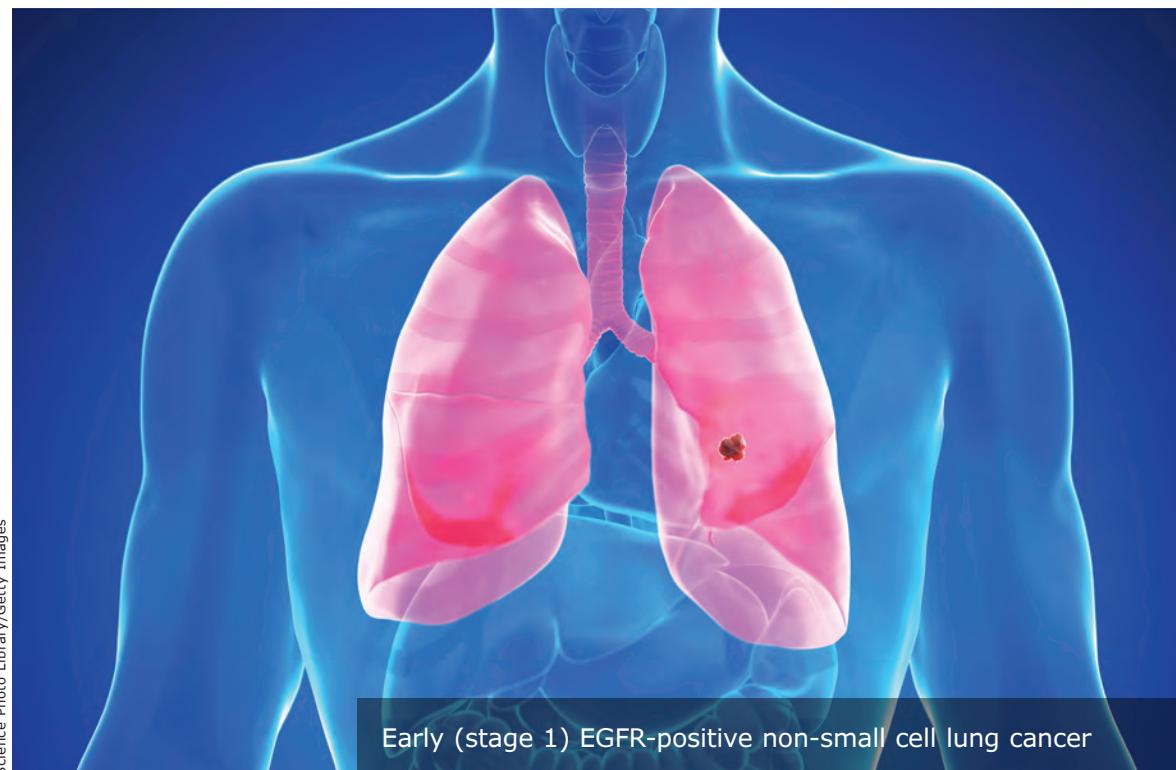




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Early (stage 1) EGFR-positive non-small cell lung cancer

Lung cancer screening rates still lag despite expanded eligibility

BY NEIL OSTERWEIL

The National Lung Screening Trial, primary results of which were published in 2011, showed that screening with low-dose computed tomography (CT) reduces lung cancer mortality.

Yet although lung cancer accounts for more deaths in the United States than breast, colorectal, and prostate cancers combined, less than 5% of Americans eligible for lung cancer screening actually underwent it in 2022.

In contrast, annual screening rates of mammography for breast cancer, PAP testing for cervical cancer, and colonoscopy/fecal immunochemical testing of eligible adults in the US

range from about 60% to 80%, according to the American Cancer Society (ACS) and the National Cancer Institute.

These sobering statistics are concerning for clinicians, especially when newly revised guidelines recommend expanding screening to more persons than ever.

In 2021, the United States Preventive Services Task Force (USPSTF) issued updated lung cancer screening guidelines that lowered the recommended starting age for screening and reduced the cumulative smoking pack-years requirement.

The updated version recommends annual lung cancer screening with low-dose CT for persons 50-80 years of age with a 20 pack-year smoking

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Catheter-directed strategy improves pulmonary artery occlusion

BY HEIDI SPLETE

Use of pharmacomechanical catheter-directed thrombolysis significantly reduced the number of pulmonary artery branches with total or subtotal occlusions in patients with acute pulmonary embolism, based on data from more than 100 individuals.

Reduced distal vascular volume is a significant predictor of 30-day and 90-day mortality in acute pulmonary embolism (PE) patients, and pulmonary obstruction is often the cause, wrote Riyaz Bashir, MD, of Temple University, Philadelphia, Pennsylvania, and colleagues.

Some studies of catheter-based treatments have shown a reduction in pulmonary artery (PA) obstruction in PE patients, but the impact has been modest, the researchers said. "The recently published RESCUE (Recombinant tPA by Endovascular Administration for the Treatment of Submassive PE Using CDT for the Reduction of Thrombus Burden) trial showed a 35.9% reduction in PA obstruction using the Refined Modified Miller Index (RMMI), the largest reduction of all published catheter studies with core lab measurement, with similar doses

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INSIDE HIGHLIGHT



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Revealing new philanthropic pillars

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history who currently smoke cigarettes or quit within the past 15 years.

The ACS updated its guidelines in 2023; the guidelines are similar to those issued by the USPSTF, but drop the years-since-quit (YSQ) requirement.

