Go to **MDedge.com/CHESTPhysician** for the latest news on the coronavirus pandemic.

CRITICAL CARE
Can Gram stains aid treatment of ventilator-associated pneumonia? // **8**

PULMONARY MEDICINE
The step test - a new tool for asthma monitoring? // **9**

SLEEP MEDICINE
Melatonin now under scrutiny for its use to treat insomnia. // **10**

VOL. 17 • NO. 5 • MAY 2022

CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

pixelfit/E+/Getty Images

Sex differences in COPD slow to be recognized, treated

BY NEIL OSTERWEIL
MDedge News

When Sigmund Freud claimed that "anatomy is destiny" he was referring to anatomical sex as a determinant of personality traits.

That notion has been widely discredited, but Freud appears to be inadvertently right in one respect: When it comes to chronic obstructive pulmonary disease (COPD), anatomy really is destiny, and sex may be as well, pulmonary researchers say.

There is a growing body of evidence to indicate that COPD affects men and women differently, and that men and women with COPD require different clinical management. Yet women are often underdiagnosed or misdiagnosed, partly because of poorly understood sex differences, but also because of cultural biases.

But before plunging any farther into the weeds, it's important to define terms. Although various investigators have used the terms "sex" and "gender" interchangeably, sex is the preferred term when referring to biological attributes of individual patients, while gender refers to personal identity.

These distinctions are important, contended Amik Sodhi, MBBS, MPH, from the division of allergy, pulmonology, and critical care medicine

COPD // *continued on page 6*

Pneumonia decision tool reduces deaths in ED patients

BY PAM HARRISON

The use of an electronic clinical decision support tool called "ePNa" reduced severity-adjusted, 30-day, all-cause mortality by 38% across 16 community hospitals in Utah, compared with predeployment levels, a 3-year, pragmatic, cluster-controlled study shows.

"We designed the ePNa specifically to require minimal input from the clinician so everything it does is already in the electronic medical record," Nathan Dean, MD, University of Utah, Salt Lake City, told this news organization.

"So it's actually putting the guideline recommendations into effect for physicians so that they can make better decisions by having all this information – it's a comprehensive best practice kind of tool where best practices are likely to make the biggest difference for patients with a high severity of illness," he added.

The study was published online in the American Journal of Respiratory and Critical Care Medicine (2022 Mar 7. doi: 10.1164/rccm.202109-2092OC).

DECISION TOOL // *continued on page 4*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Welcome Corinne Young, MSN, FNP-C, FCCP, to our editorial board.

Page 23

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

CHANGE SERVICE REQUESTED

PRSRT STD
U.S. POSTAGE
PAID
HARRISBURG PA
PERMIT 500

Knowing eosinophils count is our

EOSINOPHILOSOPHY

WHAT'S YOURS?

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

In health

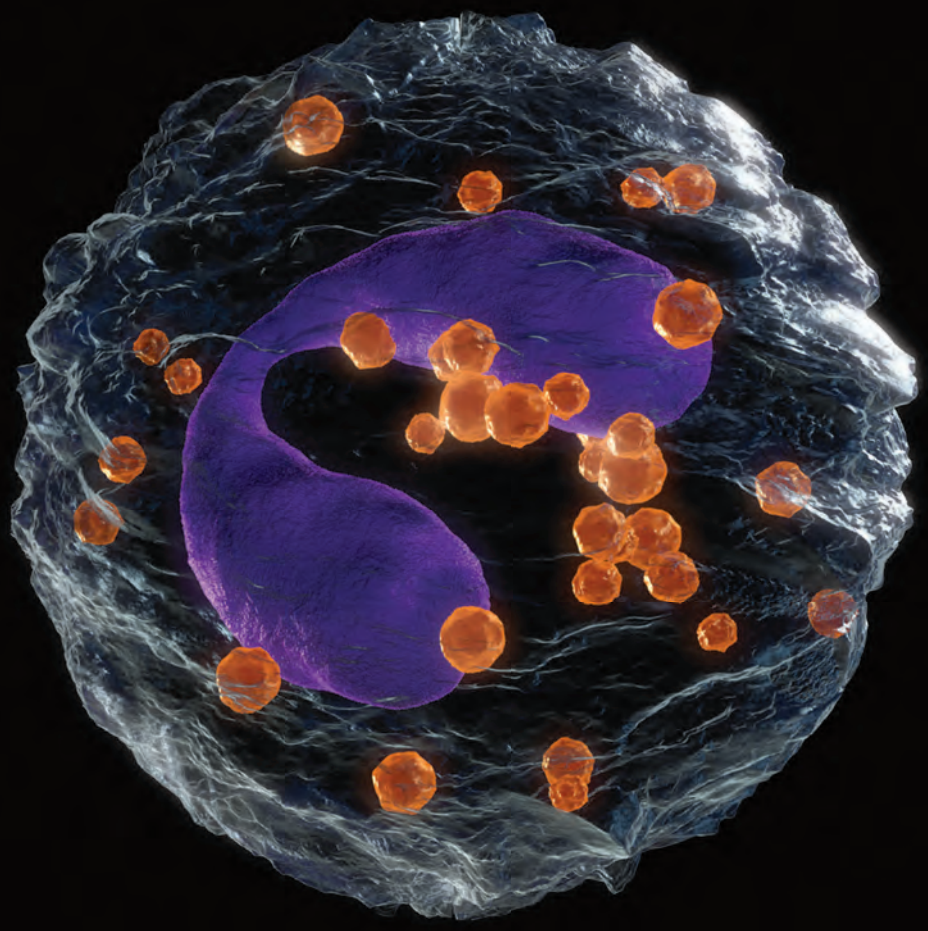
Eosinophils may contribute to overall health and immunoregulation[1-3]

In disease

Eosinophils contribute to inflammation and organ damage or dysfunction[2,3]

In diagnosis and treatment decisions

Blood and/or tissue eosinophils can serve as an important biomarker in clinical practice[4-11]



Discover more about the important role of eosinophils at **EOScounts.com**

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

DECISION TOOL

// continued from page 1

Guideline-based tool

The ePNa makes use of pneumonia guidelines of 2007 and 2019 from the American Thoracic Society/Infectious Disease Society of America. The system was deployed into six geographic clusters of 16 Intermountain hospital EDs at 2-month intervals between December 2017 and November 2018. Simultaneous deployment was impractical, as implementation of the tool takes education, monitoring, and feedback that can be facilitated by focusing on only a few hospitals at a time.

The decision support tool gathers key patient indicators including age, fever, oxygen saturation, vital signs, and laboratory and chest imaging results to offer recommendations on care, including appropriate antibiotic therapy, microbiology studies, and whether a given patient should be sent to the intensive care unit, admitted to hospital, or safely discharged home.

Investigators analyzed a total of 6,848 patients, of whom 4,536 were managed for pneumonia before the ePNa was deployed and 2,312 after deployment.

The median age of patients was 67 years (interquartile range, 50-79 years). Roughly half were female and almost all were White. "Observed 30-day all-cause mortality including both outpatients and inpatients was 8.6% before deployment versus 4.8% after deployment of ePNa," Dr. Dean and colleagues reported.

Adjusted for severity of illness, the odds ratio for lower mortality post-ePNa launch was 0.62 (95% confidence interval, 0.49-0.79; $P < .0010$) "and lower morality was consistent across hospital clusters."

Compared with patients who were discharged home, reductions in mortality were greatest in patients who were directly admitted to ICUs from the ED (OR, 0.32; 95% CI, 0.14-0.77; $P = .01$). The OR for patients admitted to the medical floor was 0.53 (95% CI, 0.25-1.1; $P = .09$), which did not reach statistical significance.

Dr. Dean explained that the reductions in mortality were seen among those with the most severe illness, in whom best practices would benefit the most. In contrast, patients who are sent home on an antibiotic are at low risk for mortality while patients admitted to the medical floor may well have another, more lethal illness from which they end up dying, rather than simple pneumonia.

"For me, this was a clear demonstration that these best practices made the biggest difference in patients who were sick and who did not have any underlying disease that was going to kill them anyway," he emphasized. On the other hand, both 30-day mortality and 7-day secondary hospital admission were higher among patients the tool recommended for hospital ward admission but who were discharged home from the ED.

Both 30-day mortality and 7-day secondary hospital admission were higher among patients the tool recommended for hospital ward admission but who were discharged home from the ED.

"This was an unexpected finding," Dr. Dean observed. However, as he explained, the authors reviewed 25% of randomly selected patients who fell into this subgroup and discovered that the ePNa tool was used in only about 20% of patients – "so doctors did not use the tool in the majority of this group."

In addition, some of these patients declined hospital admission, so the doctors may have recommended that they be admitted but the patients said no. "The hypothesis here is that if they had been admitted to the hospital, they may have had a lower mortality risk," Dr. Dean said.

Noticeable changes

Another noticeable change following the introduction of the ePNa tool was that guideline-concordant antibiotic prescribing increased in the 8 hours after patients presented to the ED, from 79.5% prior to the tool's launch to 87.9%, again after adjusting for pneumonia severity ($P < .001$). Use of broad-spectrum antibiotics was not significantly different between the two treatment intervals, but administration of antibiotics active against methicillin-resistant *Staphylococcus aureus* dropped significantly between the two treatment intervals ($P < .001$). And the mean time from admission to the ED to the first antibiotic taken was

DECISION TOOL *continued on following page*

***CHEST PHYSICIAN* IS ONLINE**

CHEST Physician *is available at chestphysician.org.*

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

CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

E-mail: chestphysiciannews@chestnet.org

FRONTLINE MEDICAL COMMUNICATIONS

FRONTLINE MEDICAL COMMUNICATIONS SOCIETY PARTNERS

EXECUTIVE EDITOR Kathy Scarbeck, MA
EDITOR Mark S. Lesney, PhD
CREATIVE DIRECTOR Louise A. Koenig

DIRECTOR, PRODUCTION/MANUFACTURING
Rebecca Slebodnik

GROUP PUBLISHER
JoAnn Wahl,
973-206-8989, cell 732-427-7617
jwahl@mdedge.com

DIRECTOR, THE MEDJOBNETWORK
Julian Knight
973-206-2317, cell 201-310-7063
jknight@mdedge.com

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

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

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

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

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

FRONTLINE MEDICAL COMMUNICATIONS

Corporate
VP, SALES Mike Guire
VP, SALES LEAD Dino Marsella
VP, MEMBER MARKETING Amy Pfeiffer
VP, SALES, STRATEGY & PARTNERSHIPS JoAnn Wahl
DIRECTOR, CIRCULATION Jared Sonners
EXECUTIVE EDITOR Patrick Finnegan

VP, PROPRIETARY CONFERENCES, MEDSCAPELIVE David J. Small, MBA

ILD progression, not diagnosis, triggers palliative care

BY HEIDI SPLETE

FROM THE JOURNAL *CHEST*® ▪ Most health care providers are comfortable recommending palliative care (PC) for their patients with interstitial lung disease (ILD), but most do so at the time of disease progression, rather than diagnosis, based on a survey of 128 clinicians.

