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## Catch-and-treat strategy identifies undiagnosed asthma and COPD

BY NEIL OSTERWEIL

**FROM ATS 2024** ■ SAN DIEGO — You can't treat patients if you can't find them. But as investigators in a randomized controlled trial showed, a case-finding method based on spirometry results can identify individuals in the community with undiagnosed chronic obstructive pulmonary disease (COPD) or asthma whose lives could be significantly improved with proper care.

Once they have been identified and randomly assigned to be treated by a pulmonologist and asthma-COPD educator according to clinical guidelines, these previously undiagnosed patients have significant improvements in health care utilization, lung function, symptoms, and

quality of life compared with patients randomly assigned to treatment by a general practitioner.

"By diagnosing people early and treating them intensively, you can really improve their quality of life," said lead investigator Shawn D. Aaron, MD, from the Ottawa Hospital Research Institute and University of Ottawa, Ontario, Canada.

Even those patients in the study who were randomly assigned to receive care from a general practice physician had improvements in lung function and quality of life, although on a smaller scale than patients assigned to a specialty team, Dr. Aaron said at the American Thoracic Society's international conference. He reported results of the study in a late-breaking oral

**CATCH** // continued on page 7

## Debate on safety of gas stoves isn't just hot air

BY NEIL OSTERWEIL

**FROM ATS 2024** ■ SAN DIEGO — While there is currently no smoking gun definitively showing that indoor nitrogen dioxide (NO<sub>2</sub>) concentrations from gas appliances are a cause of pulmonary diseases, the circumstantial evidence of the baleful effects of gas stoves on lung function is pretty compelling, said participants in a pro-con debate.

In what the moderator called "one of the most agreeable debates yet," experts presented their views on the risks that cooking with natural gas pose on pulmonary health, and discussed ways for mitigating that harm. The debate was held at the American Thoracic Society's international conference.

### Pro: Gas stoves cause lung disease

Arguing for the "pro" side, John R. Balmes, MD, of the University of California, San Francisco, and a physician member of the California Air Resources Board, began by admitting that "I would never have said gas stoves cause lung disease, but that's what they assigned me."

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# Diet, exercise improve cardiac function

BY NEIL OSTERWEIL

**FROM ATS 2024** ■ SAN DIEGO — A lifestyle intervention focused on diet and exercise can improve cardiac function and the quality of life (QOL) for patients with pulmonary arterial hypertension (PAH), results of a randomized clinical trial show. At 12-week follow-up, patients with PAH who were randomized to undergo a diet and cardiovascular exercise program had better exercise capacity and improved right ventricular and quality of life compared with patients randomized to the standard of care. In addition, for

(PHINE) study enrolled adults with group 1 PAH who were stable on PAH medications for at least 2 months. Patients with portopulmonary hypertension, New York Heart Association (NYHA) class IV heart failure, syncope, or use of supplemental oxygen greater than 4 liters per minute were excluded. The patients were screened with a graded exercise test, intravenous glucose tolerance test, and other measures at baseline, stratified by NYHA class and tricuspid annular plane systolic excursion (TAPSE) score, and randomized to an intervention arm (16 patients) or standard-of-care arm (14 patients).

The intervention consisted of supervised exercise training for 50-60 minutes on a treadmill at 80%-85% of the patient's maximum heart rate 5 days per week, plus weekly counseling on a combination low glycemic index/Mediterranean dietary pattern. The diet included olive oil as the primary fat source, three 1-ounce servings of nuts and peanuts weekly, at least three servings of fish and legumes, and no sugar-sweetened beverage, commercial bakery products, pastries, white breads, white rice, or white potatoes.

At 12 weeks, there were no statistically significant differences between the groups in either insulin sensitivity or right ventricular strain. However, patients in the intervention arm had significant improvements in mean RV function (TAPSE), improved exercise capacity (peak oxygen uptake, 6-minute walking distance), QOL (EmPHasis-10 health-related QOL score), and NYHA functional class.

Ravi Kalhan, MD, MS, of Northwestern University Feinberg School of Medicine in Chicago, who co-moderated the session but was not involved in the study, said, "We're so centered on what's the next big pharmacotherapy you can give to fix the disease, but sometimes maybe we should be pushing lifestyle interventions that are impactful, and they have biologic mechanisms — it's not just that you got in better shape, but right ventricular function also improves. I'm pretty drawn to that sort of thing," he said.

The PHINE trial was supported by National Institute of Health grants. Dr. Heresi and Dr. Kalhan reported no conflicts of interest. ■

## Dr. Gustavo A. Heresi

those participants in the diet and exercise group who lost weight, right ventricular glucose uptake improved, said Gustavo A. Heresi, MD, MS, of the division of pulmonary medicine at the Cleveland Clinic.

The intervention did not have an effect on insulin sensitivity, suggesting that insulin resistance is not a significant pathological mechanism in PAH, he said in an oral abstract session at the American Thoracic Society's international conference. "With these data, in the context of prior studies showing the benefits of exercise interventions, we believe that diet and exercise should be incorporated and thought of as part of the treatment armamentarium for [PAH]," he said.

Because abnormalities in both glucose and insulin metabolism are prevalent and associated with decreased survival in patients with PAH, Dr. Heresi and colleagues designed a trial to test if a diet and exercise intervention could improve insulin sensitivity and right ventricular function. The Pulmonary Arterial Hypertension Improvement With Nutrition and Exercise



Neil Osterweil/MDedge News

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# Dupilumab may reduce exacerbations in COPD, type 2 inflammation

BY HEIDI SPLETE

**FROM ATS 2024** ■ Dupilumab significantly reduced exacerbations and improved lung function in adults with uncontrolled chronic obstructive pulmonary disease (COPD) and type 2 inflammation, based on data from more than 900 individuals.

Data from a phase 3 trial known as NOTUS were presented at the American Thoracic Society's international conference and published simultaneously in *The New England Journal of Medicine* (NEJM).

Dupilumab, a fully human monoclonal antibody, works by inhibiting the signaling of the interleukin 4 (IL-4) and IL-13 pathways and is approved for many conditions characterized by type 2 inflammation, wrote Surya P. Bhatt, MD, of The University of Alabama at Birmingham, and colleagues in the NEJM study.

"Last year, we showed in the BOREAS trial that dupilumab was very effective in lowering exacerbation frequency in patients with COPD who continued to have frequent exacerbations despite being on maximal inhaled therapy," Dr. Bhatt said.

## 12 months of COPD, triple-inhaler therapy

In the NOTUS study, the researchers randomized 470 adults with uncontrolled COPD and type 2 inflammation (defined as a blood eosinophil count of  $\geq 300$  cells/ $\mu$ L) to 300 mg subcutaneous dupilumab and 465 to a placebo every 2 weeks. Patients were enrolled between July 2020 and May 2023.

The study population included adults aged 40-85 years with physician-diagnosed COPD for at least 12 months who had received background triple-inhaler therapy (an inhaled glucocorticoid agent plus long-acting muscarinic antagonist [LAMA]-long-acting beta-agonist [LABA] or LAMA-LABA alone) for at least 3 months and at a stable dose for at least 1 month. All participants were current or former smokers with a smoking history of at least 10 pack-years.

The primary endpoint was a reduction in the annualized rate of moderate or severe COPD exacerbations at 52 weeks.

At 52 weeks, the annualized rate of moderate or severe exacerbations was significantly lower (34%) in the dupilumab group than in the placebo group (0.86 vs 1.30,  $P < .001$ ).

Patients in the dupilumab group also saw a significantly greater improvement in lung function compared with individuals in the placebo group based on prebronchodilator forced expiratory volume in 1 second from baseline to 12 weeks (least-squares mean change of 139 mL vs 57 mL). This improvement was sustained at 52 weeks (least-squares mean change of 115 mL vs 54 mL).

Improvement in respiratory symptom severity based on the St. George's Respiratory Questionnaire was another secondary endpoint, and changes in total score were greater in the dupilumab group than in the placebo group

(least-squares mean change of 9.8 vs 6.4).

Safety outcomes were similar between the dupilumab and placebo groups, with approximately 66% of patients in each group reporting adverse events during the 52-week study period. Serious adverse events occurred in 13% and 15.9% of dupilumab and placebo patients, respectively, and adverse events resulting in death occurred in 2.6% and 1.5%, respectively. The most common

*"While the NOTUS study provides valuable insights into the efficacy and safety of dupilumab over 52 weeks, longer-term studies are needed to understand the sustained benefits and risks of continued treatment."*

– Dr. Narendra

adverse events were COVID-19, which occurred in 9.4% and 8.2% of the dupilumab and placebo patients, respectively, followed by headache, COPD, and nasopharyngitis. Major adverse cardiovascular events occurred in three patients in the dupilumab group and seven patients in the placebo group.

The findings were limited by several factors including the reduced sample size for 52-week endpoints because of the earlier analysis and the primarily White study population, the researchers noted. The study was conducted in part during the COVID-19 pandemic period, which contributed to health care disruptions and behavior changes that decreased exposure to viral respiratory infections, they wrote in their discussion. However, the results were strengthened by the large numbers and international population without other major pulmonary diseases, such as asthma, and the 34% reduction in exacerbations with dupilumab vs placebo is clinically significant, they said.

## Data may drive approval

In the BOREAS trial, dupilumab also improved lung function and quality of life, with no notable safety concerns. "As with any trial evaluating the efficacy and safety of a medication, it is important to confirm the findings in a replicative study," Dr. Bhatt said. "With NOTUS, we confirmed the findings of BOREAS," and the researchers were reassured by the substantial reduction in exacerbation frequency and the replication of key secondary outcomes, she said.

With the NOTUS study, "two randomized trials have now shown near identical reductions in exacerbation frequency in a difficult-to-treat population of patients with COPD with type 2 inflammation and frequent exacerbations," as well as a significant and meaningful improvement in lung function, Dr. Bhatt said. "We hope these trials pave for the way for regulatory body approval of dupilumab

for clinical use," she said. Looking ahead, more studies are needed to test the potential disease modification effects of dupilumab in patients with COPD, she added.

## Potential change in patient management

Approximately 20%-40% of patients with COPD have type 2 inflammation with elevated blood eosinophil count, and this subset of patients has

an increased risk for exacerbations, with worsening lung function and quality of life, said Dharani Narendra, MD, FCCP, assistant professor at Baylor College of Medicine, Houston, and a member of the *CHEST Physician* Editorial Board.



Dr. Narendra

Prior phase 3 studies have shown that dupilumab, a blocker of IL-4 and IL-13

pathways, could effectively reduce exacerbations and improve lung function in these patients, and the NOTUS study aimed to confirm the findings in a larger, more diverse population, said Dr. Narendra, who was not involved in the study.

The NOTUS study represents a paradigm shift in the management of COPD patients with type 2 inflammation, Dr. Narendra said. "This study validates the previous BOREAS trial and has shown that dupilumab reduces exacerbations, improves lung function and quality of life, and potentially slows disease progression," she said.

If approved, potential barriers to the use of dupilumab in practice include cost and insurance coverage, education and dissemination of study findings, and limited data on side effects, Dr. Narendra said.

"While the NOTUS study provides valuable insights into the efficacy and safety of dupilumab over 52 weeks, longer-term studies are needed to understand the sustained benefits and risks of continued treatment," Dr. Narendra said. "Studies comparing dupilumab with other biological agents and newer COPD treatments could provide insights into its relative efficacy and position in treatment protocols," she said.

In addition, further research into dupilumab's underlying mechanisms could provide deeper insights into the pathophysiology of type 2 inflammation in COPD and inform the development of new treatments, Dr. Narendra said. "These steps will help integrate dupilumab more effectively into clinical practice and optimize its use for COPD patients with type 2 inflammation," she noted.

Dupilumab is undergoing Priority Review by the Food and Drug Administration as an add-on maintenance therapy for adults with uncontrolled COPD and type 2 inflammation, according to a company press release.

The study was funded by Sanofi and Regeneron Pharmaceuticals.

Dr. Narendra had no financial conflicts to disclose. ■

abstract session. The study findings were also published in *The New England Journal of Medicine* (doi: 10.1056/NEJMoa2401389).

### Undiagnosed diseases

“The simple problem is that 70% of individuals with asthma or COPD are likely undiagnosed,” Dr. Aaron said. He noted that the 2007-2012 US National Health and Nutritional Examination Survey found obstructive lung disease in 13% of randomly selected US adults, but 71% of these people had never been diagnosed with asthma or COPD.

“So our questions were in this study: One, can we find adults with undiagnosed asthma or COPD in the community? The second question was: If we find them, are they sick? And the third and most important question was: Can we treat them early and improve their health outcomes?” he said.

Asthma and COPD both present with similar respiratory symptoms, including dyspnea, cough, wheeze, and/or chest tightness, and the two conditions share expiratory airflow obstruction as a common physiologic impairment that can be detected with spirometry.