“Historical and emerging data indicate that two core assumptions about YSQ with respect to continuing lung cancer risk are incorrect: first, that persons who formerly smoked are on a continuous trajectory of declining absolute risk, and second, that individuals who are past YSQ15 are no longer at sufficiently elevated risk to justify screening,” the ACS guideline developers wrote.

Stigma and access problems

Public health researchers and advocacy groups who focus on improving lung cancer screening rates



Ms. Ambrose

applaud the updated guidelines, but also express frustration that neither clinicians nor large swaths of the at-risk population seem to be getting the message.

“It really boils down to this being lung cancer, which carries a terrible stigma. It’s blame-the-smoker, when in essence this is a disease that no one deserves, and with the extraordinary life-saving benefit of screening this should have been embraced, advocated for, and supported from day one,” said Laurie Fenton Ambrose, president and CEO of the advocacy organization GO₂ for Lung Cancer, in an interview with *Chest Physician*.

Yet even with the updated ACS guidelines, which expand eligibility to an estimated 5 million additional at-risk individuals, the lack of attention and action “is tragic” she said.

Debra P. Ritzwoller, PhD, an economist and senior investigator at the Institute for Health Research at Kaiser Permanente Colorado, told *Chest Physician* that the problem is multifaceted and will require a multi-factor effort to get more eligible persons in for screening.

“If we think about mammography and colorectal cancer screening, those have been out there for decades,” she said, noting there is widespread media coverage and therefore public awareness of the benefits of screening for breast and

colorectal cancers, whereas low-dose CT scanning for lung cancer screening is not as well known.

Access to screening is also a problem for many patients, “not just access to insurance — insurance is key, obviously — but access meaning ‘do you have a primary care provider who’s going to actually engage in a conversation about this?’”

And unlike either mammography or colorectal cancer, which are recommended based on age, eligibility for lung cancer screening requires both age and smoking history.

Primary care physicians “have to have knowledge of your smoking history and engage you in a conversation about that, and more importantly, they have to have a conversation with you about the risks and benefits, shared decision-making,” Dr. Ritzwoller said.

Reducing disparities

One important step for improving lung cancer screening is reducing ethnic, racial, gender, and socioeconomic disparities, Dr. Ritzwoller and Ms. Ambrose said.

The updated USPSTF and ACS guidelines are a good start, Dr. Ritzwoller said. In an analysis published in 2021, she and colleagues compared the newly revised USPSTF guidelines with the previous iteration issued in 2013, and found the 2021 update would expand overall eligibility for screening by 53.7%, with a larger proportion of women and racial or ethnic minority groups becoming newly eligible.

The authors noted their findings were similar to those found in analyses conducted by members of the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Cancer Working Group, although the CISNET findings were based largely on clinical trial results, which tend to show more favorable outcomes than real-world, community-based studies.

However, in a separate study published in 2023 in the *American Journal of Preventive Medicine*, her group also reported that of nearly 30,000 individuals across five health care systems who were eligible for screening as of September 2019, only 28.3% were undergoing testing.

“The percentage up to date with testing among those eligible for lung cancer screening is well below estimates for other types of cancer screening, and disparities in lung cancer screening participation

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PULMONARY PERSPECTIVES® //

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Sotatercept endorsed for PAH by ICER

BY JIM KLING

In a new report, the Midwest Institute for Clinical and Economic Review's (ICER) Comparative Effectiveness Public Advisory Council concluded that the Merck drug sotatercept, currently under review by the US Food and Drug Administration (FDA), has a high certainty of at least a small net health benefit to patients with pulmonary arterial hypertension (PAH) when added to background therapy. The limited availability of evidence means that the benefit could range from minimal to substantial, according to the authors.

Sotatercept, administered by injection every 3 weeks, is a first-in-class activin signaling inhibitor. It counters cell proliferation and decreases inflammation in vessel walls, which may lead to improved pulmonary blood flow. The US FDA is considering it for approval through a biologics license application, with a decision expected by March 26.

There remains a great deal of uncertainty surrounding the long-term benefits of sotatercept. It's possible that the drug is disease-modifying,

but there isn't yet any proof, according to Greg Curfman, MD, who attended a virtual ICER public meeting on December 1, 2023, that summarized the report and accepted public comments. "I'm still wondering the extent to which disease-modifying issue here is more aspirational at this point than really documented," said Dr. Curfman, who is an associate professor of medicine at Harvard Medical School and executive editor of the *Journal of the American Medical Association*.

Current PAH treatment consists of vasodilators, including phosphodiesterase-5 inhibitors (PDE5i), guanylate cyclase stimulators, endothelin receptor antagonists (ERA), prostacyclin analogues (prostanoids), and a prostacyclin receptor agonist. The 2022 European Society of Cardiology and the European Respiratory Society clinical practice guideline recommends that low- and intermediate-risk patients should be started on ERA/PDE5i combination therapy, while high-risk patients should also be given an intravenous or subcutaneous prostacyclin analogue, referred to as triple therapy.

Sotatercept's regulatory approval hinges on the phase 3 STELLAR trial, which included 323

patients with World Health Organization functional class (WHO-FC) II and III PAH who were randomized to 0.75 mg/kg sotatercept in addition to background double or triple therapy, or background therapy alone. The mean age was 48 years, and the mean time since diagnosis was 8.8 years. About 40% received infused prostacyclin therapy at baseline. At 24 weeks, the median change in 6-minute walking distance (6mWD) was 40.8 m longer in the sotatercept group. More patients in the sotatercept group experienced WHO-FC improvement (29.4% vs 13.8%).