ILD is associated with a high mortality rate and profound symptoms that contribute to poor quality of life, Rebecca A. Gersen, MD, of Johns Hopkins University, Baltimore, and colleagues wrote.

"Nevertheless, there is often a lack of preparedness for death by both patients and providers, contributing to increased distress," they said. Clinician perspectives on the use of PC for ILD patients have not been well studied, although PC is not limited to end-of-life care and is recommended for ILD patients by professional organizations, including the American Thoracic Society. "PC is successful in improving breathlessness in chronic lung disease and can increase survival."

In a study published in the journal CHEST® (2022 Mar 16. doi: 10.1016/j.chest.2022.03.009), the researchers surveyed health care providers at 68 Pulmonary Fibrosis Foundation centers across the United States. The survey was sent and collected by email and a restricted social media platform. A total of 128 providers from 34 states completed the survey between October 2020 and January 2021. Of these, 61% were physicians, and 67% identified as White.

"There is often a lack of preparedness for death by both patients and providers, contributing to increased distress."

Overall, 95% of the respondents agreed or strongly agreed that addressing advance directives is important, but only 66% agreed or strongly agreed that they themselves addressed advance directives in the outpatient ILD clinic setting. A greater number (91%) agreed or strongly agreed that they had a high level of comfort in discussing prognosis, while 88% agreed or strongly agreed that they felt comfortable assessing a patient's readiness for and acceptance of PC. Approximately two-thirds (67%) agreed or strongly agreed that they use PC services for ILD patients. There were no significant differences in responses from clinicians who had more than 10 years of experience and those who had less.

Of the providers who referred patients to PC, 54% did so at objective disease progression, and 80% did so at objective and/or symptomatic progress; 2% referred patients to PC at initial ILD diagnosis.

Lack of resources

Health care providers who reported that they rarely referred patients to palliative care were significantly more likely to cite a lack of local PC options ($P < .01$). Those who rarely referred patients for PC also were significantly less likely to feel comfortable discussing prognoses or advance directives in the ILD clinic ($P = .03$ and $P = .02$, respectively).

Among the 23% of responders who reported that they rarely referred patients, 66% said they did not have PC at their institution.

"In addition to understanding and addressing barriers to care, educational resources may be key to improving PC delivery to the ILD population," the researchers wrote.

The study findings were limited by several factors, including voluntary participation, lack of a validated questionnaire, and use of self-reports, which may not reflect physicians' actual practice, the researchers noted. Other limitations include the use of U.S. data only, which may not generalize to countries with different health care models.

However, the results were strengthened by the use of data from providers at a range of institutions across the United States and by the high overall survey response rate, the researchers said.

"While ILD providers reassuringly demonstrate knowledge and interest in PC involvement, no current system exists to facilitate and monitor response to referral," they noted. "Future research is desperately needed to address barriers to the provision of PC in order to enhance access to a critical service in the management and care of patients with ILD."

The study was supported by the National Heart, Lung, and Blood Institute. The researchers disclosed no relevant financial relationships. ▪

DECISION TOOL *continued from previous page*

slightly faster, improving from 159.4 minutes (95% CI, 156.9-161.9 minutes) prior to the ePNa launch to 150.9 minutes (95% CI, 144.1-157.8) post deployment ($P < .001$).

"Overall outpatient disposition for treatment of pneumonia from the emergency department increased from 29.2% before ePNa to 46.9% [post ePNA]," the authors noted, while a similar increase was observed in patients for whom ePNA recommended outpatient care – from 49.2% pre-ePNA to 66.6% after ePNA.

Both hospital ward admission and admission to the ICU decreased after ePNa had been introduced. Despite a significant increase in the percentage of patients being discharged home, neither 7-day secondary hospital admission nor severity-adjusted, 30-day mortality were significantly different before versus after the introduction of ePNa, the authors stressed.

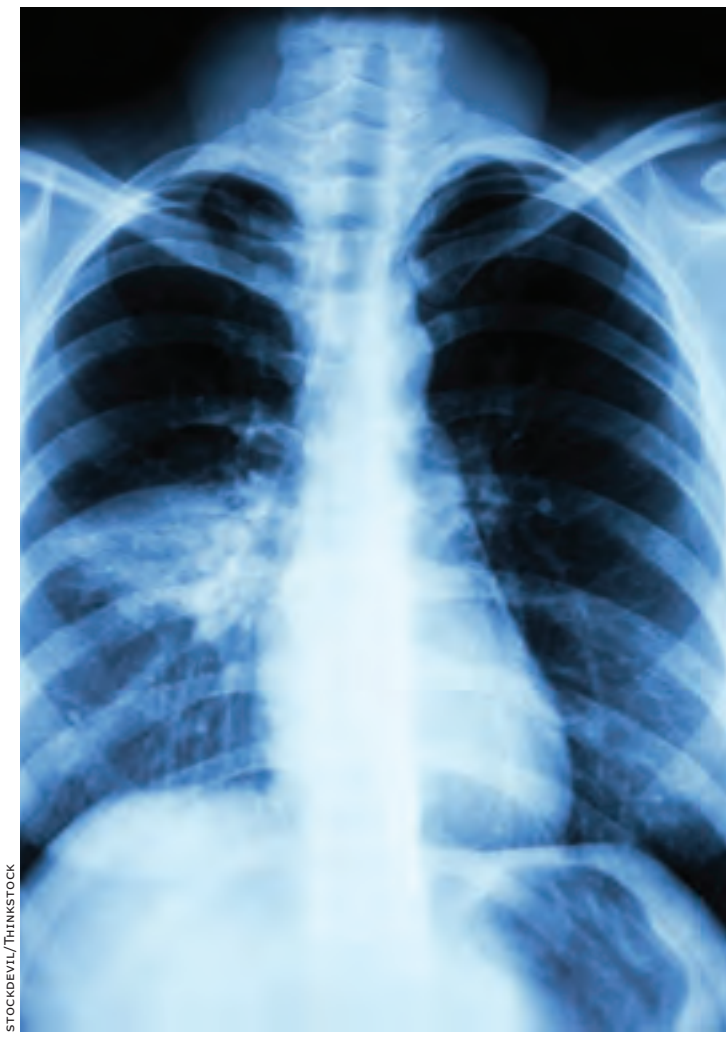
A limitation of the study was that the trial was confined to a single health care system in one region of the United States with a patient population that may differ from that in other regions.

Reason for its success

Asked to comment on the findings, Adam Balls, MD, emergency department chair, Intermountain Medical Center, Murray, Utah, suggested that the reason the ePNa tool has been so successful at improving care for pneumonia patients is that it puts the guidelines directly into the hands of individual providers and tells them what's going on. (Dr. Balls was not involved in the study.) "The tool allows us to take into consideration various clinical features – a patient's oxygen requirements and whether or not they had prior complicated pneumonias that required additional antibiotics, for example – and then it makes the best determination for not only the disposition for that patient but antibiotic treatment as well," he said in an interview.

This then allows physicians to either appropriately discharge less severely ill patients and admit those who are more ill – "and in general, just do a better job of treating pneumonia with this tool," Dr. Balls said. He himself uses the decision support tool when attending to his own patients with pneumonia, as he feels that the tool really does make his care of these patients better. "There is a disparity around how we treat pneumonia in the U.S.

"Clinicians sometimes have a bias or a preference for certain antibiotics and we may not be appropriately treating these patients with broad-spectrum antibiotics or are perhaps using antibiotics that are not as effective based on an individual patient scenario so this is definitely a user-friendly tool that hopefully can be deployed throughout other health care systems to improve the treatment of pneumonia overall," Dr. Balls emphasized. ▪



STOCKDEVIL/THINKSTOCK

COPD

// continued from page 1

at the University of Wisconsin–Madison.

"Sex is essentially a biologic construct, so it's got to do with the sex chromosomes, the genetics of that person, and it refers to the anatomic variations that can change susceptibility to different diseases," she said in an interview.

An example of sex differences or "sexual dimorphism" can be found in a recent meta-analysis of sex-based genetic associations by Megan Hardin, MD, MPH, from Brigham and Women's Hospital in Boston and colleagues (Am J Respir Cell Mol Biol. 2017 Mar;56[3]:332-41).

They reported that CELSR1, a gene involved in fetal lung development, was expressed more among women than among men and that a single nucleotide polymorphism in the gene was associated with COPD among women smokers, but not among men smokers.

The finding points to a potential risk locus for COPD in women, and could help shed light on sexual dimorphism in COPD, Dr. Hardin and colleagues said.

In contrast to sex, "gender is more of a psychosocial construct which can impact how diseases manifest themselves, how they are potentially managed, and what outcomes might occur for that particular disease," Dr. Sodhi said.

She and her colleagues recently published a review of sex and gender in common lung disorders and sleep in the journal CHEST (2022 Mar 14. doi: 10.1016/j.chest.2022.03.006), where they wrote that the "influence of sex and gender is portrayed in epidemiological data, disease pathogenesis and pathophysiology, clinical manifestations, response to treatment, access to care, and health outcomes. Hence, sex and gender should be considered in all types of research, clinical practice and educational curricula."

For example, as previously reported at the 2021 annual meeting of the American Thoracic Society, sex-specific differences in the severity of symptoms and prevalence of comorbidities in patients with COPD may point to different criteria for diagnosing cardiac comorbidities in women and men.

Those conclusions came from a retrospective analysis of data on 795 women and 1,251 men with GOLD (Global Initiative for Chronic Obstructive Lung Disease) class 1-3 disease.

The investigators looked at the patients' clinical history, comorbidities, lung function, COPD Assessment Test (CAT) scores, and modified Medical Research Council (mMRC) dyspnea score, and found significant differences between men and women for most functional parameters and comorbidities, and for CAT items of cough, phlegm, and energy.