### Study details

To identify participants, the investigators hired a commercial survey firm to contact households asking whether any member aged 18 years or older had respiratory symptoms such as shortness of breath, wheezing, increased mucus or sputum production, or prolonged cough in the past 6 months. Those who responded yes were then contacted by a trial coordinator, and the symptomatic household member was asked to complete the Asthma Screening Questionnaire over the phone. Participants aged 60 years or older and those younger than 60 years with a score of 6 or higher on the asthma screen also completed the COPD Diagnostic Questionnaire.

Those with a score of 6 or higher on the asthma screen or 20 or higher on the COPD screen were invited to undergo spirometry at a trial site.

The investigators ultimately identified 508 adults with undiagnosed asthma or COPD and randomly assigned them on an equal basis to an intervention group (253 patients) or control group (255 patients).

In the intervention group treatment was provided by a study pulmonologist and asthma-COPD educator who started guideline-based care. Patients were prescribed

inhalers and were taught how to use them, and many were given action plans that included smoking cessation aids, exercise and weight counseling, and vaccinations against influenza and pneumonia. Participants assigned to the control group would receive usual care provided by their primary care practitioner (PCP).

### Improvements abound

During the 12 months of the study, 92% of patients in the intervention group and 60% in the control group were started on new medications for their condition.

Only 13.4% of those in the intervention group received either no respiratory treatments or a short-acting beta 2 agonist only during the entire trial period compared with 49.8% of controls, “so the usual-care arm was undertreated relative to the intervention arm, and because of that under-treatment we saw a tremendous difference in the primary outcome,” Dr. Aaron said.

The primary outcome, the annualized rate of patient-initiated health care utilization for respiratory illness, was significantly lower in the intervention group, translating into an incidence rate ratio of 0.48 ( $P < .001$ ). Secondary outcomes were also better in the intervention group. For example, total scores on the St. George Respiratory Questionnaire (SGRQ) declined by 10.2 points from baseline in the intervention group compared with a 6.8-point drop in the usual-care group. The mean difference was 3.5 points ( $P = .009$ ). Lower scores on the 0-100 SGRQ scale indicate better health status.

Similarly, total scores on the COPD Assessment Test, a scale of 0-40 with lower scores indicating better health, declined by 3.8 points and 2.6 points, respectively, over 12 months, for a mean difference of 1.3 points ( $P = .03$ ). In addition, those in the intervention arm had a 119-mL improvement in forced expiratory volume in 1 second over the 12 months of the study compared with only a 22-mL improvement in the usual-care group.

### Translatable results?

Dr. Aaron acknowledged that the investigators could have chosen to keep those who were assigned to the control group unaware of their diagnosis during the study but because all patients enrolled were symptomatic, it would have been unethical to do so. All participants were informed of their diagnosis at randomization, and the information

was conveyed to each patient’s PCP as well.

In fact, many patients in the control group decided to seek treatment for either asthma or COPD after learning of their diagnosis, which may have contributed to improved outcomes in the control arm, he said.

“What this means is if you make the diagnosis early in the community, and at least have them see a PCP, they will improve their quality of life and their health status,” he concluded.

Ravi Kalhan, MD, MS, from the Northwestern University Feinberg School of Medicine in Chicago, who co-moderated the session but was not involved in the study, said that the case-finding model used in the trial would be difficult to replicate elsewhere.

“This idea of seeking out undiagnosed people by doing spirometry, so-called ‘case finding’ as they described it, testing highly symptomatic people with spirometry, is really challenging in the US, because symptoms are not collected proactively very much,” he said.

Persons with acute respiratory symptoms in the US typically seek health care at urgent care clinics or have unscheduled visits with their

PCPs, “and by all accounts those people should have spirometry, but they just don’t in the US, as best as I can tell,” he added.

He agreed that getting patients to a specialist can result in better outcomes but said that implementing a systematic approach such as the one described in the study would be extremely difficult in the fragmented US health care system.

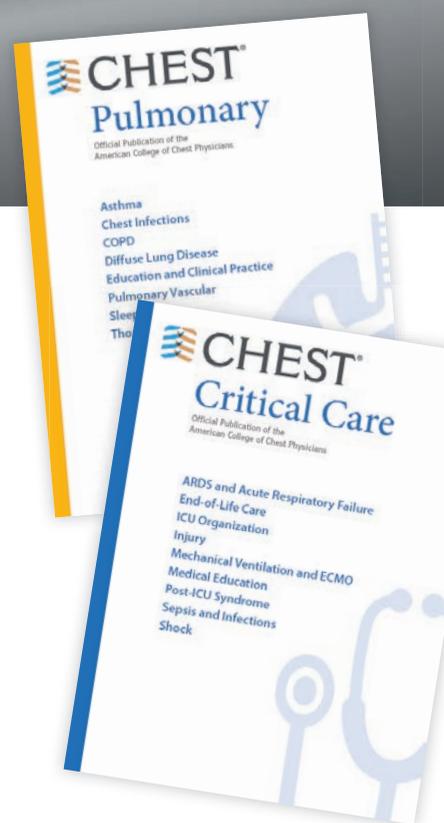
Dr. Kalhan’s co-moderator, Nuala J. Meyer, MD, MS, from the Hospital of the University of Pennsylvania, Philadelphia, said that “it was interesting that even those who were not in the intervention group but had these details passed on to their primary care physicians still had improvements,” and that it would be beneficial if PCPs were routinely informed about the results of urgent care visits. She added, however, that in the US the flow of information between urgent care clinics, primary care offices, and specialty clinics is problematic, suggesting that symptomatic patients may not always receive the additional care that they need. The study was supported by the Canadian Institutes of Health Research. Dr. Aaron, Dr. Kalhan, and Dr. Meyer all reported having no relevant disclosures. ■

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Gamely proceeding anyway, Dr. Balmes noted that natural gas — methane — is a potent greenhouse gas, and that cooking with natural gas leads to generation of NO<sub>2</sub> with high peak concentrations in the home, especially in the kitchen, but in other rooms as well.

“We know that NO<sub>2</sub> is an irritant gas that can cause bronchoconstriction, airway hyperresponsiveness, and inflammation, and there’s increased risk of asthma and COPD [chronic obstructive pulmonary disorder] exacerbations,” he said.

The US Environmental Protection Agency (EPA) outdoor ambient air standard for NO<sub>2</sub> is 100 parts per billion (ppb) or lower, which are the levels needed to prevent asthma exacerbations. In separate meta-analyses there was a 1.05 rise in asthma incidence per every 2 ppb of NO<sub>2</sub>, and an increase of 1.07 in COPD incidence for every 5 ppb of NO<sub>2</sub>, Dr. Balmes noted.

The respiratory effects of gas stoves were revealed in a 2013 meta-analysis of 10 studies from North America and Europe, which showed a pooled odds ratio for current asthma of 1.34. Building on these data, authors of a 2022 paper estimated that 13% of childhood asthma could be prevented by elimination gas cooking.

Although the causative link is missing, the evidence is abundant that natural gas isn’t good for anyone, he acknowledged.

### Con: More evidence needed

Arguing for the “con” side of the question, Meredith C. McCormack, MD, MHS, professor of medicine in the pulmonary and critical care division at Johns Hopkins University in Baltimore, said that “more definitive evidence is needed to define whether gas stoves cause lung disease.”

But Dr. McCormack didn’t let the natural gas industry off the hook, noting that a systematic review and meta-analysis of cooking with gas in high-, middle-, and low-income countries showed that domestic use of gas fuels vs electric was associated with increased risk of asthma (1.11 overall), COPD (1.15), and pneumonia (1.26).

The link between gas and risk of asthma was significant only for adults, however, and the data on the risks for COPD and for pneumonia or other respiratory infections came almost exclusively from low-income countries, she noted.



Dr. John R. Balmes

Despite the lack of evidence for a causative link, however, Dr. McCormack pointed to evidence that indoor NO<sub>2</sub> is an air pollutant that acts as a respiratory irritant, and that indoor NO<sub>2</sub> levels in homes with gas stoves have been shown to be more than twice as high as those in homes with electric stoves.

Other evidence shows that indoor NO<sub>2</sub> is associated with increased symptoms and use of rescue medications for children with asthma, and with shortness of breath, nocturnal symptoms, reduction in lung function, and exacerbations in COPD.

Still other studies have shown that exchanging a gas stove for an electric stove can reduce NO<sub>2</sub> concentrations in the home by up to 50%, but there is still a need for clinical trial evidence of a health benefit for such an exchange, she said.

And even if a gas stove is swapped out for an electric or induction range, household members with asthma are exposed to other hazards, including second-hand smoke, cooking exhaust, candle or incense burning, outdoor particulate matter that finds its way indoors, mold, and mouse or cockroach allergens, she noted.

### On common ground

Environmental interventions that can benefit all members of a household — not just those with obstructive pulmonary disease — include smoking cessation, charcoal filter-equipped air cleaners, stove hoods that vent outdoors, integrated pest management, hypoallergenic pillow and mattress covers, high-efficiency particulate air (HEPA) vacuums, and mold and radon abatement.



Dr. Meredith C. McCormack

Both Dr. Balmes and Dr. McCormack agreed in the end that gas stoves contribute to respiratory morbidity, and that both state and national policy changes are needed to support transition to cleaner indoor air, with financial incentives available for households with more modest incomes.

“For everyone, there is a climate-change mitigation imperative to transition away from gas appliances if we want to tackle the climate emergency,” Dr. Balmes said.

### End indoor combustion

George D. Thurston, ScD, professor of medicine and population health at the NYU Grossman School of Medicine, who attended the debate, said that the participants talked about NO<sub>2</sub> but didn’t touch on particulate pollution generated by gas stoves.

Burning natural gas produces particles that are very similar in composition to those produced by burning coal, oil, or diesel fuel, Dr. Thurston said, and he pointed out that interventions such as range hoods work only if they actually vent outdoors, and aren’t simply fans that recirculate the air within the home. And even when ventilation works as it should to move air out of the house, it pumps it only back into the atmosphere, where it contributes to climate change.

“We need combustion-free homes. That’s the unifying principle. We have to keep our eyes on that prize,” he said.

Dr. Balmes, Dr. McCormack, and Dr. Thurston all reported having no relevant disclosures. ■

## Moderna’s RSV vaccine approved by FDA

BY BRIAN OWENS

The US Food and Drug Administration (FDA) approved mRESVIA (mRNA-1345, Moderna), a vaccine for respiratory syncytial virus (RSV).

The mRNA vaccine is approved for adults aged 60 years or older to prevent lower respiratory tract disease caused by RSV. It is the third vaccine to be approved for RSV in the past year after Arexvy from GSK and Abrysvo by Pfizer.

“The FDA approval of our second product, mRESVIA, builds on the strength and versatility of our mRNA platform,” Stéphane Bancel, chief executive officer of Moderna, said in a news release. “mRESVIA protects older adults from the severe outcomes of RSV infection. This approval is also the first time an mRNA vaccine has been approved for a disease other than COVID-19.”

mRESVIA is a single-dose vaccine available in prefilled syringes, which the company said are designed to

maximize ease of administration, saving vaccinators’ time, and reducing the risk for administrative errors.

The approval is based on the positive results from the phase 3 ConquerRSV clinical trial, published in *The New England Journal of Medicine* in December 2023. The study, conducted in approximately 37,000 adults aged 60 years or older in 22 countries, found a vaccine efficacy against RSV lower respiratory tract disease of 83.7% after a median 3.7 months of follow-up.

An additional longer-term analysis showed continued protection over 8.6 months median follow-up. No serious safety concerns were identified. The most reported adverse reactions were injection-site pain, fatigue, headache, myalgia, and arthralgia.