Those in the sotatercept group also experienced an 84% reduction in risk for clinical worsening or death. PAH-specific quality of life scales did not show a difference between the two groups. Open-label extension trials have shown that benefits are maintained for up to 2 years. Adverse events likely related to sotatercept included telangiectasias, increased hemoglobin levels, and bleeding events.

Along with its benefits, the report authors suggest that the subcutaneous delivery of sotatercept

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remain," the investigators wrote.

Ms. Ambrose's organization advocates for removing what they view as arbitrary barriers to access, such as the minimum 15-pack-year requirement and the upper age limit of 80.

"Some members of our scientific advisory board have conducted lung cancer surgery on 80-year-olds who were absolutely able to manage that intervention at an early stage to prolong their lives," she said.

Risk-based screening

In addition to lowering the age for screening eligibility, another method for reducing disparities has been suggested by Eunji Choi, PhD, from the Quantitative Sciences Unit at Stanford University School of Medicine in Stanford, California, and colleagues.

In a study published in 2023 in *JAMA Oncology*, the authors noted that most of the currently available lung cancer risk-prediction models were created using data from predominantly White and male populations, and pointed out most studies of racial and ethnic disparities in screening have focused on eligibility rather than on actual cancer risk.

They proposed that applying a validated cancer risk-prediction model — the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial 2012 model (PLCOM2012) — to more accurately represent a diverse ethnic and racial population could

reduce racial and ethnic disparities and improve screening performance compared with the updated USPSTF criteria.

The investigators conducted a study using data from the Multiethnic Cohort Study which included 105,261 adults with a smoking history enrolled from 1993 through 1996 and followed through 2018.



Dr. Ritzwoller

They found the PLCOM2012 criteria "showed good predictive accuracy across races and ethnicities," whereas the USPSTF criteria would introduce a large disparity between African American and White persons, with eligibility-incidence ratios of 9.5 vs 20.3, respectively ($P < .001$).

In contrast, the respective eligibility-incidence ratios using the PLCOM2012 criteria were 15.9 vs 18.4, reflecting a reduction, if not elimination, of disparities.

Sex-based differences

Dr. Ritzwoller's group found the 2021 USPSTF screening recommendations would result in a 13.8% relative increase in lung cancer screening among women compared with men, an important finding given the higher lung cancer incidence among women under age 50

compared with men in the same age range, as reported by Ahmedin Jemal, DVM, PhD, and colleagues at ACS in *The New England Journal of Medicine* in 2018.

They noted that the lung cancer incidence rate among women younger than 50 was higher than that among men in the same age range, which represented a reversal of the historical pattern that could not be fully explained by sex differences in smoking.

To see whether the same pattern shift was true for more recent birth cohorts, Dr. Jemal and colleagues extended their previous analysis, adding 5 more years of data.

As they reported in an October 2023 research letter in *JAMA Oncology*, declines in incidence rates from the 2000-2004 period to the 2015-2019 period were greater among men than among women, which led to the higher incidence rate for young women.

Lobbying for access

In November 2023, representatives of the American Lung Association, GO2 for Lung Cancer, and LUNGevity Foundation ascended Capitol Hill to lobby Congress to pass legislation aimed at improving lung cancer screening rates.

One proposed bill, H.R. 4286, titled the "Increasing Access to Lung Cancer Screening Act," is intended to increase access to annual lung cancer screening by removing barriers such as prior authorization and

cost sharing for all eligible individuals, increase access to smoking cessation counseling and treatments for all Medicaid recipients, and establish a nationwide public awareness campaign about lung cancer screening and eligibility criteria.

A second bill introduced in the US Senate, titled the Women and Lung Cancer Research and Preventive Services Act (S 2245; H.R. 4534) would "require the Department of Health and Human Services to conduct an interagency review of the status of women and lung cancer, including the status of existing research and current knowledge gaps; opportunities for collaborative research to determine the causes of lung cancer and advance prevention, screening, diagnosis, and treatment; and recommendations for a national cancer screening strategy and public education campaign," according to a press release issued jointly by the advocacy groups.

"We have an extraordinary opportunity to move the cancer mortality needle by focusing on lung at this moment," Ms. Ambrose said.

Dr. Ritzwoller is employed by Kaiser Permanente. She reported support for lung cancer research from the Gordon and Betty Moore Foundation, and salary support paid to her institution by Pfizer for work outside of lung cancer. Ms. Ambrose is employed by GO₂ for Lung Cancer. She reported having no conflicts of interest to disclose. ■

of tissue plasminogen activator (tPA),” the researchers wrote.

The Bashir endovascular catheter was designed to maximize thrombus reduction via a pharmacomechanical infusion. The catheter features an expandable basket of 6 nitinol-reinforced infusion limbs. “There are three crucial goals that we want to accomplish in patients who have a severe pulmonary embolism,” Dr. Bashir said in an interview. “Those include, in the order of importance, survival, recovery of right ventricular function, and resolution of blocked pulmonary arteries; both segmental and proximal pulmonary arteries,” he said.

Most previous studies have focused on the first two goals, but they still need to evaluate the resolution of PA blockages carefully, Dr. Bashir said. “In our clinical practice, we have seen a large number of patients who develop debilitating shortness of breath from these blockages. We decided to carefully evaluate these blockages before and after pharmacomechanical catheter-directed thrombolysis with the Bashir endovascular catheter using the core lab data from the RESCUE study,” he said.