In logistic regression analysis, predictors for cardiac disease in men were energy, mMRC score, smoking status, body mass index, age, and spirometric lung function, but in women only age was significantly predictive for cardiac disease.

An example of gender effects on COPD differences in men and women is the increase in cigarette advertising aimed at women in the 1960s and the advent of women-targeted brands such as Virginia Slims, which in turn lead to increased smoking rates among women. In addition, in the developing world, where the sex/gender gap in COPD is narrowing, women tend to have greater exposure to wood smoke and cooking fuels in unventilated or poorly ventilated spaces, compared with men.

Increasing incidence among women

According to the Centers for Disease Control and Prevention, chronic lower respiratory diseases, primarily COPD, were the fourth-leading cause of death in women in the United States in 2018, following only heart disease, cancer, and accidents/injuries.

And as a CDC analysis of data from the 2013 Behavioral Risk Factor Surveillance System showed (Morb Mortal Wkly Rep. 2015 Mar 27;64[11]:289-95), women were more likely to report being told by a physician that they had COPD than did men (6.6%, compared with 5.4%).

Dr. Sodhi and colleagues noted that, at all time points examined from 2005 to 2014, women had a higher proportion than men of COPD hospitalizations and in-hospital deaths. They also noted that female sex is associated with a threefold risk for severe early-onset COPD, and that women with COPD have lower diffusion capacity of lungs for carbon monoxide, despite having higher predicted forced expiratory volume in 1 second, compared with men.

"Historically, COPD wasn't a disease that was so prevalent in women. It's been in the past 20 years that the trends have changed," said Patricia Silveyra, PhD, MSc, ATSF, associate professor of environmental and occupational health at the Indiana University, Bloomington.

"Historically, COPD wasn't a disease that was so prevalent in women. It's been in the past 20 years that the trends have changed."

The increasing prevalence of COPD among women cannot be explained by smoking alone, she said in an interview.

"It used to be thought that it was because more women smoked, but actually a lot of women who don't smoke can develop COPD, so it appears to be probably something environmental, but because it used to be a disease of older men, in the clinic there was also a bias to diagnose men with COPD, and women with asthma, so a lot of women went underdiagnosed," Dr. Silveyra said.

In their review, Dr. Sodhi and colleagues noted that women with COPD "may be underdiagnosed as a result of having different symptoms from those classically recognized. Reasons for underdiagnosis or a delay in diagnosis may also be due to lack of a formal evaluation with spirometry, women seeking care later in the course of disease, physician bias, or associated fatigue or depression misdirecting diagnostic strategies. Underdiagnosis may be associated with psychological distress and worse health-related quality of life."

Although the evidence is mixed, women tend to present more frequently with the chronic bronchitis phenotype of COPD, compared with the emphysema phenotype, and women tend to have greater degrees of pulmonary function impairment when exposed to tobacco smoke, even after controlling for differences in height and weight.

DECADE3D/THINKSTOCK

"For the same amount of exposure to tobacco smoke, females are likely to develop more severe airflow limitation at an earlier age than males, and have more exacerbation," Dr. Sodhi and colleagues wrote.

Both Dr. Silveyra and Dr. Sodhi said that reasons why men and women differ in their physiological reactions to smoke are still unknown.

Sex differences in drug responses

There is only limited evidence to indicate that women and men respond differently to various therapeutic agents, but what is clear is that more research into this area is needed, Dr. Sodhi and Dr. Silveyra said.

For example, among the few studies that have documented sex differences, one showed no sex differences in the efficacy of salmeterol/fluticasone combination therapy for reducing exacerbations or improving quality of life, whereas another showed that women were more likely than men to experience COPD symptoms or exacerbations after stopping inhaled corticosteroids, Dr. Sodhi and colleagues noted.

Both Dr. Sodhi and Dr. Silveyra emphasized the need for clinical trials that study the effects of sex on treatment outcomes in COPD, which could lead to better, more personalized therapeutic regimens that take sex and gender into account.

Dr. Sodhi and colleagues offered the following advices to clinicians: "Interaction with female patients should take into account that their symptoms may not conform to traditionally accepted presentations. Challenges exist for female patients at all levels of health care interaction and as clinicians we need to acknowledge the bias and willfully work toward recognition and elimination of unconscious and conscious bias. Empowering our patients to have frank discussions with their health care team when they perceive bias is another step to help promote equity."

The review by Dr. Sodhi and colleagues was supported by grants from the National Institutes of Health. Dr. Sodhi and Dr. Silveyra reported having no conflicts of interest to disclose. ■

IN METASTATIC NON-SMALL CELL LUNG CANCER

DON'T FORCE FIT IO IN FIRST LINE

If a patient has certain actionable mutations, first-line immunotherapy could be:

- **Ineffective**—a study showed no response for first-line IO in patients with EGFRm NSCLC[1]*
- **Sequentially harmful**—starting a TKI after IO has been shown to increase the risk of toxicity in patients with mNSCLC that harbor certain EGFR or ALK alterations[2-8†]

CONFIRM MUTATION STATUS AND EXPLORE THE POSSIBILITY OF TARGETED THERAPY. LEARN MORE AT KnowBeforeIO.com

*Phase 2, single-arm study of pembrolizumab in patients with advanced EGFRm NSCLC. 82% of enrolled patients were treatment naïve. The clinical study was stopped due to lack of efficacy after 11 of 25 planned patients were enrolled. No responses were observed (ORR was 0%) in the 10 of 11 patients treated, even in patients with PD-L1 expression ≥50%. The patient who did have a response was revealed to be EGFR wild-type upon repeat analysis.[1]

†Based on 6 studies of 3867 patients with NSCLC and EGFR sensitizing mutations, and 1 study including 345 patients with NSCLC and ALK mutations. Of the 3867 patients with EGFR mutations, 395 were treated with immunotherapy followed by EGFR TKIs. Of the 345 patients with ALK mutations, 3 were treated with immunotherapy followed by an ALK TKI. Adverse reactions, including ILD, were observed following the sequential use of IO followed by TKI therapy in patients who had actionable mutations.[2-8]

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; ILD, interstitial lung disease; IO, immuno-oncology; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

References: 1. Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. *J Thorac Oncol.* 2018;13(8):1138-1145. **2.** Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. *JAMA Oncol.* 2018;4(8):1112-1115. **3.** Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol.* 2019;30(5):839-844. **4.** Ohe Y, Kato T, Fumikazu S, et al. Real-world use of osimertinib for epidermal growth factor receptor T790M-positive non-small cell lung cancer in Japan. *Jpn J Clin Oncol.* 2020;50(8):909-919. **5.** Yamaguchi O, Kaira K, Kawasaki T, et al. Severe hepatotoxicity due to osimertinib after nivolumab therapy in patients with non-small cell lung cancer harboring EGFR mutation. *Thorac Cancer.* 2020;11(4):1045-1051. **6.** Uchida T, Kaira K, Yamaguchi O, et al. Different incidence of interstitial lung disease according to different kinds of EGFR-tyrosine kinase inhibitors administered immediately before and/or after anti-PD-1 antibodies in lung cancer. *Thorac Cancer.* 2019;10(4):975-979. **7.** Kotake M, Murakami H, Naito T, et al. Practical use of osimertinib in Japanese patients with EGFR T790M mutation positive advanced non-small-cell lung cancer [abstract]. *Ann Oncol.* 2016;27(suppl9):ix147. **8.** Lin JJ, Chin E, Yeap BY, et al. Increased hepatotoxicity associated with sequential immune checkpoint inhibitor and crizotinib therapy in patients with non-small cell lung cancer. *J Thorac Oncol.* 2019;14(1):135-140.

AstraZeneca

Can Gram stains guide antibiotics for VA-pneumonia?

BY LOUISE GAGNON

Similar outcomes in patients with ventilator-associated pneumonia (VAP) suggest that antibiotics selected by Gram staining were noninferior to those based on guidelines and also significantly decreased the use of broad-spectrum antibiotics in this patient population.

The findings were published April 8 in JAMA Network Open (doi:10.1001/jamanetworkopen.2022.6136). The multicenter, open-label, noninferiority, randomized trial, Gram Stain-Guided Antibiotics Choice for VAP (GRACE-VAP), was conducted for 2 years in intensive care units (ICUs) of a dozen tertiary referral hospitals in Japan, from April 1, 2018, through May 31, 2020.

CDC/Janice Haney Carr

The authors noted in their paper that the 2016 clinical practice guidelines for VAP published by the Infectious Diseases Society of America and the American Thoracic Society recommend antibiotic agents active against both methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* as an empirical treatment. Adherence to these guidelines may lead to overuse of broad-spectrum antibiotic agents and could be associated with the accelerated emergence of antimicrobial-resistant organisms, the authors postulated.

The study sought to answer the question: Can Gram staining be used as an alternative to established guidelines to direct antibiotic use – thereby curbing the use of broad-spectrum antibiotics – without compromising patient safety and clinical outcomes?

A total of 206 patients, with a mean age of 69, took part in the study. The same number of patients were assigned to each arm. Patients aged 15 years or older with a VAP diagnosis and a modified Clinical Pulmonary Infection Score of 5 or higher were included.

Investigators reported that 79 patients (76.7%) responded to antibiotics in the Gram stain–guided group and 74 (71.8%) responded in the guideline–based group (risk difference, 0.05; 95% confidence interval, –0.07 to 0.17; $P < .001$, for noninferiority).

There was a decrease in antipseudomonal agent use comparing the Gram stain-guided group with the guideline-based group (30.1%; 95% CI, 21.5% to 39.9%; $P < .001$). There also was a decrease in anti-MRSA agents in the Gram stain–guided group, compared with the guideline–based group (38.8%; 95% CI, 29.4% to 48.9%; $P < .001$).

The 28-day cumulative incidence of mortality was 13.6% (n = 14) in the Gram stain–guided group vs. 17.5% (n = 18) in the guideline–based group. Escalation of antibiotics according to culture results was performed in seven patients (6.8%) in the Gram stain–guided group and in one patient (1.0%) in the guideline-based group. No significant differences in study arms were observed on other measures, such as ICU-free days, ventilator-free days, and adverse events.

The authors concluded that their findings support the use of Gram staining as a strategy to manage infectious diseases and contain the development of multidrug resistant organisms (MDROs) in the setting of critical care.