Moderna has also filed for approval in multiple markets around the world, and said it expects mRESVIA to be available in the United States in time for the 2024-2025 respiratory virus season. ■

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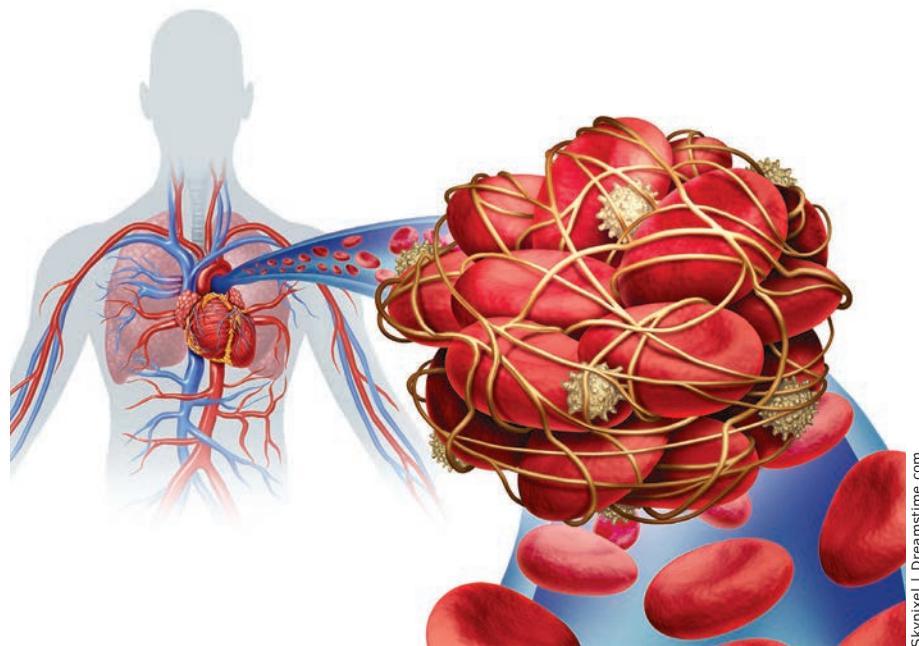
# Disparities in pulmonary embolism management

BY RICHARD MARK KIRKNER

**FROM SCAI 2024** ■ LONG BEACH, CALIFORNIA — A small fraction of patients with pulmonary embolism (PE) who are eligible for advanced therapies are actually getting them, reported investigators who conducted a big data analysis.

“Advanced PE therapy seems to be vulnerable to disparate use, and perhaps underuse,” said Sahil Parikh, MD, a cardiovascular interventionalist at the Columbia University Medical Center in New York, when he presented results from the REAL-PE study at the Society for Cardiovascular Angiography and Interventions (SCAI) 2024 scientific sessions.

The underuse of advanced PE therapies is “the controversy,” Dr. Parikh said after his presentation. “It remains unclear what the role of invasive therapy is in the management of so-called high-intermediate-risk people. There isn’t a Class 1 guideline recommendation, and there is a very rapidly evolving trend that we’re increasingly treating these patients invasively,” he said.



“However, if you come to these meetings [such as SCAI], you might think everyone is getting one of these devices, but these data show that’s not the case,” Dr. Parikh said.

The analysis mined deidentified data from Truveta, a collective of health systems that provides regulatory-grade electronic health record data for research.

The database included 105 million diagnoses made from January 1, 2018, to May 5, 2023; according to the diagnosis codes, 435,296 of these were for pulmonary embolism, and according to the procedure codes, 2072 patients — 0.48% of all patients with a PE diagnosis — received advanced therapy.

The researchers accessed data on patients treated with ultrasound-assisted catheter-directed thrombolysis or mechanical thrombectomy, identified from claims codes. Patient characteristics — age, race, ethnicity, sex, comorbidities, and diagnoses — were also accessed for the analysis. Earlier results were published in the *Journal of the Society for Cardiovascular Angioplasty Interventions*.

## Less intervention for Black patients and women

White patients were more likely to receive advanced therapy than were Black patients (0.5% vs 0.37%), Dr. Parikh reported, and women were less likely to receive advanced therapy than were men (0.41% vs 0.55%).

The only discernable differences in outcomes were in major bleeding events in the 7 days after the procedure, which affected more White patients than it did Black patients (13.9% vs 9.3%) and affected more women than it did men (16.6% vs 11.1%).

What’s noteworthy about this study is that it demonstrates the potential of advanced data analytics to identify disparities in care and outcomes, Dr. Parikh said during his presentation. “These analyses provide a means of evaluating disparities in real clinical practice, both

in the area of PE and otherwise, and may also be used for real-time monitoring of clinical decision-making and decisional support,” he said. “We do think that both novel and established therapies can benefit equally from similar types of analyses.”

## Big data signaling disparities

“That’s where these data are helpful,” Dr. Parikh explained. They provide “a real snapshot of how many procedures are being performed and in what kinds of patients. The low number of patients getting the procedure would suggest that there are probably more patients who would be eligible for treatment based on some of the emerging consensus documents, and they’re not receiving them.”

The data are “hypotheses generating,” Dr. Parikh said. “These hypotheses have to be evaluated further in more granular databases.”

REAL-PE is also a “clarion call” for clinical trials of investigative devices going forward, he said. “In those trials, we need to endeavor to enroll enough women and men, minority and nonminority patients so that we can make meaningful assessments of differences in efficacy and safety.”

This study is “real proof that big data can be used to provide information on outcomes for patients in a very rapid manner; that’s really exciting,” said Ethan Korngold, MD, chair of structural and interventional cardiology at the Providence Health Institute in Portland, Oregon. “This is an area of great research with great innovation, and it’s proof that, with these type of techniques using artificial intelligence and big data, we can generate data quickly on how we’re doing and what kind of patients we’re reaching.”

Findings like these may also help identify sources of the disparities, Dr. Korngold added.

“This shows we need to be reaching every patient with advanced therapies,” he said. “Different hospitals have different capabilities and different expertise in this area and they reach different patient populations. A lot of the difference in utilization stems from this fact,” he said.

“It just underscores the fact that we need to standardize our treatment approaches, and then we need to reach every person who’s suffering from this disease,” Dr. Korngold said. ■

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# Hold the antianaerobics in the ICU

BY NEIL OSTERWEIL

**FROM ATS 2024** ■ SAN DIEGO — Avoiding the use of antianaerobic antibiotics for empiric treatment of patients with sepsis can prevent depletion of beneficial bacteria in the gut microbiome and reduce both organ dysfunction and in-hospital mortality, a critical care specialists contends. “You may not be personally moved by a 2%-5% absolute difference in mortality, but sepsis is so common and so lethal that even small differences in outcomes can actually translate into enormous public health implications,” said Robert P. Dickson, MD, a pulmonary and critical care specialist at the University of Michigan in Ann Arbor.



Dr. Dickson

If instead of prescribing piperacillin-tazobactam (Zosyn; pip-tazo) for sepsis, critical care specialists were to switch to cefepime “even if you make very conservative assumptions like a modest effect size, you’re still talking about [saving] thousands of lives a year,” he said in a symposium at the American Thoracic Society’s international conference.

Most patients with sepsis in a medical ICU with respiratory, urinary, or bloodstream sources of infection do not have indications for antianaerobic antibiotics, and there are no head-to-head clinical trials demonstrating a benefit for one anti-sepsis antibiotic strategy over another, he said.

“In contrast, every observational study between antianaerobic and non-antianaerobic shows benefits to the anaerobe-sparing [drugs], and it’s been shown with animal models too. So to my mind, it’s already practice changing. I need to be talked into giving antianaerobic antibiotics for septic patients” he said.

There are three basic approaches to focusing on the gut microbiome as a therapeutic target. The hardest is attempting to engineer an ecosystem — a complex task that has never been shown to work in either the gut or in the ICU, Dr. Dickson said. A second approach, the use of probiotics to repopulate the gut with beneficial bacteria, is largely futile in the ICU, as the large majority of patients are on antibiotics and can’t be safely

**Eugene Yuriditsky, MD, FCCP comments:** The current report addresses an important question in critical care medicine: Should antianaerobic coverage be included in empiric antibiotic selection? The article highlights a recent publication by Chanderraj and colleagues and features an interview with Dr. Robert P. Dickson, the senior author. In the retrospective study including over 3,000 patients, those treated with an antianaerobic regimen (primarily piperacillin-tazobactam [pip-tazo]), experienced higher rates of ventilator-associated pneumonia, nosocomial infection, and decreased survival compared to patients treated without antianaerobic coverage (primarily cefepime and vancomycin).<sup>1</sup> Corroborating the findings, Chanderraj et al. performed a separate retrospective analysis of over 7,500 patients demonstrating that treatment with pip-tazo was associated with higher mortality (5% absolute difference) and duration of organ dysfunction when compared with cefepime.<sup>2</sup>

The authors indicate prior experimental and observational studies have demonstrated that anti-anaerobic coverage was associated with expansion of enteric pathogens in hospitalized patients and that pip-tazo is particularly disruptive of gut microbiota.<sup>1</sup> Based on a sub-study and a murine model, the authors hypothesized that disruption of gut microbiota and altered respiratory microbiology were among the explanations for their findings.<sup>1</sup> Importantly, the mortality difference was not fully attributed to infection risk. Proposed future work should therefore include translational studies to explore additional mechanistic links as well as subject



the study findings to a randomized trial. Anti-microbial therapy among hospitalized patients is frequently overprescribed and anti-anaerobic coverage often deemed unnecessary.<sup>3</sup> The two manuscripts by Chanderraj et al suggest potential harm. Recently, Bai and colleagues analyzed patients with community-acquired aspiration pneumonia and found that extended anaerobic coverage did not offer<sup>2</sup> mortality benefit and increased rates of *Clostridium difficile* when compared with limited anaerobic coverage.<sup>4</sup>

How should the results of the aforementioned studies inform our clinical practice? The incidence of anaerobic infections is likely overestimated. The weight of evidence suggests that withholding empiric anti-anaerobic coverage may improve clinical outcomes and lead to less disruption of gut microbiota. While there is a cohort of patients who may benefit from anti-anaerobic coverage, this approach is not likely appropriate for the majority of critically ill patients without an identified source or organism. The current evidence should be incorporated into clinical practice and antibiotic stewardship as we hope to see randomized controlled trials more definitively shed light on this question and elucidate the best approach to empiric antibiotic therapy in critically ill patients.

*Dr. Yuriditsky is a member of the CHEST Physician Editorial Board.*

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weaned off of them while in critical care. The third and easiest approach is to minimize dysbiosis in the first place. Anaerobic bacteria in the gut have been shown in several different disease states and animals models to be protective against pneumonia, organ failure, and death.

To see whether antianaerobic antibiotics could increase risk for adverse outcomes in the ICU, Dr. Dickson and colleagues previously conducted a retrospective study of 3032 mechanically ventilated patients in their center who received antibiotics with or without anaerobic coverage in the first 72 hours. They found that patients treated with early antianaerobic antibiotics had decreased ventilator-associated pneumonia-free survival (hazard ratio [HR], 1.24), infection-free survival (HR, 1.22), and overall survival (HR, 1.14) compared with patients who received antibiotics without anaerobic cover.

In a subcohort of 116 patients for whom gut microbiota data compositions were available, those who

received antianaerobic antibiotics had decreased initial gut bacterial density ( $P = .00038$ ), increased microbiome expansion during hospitalization ( $P = .011$ ), and domination of the microbiome by Enterobacteriaceae species ( $P = .045$ ). They also found that Enterobacteriaceae were enriched among respiratory pathogens in antianaerobic treated patients, and that in murine models, treatment with antianaerobic antibiotics increased susceptibility to Enterobacteriaceae pneumonia and increased the risk of death from non-infectious injuries.

In the ACORN (Antibiotic Choice on Renal Outcomes) trial in November 2023, there were no differences in the highest stage of acute kidney injury or death in the first 14 days between pip-tazo and cefepime. Remarking on the results, lead investigator Edward T. Qian, MD, MSc, from Vanderbilt University in Nashville, Tennessee, said, “I think the big takeaway is that you should feel comfortable starting

or using pip-tazo for your patients who are coming into the hospital and receiving empiric antibiotics for acute infection.”

But as Dr. Dickson’s group reported recently in *JAMA Internal Medicine*, a 15-month pip-tazo shortage allowed the investigators to conduct a natural experiment comparing 90-day outcomes among 7569 patients with sepsis who received vancomycin plus either pip-tazo or cefepime. They found in an instrumental variable analysis that pip-tazo was associated with an absolute increase in mortality at 90 days of 5.0%, and that patients who received this antianaerobic antibiotic had 2.1 fewer organ failure-free days, 1.1 fewer ventilator-free days, and 1.5 fewer vasopressor-free days.

The work of Dr. Dickson and colleagues is supported by National Institute of Health and Agency for Healthcare Research and Quality grants. He reported no other relevant disclosures. Dr. Thornton had no relevant disclosures. ■

# New drug offers hope for CPAP-free nights for OSA

BY DAVID BRZOSTOWICKI

**R**oughly 30 million to 40 million people in the United States have OSA. Because they are cumbersome and often uncomfortable, many OSA patients don't use their continuous positive airway pressure (CPAP) machine.

"In my patients, I'd say a quarter of them don't get compliant on the machine and require other treatments," said David Kuhlmann, MD, medical director of sleep medicine at Bothwell Regional Health Center in Sedalia, Missouri. That's often because they "just don't want to wear a mask at night." For Dr. Kuhlmann, who's also a spokesperson for the American Academy of Sleep Medicine, no other treatment can replace something that continually supplies air throughout the night. But that may be changing.