In the current study published in *JACC: Advances* (2023 Nov. doi: 10.1016/j.jacadv.2023.100670), the researchers used baseline and 48-hour posttreatment contrast-enhanced chest computed tomography angiography of adult PE patients with right ventricular dilatation.

The study population included 107 adults with acute intermediate-risk PE who were treated with pharmacomechanical catheter-directed thrombolysis (PM-CDT) at 18 sites in the United States. Of these, 98 had intermediate

high-risk PE with elevated troponin and/or brain-type natriuretic peptide (BNP) levels and 102 had bilateral PE.

The primary endpoint was the change in the number of segmental and proximal PA branches with total or subtotal occlusions (defined as > 65%) after 48 hours compared to baseline. Occlusions were assessed using McNemar’s test.

Patients with bilateral PE received two Bashir catheters; those with unilateral PE received one catheter each.

Each patient received a pulse spray of 2 mg of recombinant tPA (r-tPA) into each lung, followed by 5 mg of r-tPA over 5 hours; the total dose was 7 mg of r-tPA for patients with unilateral PEs and 14 mg for those with bilateral PEs, the researchers said. The median times for catheter placement and total procedure were 15 minutes and 54 minutes, respectively.

The number of segmental PA branches with total or subtotal occlusions decreased significantly, from 40.5% at baseline to 11.7% at 48 hours, and proximal PA branch total or subtotal occlusions decreased significantly, from 28.7% at baseline to 11.0% at 48 hours ($P < .0001$ for both).

The magnitude of the reductions in both total and subtotal occlusions of segmental arteries was significantly correlated with the extent of right ventricle recovery (measured by the reduction in right ventricular/left ventricular ratio) with a correlation coefficient of 0.287 ($P = .0026$); however, this correlation was not observed in the proximal PA arteries (correlation coefficient 0.132, $P = .173$).

One major bleeding event occurred within 72 hours in a

patient who also experienced a device-related left common iliac vein thrombosis while not taking anticoagulation medication, and one death unrelated to PE occurred within 30 days. “The two findings that surprised me include, first, a more than 70% reduction in total and subtotal occlusions in the segmental arteries with such a low dose of r-tPA and, second, the resolution of the blockages was seen not only in the arteries where the device was placed but also at remote sites away from the location of the catheter,” Dr. Bashir told this news organization.

The findings were limited by several factors including the lack of long-term clinical follow-up outcomes data and lack of comparison groups who underwent other treatments.

However, “This study implies that we now have a safe therapy for these patients that improves survival and right ventricular recovery in addition to dramatically improving blocked pulmonary arteries,” Dr. Bashir said.

As for additional research, “we need all the current and future prospective pulmonary embolism studies to include an assessment of pulmonary artery blockage resolution as an essential endpoint,” he said.

Catheter treatment options

The current study, a subgroup analysis of the RESCUE trial, was one of the first to examine the impact of catheter-directed lysis on distal occlusions, study coauthor Parth M. Rali, MD, said in an interview.

To this point, literature has been limited to evaluation for proximal disease, said Dr. Rali, director of thoracic surgery and medicine and part of the Pulmonary Embolism

Dharani Narendra, MD, FCCP,
comments:

“Although the article shows benefit from PA size dimension, it would be imperative to see patient outcomes such as all-cause mortality, pulmonary hypertension.”

Dr. Narendra is a member of the CHEST Physician Editorial Board.



Response Team at Temple University Hospital, Philadelphia.

Dr. Rali said he was encouraged to see confirmation that the BEC catheter, because of its design, works in patients with proximal or distal occlusive disease.

In clinical practice, “the catheter provides an additional option for care in patients with multiple distal occlusive disease when a systemic tissue plasminogen activator may put patient at high bleeding risk,” Dr. Rali said.

Looking ahead, a prospective, observational multicenter study would be useful to validate the findings from the post hoc analysis of the current study, he noted.

The study was sponsored by the National Heart, Lung, and Blood Institute, Commonwealth of Pennsylvania, and Thrombolix, a medical device company developing interventional catheter-based therapies for the rapid and effective treatment of acute venous thromboembolic disorders. Dr. Bashir is a cofounder and has an equity interest in Thrombolix. Dr. Rali disclosed serving as a consultant for Thrombolix, Inari Medical, Viz AI, and ThinkSono. ■

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may be less burdensome to patients than some other PAH treatments, especially inhaled and intravenous prostanoids. “However, uncertainty remains about sotatercept’s efficacy in sicker populations and in those with connective tissue disease, and about the durability of effect,” the authors wrote.

A lack of long-term data leaves open the question of its effect on mortality and unknown adverse effects.

Using a de novo decision analytic model, the authors estimated that sotatercept treatment would lead to a longer time without symptoms at rest and more quality-adjusted life-years, life-years, and equal-value life-years. They determined the health benefit price benchmark for sotatercept to be between \$18,700 and \$36,200

per year. “The long-term conventional cost-effectiveness of sotatercept is largely dependent on the long-term effect of sotatercept on improving functional class and slowing the worsening in functional class; however, controlled trial evidence for sotatercept is limited to 24 weeks. Long-term data are necessary to reduce the uncertainty in sotatercept’s long-term effect on improving functional class and slowing the worsening in functional class,” the authors wrote.