"In the GRACE-VAP trial, we used the time-honored Gram stain technique as part of the daily management of infectious diseases. We believe that the trial results are acceptable and have the potential to change the strategy of antibiotic choice worldwide," the authors wrote.

Benjamin D. Galvan, MLS(ASCP), CIC, an infection preventionist with a professional background in clinical microbiology, noted that Gram staining is more accessible and significantly less costly than the rapid polymerase chain reaction testing certain institutions use to rapidly identify MDROs to help tailor therapy.

But one of the pitfalls with relying on Gram stain collection to guide antibiotic use is that it is operator dependent and subject to extrinsic factors, like prior antibiotic use, he pointed out.

"If it is not collected, set up, and read properly, the Gram stain is not going to necessarily be reliable" said Mr. Galvan, also a member of the national communications committee for the Association for Professionals in Infection Control and Epidemiology. He added that the sample in the was not representative of institutions dealing with elevated rates of multidrug resistance.

"Even from their own results, they were looking at hospitals that have a low rate of multidrug resistance," he said. "It was not clear if MRSA or just *Staphylococcus aureus* was identified in significant quantities upon review, and they recognized a lower-than-expected number of isolates of *Pseudomonas aeruginosa*."

Establishing antibiotic treatment from the results of Gram-stain collection may not be sufficiently comprehensive, he said.

"Generally speaking, basing it (antibiotic therapy) solely off of a Gram stain is not looking at the whole picture," said Mr. Galvan, noting that the 2016 IDSA guidelines call for an evaluation of the clinical status, including risk, of the individual patient, as well as locally available antibiotic resistance data.

Moreover, the evidence-based IDSA guidelines are in place to help address the issue of antimicrobial resistance trends, already recommending tailoring empiric antibiotic therapy based upon the levels of resistance in the local population, according to Mr. Galvan.

While the study suggests that this Gram-stain–driven tailoring of empiric antibiotic therapy may be noninferior to current guidelines in health care settings with low MDRO rates, its utility may not be suitable in hospitals that are already dealing with high rates of MDROs, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, or severe clinical cases of VAP, Mr. Galvan explained.

The researchers and Mr. Galvan disclosed no relevant financial relationships. ■

David Bowton, MD, FCCP, comments: The GRACE-VAP trial examined the utility of employing the results from Gram-stained respiratory secretions vs. guideline-based antibiotic prescribing on clinical outcome and the use of broad-spectrum antibiotic therapy. They found that by restricting anti-pseudomonal and anti-MRSA to patients with gram-negative rods or gram-positive cocci in clusters, respectively, there was no difference in clinical outcome 7 days after the end of therapy. The use of anti-pseudomonal and anti-MRSA antibiotics was reduced by 30% to 40%, and there was no difference in 28-day mortality.

I have several concerns that mitigate the broad applicability of these findings. The incidence of resistant organisms in sputum cultures was relatively low (< 20% overall). A numerically higher number of patients in the guideline group had received antibiotics prior to enrollment, which is a recognized predisposition to resistant organisms and higher mortality. The 28-day mortality of patients diagnosed with VAP was only 16%, which is considerably lower than most series of VAP, raising the question of how ill these patients were and the accuracy of the diagnosis of VAP. The diagnosis of VAP was based on a CPIS score of > 5. The clinical diagnosis of VAP is notoriously inaccurate, and even using a higher CPIS score of 6 or greater, the ROC curve for accurate diagnosis based on quantitative cultures is little better than a coin toss (Schurink CAM et al. Intensive Care Med. 2004;30:217). While quantitative cultures are not a "gold standard" for VAP diagnosis, when antibiotics are discontinued when quantitative cultures are negative, there is no adverse impact on outcomes (Fagon J-Y, et al. Annals of Internal Medicine. 2000;132:621). If you do not have VAP, VAP therapy is unlikely to have a beneficial effect on outcome. Further, optimal interpretation of Gram-stained sputum requires rapid smearing, heat fixing, and staining of the specimen followed by ensuring that the smear is high quality (few epithelial cells with leukocytes present). These steps are not consistently ensured in most ICUs. While the authors state that the Gram-stained specimens were classified by the Miller and Jones and the Geckler schema, there are no data provided as to the quality of the collected specimens and how these data might have been used. It would be unusual for all enrolled patients to have high-quality specimens, yet no patient appears to have been excluded from randomization or analysis.

Step test signals exercise capacity in asthma patients

BY HEIDI SPLETE
MDedge News

The incremental step test is a highly reliable measure of exercise capacity in patients with moderate to severe asthma, based on data from 50 individuals.

Asthma patients often limit their physical exercise to avoid respiratory symptoms, which creates a downward spiral of reduced exercise capacity and ability to perform activities of daily living, wrote Renata Cléia Claudino Barbosa of the University of São Paulo and colleagues. "However, exercise training has been shown to be an important adjunctive therapy for asthma treatment that improves exercise capacity and health-related quality of life," they wrote.

Step tests have been identified as a simpler, less-costly alternative to cardiopulmonary exercise tests to measure exercise capacity in patients with chronic obstructive pulmonary disease, but their effectiveness for asthma patients has not been investigated, the researchers said.

"Exercise training has been shown to be an important adjunctive therapy for asthma treatment that improves exercise capacity and health-related quality of life."

In a study published in Pulmonology (2022 Feb 24. doi: 10.1016/j.pulmoe.2022.02.002), the researchers recruited 50 adults with moderate or severe asthma during routine care at a university hospital. The participants had been clinically stable for at least 6 months, with no hospitalizations, emergency care, or medication changes in the past 30 days. All participants received short-acting and long-acting bronchodilators and inhaled corticosteroids. The patients ranged in age from 18 to 60 years, with body mass index measures from 20 kg/m^2 to 40 kg/m^2.

Participants were randomized to tests on 2 nonconsecutive days at least 48 hours apart. On the first day, patients completed asthma control questionnaires and lung function tests, then performed either a cardiopulmonary exercise test (CPET) or two incremental step tests (IST-1 and IST-2). On the second day, they performed the other test. Participants were instructed to use bronchodilators 15 minutes before each test.

The step test involved stepping up and down on a 20–cm high wooden bench.

Overall, the peak oxygen (VO_2) uptakes were 27.6 mL/kg per minute for the CPET, 22.3 mL/kg per minute for the first IST, and 23.3 mL/kg per minute for the second IST.

"The IST with better performance regarding the peak VO_2 value was called the best IST (b-IST)," and these values were used for validity and interpretability analyses, the researchers wrote.

ASTHMA *continued on following page*

ASTHMA *continued from previous page*

In a reliability analysis, the intraclass correlation coefficient (ICC) was 0.93, the measurement error was 2.5%, and the construct validity for peak VO_2 was significantly more reliable than the CPET ($P < 0.001$), the researchers said. The ICC for total number of steps was 0.88.

Notably, "the present study also demonstrated that IST is not interchangeable with the CPET since the subjects with moderate to severe asthma did not reach the maximal exercise capacity," the researchers said. However, "we believe that the IST is superior to walking tests in subjects with asthma because it is an activity that requires greater ventilation in a subject's daily life," they said.

The study findings were limited by several factors including the relatively small study population and the small number of male patients, which may limit generalizability to males with asthma or other asthma endotypes, the researchers said. However, the results were strengthened by the randomized design, and support the value of the IST as a cost-effective option for assessing exercise capacity, preferably with two step tests to minimize the learning effect, they said.

Additional research is needed to determine whether IST can assess responsiveness to pharmacological and nonpharmalogical treatments in asthma patients, they noted.

The study was supported by the São Paulo Research Foundation, Conselho Nacional de Pesquisa, and Coordination of Improvement of Higher Level Personnel–Brazil. The researchers had no conflicts to disclose. ■

Sachin Gupta, MD, FCCP, comments: Though functional capacity testing is not commonly used in the management of asthma as it is with chronic obstructive pulmonary disease, pulmonary arterial hypertension, and heart failure, it can provide rich insights into a patient's physiology. Perhaps one day soon we will know the performance of the incremental step test in determining outcomes compared with other biomarkers.

SLEEP MEDICINE

Many turn to melatonin for insomnia despite risks

BY LAURA LILLIE

The American Academy of Sleep Medicine is looking into the safety of melatonin. And while the assessment of the evidence is underway, the academy recommends that melatonin not be used for insomnia in adults or children.

Muhammad Adeel Rishi, MD, vice chair of the public safety committee for the American Academy of Sleep Medicine, said there are important reasons to not use melatonin for insomnia until more information is available.

Melatonin affects sleep, but also influences other functions. "It has an impact on body temperature, blood sugar, and even the tone of blood vessels," Dr. Rishi said. And because melatonin is available over the counter, it hasn't been approved as a medicine by the FDA. A previous study of melatonin products, for instance, flagged problems with inconsistent doses, and prompted calls for more FDA oversight.

While melatonin plays a role in setting the sleep and wake cycle, serotonin is also at work. Serotonin is involved in mood and helps with deep REM sleep. But adding serotonin in unknown amounts could be unhealthy. It can be dangerous to use a product as a medication when doses can be so off and there are unknown byproducts in it. Serotonin can influence the heart, blood vessels, and brain, and people taking medication for mood disorders could be affected by the serotonin in their sleep aid, Dr. Rishi warns.

Another worry is whether melatonin interferes with puberty in children – which is also a question researchers at the Children's Hospital of Eastern Ontario in Ottawa are asking (Nat Sci Sleep. 2019;11:1-10). While short-term melatonin use is considered safe, the researchers reported, concerns that long-term use might delay children's sexual maturation require more study.

Melatonin will probably need to be regulated by the FDA – especially for children – Dr. Rishi pointed out. And what place, if any, it will have for managing chronic insomnia is "a big question mark." ■

The quest for a good night's sleep: An update on pharmacologic therapy for insomnia

BY MICHAEL PELEKANOS, MD; AND OLIVER SUM-PING, MD

Insomnia is one of the most common complaints in medicine, driving millions of clinic visits each year (Table 1). It is estimated that approximately 30% of individuals report at least short-term insomnia symptoms and 10% report chronic insomnia. These rates are even higher in groups that may be more susceptible to insomnia, including women, the elderly, and those of disadvantaged socioeconomic status (Ohayon MM. *Sleep Med Rev*. 2002;[2]:97-111). While most patients with insomnia find their sleep difficulties self-resolve within 3 months, a substantial number of patients will find their insomnia to persist for longer and require intervention (Sateia MJ et al. *J Clin Sleep Med*. 2017;13[2]:307-49).