## New pill in OSA?

Could there be a new approach — a pill — that eases OSA symptoms and replaces more conventional treatments? That's the goal of researchers at Apnimed, a company that's developed a new oral drug for OSA. Currently called AD109, the drug combines aroxybutynin and atomoxetine.

Aroxybutynin is used to treat symptoms of an overactive bladder, while atomoxetine is used to treat attention-deficit/hyperactivity disorder.

"The drug is unique in the sense that, currently, there's no approved drug for the treatment of sleep apnea," said Douglas Kirsch, MD, medical director of sleep medicine at Atrium Health in Charlotte, North Carolina. "AD109 keeps the airway from collapsing during the night. And that function is through a combination of drugs, which, in theory, both help keep the airway a little bit more open, but also helps keep people asleep."

AD109 is currently in phase 3 trials, and based on results of phase 2 studies, "AD109 showed

clinically meaningful improvement in [OSA], suggesting that further development of the compound is warranted," according to the study's published data.

But there's something to consider when looking at these results.

## Evaluating AD109's results

One promising result out of the phase 2 trials was the lack of major side effects in people who took the drug. "What you are kind of hoping for from a phase 2 trial, both from a set safety perspective and an efficacy perspective, is that it did change the level of sleep apnea when compared to placebo," said Dr. Kirsch, who's also a former president of the American Academy of Sleep Medicine.

For phase 2 trials, patients were separated into groups after they were tested to see how severe their OSA was, using the apnea-hypopnea index (AHI). Dr. Kuhlmann said there are two big things they noticed: The AHI dropped in patients given two different doses of the drug. Those in the group that took the lower dosage actually saw "clinically significant improvement in fatigue."

For those with an index score of 10-15 (mild), 77% had their scores lowered to below 10. But only 42% with a score of 15-30 (moderate) were able to get below 10. And only 7% of those with a score of over 30 were able to get all the way down to 10 or below.

Regarding some of the index score drops, Dr. Kuhlmann said, "If you drop from an AHI of 20-10, that's still OSA if you have diabetes, high blood pressure, depression, daytime sleepiness, or insomnia."

Phase 3 should include a broader range of people.

"Phase 2 provides a proof of concept ... phase 3 is a little bit broader ... you can open the use of the drug to more people," Dr. Kirsch said.

## Sreelatha Naik, MD,

**comments:** In sleep medicine, we are cautiously optimistic looking to pharmacotherapy to address OSA and its impact. This may be the paradigm shift that is needed in OSA treatment.



*Dr. Naik is a member of the CHEST Physician Editorial Board.*

## A significant omission

The AD109 phase 2 trial did not include a crucial element sleep experts look at in how well treatments work: oxygen saturation.

Dr. Kuhlmann was skeptical of this omission. Instead of reporting the minimum oxygen saturation, Apnimed used something called "hypoxic burden," he said. "They didn't give us oxygen saturation information at all. But there's a big difference between somebody who has a minimum oxygen saturation of 89% and went from an AHI of 20 to 12... which sounds great... but had minimum oxygen saturation stay the same after."

In explaining the importance of hypoxic burden, Dr. Kirsch said, "If 99% of a sleep study was at 90% and above, but there was one dip at 80%, that's not the same as spending 45 minutes below 88%. What you really want to talk about is how much or how long does that oxygen get low?" Until phase 3 data are out, it's not possible to say where AD109 can work for those across severities. "Like any form of data, there are going to be targeted populations that may do better ... with

CPAP-FREE *continued on following page*

# CPAP underperforms: The sequel

BY AARON B. HOLLEY, MD, FCCP

**A** few months ago, I posted a column on continuous positive airway pressure (CPAP) with the title, "CPAP Oversells and Underperforms." To date, it has 90 comments, which are almost all negative. I'd like to address some of the themes expressed in the posts. Most comments were personal testimonies to the miracles of CPAP. CPAP can provide significant improvements in daytime sleepiness and quality of life. But several comments warrant a more in-depth discussion. The original piece focuses on CPAP and cardiovascular (CV) outcomes but made no mention of atrial fibrillation (AF) or ejection fraction (EF). The effects of CPAP on each are touted by

cardiologists and PAP-pushers alike and are drivers of frequent referrals. It's my fault for omitting them from the discussion. AF is easy. The data are identical to all other things CPAP and CV. There's hypoxia, intrathoracic pressure swings, sympathetic surges, and sleep state disruptions. It's easy to get from there to arrhythmogenesis. There's lots of observational noise, too, but no randomized proof that CPAP alters this relationship. I found four randomized controlled trials (RCTs) that tested CPAP's effect on AF. They were all negative. One even found a signal for more adverse events in the CPAP group. In medicine, the burden of proof falls on demonstrating efficacy. If we treat before concluding that a therapy works, we risk wasting time, money, medical resources, and the

energy required for behavior change. In their response to letters to the editor, the authors of the third RCT summarize the CPAP, AF, and CV disease data, and come out against screening patients with AF for OSA. The story for CPAP's effects on EF is similar though muddier. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for heart failure cite a meta-analysis showing that CPAP improves left ventricular EF. In 2019, the American Academy of Sleep Medicine (AASM) CPAP guidelines included a systematic review and meta-analysis that found that CPAP has no effect on left ventricular EF in patients with or without heart failure. The ACC/AHA cited review had broader inclusion, significantly more patients, and more

heterogeneity (I2 in the 80%-90% range). The AASM analysis achieved 0% heterogeneity but included fewer than 100 patients. Across both, the improvement in EF was 2%-5% at a minimally clinically important difference of 4%. The cemetery for discarded medical therapies is crowded, but there's room for CPAP, at least when it comes to improving CV outcomes. ■

*Dr. Holley is a professor in the department of medicine, Uniformed Services University, Bethesda, Maryland, and a physician at Pulmonary/Sleep and Critical Care Medicine, MedStar Washington Hospital Center, Washington. He disclosed ties to Metapharm and WebMD, and he is a member of the CHEST Physician Editorial Board.*

# Patients with CF experience poor sleep, depression

BY HEIDI SPLETE

**FROM ATS 2024** ■ Nonrespiratory symptoms including poor sleep, fatigue, pain, anxiety, and depressive symptoms were prevalent among adults with cystic fibrosis (AwCF) and persisted after 1 year of follow-up, based on data from more than 200 individuals in a study presented at the American Thoracic Society 2024 international conference.

“People with cystic fibrosis have qualitatively reported burden from extrapulmonary symptoms that were not being addressed by their health care providers; this is the first study to examine these symptoms concurrently in a large sample over time,” said lead author Kristin A. Riekert, PhD, of Johns Hopkins University, Baltimore, in an interview.

Previous cross-sectional studies have shown a high prevalence of poor sleep quality, fatigue, pain, depression, and anxiety among AwCF, but longitudinal data showing the persistence of symptoms are lacking, Dr. Riekert and colleagues noted in their abstract.

## Sleep quality, anxiety, and other assessments

The researchers recruited a total of 236 AwCF aged 18 years and older from two cystic fibrosis (CF) centers between April 2021 and August 2022. They examined the prevalence of poor sleep quality, fatigue, pain, depression, and anxiety in AwCF on the basis of five assessments: at baseline and at 3, 6, 9, and 12 months.

Participants were assessed via an online survey using the Fatigue Severity Scale (cutoff, > 4), Pittsburgh Sleep Quality Index (cutoff, > 5), Patient Health Questionnaire (cutoff, > 9), Generalized Anxiety Disorder (cutoff, > 9), and PROMIS Pain Intensity (cutoff, > 50 T score).

Chronic symptoms were defined as positive scores on four or more assessments for individuals who completed four or five time-point assessments. The mean age of the participants was 37 years, 52% were women, 95% were non-Hispanic White, and 86% had been prescribed CF modulator therapy.

*The study findings suggest that clinicians should assess people with CF for chronic fatigue and poor sleep along with depression and anxiety and provide treatment or referral.*

– Dr. Riekert

At 12 months, 62% of participants reported poor sleep, and 34% reported fatigue. In addition, 17% reported depressive symptoms, 14% reported anxiety symptoms, and 7% reported pain at 12 months.

Overall, 49% of participants met the criteria for chronic poor sleep quality, and 29% met the criteria for chronic fatigue, with positive assessments at four or more time points over the course of a year. In addition, 40%, 30%, and 18% of participants reported taking medication in the past 7 days for pain, mental health, and sleep, respectively.

The findings suggest that patients with CF might benefit from routine assessments of nonpulmonary symptoms in clinical care and from access to health care providers, including mental health professionals, to address nonpulmonary concerns, the researchers wrote in their abstract.

“We delayed starting the study until elexacaftor/tezacaftor/ivacaftor (ETI) was FDA [Food and Drug Administration]-approved because there was an assumption that people with CF would have

less fatigue because of respiratory improvements from ETI,” Dr. Riekert told this news organization. “Instead, the prevalence of fatigue and poor sleep quality was higher and more chronic than we had anticipated,” she noted.

However, “we were pleasantly surprised that depression and anxiety, while still prevalent, were less prevalent and chronic than previously reported,” Dr. Riekert said in an interview. “We attribute this to the CF Foundation’s mental health initiative that has increased the frequency of annual screening for depression and anxiety and provided resources to help people with cystic fibrosis obtain mental health services,” she said.

The study findings suggest that clinicians should assess people with CF for chronic fatigue and poor sleep along with depression and anxiety and provide treatment or referral, Dr. Riekert said. “For example, cognitive-behavioral therapy can effectively treat all the symptoms that were measured in our study,” she noted.

Limitations of the study include the lack of data on how the nonrespiratory symptoms interact with respiratory symptoms or pulmonary exacerbations, Dr. Riekert said. “While we assessed these symptoms five times, it was for a year; longer-term follow-up seems merited given our findings,” she said. In addition, “we need to study approaches to make cognitive-behavioral therapy and other therapy more accessible for people with cystic fibrosis,” Dr. Riekert said.

## Targeting nonpulmonary dimensions of CF care

The current study highlights an aspect of quality of life that is often forgotten when managing adults with CF and may affect their well-being despite effective therapy

to improve function and prolong life, said Wissam Chatila, MD, professor of thoracic medicine and surgery at the Lewis Katz School of Medicine at Temple University, Philadelphia, in an interview.

The high incidence of poor sleep, fatigue, depression, and anxiety seen in the current study was “somewhat surprising,” Dr. Chatila said. Also somewhat surprising was the chronicity of the symptoms considering the cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies (designed to correct the malfunctioning protein made by the CFTR gene) that have changed the face of CF, he noted.

However, recent growth in the number of adult patients with CF (more than 50% in certain countries) has led to a change in pathologies that physicians have to manage, and the current study addresses some of the emerging pathologies, Dr. Chatila said.

“Beyond demonstrating survival data from registries and other epidemiologic studies, this study sheds light on the need to address patient-reported outcomes that may or may not be directly related to the pulmonary and GI effects of the CFTR modulators,” he said. “Recognizing the extent of the dysfunction that many CF patients continue to suffer from will eventually lead to identifying factors that contribute to poor outcomes and the mechanisms involved,” he added.

Overall, the current study illustrates the potential benefits of offering personalized medicine to adults with CF that improves not only their physical function but also their mental health, Dr. Chatila said.

The study was funded by the Cystic Fibrosis Foundation. Dr. Riekert had no financial conflicts to disclose. Dr. Chatila had no financial conflicts to disclose. ■

CPAP-FREE continued from previous page

any drug, you’re unlikely to fix everything ... Until we see that phase 3 data ... you really can’t say for sure,” Dr. Kirsch said.

“It seems AD109 treats more of a milder spectrum than maybe the ones who would get the most benefit,” Dr. Kuhlmann said. He said AD109 may still work well for a number of people, but it’s important to understand a pill can’t be compared to CPAP. Dr. Kuhlmann said he’d like to see a medication, including AD109, that could measure up to oral appliances or anything that treats mild to moderate cases and “have some clinical scales associated with it that are positive.” Besides AD109, Dr. Kirsch said, “I think we are potentially

on the precipice of having some drugs that may help with sleep apnea in the coming years.”

The American Academy of Sleep Medicine estimates up to 80% of people with OSA remain undiagnosed. Cigarette smoking, high alcohol intake, drugs, or neurological disorders are common risk factors.

But most importantly, it’s anything that decreases muscle tone around the upper airway or changes in structural features that narrow the airway.

Dr. Kuhlmann also stressed the importance of weight issues linked to OSA. “It’s a very common condition, especially as people are getting older and heavier... you have loss of muscle tone

to your entire body, including the upper airway muscles.” ■

## Sources

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# AI could change imaging for bronchoscopy

BY JAVIER COTELO, MD

**A**rtificial intelligence (AI) can enhance endobronchial ultrasound (EBUS) image processing and new techniques such as cryoEBUS to achieve significant diagnostic and prognostic breakthroughs in interventional pulmonology and general pulmonology.