During the online meeting, Dr. Curfman took note of the fact that the STELLAR trial reported a median value of increase in 6mWD, rather than a mean, and the 40-minute improvement is close to the value accepted as clinically meaningful. “So that tells us that half the patients had less than a clinically important improvement in the 6-minute walk distance. We should be putting that

in perspective,” Dr. Curfman said.

Another attendee pointed out that the open-label PULSAR extension trial showed that the proportion of patients in the sotatercept arm who were functional class I rose from 7.5% at the end of the trial to 20.6% at the end of the open-label period and wondered if that could be a sign of disease-modifying activity. “I think that’s a remarkable piece of data. I don’t recall seeing that in any other open label [trial of a PAH therapy] — that much of an improvement in getting to our best functional status,” said Marc Simon, MD, professor of medicine and director of the Pulmonary Hypertension Center at the University of California, San Francisco, who was a coauthor of the report.

Dr. Curfman has no relevant financial disclosures. Dr. Simon has consulted for Merck. ■

Olympus provides recall correction for bronchoscopes to reduce fire risk

BY HEIDI SPLETE

A series of Olympus bronchofiberscopes and bronchovideoscopes have been recalled by the manufacturer because of a risk for burns and fire, according to a statement from the US Food and Drug Administration (FDA).

However, “this recall is a correction, not a product removal,” according to the FDA. Clinicians do not need to cease using these devices, but they must be mindful of the risks and take the precautions outlined by Olympus.

“While health care providers may choose to continue using the Olympus bronchofiberscopes and bronchovideoscopes, to maximize patient safety and mitigate any potential risk to patient health, the FDA and Olympus advise users not to perform high-frequency cauterization while supplying oxygen, and carefully follow the warnings provided in the Olympus operators manual and highlighted in its October 12, 2023, letter to customers,” an FDA spokesperson said.

The recall affects Olympus bronchofiberscopes and bronchovideoscopes distributed between January 1, 2001, and September 11, 2023. According to the FDA statement, use of these devices may cause serious adverse events to patients and to clinicians. Patients treated with these devices could experience critical burns in the airways or lungs, airway bleeding, breathing difficulty, apnea, loss of consciousness, or death. Health care workers using the devices also may be affected in the event of combustion.

On October 12, 2023, Olympus sent an Urgent Medical Device Corrective Action letter. This letter outlined the risks associated with the devices as follows:

“There is a risk of endobronchial combustion if high-frequency cauterization is performed while supplying oxygen [and/or] the electrode section of the electrosurgical accessory is too close to the distal end of the endoscope.”

To mitigate this risk, Olympus reminds clinicians to heed the warnings found in the device operations manuals, notably these three:

- Do not perform high-frequency cauterization while supplying oxygen.
- Confirm that the electrode section of the electrosurgical device used with the endoscope is at a safe distance from the distal end of the endoscope.
- Use the Olympus bronchoscopes with compatible high-frequency therapy equipment only as described in the operations manual.

The letter also asks facilities that have purchased any of the affected bronchoscopes to ensure all personnel are “completely knowledgeable and thoroughly aware” of the warnings stated in the operations manual.

Olympus explains

“Olympus Corporation initiated this Field Corrective Action (FCA) to address complaints of endobronchial combustion occurring when high-frequency-compatible bronchoscopes are used during therapeutic procedures in combination with high-frequency therapy equipment,” a spokeswoman for Olympus said in an interview.

“This corrective action was taken following a thorough assessment of adverse event complaints involving serious patient injury; Olympus takes these complaints very seriously. Patient safety is our top priority,” the spokeswoman said.

The products are not being removed, and no

labeling changes are being made at this time, she said.

The bottom line for clinicians: “Users can continue to use Olympus bronchoscopes according to the instructions provided in the operation manual and the customer letter,” the Olympus spokeswoman said. “This is not a removal action. There are no changes to the existing operation manual regarding compatibility of bronchoscopes with high-frequency therapy equipment,” she said.

“In terms of actions going forward, in addition to the communication provided through this Field Corrective Action, which is intended to remind users of recommendations on oxygen use and clarify the appropriate distance while using high-frequency therapy equipment, the root cause and potential contributing factors are currently under investigation through a formal CAPA [Corrective Action Preventative Action] process. Olympus will take any appropriate enhancement action based on investigation results,” according to the Olympus spokeswoman.

In 2016, this news organization reported that Olympus made medical headlines by recalling its TJF-Q180V duodenoscope in the wake of Congressional investigations after the product was linked to spreading bacterial infections because of design flaws.

United States customers can contact Olympus by phone at 1-800-848-9024 (option 1) with questions about the recall, and health care professionals and consumers may report adverse reactions or quality problems associated with the devices to MedWatch: The FDA Safety Information and Adverse Event Reporting Program via an online form, regular mail, or fax. ■

More evidence suggests that ‘long flu’ is a thing

BY DAMIAN MCNAMARA

More evidence points to “long flu” being a real phenomenon, with a large study showing symptoms persist 4 weeks or more after some are hospitalized for the flu.

Researchers compared long flu to long COVID-19 and found long flu happened less often and was less severe overall. This difference could be because the flu mostly affects the lungs whereas COVID can affect any number of organ systems.

Both long flu and long COVID were linked to a greater burden of health loss, compared to either initial infection.

“I think COVID and long COVID made us realize infections have long-term consequences, and often the toll of those long-term consequences is much larger than the toll of acute

disease,” said Ziyad Al-Aly, MD, senior author of the study and chief of research and development at the VA St. Louis Health Care System.