Dr. Pelekanos

For individuals requiring treatment, cognitive behavioral therapy for insomnia (CBT-I) is considered first-line therapy by the American Academy of Sleep Medicine for both acute and chronic insomnia. Unfortunately, obtaining CBT-I for a patient is often a challenge as the number of trained therapists offering this service is limited, resulting in long wait times or, in some cases, a complete lack of access to this treatment option. Judicious use of sedative-hypnotic medications may be a reasonable alternative for patients with insomnia who are unable to undergo CBT-I, who are still symptomatic despite undergoing CBT-I, or, in some cases, as a temporary treatment (Sateia MJ et al. *J Clin Sleep Med*. 2017;13[2]:307-49).

Current medications used to treat insomnia are listed in Tables 2 and 3, some of which carry an FDA approval to be used as a hypnotic, while others are used in an off-label manner.

Cautions abound with use of many of these medications. Common concerns include safety, particularly for elderly patients and long-term use, and the potential for developing tolerance and dependence.

Cautions abound with use of many of these medications. Common concerns include safety, particularly for elderly patients and long-term use, and the potential for developing tolerance and dependence.

Most medications that have been used for insomnia have been available for decades, but, in recent years, a new class of hypnotics has emerged. Dual orexin receptor antagonists (DORAs) are the newest class of FDA-approved medications (Table 4).

Orexin is a neuropeptide found primarily in the lateral hypothalamus and binds to the orexin 1 and orexin 2 receptors leading to a number of downstream effects, including stimulating wakefulness. Loss of orexin-generating neurons has been implicated as the cause of type 1 narcolepsy, and antagonism of their effects can facilitate sleep by suppressing wakefulness. The first medication in the DORA class to be FDA-approved was suvorexant in 2014, followed by lemborexant's FDA approval in 2019. These are both indicated for treating sleep onset and sleep maintenance insomnia and have been shown to improve both subjective and objective measures of sleep. The most common side effects reported for both suvorexant and lemborexant are headache and somnolence, with morning-after sleepiness being a frequent complaint.

In January 2022, a new medication in the DORA class named daridorexant was approved by the FDA (Table 5).

Daridorexant, like its DORA counterparts, has been shown to have efficacy in improving subjective and objective markers of insomnia. This has included polysomnographic measures of wake after sleep onset and latency to persistent sleep, as well as subjective total sleep time. Importantly, in addition to positive sleep outcomes, improvements with daytime function have also been observed with this medication (Mignot E et al. *Lancet Neurol*. 2022;21[2]:125-39). Daridorexant's half-life of approximately 8 hours is shorter than that of the other available DORAs, leading to fewer day-after effects. The combination of effectiveness for sleep initiation and maintenance without daytime impairment distinguishes daridorexant from the other DORAs and even other classes of sleep medication.

Safety, especially in patients age 65 and older, is an important concern with sleep medication, particularly with respect to polypharmacy, over-sedation, increased fall risk, and cognitive impairment, but daridorexant's available safety data suggest a favorable safety profile (Zammit G et al. *Neurology*. 2020;94[21]:e2222-32).

Daridorexant at the highest dose available, 50 mg, did not worsen respiratory function, in terms of the apnea-hypopnea index and oxygen saturation in individuals with

INSOMNIA *continued on page 19*

TABLE 1

ICSD-3 diagnostic criteria for insomnia disorder

Patient (or caregiver) reports more than one of the following symptoms:
• Difficulty falling sleep • Trouble staying asleep • Difficulty going to bed at a reasonable time • Waking up before one's anticipated wake time • Trouble sleeping without a caregiver or parent involvement
Patient (or caregiver) reports more than one associated daytime symptom:
• Fatigue • Sleepiness • Cognitive deficits (memory, concentration, attention problems) • Lack of drive or motivation • Performance deficits in work, school, family, or society • Increased mistakes and accidents • Mood disturbances • Behavior disturbances • Worry or anxiety about sleep
There must be an effort to achieve sufficient sleep and the sleep environment needs to be conducive to sleep.
Short-term insomnia disorder • ≥ 3 nights per week for < 3 months Chronic insomnia disorder • ≥ 3 nights per week for > 3 months
Symptoms are not a consequence of another sleep disorder.

TABLE 2

FDA-approved medications

Medication	Dosage
Benzodiazepines	
Triazolam	0.125-0.25 mg
Temazepam	7.5-30 mg
Estazolam	1-2 mg
Quazepam	7.5mg-15 mg
Flurazepam	15-30 mg
Nonbenzodiazepine receptor agonists	
Zaleplon	5-10 mg
Zolpidem	5-10 mg
Zolpidem (ER)	6.25-12.5 mg
Zolpidem sublingual lozenge	1.75-3.5 mg
Zolpidem sublingual tablet	5-10 mg
Zolpidem oral spray	5-10 mg
Eszopiclone	1-3 mg
Melatonin receptor agonist	
Ramelteon	8 mg
Tricyclic antidepressant	
Doxepin	3-6 mg
Dual orexin receptor antagonists	
Suvorexant	5-20 mg
Lemborexant	5-10 mg
Daridorexant	25-50 mg

TABLE 3

Off-label medications

Medication	Dosage
Benzodiazepines	
Alprazolam	0.25-0.5 mg
Lorazepam	0.5-2 mg
Diazepam	2-10 mg
Sedative antidepressants	
Trazodone	25-150 mg
Mirtazapine	7.5-45 mg
Tricyclic antidepressants	
Amitriptyline	10-30 mg
Nortriptyline	10-30 mg
Alpha 2 delta ligand	
Gabapentin	300-1,200 mg
Antihistamines	
Diphenhydramine	25-50 mg
Doxylamine	25-50 mg
Hydroxyzine	25-100 mg
Melatonin receptor agonist	
Melatonin	0.5-5 mg
Atypical antipsychotic	
Quetiapine	25-75mg

TABLE 4

Dual orexin receptor antagonists

Medication	Dosage	FDA approval
Suvorexant	5-20 mg	2014
Lemborexant	5-10 mg	2019
Daridorexant	25-50 mg	2022

30% of infected patients found to develop long COVID

BY RALPH ELLIS

About 30% of COVID-19 patients developed the condition known as long COVID, University of California, Los Angeles, researchers said in a study published in the Journal of General Internal Medicine (2022 Apr 7. doi: 10.1007/s11606-022-07523-3).

The UCLA researchers studied 1,038 people enrolled in the UCLA COVID Ambulatory Program between April 2020 and February 2021 and found that 309 developed long COVID. A long-COVID diagnosis came if a patient answering a questionnaire reported persistent symptoms 60-90 days after they were infected or hospitalized. The most persistent symptoms were fatigue (31%) and shortness of breath (15%) in hospitalized participants. Among outpatients, 16% reported losing sense of smell.

The study's findings differ from earlier research. The University of California, Davis, for example, estimated that 10% of COVID-19 patients develop long-haul symptoms. A 2021 study from Penn State University found that more than half of worldwide COVID-19 patients would develop long COVID (JAMA Netw Open. 2021;4[10]:e2128568).

Part of the discrepancy can blamed on the fact there is no official, widely accepted definition of long COVID. The CDC has said it means patients who experience "new, returning, or ongoing health problems 4 or more weeks after an initial infection" by the coronavirus. The UCLA study, meanwhile, included patients still having symptoms 60-90 days after infection.

Still, the UCLA research team looked at demographics and clinical characteristics in an attempt to develop effective treatments.

People with a history of hospitalization, diabetes, and higher body mass index were most likely to develop long COVID, the researchers said. "Surprisingly, patients with commercial insurance had double the likelihood of developing [long COVID] compared to patients with Medicaid," they wrote. "This association will be important to explore further to understand if insurance status in this group is representing unmeasured demographic factors or exposures."

Older age and socioeconomic status were not associated with long COVID in the study – a surprise because those characteristics are often linked with severe illness and higher risk of death from COVID-19.

Weaknesses in the study included the subjective nature of how patients rated their symptoms and the limited number of symptoms evaluated.

"This study illustrates the need to follow diverse patient populations ... to understand the long COVID disease trajectory and evaluate how individual factors ... affect type and persistence of long COVID symptoms," said Sun Yoo, MD, health sciences assistant clinical professor at UCLA. ■

COVID-19

One in four feel fully recovered after hospitalization

BY ROB HICKS, MBBS

In a new U.K. study of more than 2,000 patients, presented at this year's European Congress of Clinical Microbiology & Infectious Diseases, and published in The Lancet Respiratory Medicine (2022.doi: 10.1016/S2213-2600[22]00127-8), only one in four patients reported feeling fully well 1 year after COVID-19 hospitalization.

The researchers assessed 2,320 participants discharged from 39 U.K. hospitals between March 7, 2020, and April 18, 2021, via patient-reported outcome measures, physical performance, and organ function at 5 months and at 1 year after hospital discharge. All participants were assessed at 5 months after discharge and 807 participants (33%) completed both the 5-month

RECOVERED *continued on following page*

RECOVERED *continued from previous page*

and 1-year visits at the time of the analysis. The 807 patients were mean age of 59 years, 36% were women, and 28% received invasive mechanical ventilation. The proportion of patients reporting full recovery was similar between 5 months (26%) and 1 year (29%).

Being female, obese, and having had mechanical ventilation in hospital makes someone 32%, 50%, and 58%, respectively, less likely to feel fully recovered 1 year after COVID-19 hospitalization, the authors said.

The authors said fatigue, muscle pain, physically slowing down, poor sleep, and breathlessness were most common ongoing long COVID symptoms. The total number and range of ongoing symptoms at 1 year was "striking," positively associated with the severity of long COVID, and emphasizes the "multisystem nature of long COVID."

An earlier publication from this study identified four groups or "clusters" of symptom severity at 5 months, which were confirmed by this new study at 1 year, the authors said. They reported that 20% had very severe physical and mental health impairment, 30% had severe physical and mental health impairment, 11% had moderate physical health impairment with cognitive impairment, and 39% had mild mental and physical health impairment.

They added that having obesity,

reduced exercise capacity, a greater number of symptoms, and increased levels of C-reactive protein were associated with the "more severe clusters." In both the very severe and the moderate with cognitive impairment clusters, levels of interleukin-6 (IL-6) were higher when compared with the mild cluster.