Pulmonologists are witnessing a surge in new technologies for endoscopy and pulmonology in general.

Some, such as AI, robotic bronchoscopy, radiomics, or improvements in electromagnetic bronchial navigation, are minimally invasive diagnostic techniques that significantly enhance the characterization of lung lesions, said Virginia Pajares, MD, a member of the Catalan Society of Pulmonology and coordinator of the Bronchoscopy Unit at Hospital de Sant Pau in Barcelona, Spain. She spoke at the XLI Pneumological Day of the Catalan Society of Pulmonology in Vilanova i la Geltrú, Spain.

Regarding AI, pulmonologists “already have platforms that enable the calculation of the malignancy risk of lung lesions and mediastinal adenopathies. In addition, some devices that allow for an initial radiological assessment of lung nodules are starting to be used,” Dr. Pajares said.

## Radiomics: Histology and markers

The field of radiomics, a branch of AI that facilitates the characterization of lung lesions, may prove useful in future histological differentiation or molecular marker assessment. “At an endoscopic level, some studies have confirmed the ability of AI applied to imaging to differentiate between benign and malignant lesions, although currently the studies are limited and in the initial stages,” Dr. Pajares said. “AI in interventional pulmonology will be highly beneficial in image interpretation and patient assessment for those who require more invasive diagnostic techniques or for follow-up.”

Regarding the application of AI in medicine, “we lack knowledge and require specific training, especially concerning the learning curve of different technologies, such as electromagnetic navigation, cryoEBUS, or robotic bronchoscopy, which require significant training efforts,” Dr. Pajares said. “The use



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of AI without a specific goal, that is, creating a mathematical algorithm and feeding it with clinical patient data without control and validation, can lead to inaccurate conclusions. Additionally, we need to determine how to input patient data into these systems to avoid ethical issues, and, of course, legislation on this matter is essential.”

## Electromagnetic navigation

Bronchial electromagnetic navigation is a bronchoscopic technique that allows access to peripheral lung lesions. “It involves virtual route planning using the patient’s chest CT scan and subsequently performing bronchoscopy with navigation using a dirigible electromagnetic probe that allows access to the lesion,” Dr. Pajares explained. “Currently, we have navigators that can incorporate imaging techniques (fluoroscopy or cone-beam CT) to immediately correct discrepancies observed during navigation.”

These new technologies enable a greater number of precise diagnoses and may bring greater patient safety. Studies like NAVIGATE, which was published in 2022 by Folch and colleagues, confirm the diagnostic possibilities and performance of electromagnetic navigation.

In this prospective study, which followed patients for 24 months, the indications are broad. “Its most common use is as a diagnostic technique for peripheral lung nodules and for marking lung lesions for surgical resection or marking for radiotherapy field fiducial placement,” Dr. Pajares said. “Results are also beginning to be published on

the treatment of lung lesions using electromagnetic navigation ablation, demonstrating its safety and efficacy in this area.”

## Nonsolid imaging

The challenges in navigation include “improving the diagnosis of lung lesions that are nonsolid, known as ground-glass opacities, and verifying it as an additional treatment option for lung nodules in patients who are not candidates for surgical resection,” Dr. Pajares said.

*Liquid biopsy, a recent laboratory technology unrelated to bronchoscopy, allows the analysis of blood/pleural fluid samples that were extracted using the aforementioned technologies to locate tumor cells and differentiate between malignancy and benignity.*

Tess Kramer, PhD, of Amsterdam University Medical Center, Amsterdam, the Netherlands, advocates for the combined use of different technologies to have a beneficial impact on patients’ clinical outcomes.

Robotic bronchoscopy has been implemented in the United States for several years, enhancing the precision of lung nodule diagnosis. However, “currently, there are no clear differences in the diagnostic performance of robotic bronchoscopy compared with navigation in general. Soon, there will be studies to assess in which type of nodules

one technique may be more cost-effective.” No local centers have this technology yet, “although some are already evaluating the acquisition of robotic bronchoscopy; it’s only a matter of time,” Dr. Pajares said.

Improvements in echobronchoscopy technology include high-quality image processors and smaller device calibers with greater angulation to diagnose lesions and hard-to-reach adenopathies. From an imaging perspective, AI, combined with the creation of risk calculators, could enable the prediction of lymph node malignancy.

Moreover, the use of small-caliber cryoprobes (1.1 mm) for obtaining samples of adenopathies (cryoEBUS) has enhanced diagnosis by enabling larger tissue samples. Current studies are being conducted to confirm the utility of cryoEBUS in pathologies requiring extensive molecular and immunohistochemical studies for diagnosing lymphoproliferative syndromes or neoplasms.

In a different context, liquid biopsy, a recent laboratory technology unrelated to bronchoscopy, allows the analysis of blood/pleural fluid samples that were extracted using the aforementioned technologies to locate tumor cells and differentiate between malignancy and benignity.

Dr. Pajares declared no relevant financial relationships. ■

*This story was translated from the Medscape Spanish edition using several editorial tools, including AI, as part of the process. Human editors reviewed this content before publication.*

# Top reads from the CHEST journal portfolio

## Journal CHEST®

### Does Rheumatoid Arthritis Increase the Risk of COPD?

By: Chiwook Chung, MD, and colleagues

This study utilizing the Korean National Health Insurance Database suggests that patients with rheumatoid arthritis (RA) face a significantly higher risk of developing COPD compared with the general population. Notably, individuals with



Ms. Young

seropositive RA exhibit a greater risk of COPD onset than those with seronegative RA. Although smoking history didn't affect the relationship between RA and COPD, monitoring respiratory symptoms and pulmonary function in patients with RA, especially patients who are seropositive, is crucial. These findings underscore the importance of interdisciplinary collaboration between rheumatologists and pulmonologists to enhance early detection and management strategies for pulmonary complications in patients with RA. – Commentary by Corinne Young, MSN, FNP-C, FCCP, Member of the CHEST Physician Editorial Board

## CHEST Pulmonary®

### The Lung Cancer Prediction Model “Stress Test”

By: Brent E. Heideman, MD, and colleagues

Current lung cancer prediction models have limited utility in high-risk patients referred for diagnostic biopsy. In a study of 322 indeterminate pulmonary nodules, the Brock, Mayo Clinic, Herder, and Veterans Affairs models showed modest discrimination between benign and malignant nodules (AUCs 0.67-0.77). The models performed poorly for low-risk patients (negative predictive values 63%-71%) and suboptimally for high-risk patients (positive predictive values 73%-87%), suggesting referring physicians use additional clinical information not captured in these models to identify high-risk patients needing biopsy. New prediction models and biomarkers specifically developed and calibrated for high-risk populations are needed



Dr. Miller

to better inform clinical decision-making. Incorporating interval imaging to assess changes in nodule characteristics could potentially improve model performance. Tailored risk assessment tools are crucial for optimizing management and reducing unnecessary invasive procedures in this challenging patient population. – Commentary by Russell Miller, MD, Member of the CHEST Physician Editorial Board

## CHEST Critical Care®

### Characterizing Cardiac Function in ICU Survivors of Sepsis

By: Kevin Garrity, MBChB, and colleagues

While chronic cardiac dysfunction is one of the proposed mechanisms of long-term impairment post critical illness, its prevalence, mechanisms, and associations with disability following admission for sepsis are not well understood. Garrity and



Dr. Yuriditsky

colleagues describe the Characterization of Cardiovascular Function in ICU Survivors of Sepsis (CONDUCT-ICU) protocol, a prospective study including two ICUs in Scotland aimed to better define cardiovascular dysfunction in survivors of sepsis. Designed to enroll 69 patients, demographics, cardiac and inflammatory biomarkers, and echocardiograms will be obtained on ICU discharge with additional laboratory data, cardiac magnetic resonance imaging, and patient-reported outcome measures to be obtained at 6 to 10 weeks. This novel multimodal approach will provide understanding into the role of cardiovascular dysfunction following critical illness as well as offer mechanistic insights. The investigators hope to obtain operational and pilot data for larger future studies.

– Commentary by Eugene Yuriditsky, MD, FCCP, Member of the CHEST Physician Editorial Board

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## CRITICAL CARE COMMENTARY

## Use of albumin in critically ill patients

BY NICOLE RELKE, MD,  
MARK HEWITT, MD,  
BRAM ROCHWERG, MD, AND  
JEANNIE CALLUM, MD

Intravenous albumin is a human-derived blood product studied widely in a variety of patient populations. Despite its frequent use in critical care, few high-quality studies have demonstrated improvements in patient-important outcomes. It is important for intensivists to think critically about prescribing albumin and individualize the prescription for each patient, as albumin use is not without risk. Compared with crystalloids, albumin increases the risk of fluid overload and bleeding and infections in patients undergoing cardiac surgery. In addition, albumin is costly, and its production is fraught with donor supply chain ethical concerns (the majority of albumin is derived from paid plasma donors).

Albumin use is highly variable between countries, hospitals, and even clinicians within the same

specialty due to several factors, including the perception of minimal risk with albumin, concerns regarding insufficient short-term hemodynamic response to crystalloid, and lack of high-quality evidence to inform clinical practice. We will discuss when intensivists should consider albumin use (with prescription personalized to patient context) and when it should be avoided due to the concerns for patient harm.

An intensivist might consider albumin as a reasonable treatment option in patients with cirrhosis undergoing large volume paracentesis to prevent paracentesis-induced circulatory dysfunction, and in patients with cirrhosis and spontaneous bacterial peritonitis (SBP), as data suggests use in this setting leads to a reduction in mortality. Clinicians should be aware that even for these widely accepted albumin indications, which are supported by published guidelines, the certainty of evidence is low, recommendations are weak (conditional), and,



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therefore, albumin should always be personalized to the patient based on volume of paracentesis fluid removed, prior history of hypotension after procedures, and degree of renal dysfunction.

There are also several conditions for which an intensivist might consider albumin and for which

albumin is commonly administered but lacks high-quality studies to support its use either as a frontline or rescue fluid therapy. One such condition is type 1 hepatorenal syndrome (HRS), for which albumin is widely used; however, there are no randomized controlled trials that have compared albumin with

Trial	Population; intervention	Primary outcome	Primary outcome: albumin	Primary outcome: comparator	RR; 95% CI; P-value	Comments
<i>Sepsis or general ICU population</i>						
2004 SAFE Study	Patients in ICU; 4% albumin vs. 0.9% normal saline	Death from any cause at 28 days	726/3497 (20.9%)	729/3500 (21.1%)	0.99; 0.91-1.09; P=0.87	No difference in organ failure, length of ICU or hospital stay, duration of RRT or mechanical ventilation. Decreased mortality in a post-hoc analysis of patients with severe sepsis and trauma. Increased mortality in patients with TBI.
Caironi et al. (2014) ALBIOS Study	Severe sepsis; 20% albumin + crystalloid vs. Crystalloid alone	Death from any cause at 28 days	285/895 (31.8%)	288/900 (32.0%)	1.00; 0.87-1.14; P=0.94	Secondary outcomes not different (organ dysfunction, mortality at 90 days)
<i>Cirrhosis</i>						
China et al. (2021) ATTIRE Study (China et al., 2021)	Decompensated cirrhosis (inpatient), albumin <30g/L; 20% albumin vs. standard care	New infection, kidney dysfunction, death 3-15 days after treatment initiation	113/380 (29.7%)	120/397 (30.2%)	0.98; 0.71-1.33; P=0.87	Increased serious or life-threatening adverse events in the albumin group (pulmonary edema, fluid overload)
Sort et al. (1999)	Cirrhosis and SBP; Cefotaxime + albumin vs. cefotaxime alone	a) Renal impairment b) In-hospital mortality	a) 6/63 (10%) b) 6/63 (10%)	a) 21/63 (33%) b) 18/63 (29%)	a) P=0.002 b) P=0.01	No explicit fluid resuscitation the control arm
<i>Cardiac surgery</i>						
Pesonen et al. (2022) ALBICS Study	On-pump cardiac surgery; 4% albumin vs. ringers acetate as CPB prime and perioperative volume replacement	Major adverse event at 90 days (death, MI, acute heart failure, resternotomy, AKI, stroke, bleeding, arrhythmia, infection)	257/693 (37.1%)	234/693 (33.8%)	1.10; 0.95-1.27; P=0.20	Increased incidence of bleeding, resternotomy, infection in the albumin group. Lower incidence of myocardial injury in the albumin group.