“I know, having studied long COVID for the past 4 years, I should not be surprised. But I am in awe of what these infections can do to the long-term health of affected individuals,” said Dr. Al-Aly, who is also a clinical epidemiologist at Washington University in St. Louis.

Dr. Al-Aly and colleagues Yan Xie, PhD, and Taeyoung Choi, MS, analyzed US Department of Veterans Affairs medical records. They compared 81,280 people hospitalized with COVID to 10,985 people hospitalized with the flu before the COVID pandemic. They checked up to 18 months after initial infections to see who developed long flu or long COVID.

The study was published online in *The Lancet Infectious Diseases* (2023 Dec 14. doi: 10.1016/S1473-3099[23]00684-9).

It’s an interesting study, said Aaron E. Glatt, MD, chairman of the Department of Medicine and a hospital epidemiologist at Mount Sinai South Nassau in Oceanside, New York, who was not part of the research. “There is a concern with many viruses that you can have long-term consequences,” said Dr. Glatt, who is also a fellow of the Infectious Diseases Society of America. He said the possibility of long-term symptoms with the flu is not new, “but it’s nice to have more data.”

People hospitalized with COVID had a 50% higher risk of death during the study than those hospitalized with the flu. Put another way,

for every 100 people admitted to the hospital with COVID, 8 more died than those hospitalized with the flu over the following 18 months. Hospital admissions and intensive care unit admissions were also higher in the long COVID group — 20 more and 9 more people, respectively, for every 100 COVID hospital admissions.

More research is needed, Dr. Glatt said. A prospective study of antiviral treatments, for example, would be useful, he said. Dr. Al-Aly and colleagues would like to do more studies. “We need to more deeply understand how and why acute infections cause long-term illness,” he said. He wants to investigate ways to prevent and treat the long-term effects. “Much remains to be done, and we are committed to doing our best to develop those answers.” ■

Monitoring tech for pulmonary disorders moving beyond wearables

BY RICHARD MARK KIRKNER

The smartphone and smartwatch have spun off multiple apps and platforms for remotely monitoring a host of diseases, including pulmonary diseases and sleep disorders, but, like any emergent technology, pitfalls come with the potential.

In recent months, researchers have reported on an artificial intelligence (AI)-aided home stethoscope to monitor asthma



Dr. Louis

exacerbations and an ingestible electronic capsule, which has shown some facility for continuous, remote monitoring of sleep apnea and opioid-induced respiratory depression. “Smartphones and wearable technology in health care are here to stay,” said Mariam Louis, MD, FCCP, pulmonologist and sleep medicine physician at the University of Florida Health and Chair of the Non-respiratory Sleep Section of the Sleep Medicine Network with the American College of Chest Physicians.

“It is an exciting field, as it encourages patients to be actively involved in their medical care and can potentially offer more real-time feedback regarding the patient’s medical conditions,” she said. “There are currently many apps being used to monitor sleep and other diseases. However, the technology is still rudimentary, and more research is needed to see if these apps are accurate and dependable.”

Trackers overestimate sleep

Recent studies have reported on the accuracy of 18 wearable sleep-tracker devices, finding they overestimated sleep duration by 19 minutes on average (*Sleep*. 2023 Nov 8. doi: 10.1093/sleep/zsad288). Researchers in the United States also reported on the first human trial of an ingestible pill for monitoring sleep apnea that sends data to a receiving device up to 6 feet away (*Device*. 2023 Nov 17. doi: 10.1016/j.device.2023.100125), and a group in Poland reported an AI-aided home stethoscope provided reliable

information on asthma exacerbations in 149 patients (*Ann Fam Med*. 2023;21:517-25).

All of these technologies aim to overcome challenges with traditional devices, such as polysomnography (PSG) for evaluating sleep. Jaques Reifman, PhD, a senior research scientist at the US Army Medical Research and Development Command in Fort Detrick, Maryland, led the study of 18 wearable sleep trackers. “Both polysomnography and sleep-tracking devices in a sense are attempting to reach the same goal: They’re trying to estimate certain sleep parameters,” Dr. Reifman said. “But they use very different signals,” he added, noting PSG uses electroencephalography (EEG) to measure electrical signals in the skull whereas most sleep trackers used an accelerometer to measure body movement. “As your wrist moves around, it determines if you are moving or not,” Dr. Reifman said. “Each of them have their pluses and minuses,” he added. PSG, while it’s considered the gold standard for measuring sleep, isn’t a consumer product. “It generally requires a very sophisticated data acquisition system; they are laden with motion artifacts and you have to have software to remove them before you analyze the data,” Dr. Reifman said. “They generally require an expert to interpret the results, although there are a few AI-based algorithms that you can provide the EEG signals to and it does score those stages for you”

Sleep trackers, on the other hand, are consumer products. “They can be used outside the lab, and you can use them to record for long periods of time, which is not really possible with PSG,” Dr. Reifman said. “They are low cost, they are easy to use, small size, and folks have developed algorithms that can directly tell the consumer you slept 7 hours last night. In that sense, they’re comfortable to use as opposed to using an almost-like shower cap with the EEG and face sensors as part of the PSG montage.”

However, what sleep trackers offer in convenience, they lack in accuracy. “There are things they just cannot do based on the limitations of the signals they use,” Dr. Reifman said.