"The limited recovery from 5 months to 1 year after hospitalisation in our study across symptoms, mental health, exercise capacity, organ impairment, and quality-of-life is striking," the researchers noted.

"In our clusters, female sex and obesity were also associated with more severe ongoing health impairments including reduced exercise performance and health-related quality of life at one year," and suggested that this potentially highlighted a group that "might need higher intensity interventions such as supervised rehabilitation," they added.

There are no specific therapeutics for long COVID, the researchers said, noting that "effective interventions are urgently required." The persistent systemic inflammation identified, particularly in those in the very severe and moderate with cognitive impairment clusters, suggested that these groups "might respond to anti-inflammatory strategies," the authors wrote.

They warned that without effective treatments, long COVID could become a "highly prevalent new long-term condition." ■

References: 1. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020. **2.** Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. December 2020.

FDA OKs COVID-19 breath test for specific settings

BY DAMIAN MCNAMARA

The US Food and Drug Administration (FDA) has granted emergency use authorization to a first-of-its-kind test that can detect SARS-CoV-2 in the breath in less than 3 minutes. The COVID-19 Breathalyzer test (InspectIR Systems) will be available only in licensed test settings, therefore it is not currently meant for home use. That's one reason why the impact of the test may be limited, said William Schaffner, MD. The manufacturer claims it can produce about 100 testing instruments a week; "it's not as though they are producing 10,000," he said.

Also, the capacity is limited – each testing system can evaluate 160 breath samples per day.

"So this can't be used at a concert or a big ball game or something like that," said Dr. Schaffner,

who is at Vanderbilt University Medical Center, Nashville, Tenn.

It is more likely the COVID-19 breath test will be used in "an average doctor's office or clinic ... a circumstance where the capacity of the machine would be appropriate," he said. "[The] authorization is yet another example of the rapid innovation occurring with diagnostic tests for COVID-19," Jeff Shuren, MD, JD, director of the FDA's Center for Devices and Radiological Health, stated in a news release.

The breath test was evaluated in a study with 2,409 people, including participants with and without COVID-19 symptoms. The test identified 91.2% of positive samples and 99.3% of negative samples, so it has high sensitivity and specificity. A negative result means people are likely truly negative, because the test had a 99.6% negative predictive value, the FDA notes. People who test positive should consider a confirmatory laboratory test. In a separate study specific to the Omicron variant, the test's performance was similar.

"How much training does it actually take for somebody to run this?" Dr. Schaffner asked. Someone licensed for testing is needed to supervise – which is why this is not a home assay – as well as a technician trained to run and interpret the results. Dr. Schaffner added, "We'll just have to see how well it actually works in the real world."

Dr. Schaffner had no relevant disclosures. ■

Gastrointestinal Perforation [*see Warnings and Precautions*].

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients, 332 patients with chronic fibrosing ILDs with a progressive phenotype, and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%). The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death. Adverse reactions leading to permanent dose reductions were reported in 33% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (16%). Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%). The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%). Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.
[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal [*see Warnings and Precautions*], pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration]*. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [*see Warnings and Precautions*]. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and

COVID-19 again the third-leading cause of U.S. deaths

BY RALPH ELLIS

COVID-19 was the third-leading cause of death in the United States in 2021 for the second straight year, with only heart disease and cancer causing more deaths, the Centers for Disease Control and Prevention (CDC) said April 22.

About 693,000 people died of heart disease in 2021, with 605,000 dying of cancer and 415,000 of COVID, the CDC said, citing provisional data that might be updated later.

Unintentional injuries were the fourth-leading cause of death, increasing to 219,000 in 2021 from 201,000 in 2020. Influenza and pneumonia dropped out of the top 10 leading causes of death and suicide moved into 10th place.

Overall, about 3,458,697 deaths were reported in the United States in 2021. The age-adjusted death rate was 841.6 deaths per 100,000 people, an increase of 0.7% from 2020. The 2021 death rate was the highest since 2003, the CDC said.

About 693,000 people died of heart disease in 2021, with 605,000 dying of cancer and 415,000 of COVID.

The overall number of COVID deaths in 2021 increased around 20% over 2020, when around 384,000 people died from the virus, the CDC said. COVID deaths in 2021 peaked for the weeks ending Jan. 16 and Sept. 11, following holiday periods.

Blacks accounted for 13.3% of COVID deaths in 2021 and Hispanics 16.5%, down several percentage points from 2020, the CDC said (Morb Mortal Wkly Rep. 2022 Apr 22. doi: 10.15585/mmwr.mm7117e2). Asians made up 3.1% of COVID deaths for 2021, a drop from 3.6% in 2020.

Whites accounted for 65.2% of COVID deaths in 2021, an increase from 59.6% in 2020. Non-Hispanic American Indian/Alaskan Native and non-Hispanic Black or African American had the highest overall death rates for COVID.

The number of COVID deaths among people aged 75 years and older dropped to 178,000 in 2021 from around 207,000 in 2020. Among people aged 65-75, about 101,000 died of COVID in 2021, up from around 76,000 in 2020.

"The results of both studies highlight the need for greater effort to implement effective interventions," the CDC said in a statement. "We must work to ensure equal treatment in all communities in proportion to their need for effective interventions that can prevent excess COVID-19 deaths."

Since the pandemic began, about 991,000 people in the United States have died from COVID-related causes, the most among all nations in the world. ■

NETWORKS

Cardiac arrest; latent TB; lung cancer; and more ...

PULMONARY VASCULAR AND CARDIOVASCULAR NETWORK
Cardiovascular medicine & surgery section

Targeted temperature management (TTM) after cardiac arrest: How cool?

Recent randomized control trials, TTM2 (Dankiewicz J. *N Engl J Med*. 2021;384:2283) and HYPERION (Lascarrou J-B. *N Engl J Med*. 2019;381:2327), of therapeutic hypothermia, as opposed to normothermia, in patients who remain comatose after return of spontaneous circulation (ROSC) after cardiac arrest have produced conflicting results regarding survival and neurologic benefit. TTM2 reported no benefit to cooling to 33°C, while HYPERION found improved neurologic outcome at 90 days in patients cooled to 33°C. The European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) recently released an evidence review and guideline for adults who remain comatose after cardiac arrest (Sandroni C. *Intensive Care Med*. 2022;48:261). These guidelines recommend continuous monitoring of core temperature in all patients who remain comatose after cardiac arrest, and preventing fever (>37.7°C) for 72 hours, but with no recommendation of target temperature of 32°C vs 36°C.

Differences in patient populations, presenting rhythm during arrest, duration of CPR, and time to target temperature likely each contribute to the disparate conclusions of previous trials. For example, HYPERION enrolled patients with out of hospital cardiac arrest with initial nonshockable rhythms and found benefit to cooling to 33°C. In comparison, TTM2 enrolled all patients with ROSC following arrest (regardless of rhythm), including patients with in-hospital cardiac arrest and found no benefit in therapeutic cooling. Differences in patient populations are underscored by the widely differing percentage of patients with good neurologic outcome in their respective control groups: approximately 30% in the TTM2 trial and 6% in HYPERION. The guidelines leave significant room for clinical judgment in employing therapeutic cooling but encourage the continuous monitoring of core temperature and active avoidance of fever.

Fiore Mastroianna, MD
Section Member-at-Large

CHEST INFECTIONS & DISASTER RESPONSE NETWORK
Chest infections section

Update on LTBI treatment: Ensuring success by simplifying, shortening, and completing treatment

My patient has a positive IGRA test result – what's next?

If TB disease is ruled out by clinical, radiographic, and microbiologic assessment (if indicated), then latent TB infection (LTBI) is established, and treatment should be offered, guided by shared-decision making between provider and patient.

What options are available? While the former standard 9-month regimen of isoniazid-monotherapy can be shortened to 6 months, shorter rifamycin-based regimens are now preferred in most cases and include:

4 months rifampin daily, 3 months isoniazid plus rifampin daily, or 3 months isoniazid plus rifapentine weekly. In addition, 1 month of isoniazid plus rifapentine daily has recently been shown to be effective in people with HIV.

Dr. Kurz

Dr. Patrawalla

How to choose? Rifamycin-based regimens have been shown to have less hepatotoxicity and higher completion rates. Drug-drug interactions are of potential concern, for example, in patients receiving anticoagulation or treatment for HIV. The clinician should be aware of rifamycins causing a flu-like illness that may be treatment-limiting. In patients with known contact to drug-resistant TB, regimens are individualized.

How to monitor? Adherence and completion are the keys to success. Directly observed therapy may be indicated in certain scenarios. Baseline and monthly blood work is recommended for people with risk factors for hepatic or bone marrow toxicity. More importantly, patients should be instructed to discontinue LTBI medications and call the clinician with any new symptoms. HIV testing should be offered to all patients if status is unknown. Clinicians are encouraged to reach out to one of four regional TB Centers of Excellence for guidance (www.cdc.gov/tb/education/tb_coe/default.htm).

Sebastian Kurz, MD, FCCP
Amee Patrawalla, MD, MPH, FCCP
Section Members-at-Large

References

1. Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations. A Guide for Health Care Providers and Public Health Programs. Copyright © 2021 by the National Society of Tuberculosis Clinicians and National Tuberculosis Controllers Association
2. Shah, D. Latent tuberculosis infection. *N Engl J Med*. 2021;385:2271-80.
3. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017 Jan 15;64(2):111-115.
4. Swindells et. al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380:1001-11.

THORACIC ONCOLOGY & CHEST PROCEDURES NETWORK
Lung cancer section

Adjuvant and neoadjuvant therapies in early stage lung cancer

Since the discovery of the epidermal growth factor receptor (EGFR) mutation in 2004 and the development of checkpoint blockade in 2006, personalized treatment options for non–small cell lung cancer (NSCLC) have exploded, but targeted systemic therapy medications were only recommended among patients with metastatic or locally advanced disease (Rivera MP, Matthay RA. *Clin Chest Med*. 2020;41[1]:ix-xi). However, in November 2020, the National Comprehensive Cancer Network (NCCN) updated guidelines to recommend EGFR testing in surgically resected stage IB-IIIA adenocarcinoma, and to consider adjuvant osimerintib in those who were mutation-positive (NCCN. Nov 2020). Interim analysis of an ongoing phase-3 trial showed 89% of patients in the osimertinib group were alive and disease-free at 24

NETWORKS *continued on following page*

INSOMNIA *continued from page 11*

mild-moderate obstructive sleep apnea regardless of sleep stage (Boof ML et al. *Sleep*. 2021;44[6]:zsaa275). However, more safety and longitudinal data are needed to have a fuller understanding of any potential limitations of this medication.