**Table 1:** Summary of select randomized controlled trials of intravenous albumins.

AKI = Acute kidney injury, CPB = cardiopulmonary bypass, ICU = intensive care unit, MI = myocardial injury, RRT = renal replacement therapy, SBP = spontaneous bacterial peritonitis, TBI = traumatic brain injury

placebo. Instead, all studies examining this indication have included albumin in both treatment and control arms, while evaluating a variety of drug therapies that included terlipressin, midodrine, and octreotide. This does not allow for evaluation of albumin and its effect on outcomes in HRS. Intensivists should be aware of the concerns that the combination of terlipressin, an agent commonly used for HRS, and albumin may increase the risk of respiratory failure, fluid overload, and mortality. Albumin could also be considered in patients with sepsis after a trial of crystalloid, another indication lacking randomized controlled trial data. There are studies examining albumin as a frontline volume replacement in patients with sepsis, and this is recommended against in clinical practice guidelines, given no evidence of benefit. Lastly, albumin could be considered in patients with, or at high risk for, intradialytic hypotension, although there are no clinical studies demonstrating superiority of this approach over other fluid alternatives, and consideration should first be given to less costly alternative strategies (for example, oral midodrine, high dialysate sodium, lower dialysate

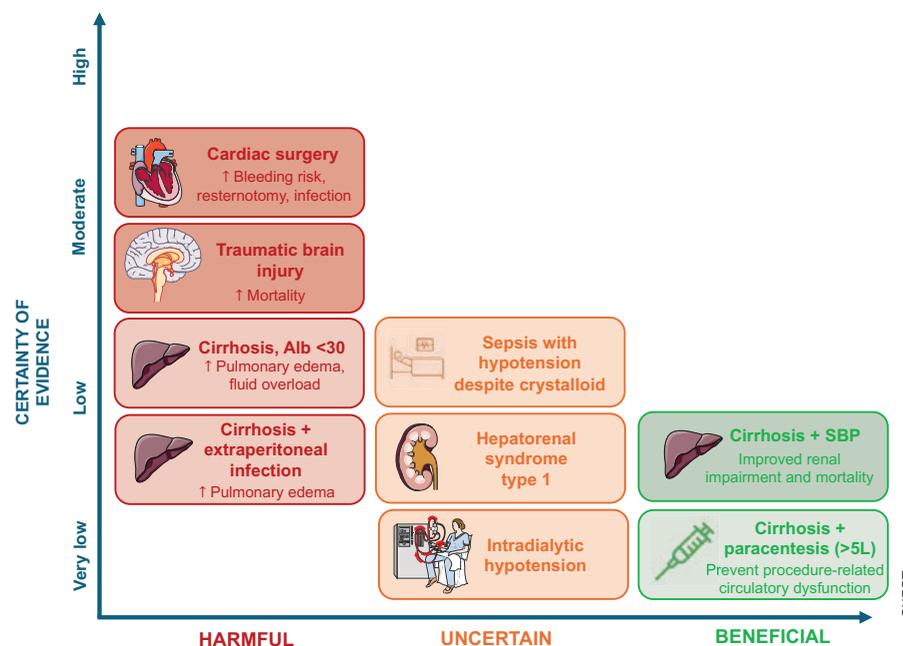
temperature, isolated ultrafiltration). As with any intervention, the use of albumin is associated with risks. In patients undergoing on-pump cardiac surgery, the ALBICS study showed that albumin did not reduce the risk of major adverse events and, instead, increased risk of bleeding, re-sternotomy, and infection. The ATTIRE trial showed that in patients hospitalized with decompensated cirrhosis and serum albumin <30 g/L, albumin failed

to reduce infection, renal impairment, or mortality while increasing life-threatening adverse events, including pulmonary edema and fluid overload. Similarly, in patients with cirrhosis and extraperitoneal infections, albumin showed no benefit in reducing renal impairment or mortality, and its use was associated with higher rates of pulmonary edema. Lastly, critically ill patients with traumatic brain injury (TBI) who received fluid resuscitation

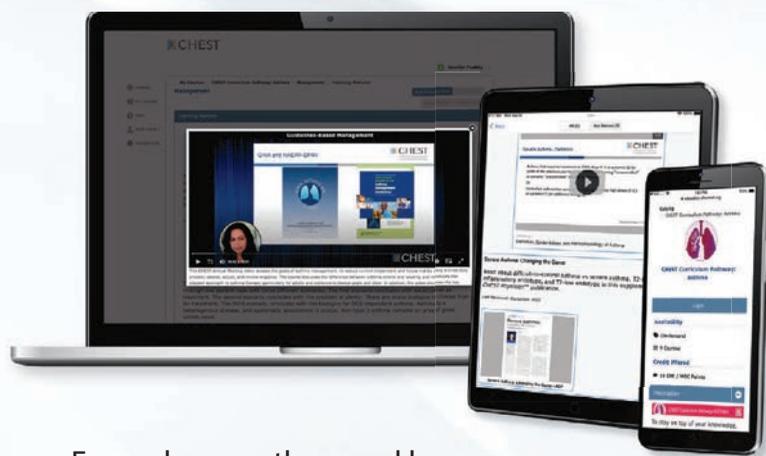
with albumin have been shown to experience higher mortality compared with saline. Thus, based on current evidence, intravenous albumin is not recommended for patients undergoing cardiac surgery (priming of the bypass circuit or volume replacement), patients hospitalized with decompensated cirrhosis and hypoalbuminemia, patients hospitalized with cirrhosis and extraperitoneal infections, and critically ill patients with TBI.

Overall, intravenous albumin prescription in critical care patients requires a personalized approach informed by current best evidence and is not without potential harm. High-quality evidence is currently lacking in many clinical settings, and large randomized controlled trials are underway to provide further insights into the utility of albumin. These trials will address albumin use in the following: acute kidney injury requiring renal replacement therapy (ALTER-AKI, NCT04705896), inpatients with community-acquired pneumonia (NCT04071041), high-risk cardiac surgery (ACTRN1261900135516703), and septic shock (NCT03869385).

All references are available online at [chestphysician.org](http://chestphysician.org). ■



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## NETWORKS

# RSV vaccine recommendations, nonidiopathic pulmonary fibrosis, PICS, and more

## AIRWAYS DISORDERS NETWORK Asthma and COPD Section Expanding recommendations for RSV vaccination

Respiratory syncytial virus (RSV) has been increasingly recognized as a prevalent cause of lower respiratory tract infection (LRTI) among adults in the United States. The



Dr. Krongold



Dr. Conroy

risk of hospitalization and mortality from RSV-associated respiratory failure is higher in those with chronic lung disease. In adults aged 65 years or older, RSV has shown to cause up to 160,000 hospitalizations and 10,000 deaths annually.

In 2023, the US Food and Drug Administration approved the adjuvanted RSVPreF3 vaccine (Arexvy, GSK) and the bivalent RSVPreF vaccine (Abrysvo, Pfizer). Both vaccines have been shown to significantly reduce the risk of developing RSV LRTI and are currently recommended for single-dose administration in adults 60 years or older—irrespective of comorbidities.

RSV has been well established as a major cause of LRTI and morbidity among infants. Maternal vaccination with RSVPreF in patients who are pregnant is suggested between 32 0/7 and 36 6/7 weeks of gestation if the date of delivery falls during RSV season to prevent severe illness in young infants in their first months of life. At present, there are no data supporting vaccine administration to patients who are pregnant delivering outside of the RSV season.

What about the rest of the patients? A phase 3b clinical trial to assess the safety and immunogenicity of the RSVPreF3 vaccine in individuals 18 to 49 years of age at increased risk for RSV LRTI, including those with chronic respiratory diseases, is currently underway with projected completion in April 2025 (clinical trials.gov; ID

NCT06389487). Additional studies examining safety and immunogenicity combining RSV vaccines with PCV20, influenza, COVID, or Tdap vaccines are also underway. These outcomes will be significant for future recommendations to further lower the risk of developing LRTI, hospitalization, and death among patients less than the age of 60 with chronic lung diseases.

*All references available online at [chestphysician.org](http://chestphysician.org).*

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## DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK Interstitial Lung Disease Section

### Short telomere length and immunosuppression: Updates in non-idiopathic pulmonary fibrosis interstitial lung disease

Interstitial lung diseases (ILDs) are a diverse group of relentlessly progressive fibroinflammatory disorders. Pharmacotherapy includes antifibrotics and immunosuppres-



Dr. Chhabria



Dr. Boente

sants as foundational strategies to mitigate loss of lung function. There has been a growing interest in telomere length and its response to immunosuppression in the ILD community.

Telomeres are repetitive nucleotide sequences that “cap” chromosomes and protect against chromosomal shortening during cell replication. Genetic and environmental factors can lead to premature shortening of telomeres. Once a critical length is reached, the cell enters senescence. Short telomere length has been linked to rapid progression, worse outcomes, and poor

response to immunosuppressants in idiopathic pulmonary fibrosis (IPF).

Data in patients with non-IPF ILD (which is arguably more difficult to diagnose and manage) were lacking until a recent retrospective cohort study of patients from five centers across the US demonstrated that immunosuppressant exposure in patients with age-adjusted telomere length <10th percentile was associated with a reduced 2-year transplant-free survival in fibrotic hypersensitivity pneumonitis and unclassifiable ILD subgroups. This study was underpowered to detect associations in the connective tissue disease-ILD group. Interestingly, authors noted that immunosuppressant exposure was not associated with lung function decline in the short telomere group, suggesting that worse outcomes may be attributable to unmasking extrapulmonary manifestations of short telomeres, such as bone marrow failure and impaired adaptive immunity. Studies like these are essential to guide decision-making in the age of personalized medicine and underscore the necessity for prospective studies to validate these findings.

*All references available online at [chestphysician.org](http://chestphysician.org).*

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## SLEEP MEDICINE NETWORK Nonrespiratory Sleep Section

### Post-intensive care syndrome and insomnia

There has been a recent interest in post-intensive care syndrome (PICS), as an increasing number of patients are surviving critical illness. PICS is defined as “new onset or worsening of impairments in physical, cognitive, and/or mental health that arises after an ICU stay and persists beyond hospital discharge. We know that poor sleep is a common occurrence in the ICU, which can contribute to cognitive impairment and could be due to various risk factors, including age, individual comorbidities, reason for admission, and ICU interventions. Sleep impairment after hospital discharge



Dr. Boppa



Dr. Louis

is highly prevalent for up to 1 year after hospitalization.

The most common sleep impairment described after hospital discharge from the ICU is insomnia, which coexists with anxiety, depression, and posttraumatic stress disorder. When patients are seen in a post-ICU clinic, a multimodal strategy is needed for the treatment of insomnia, which includes practicing good sleep hygiene, cognitive behavioral therapy for insomnia (CBT-I), and pharmacotherapy if indicated.

Since the American Academy of Sleep Medicine (AASM) 2021 clinical practice guideline on behavioral and psychological treatments for chronic insomnia, which made a strong recommendation for CBT-I, we continue to face barriers to incorporating CBT-I into our own clinical practice. This is due to limited access to CBT-I psychotherapists and patients’ lack of knowledge or treatment beliefs, among other reasons. However, there are numerous digital CBT-I platforms that patients can freely access from their mobile phone and are listed in the AASM article, “Digital cognitive behavioral therapy for insomnia: Platforms and characteristics,” which can help with treatment of insomnia.

For patients who are seen in post-ICU clinics, the first step in treating insomnia is discussing good sleep hygiene, providing resources for CBT-I (digital or in person), and treating coexistent psychiatric conditions.

*All references available online at [chestphysician.org](http://chestphysician.org).*

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Section Chair

NETWORKS continued on following page

# Coding & billing: A look into G2211 for visit complexities

BY KATINA NICOLACAKIS, MD

Member, Joint ATS/CHEST Clinical Practice Committee, ATS RUC Advisor

To continue to bring awareness to our members, we once again discuss this new add-on Healthcare Common Procedure Coding System code finalized by the Centers for Medicare & Medicaid Services (CMS) for January 1, 2024. This add-on code is for new (99202-99205) and established (99212-99215) office visits. CMS created this add-on code to address the additional costs and resources associated with providing longitudinal care.

**G2211** – Visit complexity inherent to evaluation and management (E/M) associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient's single, serious condition, or a complex condition (Add-on code; list separately in addition to office/outpatient (O/O) E/M visit, new or established)

The documentation should demonstrate the intent and need for ongoing care. Otherwise, no additional documentation is required. CMS pays \$16.04 for each service (wRVU = 0.33). It may be reported each time the patient is seen, and there is currently no limit to how often it may be used. Also, there is no additional copay requirement for patients.