The study was a meta-analysis of 14 different studies that evaluated 18 different sleep-tracking devices in 364 patients. The meta-analysis

found wide variability in accuracy between devices; for example, a 75-minute overestimation of sleep with one device and a 1-minute overestimation with another. And different studies reported variations with the same tracker or different models of a tracker. The Fitbit Charge 2, for example, was found to underestimate sleep by 12 minutes in one study and overestimate sleep by 9 minutes in another, while the Fitbit HR Charge was found to overestimate sleep by 52 minutes in a third study.



Dr. Reifman

The meta-analysis found while sleep trackers have high sensitivity (>90%), they had a relatively low specificity (<50%), Dr. Reifman noted. “Because they are mainly based on the acceleration of your wrist, if you are laying down in bed and motionless after a few minutes the device is going to think you’re asleep when in reality you’re just motionless, daydreaming or trying to go to sleep but not sleeping, so the specificity to sleep is not high,” he said.

The devices have obstacles to overcome before they’re more widely used, Dr. Louis said. “All of these technologies are proprietary,” she said. “As such, little is known about the algorithms used to come up with the diagnosis or other conclusions. In addition, the majority of the data cannot be analyzed independently by the providers, limiting some of the usage of these devices for now.”

Ingestible capsule tracking

To overcome some of those challenges, researchers from the Massachusetts Institute of Technology (MIT) and West Virginia University have worked with Celero Systems to develop a pill-sized capsule which collects vitals data from inside the gastrointestinal tract. The first-in-human study of 10 patients reported the data captured by the pill aligned with that gathered with standard sleep metrics and that it could detect sleep apnea episodes. The study described the vitals-monitoring (VM) pill as a wireless device with a custom configuration of four off-the-shelf integrated circuits

— a microcontroller, accelerometer, memory component, and radio signal — and electronic sensors for ballistic measurements from within the GI tract. The accelerometer measures movement of the abdomen during breathing.

In the VM pill study, 3 of the 10 human volunteers had a diagnosis of either central or obstructive sleep apnea and wore a continuous positive airway pressure device during the study. The patients also had PSG. The study found that the heart rate accuracy of the VM pill was within 2.5 beats per minute of the PSG measure. The study found no significant difference in the ability of the VM pill to accurately measure respiratory rate with or without CPAP.

Since study completion, the device has been evaluated in another 10 patients, Ben Pless, CEO of Celero Systems, the company developing the VM pill and a coauthor of the study, said in an interview. All patients passed the capsule without any adverse events, he said.

The capsule carries the advantages of an implantable device without the surgery, Mr. Pless said. “In addition to the product being inside body, it is very good at measuring core temperature, and of course, there are diurnal variations in core temperature,” he said. “Even though this was not in the paper, we found the combination of monitoring respiration and core temperature is a very powerful way to do sleep staging in a completely unobtrusive and discreet way.”

The first study evaluated the overnight use of the VM pill, but future studies will evaluate longer duration of the device, first up to a week and then extending out to a month, with the goal of collecting data through the entire duration, Mr. Pless said.

“If you want to do ongoing monitoring for events that may have a low incidence, for example COPD exacerbations or some asthma which does not occur every day and you want to do long-term monitoring, an ingestible format where you ultimately take one capsule and you’re monitored for a month in a completely unobtrusive way would be a great way to do patient monitoring,” he said. This platform could also collect multnight data for sleep studies, he added.

“While this is an exciting

WEARABLES continued on following page

Noninvasive AI-driven tool speeds IPF diagnosis

BY WALTER ALEXANDER

When clinicians suspect lung fibrosis and its most devastating form, idiopathic pulmonary fibrosis (IPF), a noninvasive artificial intelligence (AI)-driven digital diagnostic tool may identify subtype classifications facilitating treatment at earlier disease stages. In January, the tool, Fibresolve, developed by digital biomarker company IMVARIA, received the first US Food and Drug Administration (FDA) marketing authorization of a Breakthrough Designated AI diagnostic tool. The American Medical Association also adopted relevant CPT (Current Procedural Terminology) billing codes, according to a press release.

Diagnosis and treatment of inflammation and fibrosis driving IPF are often delayed, Joshua Reicher, MD, CEO of IMVARIA and adjunct clinical professor at Stanford University said. “There are multiple challenges with this condition. Part of the delay is lack of access to local experts. Another is vague presenting symptoms, which can overlap with other conditions. The published median average delay in diagnosis is about 2.2 years, but it’s often longer.” Conventional diagnosis is “fairly straightforward,” Dr. Reicher said, for determining some form of lung fibrosis. “The critical element is to

find out what type of lung fibrosis and begin therapy. The focus with Fibresolve is on improving noninvasive sensitivity, especially for the cases that are indeterminate and challenging,” he said.

Will adjunctive diagnostic use of Fibresolve obviate the need for invasive confirmatory tests? Dr. Reicher was cautious. “It puts complementary information in the hands of the physician. It’s really up to clinicians to decide if they have sufficient information to avoid biopsy.” The uniqueness of Fibresolve, Dr. Reicher said, is it is widely accessible and does not require hyper-specialized providers. “You can use it at any center [with] standard CT scans.”

Fibresolve also conducts its software analysis centrally. “Part of our goal is to reduce the burden on clinicians, and we try to offload as much of the technical work from them as we can.” Clinicians send images to IMVARIA, and a report is generated with outputs identifying the specific classification. Dr. Reicher said Fibresolve’s deep learning algorithm was trained on thousands of cases. “We’re very confident in the results it puts out,” he said. “This is the first FDA-authorized diagnostic tool of any type in lung fibrosis. We think this supports doctors and patients in areas where there’s a high unmet need,” he said. ■

WEARABLES *continued from previous page*

technology, there is much more to diagnosing sleep apnea than just heart rate and breathing,” Dr. Louis said. “During a sleep study, we look at oxygen levels, snoring, and many other variables.”