While we continue to recommend CBT-I as the first-line treatment whenever possible for patients with insomnia, not all patients have access to this treatment and not all patients will respond satisfactorily to it. Thus, pharmacologic treatment can continue to play an important role in the management of some patients' insomnia. Each class of medications used for treating insomnia features a unique constellation of advantages and limitations, meaning that the more available options, the greater the chances of finding an option that will be both effective and safe for a particular patient. The growing DORA class, especially its newest available entrant, daridorexant, represent a continued expansion of the armamentarium of options against insomnia. ■

Dr. Pelekanos and Dr. Sum-Ping are with the Division of Sleep Medicine, Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, California.

TABLE 5

Daridorexant

Absorption	T_{max} 1-2 hours
Metabolism	Metabolized primarily by CYP3A4
Drug interactions	Strong-moderate CYP3A4 inhibitors/inducers
Side effects	Headache, somnolence, fatigue, dizziness, nausea, nasopharyngitis, sleep paralysis, hypnogogic/hypnopompic hallucinations, cataplexy-like symptoms, and complex sleep behaviors
Contraindications	Avoid use in patients with narcolepsy or severe hepatic impairment

NETWORKS *continued from previous page*

months compared with 52% in the placebo group (hazard ratio 0.20, *P* < .001) (Wu YL, et al. *N Engl J Med*. 2020;383[18]:1711-23).

The FDA has also recently approved the use of neoadjuvant and adjuvant immunotherapy in combination with platinum-based chemotherapy. Nivolumab is now approved as neoadjuvant therapy in patients with resectable IB-IIIA NSCLC regardless of PDL-1 status. The Checkmate-816 trial showed increased median event-free survival in the immunotherapy plus chemotherapy group of 31.6 months vs 20.8 months in the chemotherapy-only group (FDA.gov. 2022, Mar 4). Atezolizumab is also now approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells. Median disease-free survival was not reached in patients in the atezolizumab groups vs 35.3 months in the best supportive care group (FDA.gov. 2021, Oct 15). With so many advances in the personalized treatment among all stages of NSCLC, this is a hopeful new chapter in the care of patients with NSCLC.

Dr. Ghosh

More information: https://www.nccn.org/guidelines/guidelines-process/transparency-process-and-recommendations/GetFileFromFileManager?fileManagerId=11259

Sohini Ghosh, MD
Section Member-at-Large

DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK

Lung transplant section

Continuous distribution for lung transplant: Overhauling the wait list

Determining how to allocate the scarce resource of donor lungs to patients is a difficult task and evaluated continuously for potential improvement. Since 2005, in the United States, lung transplant recipients have been selected based primarily on location within a Donor Service Area and by lung allocation score (LAS), a composite score of urgency for transplant. This was updated in 2017 to an allocation by highest LAS within 250 nautical miles from the donor hospital. Factors such as blood type compatibility and height are also considered. Implementation of the LAS improved the sickest patients' access to transplants while not worsening 1-year mortality (Egan TM. *Semin Respir Crit Care Med*. 2018;39[02]:126-37). Unfortunately, geographic hard boundaries mean a high proportion of low LAS (<50) patients receive local donors while high LAS patients receive national offers or die while on the waitlist (Iribarne A, et al. *Clin Transplant*. 2016:30:688-93).

Dr. Turner

Dr. Frye

A new model that employs continuous distribution has been developed based on concerns regarding equity and improving allocation. This model would prioritize patients based on factors including medical priority, efficient management of organ placement (distance), expected posttransplant outcomes, and patient access (equity). By creating a composite of these without a geographic boundary, patients would be considered more on urgency within realistic constraints of distance and outcomes.

The Organ Procurement and Transplantation Network has officially approved continuous distribution, with implementation planned for 2022; details regarding the new scoring system are to be published and further research will need to be undertaken to determine if it meets the goal of overall improvement in patient access, equity, and outcomes.

Grant A. Turner, MD, MHA
Laura Frye, MD
Section Members-at-Large

CRITICAL CARE NETWORK

Non-respiratory critical care section

Update from the non-respiratory critical care section

As you've probably noticed, there have been some changes here at CHEST involving the Networks. Leadership here at CHEST has been hard at work restructuring the networks to make them more closely aligned with relevant clinical disciplines, and, ultimately, allow for greater participation. I am proud to have been given stewardship of the new Non-Respiratory Critical Care Section of the Critical Care Network.

So, what exactly is Non-Respiratory Critical Care? Well, that's where I need your help. You see this Network is meant to reflect the needs and wants of CHEST members like you. We need you, dear readers, to join in this venture and help us guide the content that this section will ultimately create for our members.

Dr. Ramachandran

If you're interested in critical care, but you don't see your particular area of interest anywhere else in the current structure ... guess what? You've found the right place!

My Infectious Diseases and Nephro peeps? Welcome! Are you a surgical or anesthesia intensivist? Don't be shy. ECMO people, let's hear some chatter! Is therapeutic hypothermia your thing? Come on in. The water's freezing, 33 degrees just like you folks like it. Or is it 36? Not sure. Anyway, see what I'm talking about? We really need your help!

If you're interested in critical care, but you don't see your particular area of interest anywhere else in the current structure ... guess what? You've found the right place!

You can get involved by clicking on the Membership & Community tab at the CHEST website. Once you're a member, you can even nominate yourself to run for the Steering Committee elections, which are held periodically. Hope to see you soon!

Deep Ramachandran, MD, FCCP
Section Chair

SLEEP MEDICINE NETWORK

Non-respiratory sleep section

Unusual suspects? Breakthrough in the treatment of idiopathic hypersomnia

Idiopathic hypersomnia (IH) is a rare and debilitating disorder defined by its excessive daytime sleepiness, sleep inertia, prolonged nighttime sleep, and long, unrefreshing naps (AASM. ICSD 3rd ed. 2014).

Gamma-aminobutyric acid (GABA) is one of the main inhibitory neurotransmitters in the nervous system. It is through the potentiation of GABA that substances such as alcohol and benzodiazepines yield their effects. It is also hypothesized that the "brain fog" experienced in IH may be a consequence of either higher levels of an endogenous benzodiazepines in the cerebral spinal fluid or the presence of a GABA-enhancing peptide (Rye DB. *Science Transl Med*. 2012;Med 4:161ra151).

Sodium oxybate (SXB), a compound that likely has its therapeutic effect through the potentiation of GABA receptors, is an effective treatment option for cataplexy and sleepiness in narcolepsy. Although there may be some overlap between narcolepsy and IH in both diagnosis and treatment (Bassetti C, et al. *Brain*. 1997;120:1423), it would perhaps be entirely counterintuitive (given SXB's pharmacology) to imagine using SXB as a plausible treatment option in IH. It was, however, investigated in the treatment of refractory hypersomnia and IH. In the retrospective study looking at 46 subjects treated with SXB, 71% experienced improvement of their severe sleep inertia, 55% had a decrease in their excessive daytime sleepiness, and 52% reported a shortened nighttime sleep time (Leu-Semenescu S, et al. *Sleep Med*. 2016;17:38).

In a recent double-blind, randomized control trial, the lower-sodium oxybate (LXB) was trialed in 154 patients with IH. It demonstrated statistically significant and clinically meaningful improvements (compared with placebo) in the Epworth Sleepiness Scale score (*P* <.0001) and in the Idiopathic Hypersomnia Severity Scale (*P* <.0001). The effects were seen both during the up titration of LXB and the benefits were maintained during the stable phase of the intervention (Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53). In August 2021, LXB (initially launched in 2020 for the treatment of narcolepsy) is now the first FDA-approved medication to treat IH in adults. It is curious, however, that LXB's understood therapeutic effects are secondary to the "potentiation" of the very GABA receptor we have believed to be the root cause of the debilitating symptoms in IH. Could this discovery lend to further insights into the origins of this condition?

Ruckshanda Majid, MD, FCCP
Section Member-at-Large ■

President's report

BY DAVID SCHULMAN, MD, MPH, FCCP

Dr. Schulman

There is little I enjoy more than an opportunity to get together with old friends.

I write this missive on the return trip from a week of CHEST leadership meetings held last month, and I find myself filled with joy, awe, and great appreciation for the hard work our volunteers contribute to making the American College of Chest Physicians an extraordinarily productive and successful organization.

This year's meetings meant more than any I can ever recall from the past, in the context of a return to in-person gatherings that let our members share laughs, stories, and even a game or two of laser tag in the context of celebrating good times and friendship. And while some great works were accomplished by our committees, some of which I will enumerate below, the highlight of the week was definitely the esprit de corps that was on broad display.

Our Membership Committee meeting was led by Vice-Chair Marie Budev, DO, FCCP. While this committee is tasked with the critical duty of reviewing applications for the prestigious FCCP designation, they are just as importantly tasked with promoting membership to our domestic and international colleagues. This is a challenging task, because different members prioritize the variety of benefits from CHEST differently; some focus on access to our educational offerings, both throughout the year and at our annual meeting, while others find greater value in the chance to network with colleagues from around the world and to participate in leadership in an international society. Making sure that we are helping our members realize these benefits, while also identifying (and potentially enhancing) those opportunities in which members are most interested is a challenging task and I very much enjoyed watching these folks brainstorm ways that we could further increase the value of joining CHEST for current and potential future members.

The Guidelines Oversight Committee, chaired by Lisa Moores, MD, FCCP, is responsible for the oversight of CHEST's evidence-based guidelines. As our clinical guidelines are among the most highly regarded of all of the things we publish, the members of this committee take special care to ensure that the subjects selected for review as part of the guideline process meet strict criteria. They receive dozens of proposals for new guidelines each year and carefully examine each one to identify the potential public health impact, to ensure the availability of literature in the space worthy of review, and to provide the opportunity to illuminate areas where there are significant clinical uncertainties, often due to new treatments or diagnostic tests.

Watching committee members meticulously debate the merits of the many good ideas received to finalize a short list of topics for guideline development in the coming year was incredibly informative and validated my longstanding perception that our members are some of the best clinical minds in the pulmonary, critical care, and sleep fields in the world.

The Professional Standards Committee (PSC), chaired by Scott Manaker, MD, PhD, FCCP, has the important duty of developing CHEST's conflict of interest (COI) policy, as well as reviewing all potential COI among CHEST leaders and members of our guideline panels. While this may sound a little dry, the fascinating part of this meeting was the ongoing discussion of what constitutes a meaningful COI.