## Do's and don'ts

Do report in the following situations when longitudinal care is provided:

- The provider has or intends to have a long-term, ongoing relationship with the patient (ie, G2211 can be used for a new patient visit)

- Audio/video virtual visits
- May be reported with Prolonged Care Services G2212
- When advanced practice providers or physician colleagues in the same specialty practice see the patient (ie, if you see the patient for an urgent visit, but the patient is usually followed by your partner, you can still use G2211)
- When working with graduate medical education trainees (along with the -GC modifier), and as long as the conditions described in the description of G2211 are met

Do NOT report in the following situations:

- If modifier -25 is appended to the E/M service when another service is provided on the same day (eg, pulmonary function tests, 6-minute walk tests, immunization)
- Audio-only virtual visits, hospital, skilled nursing facility, or long-term acute care hospital
- If the patient is not expected to return for ongoing care
- If the reason for longitudinal care does not include a "single, serious condition or a complex condition" (eg, annual visits for a stable 6 mm lung nodule)

CMS expects that this will be billed with 38% of all E/M services initially and potentially up to 54% over time. We feel this is reimbursement for the work being done to care for our patients with single, serious, or complex conditions. Both Medicare and Medicare Advantage plans are expected to reimburse for this service. Whether other payers will do the same is unclear, but it will become clear with time and further negotiation at the local level. In the meantime, members are encouraged to report this code for all appropriate patient encounters.

## Questions and answers — G2211

**Question:** What private insurances cover G2211?

**Answer:** As of March 1, 2024, four national payers have confirmed coverage of G2211:

- Cigna (Medicare Advantage only),
- Humana (commercial and Medicare Advantage),
- United Healthcare (commercial and Medicare Advantage), and
- Aetna (Medicare Advantage).

**Question:** What needs to be documented for G2211?

**Answer:** CMS states, "You must document the reason for billing the office and outpatient (O/O) and evaluation and management (E/M). The visits themselves would need to be medically reasonable and necessary for the practitioner to report G2211. In addition, the documentation would need to illustrate medical necessity of the O/O E/M visit. We [CMS] haven't required additional documentation."

American Thoracic Society (ATS) and CHEST also recommend including a detailed assessment and plan for the visit, as well as any follow-up. The complexity of the visit should be clear in your documentation to support the medical necessity for reporting the G2211.

**Question:** How can a provider show that a new patient visit (99202-99205) is part of continuing care?

**Answer:** The treating practitioner should make sure their documentation supports their intent to provide ongoing care to the patient. Establishing such intent goes beyond a statement that the provider plans to provide ongoing care or schedule a follow-up visit. The circumstances of

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## THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK Interventional Procedures Section Diagnostic yield reporting of bronchoscopic peripheral pulmonary nodule biopsies: A call for standardization

More than 1.5 million Americans are diagnosed with an incidental CT scan-detected lung nodule annually. Advanced bronchoscopy, as a diagnostic tool for evaluation of these nodules, has evolved rapidly, incorporating a range of techniques and tools beyond CT scan-guided biopsies to assess peripheral lesions. The primary goal is to provide patients with accurate benign or malignant diagnoses. However, accurately determining the effectiveness of innovative technologies in providing a diagnosis remains



Dr. Riestra Guiance



Dr. Shojaee

challenging, in part due to limitations in study design and outcome reporting, along with the scarcity of comparative and randomized controlled studies. Current literature shows significant variability in diagnostic yield definition, lacking generalizability.

To address this issue, an official research statement by the American Thoracic Society and CHEST defines the diagnostic yield as "the proportion of all individuals

undergoing the diagnostic procedure under evaluation in whom a specific malignant or benign diagnosis is established." To achieve this measure, the numerator includes all patients with lung nodules in whom the result of a diagnostic procedure establishes a specific benign or malignant diagnosis that is readily sufficient to inform patient care without additional diagnostic workup, and the denominator should include all patients in whom the procedure was attempted or performed. This standardized definition is crucial for ensuring consistency across studies, allowing for comparison or pooling of results, enhancing the reliability of diagnostic yield data, and informing clinical decisions.

The adoption of standardized outcome definitions is essential to critically evaluate modern,

minimally invasive procedures for peripheral lung nodules diagnosis and to guide patient-centered care while minimizing the downstream effects of nondiagnostic biopsies. Clear, transparent, and consistent reporting will enable physicians to choose the most appropriate diagnostic tools, improve patient outcomes by reducing unnecessary procedures, and expedite accurate diagnoses. This initiative is a crucial first step toward creating high-quality studies that can inform technology implementation decisions and promote equitable health care.

All references available online at [chestphysician.org](http://chestphysician.org).

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# Bringing trainee wellness to the forefront

## Researching the impact of reflection in medical training

BY KATLYN CAMPBELL

Communications Specialist, CHEST

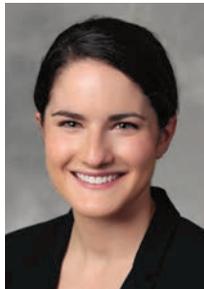
Before the spread of COVID-19, and increasingly during the pandemic, Ilana Krumm, MD, noticed a burgeoning focus on wellness for trainees and how to combat burnout in the medical space.

But Dr. Krumm also noticed that most of the existing programs focused on the individual level, rather than the system level. The onus was on the trainees to manage their wellness and burnout.

“I wanted to look at something that could be instituted at a systems level as opposed to putting all the burden of this wellness on the resident, as someone who already has a huge burden of work, stress, and time constraints as they try to learn their discipline,” Dr. Krumm said. “Asking them to meditate on their own time seemed very impractical.”

Eager to research this idea, Dr. Krumm applied for the CHEST Research Grant in Medical Education.

“The fact that CHEST is willing to support medical education research is really important for all those trying to better the educational environment. Although there’s a movement toward more support for medical education research and more recognition of its value, I think the fact that CHEST has already done so has helped advance the field and the support for the field as a whole,”



Dr. Krumm

Dr. Krumm said.

With the support of a CHEST medical education research grant, and under the mentorship of Rosemary Adamson, MBBS, Dr. Krumm began studying how incorporating a system-level program called Reflection Rounds could help trainees alleviate burnout.

“Having the support from a reputable institution like CHEST inherently gave the work that I was doing value,” Dr. Krumm said. “It gave folks an understanding that this research in medical education has importance.”

*“What I’ve learned from this project will make me a better leader in the ICU, not only in taking care of critically ill individuals but also in taking care of the team doing that work.”*

– Dr. Krumm

Dr. Krumm’s project focused on the monthly Reflection Rounds between the ICU, palliative care, and chaplaincy staff that were held at the Seattle VA Medical Center, where residents could discuss the challenges of caring for critically ill patients during a protected time. While similar interventions around death and dying have been shown to help residents reduce burnout in medical intensive care rotations, it was unknown which aspects of these sessions would be most effective.

Participant interviews were conducted before

and after the residents’ monthly sessions to understand the impact these sessions had on wellness and burnout levels.

“With the grant funding from CHEST, our team was able to purchase the recording equipment, transcription, and software necessary to complete a thorough qualitative research project, which greatly accelerated the project timeline,” she said.

Through these interviews, Dr. Krumm’s team identified three key themes that shed light on the impact of Reflection Rounds.

### 1. Cultural precedent

Participants were encouraged to participate as little or as much as they wanted during the session. Despite some residents being less vocal during these discussions, every resident agreed that this type of session set an important cultural precedent in their program and acknowledged the value of a program that encouraged space for decompression and reflection.

### 2. Shared experiences

During this project, many residents experienced an increased sense of isolation, as COVID-19 precautions were stricter in the ICU. Having this protected time together allowed residents to discover their shared experiences and find comfort in them while feeling supported.

“A lot of residents commented that it was nice to know that others were going through this as well or that they were also finding this particular instance difficult,” Dr. Krumm said.

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the visit should support the extra work involved in becoming the focal point of the patient’s care or providing ongoing care for a serious or complex condition.

**Question:** Dr. Red works at a primary care practice, is the focal point for a patient’s care, and has reported G2211. If Dr. Yellow, who is in the same specialty, or Mr. Green, a nurse practitioner, is covering for Dr. Red, and the patient comes in for a visit, can they report G2211 for that visit?

**Answer:** Yes. The same specialty/same provider rules would apply in this situation. But remember that Dr. Yellow’s or Mr. Green’s documentation for that encounter must support the code.

**Question:** Can a resident report G2211 under the primary care exemption?

**Answer:** Yes, according to CMS staff,

so long as the service and the documentation meet all the requirements for the exemption and the visit complexity code. For example, the resident can only report low-level E/M codes, and the resident must be “the focal point for that person’s care.”

**Question:** Are there frequency limits for how often we can report G2211, either for a single patient in a given time period or by a provider or a practice?

**Answer:** Not at this time, but make sure your providers are following the rules for reporting the code. “There’s got to be documentation that suggests why the practitioner believes they are treating the patient on this long-standing, longitudinal trajectory, and we’ll be able to see how that interaction is happening,” senior CMS staff said. CMS staff further issued a subtle warning to providers by reminding them that CMS has a very strong integrity program. Your practice can avoid

problems with thorough training, frequent chart review, and encouraging the team to ask questions until you feel that everyone is comfortable with the code.

**Question:** Are there any limits on the specialties that can report the code? Is it just for primary care providers?

**Answer:** No. Remember that a provider who is managing a single serious or complex condition can also report the code. But CMS expects the documentation to support the ongoing nature of the treatment. If a patient sees a provider as a one-off encounter, perhaps to manage an acute problem, that visit wouldn’t qualify. But if the provider clearly manages the patient’s condition, the encounters could qualify.

**Question:** Will CMS issue a list of conditions that meet the code’s serious or complex condition

requirement?

**Answer:** CMS has included the examples of HIV and sickle cell anemia in existing guidance, and it plans to issue a few more examples “that help folks understand what is expected.” However, it won’t be a complete list of every condition that might qualify. ■

*Originally published in the May 2023 issue of the American Thoracic Society’s ATS Coding & Billing Quarterly. Republished with permission from the American Thoracic Society.*

## In Memoriam

CHEST has been informed of the following death of a CHEST member. We remember our colleague and extend our sincere condolences.

William J. Wylie, MD

# How physician mortgage loans work for doctors

BY ALEXANDRA FROST

**T**ell someone you're a doctor, and the reaction is often: "You must be rich." But physicians who are just finishing medical school or are in their early careers might feel far from it. The average medical school debt is more than \$200,000, with total debts including undergrad climbing well north of \$250,000.

That leaves house-hunting physicians in a predicament. A key factor for lending institutions is the "debt to income" ratio, a calculation which indicates if you already have too much debt to pay your mortgage. That single equation could eliminate you from lenders' mortgage requirements.

But young doctors are also in a unique situation. Yes, they carry above-average levels of debt, but they are on a path to substantial income in future years. That's where the physician mortgage loan (PML) becomes a useful option.

## What is a physician mortgage loan?

A PML is designed to help physicians access mortgages despite large amounts of debt. They are also sometimes available to dentists, veterinarians, podiatrists, and others, according to Stephen Chang, MD, a radiologist, and a managing director at Acts Financial Advisors in McLean, Virginia.

The key features, according to James M. Dahle, MD, an emergency physician and founder of The White Coat Investor, include:

- No required down payment, which is typically 20% with a conventional loan.
- No private mortgage insurance (PMI). This is often a requirement of traditional loans, designed to protect the lender if the buyer misses payments. PMLs don't involve PMI even if you don't put

down 20%.

- No pay stubs. With a conventional loan, pay stubs are often required to prove income level and reliability. PMLs will often allow an employment contract in place of those.
- Different consideration of the student loan burden.

Those are the upsides, of course, but there may be downsides. Dr. Dahle said a PML might involve slightly higher rates and fees than a conventional mortgage does but not always.

## Who is best suited for a physician mortgage loan?

Financial advisers caution that everyone should first consider their full financial picture before applying for a mortgage, PML or otherwise. "If you don't have the money saved for a down payment, one can ask if you are financially prepared to purchase a home," said Cobin Soelberg, MD, an anesthesiologist and owner of Greeley Wealth Management, a financial planning firm serving physician families in Bend, Oregon.

If your savings are slim, you might need to build those accounts further before pursuing home ownership and the expenses that come along with it. Your credit score can contribute to the equation. "With any loan product, we always recommend working to optimize your personal credit score as soon as possible before applying for a loan," said Mark P. Eid, MD, a dermatologist and co-managing director (with Dr. Chang) at Act Financial Advisors. "Once you get into the high 700s, you've typically qualified for the best interest rates, so while that perfect 850 is nice to achieve, it's by no means necessary."

Also, assess your reasons for purchasing a home and whether it will fit your lifestyle in the coming years. "The main reason that [my wife and I] wanted to buy a home

was for stability," said Jordan Frey, MD, founder of The Prudent Plastic Surgeon. "After living in apartments for years, we wanted a place that was truly our own. We definitely felt disappointed and frustrated when worrying that our student debt may limit our ability to do this."

Like many physicians, Dr. Frey had taken on a huge amount of debt, to the tune of half a million dollars in student loans and credit card debt when he finished training in 2020. The question Dr. Frey and his wife wrestled with was: "How much debt should we take on in addition to what we already have?"

