonary Rehabilitation Programs Among People With COPD.**

By Sarah Hug, BSc, et al.

**Prevalence and Outcomes of Previously Healthy Adults Among Patients Hospitalized With Community-Onset Sepsis.**

By Mohammad Alrawashdeh, PhD, MSN, et al.



**Screening Strategies for Pulmonary Hypertension in Patients With Interstitial Lung Disease: A Multidisciplinary Delphi Study.**

By Franck F. Rahaghi, MD, et al.

**Race- and Ethnicity-Based Spirometry Reference Equations: Are They Accurate for Genetically Admixed Children?**

By Jonathan Witonsky, MD, et al.

**No VTE Recurrence After 1-Year Follow Up of Hospitalized Patients With COVID-19 and a VTE Event: A Prospective Study.**

By Maxime Delrue, MD, PhD, et al.

**Patient Perspectives on Longitudinal Adherence to Lung Cancer Screening.**

By Anna Holman, BS, et al.

SIMULATION COURSES

CHEST®



September 8-10, 2022 | CHEST Headquarters

### Difficult Airway Management

Confidently manage airways in critically ill patients

During this 3-day training, you will learn:

- Airway management for critically ill patients using evidence-based methods and crew resource management concepts
- Systemic approaches to patient, equipment, and drug preparation before intubation
- How to perform a direct laryngoscopy in a clinical environment
- Use of videolaryngoscopes, extraglottic devices, and cricothyrotomy in difficult or failed airways

REGISTER | [chestnet.org/AirwayManagement2022](https://chestnet.org/AirwayManagement2022)



## Find their path faster.

Personalize lung cancer care sooner so treatment plans can be initiated as early as possible.

Now you can access valuable blood-based genomic and proteomic insights to characterize tumor mutations and patient immune response to cancer within 72 hours. IQLung™ testing from Biodesix® helps you optimize personalized treatment decisions faster, to ensure each patient has the best chance to fight lung cancer.

Move each patient onto the right path for them.



Take the first step at [Biodesix.com/IQLung](https://Biodesix.com/IQLung)