As one would expect, many of the best medical experts in the world have relationships with pharmaceutical and medical device companies that often seek the counsel and participation of high-performing, high-volume clinicians for research trials. CHEST has extremely strict rules with regard to COIs among its many levels of leadership, but the question of what constitutes a potentially problematic COI for the large number of folks who volunteer their time and energy to teach at one of our many courses is an interesting (albeit possibly philosophical) question. Since PSC members cannot observe every CHEST faculty interaction, we rely on our members

REPORT *continued on following page*

Coming together for a night of philanthropy and fun

Although attendees will be watching "The Test of the Champion" with bated breath, the upcoming Belmont Stakes Dinner and Auction on June 11 in New York City is about much more than a famous horse race. It's about community – the vibrant community of clinicians, patients, advocates, and more who support the mission to crush lung disease.

The event started small several years ago with a Sunday brunch at the home of CHEST President-Elect Doreen Addrizzo-Harris, MD, FCCP, where attendees gathered to learn more from their host about the CHEST Foundation's many initiatives.

However, over the years, Dr. Addrizzo-Harris leaned on her own community of colleagues, family, friends, and patients to build an event that now boasts hundreds of attendees. But despite all that has changed, the Belmont Stakes Dinner and Auction is still dedicated to raising awareness about the CHEST Foundation and fundraising for initiatives to develop patient education and improve care.

In addition to a plated dinner, silent auction, cocktail reception, and rooftop after-party, this year's event will feature speeches from two long-time patient advocates living with chronic lung conditions, Fred Schick and Betsy Glaeser.

For Dr. Addrizzo-Harris, spotlighting that unique patient perspective is particularly meaningful because the core focus of CHEST and the CHEST Foundation is to improve care and, by extension, patients' lives.

Visit foundation.chestnet.org to read a blog post with more information about Schick and Glaeser's work advocating for others with lung disease, find more details about the Belmont Stakes Dinner and Auction, and reserve your seat for this night of philanthropy and fun. ■

REPORT *continued from previous page*

to let us know if they perceive any potential bias in faculty teaching (and we so very much appreciate those of you who bring the extremely rare concerns to our attention!), but this is an area that we continue to watch very closely, as we continue to ensure that all CHEST education is accurate, unbiased, and the best available throughout the world.

The reformulated Council of Networks met under the leadership of Angel Coz Yataco, MD, FCCP, and Cassie Kennedy, MD, FCCP, to discuss how to best engage our members in the new structure, which comprises seven Networks and 22 component Sections. The Council's primary charges are to develop educational content, to review project applications from Sections, and to serve as expert consultants to the President and others in their specific clinical domains.

While the new configuration provides a significant increase in leadership positions for our members, as well as more formal opportunities to cultivate relationships across different Sections, I have received a few emails from colleagues who were concerned about elimination of certain former Networks, or the placement of a specific Section under a specific Network. Some of these concerns were discussed at the April meeting. While there will be some growing pains, listening to the thoughtful discussion that ensued validated my belief that Drs. Coz and Kennedy are the right folks to be leading the Council as it matures into this new and stronger structure.

While I also had the opportunity to hear reports from the Training and Transitions Committee, the Education Committee, and the Council of Global Governors, I wanted to briefly mention the Scientific Program Committee and its Innovations Group.

While we are looking forward to seeing everyone in Nashville this October, I cannot tell you how excited I am about some of the new things we have in store for our first in-person annual meeting in 3 years. (Literally ... I am absolutely sworn to secrecy!) But under the leadership of Program Chair Subani Chandra, MD, FCCP, and my two other "Chief Fun Officers" Aneesa Das, MD, FCCP, and William Kelly, MD, FCCP, I can say that attendees are going to be in for a heck of a lot of fun. Oh, and there's going to be some education there, also.

In closing, I want to reiterate how much of a pleasure and privilege it has been to sit in the President's chair over the first few months of 2022. If any of the committees I've described sound interesting to you, please strongly consider throwing your hat into the ring when nominations open up in the coming months. Getting involved at CHEST has been one of the best experiences of my career, and I expect you'll feel the same way after you join in the fun.

As always, I remain available to you, either by emailing me at president@chestnet.org or messaging me on Twitter @ChestPrez. And, please come find me in Nashville in October, either to say hello, or to challenge me to a game of laser tag. ... I'm not very hard to beat.

Until next time,
David

This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP
Editor in Chief

Genetic Associations and Architecture of Asthma-COPD Overlap. *By Catherine John, et al.*

Emerging Nonpulmonary Complications for Adults With Cystic Fibrosis. *By Dr. Melanie Chin, et al.*

Aspirin as a Treatment for ARDS: A Randomized, Placebo-Controlled Clinical Trial. *By Dr. Philip Toner, et al.*

PICU in the MICU: How Adult ICUs Can Support Pediatric Care in Public Health Emergencies. *By Dr. Mary A. King, et al.*

Association of BMI and Change in Weight With Mortality in Patients With Fibrotic Interstitial Lung Disease. *By Dr. Alessia Comes, et al.*

Off-Label Use and Inappropriate Dosing of Direct Oral Anticoagulants in Cardiopulmonary Disease. *By Dr. Ayman A. Hussein, et al.*

Introducing our new *CHEST Physician* editorial board member

Welcome to Corinne Young, MSN, FNP-C, FCCP, who recently joined the *CHEST Physician* editorial board to represent and advocate for the perspective of advanced practice providers on the interdisciplinary team.

Young is a nurse practitioner and director of APP and Clinical Services for Colorado Springs Pulmonary Consultants in Colorado. She also is the founder and president of the Association of Pulmonary Advanced Practice Providers, which she created with support from CHEST staff and leaders, who encouraged her to create a community around advocating for and developing credentialing opportunities for this population.

The idea began early in Young's career. After joining CHEST and attending educational events, she was struck by the lack of standardization in practice among APPs.

"Every time I would be at the CHEST meeting, if I happened to bump into another APP, I would assault them with questions because I didn't know what the norm was—and come to find out, nobody did," she said. "Our organization came out of that, and our goal is to eventually standardize the education and knowledge base of APPs."

Because there is not an option for a national certification specifically for pulmonary medicine for APPs, Young instead attained the FCCP to demonstrate her clinical competency and knowledge. She also immersed herself in the education and community of CHEST, working on the former Clinical Research & Quality Improvement NetWork Committee and Interprofessional Team NetWork Committee, serving on the Scientific Program Committee, and developing patient education on asthma, among other projects.

Corrine Young, MSN, FNP-C, FCCP

Now, as a member of the *CHEST Physician* Editorial Board, Young hopes to build awareness among clinicians of the importance of APPs on the care team and to support another option for APPs to access high-quality education and content to help them build their knowledge and enhance the care they deliver.

"It's important that *CHEST Physician* is interested in an APP perspective being included," she said. "It's validation that we're part of the team, that we're included in all aspects of care including areas outside of direct care: in education, in the literature. ... That they feel our contributions are important."

When she isn't working with CHEST or caring for patients, Young and her husband competitively team rope, a rodeo event in which two people work together to rope a steer. Although they were unable to attend, they qualified for the world series in the sport last year, and hope to qualify again this year.

Please join us in welcoming Corinne Young to the *CHEST Physician* Editorial Board. ■

Supporting the Harold Amos Medical Faculty Development program

In 2020, the CHEST Foundation embarked on a bold new initiative to build trust, identify and remove barriers, and promote health care access for all in order to help fight lung disease. As part of that, we recognize that racial and ethnic minorities have been underrepresented in medical professions, contributing to these barriers to patient care.

We recognize that advocating for these groups and increasing the number of medical professors who represent people of color, ethnic minority groups, or who come from an historically disadvantaged community also increases the number of role models in our communities and can help stimulate greater interest among minority students in the health care professions. This year, CHEST is joining the American Thoracic Society (ATS) and the American Lung Association (ALA) in funding the Harold Amos Medical Faculty Development program, and the CHEST Foundation will be raising funds to support these fellowship recipients.

Harold Amos, PhD, was the first African American to chair a department, now the Department of Microbiology and Medical Genetics, of the Harvard Medical School. Dr. Amos worked tirelessly to recruit and mentor minority and disadvantaged students to careers in academic medicine and science. He was a founding member of the National Advisory Committee of the Robert Wood Johnson Foundation's Minority Medical Faculty Development Program in 1983 and served as the Program's National Program Director between 1989 and 1993. Dr. Amos remained active with the program until his death in 2003.

This program exists to continue Dr. Amos's legacy and to increase the number of faculty from historically disadvantaged backgrounds who can achieve senior rank in academic medicine, dentistry, or nursing and who will encourage and foster the development of succeeding classes of such physicians, dentists, and nurse-scientists. The impact of this program is clear.

Key results

- Over the past 30 years, 241 scholars had completed all 4 years of the program (as of 2012). More than three-quarters remained in academic medicine, including 57 professors, 76 associate professors, and 56 assistant professors.
- Many program alumni have earned professional honors and become influential leaders in the health care field. For example, three direct institutes at the National Institutes of Health, and 10 have been elected to the Institute of Medicine.
- Alumni have received hundreds of awards and honors, including a MacArthur Fellowship "genius" award.
- Alumni have reached positions of influence in academia that enable them to help correct the underrepresentation of minorities in the health professions and address health disparities.

Former scholars are:

- Members of admission, intern, and faculty selection committees
- On review boards for clinical protocols and research studies
- Officers of professional societies and on editorial boards of academic journals

CHEST is proud to join with ATS and ALA to support this incredible program. We recognize that the impact on the past is only the start. By supporting this initiative, we are also looking to address the challenges of the future as the health care landscape continues to evolve. Ensuring that this program reaches the right groups and continues to promote Dr. Amos's legacy is integral not only to the success of the program but also to aid us in being able to care for our diverse and unique patient populations.

The CHEST Foundation is raising funds to support future fellowship recipients. Join us at our next Viva la Vino wine tasting event on July 14 at 7:00 PM CT. All proceeds go to benefit this important initiative, and you can learn more about the work the Foundation does in a relaxed, social environment. ■

INDEX OF ADVERTISERS

IQlung™
TREATMENT GUIDANCE

Find their path faster.

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

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

Take the first step at **Biodesix.com/IQLung**