## What are the risks? What's in the fine print?

The eased limitations of PMLs come with potential pitfalls, and physicians should not imagine that they have unlimited buying power.

"Many physicians buy more expensive or bigger houses than they need simply because banks are willing to lend physicians money," Dr. Soelberg warns. "So, the doctor gets locked into a large mortgage and cannot build wealth, save for retirement, and repay their student loans."

As you shop around, beware of omissions and scams. When meeting with lenders, Dr. Frey recalled that some didn't even present PMLs as an option, and others presented them with unfavorable terms. He was careful to look for disadvantages hidden in the fine print, such as a potential "big hike in the rate a year later."

But sometimes, a scam is not outright deception but is more like temptation. So it's important to have your own best interests in mind without relying on lenders' advice. "When we were shopping around, some mortgage lenders would [offer] \$1.5 million, and we thought 'that makes no sense,'" Dr. Frey said. "[Physicians] have

big future income, which makes us attractive to these lenders. No one in their right mind would give a mortgage like this to anyone else. They aren't worried about whether it's a smart decision for you or not."

## What other red flags should you look out for?

Dr. Frey recommends medical professionals beware of these red flags when shopping for PMLs:

- A request for any type of collateral, including your medical practice
- A rate that is much higher than others
- A lender is pushing you to borrow a higher amount
- A lender attempts to influence your decision about the size of your down payment

Remember, if you are choosing an adjustable-rate mortgage (ARM), your rate will recalibrate on the basis of the market's rates — for better or worse. This means that your payment might be higher or lower, taking current interest rates into account. Looking back, Dr. Frey said he might reconsider his decision to use a 10-year ARM. He and his wife chose it because the rate was low at the time, and they planned to pay off the mortgage quickly or move before it went up. But the uncertainty added an element of pressure.

## How can PMLs contribute to overall financial health?

Dr. Frey said his physician mortgage was "a huge advantage," allowing him and his wife to put 0% down on their home without PMI. But most importantly, it fit within their overall financial plan, which included investing. Used strategically and intentionally, PMLs can put you on a more predictable financial path. And with less money stress, buying a home can be an exciting milestone as you plan your future and put down roots in a community. ■

TRAINEE *continued from previous page*

### 3. Ritual

At the opening of each hour-long session, participants were invited to light a candle and say aloud or think to themselves the name of a patient they had lost, had a hard time with, or cared for during their time in the ICU.

"Every single person pointed to that moment as meaningful and impactful," Dr. Krumm said.

This ritual gave the residents time to center and have a common focus with their peers to think about patient stories that they were carrying with them.

"Maybe just incorporating a small moment like that, a point of reflection, could potentially have a big impact on the weight we carry as providers who care for [patients who are] critically ill," Dr. Krumm said. "What I've learned from this project will make me a better leader in the ICU, not only in taking care of critically ill individuals but also in taking care of the team doing that work."

Dr. Krumm credits the CHEST grant funding and subsequent research project with helping her join a highly competitive fellowship program at the University of California San Francisco, where

she can continue to conduct research in the field of medical education.

"I am working closely with medical education faculty and peers to design new research studies and further establish myself in the field of medical education, leading to my ultimate goal of becoming a program director at a strong med-ed-focused program." ■

*This article was adapted from the Spring 2024 online issue of CHEST Advocates. For the full article—and to engage with the other content from this issue—visit [chestnet.org/chest-advocates](http://chestnet.org/chest-advocates).*



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## LUNG CANCER

# 'Practice changing' results for osimertinib in unresectable stage III EGFR+ NSCLC

BY M. ALEXANDER OTTO, PA, MMS

**FROM ASCO 2024** ■ CHICAGO — Osimertinib (Tagrisso) may soon have approvals across all stages of epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC).

The third-generation EGFR tyrosine kinase inhibitor (TKI) already carries indications for metastatic disease and for adjuvant use in earlier-stage EGFR-mutated NSCLC.

Results from the phase 3 LAURA trial, presented at the American Society of Clinical Oncology annual meeting and funded by AstraZeneca, will likely lead to an approval for the remaining indication: unresectable stage III disease.

Among patients randomized to either osimertinib or placebo following definitive chemoradiation, osimertinib extended median progression-free survival by 33.5 months compared with placebo — 39.1 vs 5.6 months, respectively (hazard ratio, 0.16;  $P = .001$ ).

The news was greeted with a standing ovation at the meeting where it was presented by lead investigator and medical oncologist Suresh S. Ramalingam, MD, a lung cancer specialist at Emory University, Atlanta.

David R. Spigel, MD, a discussant on the trial, called the results “outstanding.”

“To have an 84% reduction in the risk of cancer progression or death is meaningful,” said Dr. Spigel, a medical oncologist at the Sarah Cannon Research Institute, Nashville, Tennessee, who reported ties to AstraZeneca. “This will be practice changing as soon as the label gets expanded.”

In the trial, investigators randomized 216 patients with unresectable stage III EGFR-mutated NSCLC who had not progressed after definitive platinum-based chemoradiation to receive either 80 mg osimertinib ( $n = 143$ ) or placebo ( $n = 73$ ). Baseline characteristics were generally balanced between the study arms, with a mostly even split between stage III subtypes.

Patients were staged by biopsy or CT at baseline plus MRI to confirm the absence of brain lesions. Subsequent imaging was repeated at regular intervals.

Twelve-month progression-free survival, assessed by blinded independent central review, was 74% with osimertinib vs 22% with placebo. At 24 months, the rates were 65% and 13%, respectively.

*Nearly a third of patients with NSCLC present with stage III disease, and the majority are unresectable. Of those, about a third are EGFR mutated.*

The progression-free survival benefit held across numerous subgroups but was statistically significant only among Asian individuals, who made up over 80% of both study arms.

Although the data are immature, osimertinib is also showing a trend toward improved overall survival, despite 81% of placebo patients crossing over to osimertinib after progression, Dr. Ramalingam reported. Mature overall survival results are expected within 2 years.

Based on these results, “osimertinib will become the new standard of care” after definitive chemoradiation in this patient population, Dr. Ramalingam said.

EGFR mutation testing “is now critical for stage III patients to ensure optimal” treatment, he added. Nearly a third of patients with NSCLC present with stage III disease, and the majority are unresectable. Of those, about a third are EGFR mutated.

Placebo was a fair comparator in the trial, Dr. Ramalingam stressed. While the current standard of care for unresectable stage III disease is 1 year of durvalumab after chemoradiation, durvalumab has proven ineffective in EGFR-mutated disease and often isn't used in the setting.

NSCLC continued on following page

# LDCT lung cancer screening may find undiagnosed comorbidities

BY HEIDI SPLETE

**L**ung cancer screening with low-dose CT (LDCT) can effectively evaluate a high-risk population for undiagnosed chronic obstructive pulmonary disease (COPD) and airflow obstruction, based on data from a new study of approximately 2000 individuals. Previous research suggests approximately 70%-90% of individuals with COPD are undiagnosed, especially populations who may be less likely to undergo screening, said Michaela A. Seigo, DO, at Temple University Hospital, Philadelphia, in a study presented at the American Thoracic Society 2024 international conference.

Although the current guidance from the United States Preventive Services Task Force (USPSTF) recommends against universal COPD screening in asymptomatic adults, the use of LDCT may be an option for evaluating a high-risk population, researchers noted. They reviewed data from 2083 adults enrolled in the Temple Healthy Chest Initiative, a lung cancer screening program, combined with detection of symptoms and comorbidities.

## Baseline LDCT screening

Study participants underwent baseline LDCT between October 2021 and October 2022. The images were reviewed by radiologists for pulmonary comorbidities including emphysema, airway disease, bronchiectasis, and interstitial lung disease. In addition, 604 participants (29%) completed a symptom survey, and 624 (30%) underwent spirometry. The mean age of the participants was 65.8 years and 63.9 years (with and without a history of COPD, respectively). Approximately half of the participants in both groups were female.

Overall, 66 of 181 (36.5%) individuals previously undiagnosed with COPD had spirometry consistent with airflow obstruction (forced expiratory volume in 1 second/forced vital capacity, < 70%). These individuals were more

likely to be younger, male, current smokers, and Hispanic or other race (not Black, White, Hispanic, or Asian/Native American/Pacific Islander).

Individuals without a reported history of COPD had fewer pulmonary comorbidities on LDCT and lower rates of respiratory symptoms than those with COPD. However, nearly 25% of individuals with no reported history of COPD said that breathing issues affected their “ability to do things,” Dr. Seigo said, and a majority of those with no COPD diagnosis exhibited airway disease (76.2% compared with 84% of diagnosed patients with COPD). In addition, 88.1% reported ever experiencing dyspnea and 72.6% reported experiencing cough; both symptoms which are compatible with a COPD diagnosis, researchers said.

“We detected pulmonary comorbidities at higher rates than previously published,” Dr. Seigo said. The increase likely reflects the patient population at Temple, which includes a high percentage of city-dwelling, lower-income individuals, minorities, and persons of color, she said. However, “these findings will help clinicians target the most at-risk populations for previously undiagnosed COPD,” Dr. Seigo said.

Looking ahead, Dr. Seigo said she sees a dominant role for artificial intelligence (AI) in COPD screening. “At-risk populations will get LDCT scans, and AI will identify pulmonary and extrapulmonary comorbidities that may need to be addressed,” she said. A combination of symptom detection and access to screening offers an “opportunity to intervene earlier and potentially save lives,” she said.

## Earlier COPD intervention

The current study examines the prevalence of undiagnosed COPD, especially among low-income and minority populations, in an asymptomatic high-risk group. “By integrating lung cancer CT screening with the detection of pulmonary comorbidities on LDCT

and respiratory symptoms, the current study aimed to identify individuals with undiagnosed COPD,” said Dharani K. Narendra, MD, FCCP, Assistant Professor at Baylor College of Medicine, Houston, and a member of the *CHEST Physician* Editorial Board. “The study highlighted the feasibility and potential benefits of coupling lung cancer screening tests with COPD detection, which is noteworthy, and hits two targets with one arrow — early detection of lung cancer and COPD — in high-risk groups, Dr. Narendra said.

“Although the USPSTF recommends against screening for COPD in asymptomatic patients, abnormal pulmonary comorbidities observed on CT chest scans could serve as a gateway for clinicians to screen for COPD,” Dr. Narendra said. “This approach allows for early diagnosis, education on smoking cessation, and timely treatment of COPD, potentially preventing lung function deterioration and reducing the risk of exacerbations.”

The finding that one third of previously undiagnosed and asymptomatic patients with COPD showed airflow obstruction on spirometry is consistent with previous research, Dr. Narendra said. “Interestingly, in questions about specific symptoms, undiagnosed COPD patients reported higher rates of dyspnea, more cough, and breathing difficulties affecting their daily activities, at 16.1%, 27.4%, and 24.5%, respectively, highlighting a lower perception of symptoms,” she said.

Future studies should include investigating specific barriers to screening among different high-risk groups and tailoring interventions to improve screening uptake and adherence, Dr. Narendra said. “By addressing these research gaps, health care providers can optimize screening programs and enhance the overall health of urban, high-risk populations,” Dr. Narendra added.

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

NSCLC continued from previous page

If the control arm had been on durvalumab, patients would have needed to wait until it was safe to give them an EGFR TKI after progression, which didn’t seem to be in their best interest, he told this news organization.

A total of 68% of patients receiving placebo developed new lesions during the study, including brain metastases in 29%. New lesions developed in 22% of those on osimertinib, with new brain lesions in 8%.

The incidence of radiation pneumonitis, the most common adverse event, was 48% with osimertinib and 38% with placebo. Skin

rash, diarrhea, and other known TKI side effects were also more common with osimertinib.

Treatment-related grade 3 or worse adverse events occurred in 13% of osimertinib patients vs 3% of placebo patients. Overall, 8% of osimertinib patients developed interstitial lung disease; most cases were low grade, but one person died.

About half of patients interrupted osimertinib dosing because of side effects, with a minority discontinuing.

Another study discussant, medical oncologist Lecia Sequist, MD, called the results “practice changing” and said the findings support immediate

consolidation with osimertinib instead of waiting for patients to progress.

Dr. Sequist, who reported ties to AstraZeneca, noted that patients were treated with osimertinib until progression, not for a limited duration as in past EGFR TKI trials, raising the possibility of indefinite, life-long treatment.

Treating until progression acknowledges the fact that for most patients, unresectable stage III NSCLC can’t be cured. However, she said a minority of patients might not need indefinite treatment — an important cohort to identify, given the drug costs more than \$18,000 a month.

The study was funded by osimertinib maker AstraZeneca. Investigators included employees. Dr. Ramalingam, Dr. Spigel, and Dr. Sequist are advisers for and disclosed research funding from AstraZeneca. Dr. Spigel also disclosed travel funding. ■

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