Mr. Pless

AI-aided stethoscope

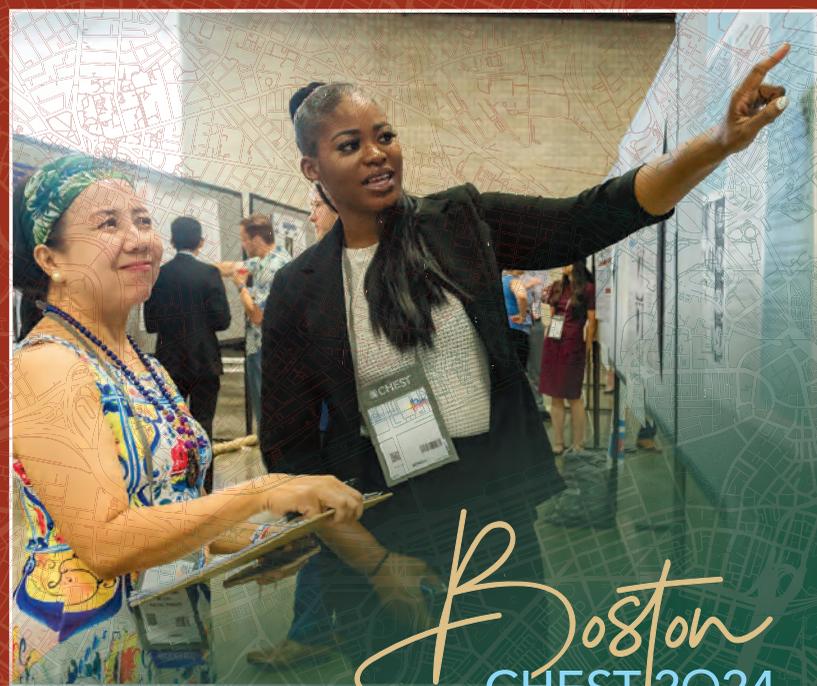
The AI-aided stethoscope demonstrated an ability to collect reliable information on asthma exacerbations, the study in Poland

found. The study enrolled patients of various ages with asthma, using the AI-aided stethoscope to monitor asthma-related physiologic parameters at home for 6 months. The stethoscope recorded auscultatory sounds from standard chest point and sent them to

an application in which an AI module analyzed the recordings. Researchers trained the module using 10,000 respiratory sound recordings.

The study showed parameters — wheezes, rhonchi, coarse and fine crackles, heart rate, respiratory rate, and inspiration-to-expiration duration ratio — measured with the AI-aided stethoscope can detect asthma exacerbations without obtaining peak expiratory flow measurements. It also showed a potential to make asthma diagnosis more straightforward in younger children.

“As we learn more and refine these technologies, we will be able to offer more patient centered, precise medicine to our patients, tailored specifically to their needs,” Dr. Louis said. “AI will play a part in the future.” Dr. Louis and Dr. Reifman have no relevant relationships to disclose. Mr. Pless is CEO of Celero Systems, a privately held company in Lincoln, Massachusetts. ■



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Systemic bias in AI models may undermine diagnostic accuracy

BY HEIDI SPLETE

Systematically biased artificial intelligence (AI) models did not improve clinicians' accuracy in diagnosing hospitalized patients, based on data from 450 clinicians.

"AI could support clinicians in their diagnostic decisions of hospitalized patients but could also be biased and cause potential harm," said Sarah Jabbour, MSE, a PhD candidate in computer science and engineering at the University of Michigan, Ann Arbor. "Regulatory guidance has suggested the use of AI explanations could mitigate these harms, but the effectiveness of using AI explanations has not been established," she said.

To examine whether AI explanations can be effective in mitigating the potential harms of systemic bias in AI models, Ms. Jabbour and colleagues conducted a randomized clinical vignette survey study. The survey was administered between April 2022 and January 2023 across 13 states, and included hospitalist physicians, nurse practitioners, and physician assistants. The results were published in *JAMA* (2023 Dec 19. doi: 10.1001/jama.2023.22295). Participants were randomized to AI predictions with AI explanations (226 clinicians) or without AI explanations (231 clinicians). The

primary outcome was diagnostic accuracy for pneumonia, heart failure (HF), and chronic obstructive pulmonary disease (COPD), defined as the number of correct diagnoses over the total number of assessments, the researchers wrote. Clinicians viewed nine clinical vignettes of patients hospitalized with acute respiratory failure, including their presenting symptoms, physical examination, laboratory results, and chest radiographs. Clinicians viewed two vignettes with no AI model input to establish baseline diagnostic accuracy. They made three assessments in each vignette, one for each diagnosis. The order of the vignettes was two without AI predictions (to establish baseline diagnostic accuracy), six with AI predictions, and one with a clinical consultation by a hypothetical colleague. The vignettes included standard and systematically biased AI models.

The baseline diagnostic accuracy was 73% for the diagnoses of pneumonia, HF, and COPD. Clinicians' accuracy increased by 2.9% when they viewed a standard diagnostic AI model without explanations and by 4.4% when they viewed models with AI explanations. However, clinicians' accuracy decreased by 11.3% after viewing systematically biased AI model predictions without explanations compared with

baseline, and biased AI model predictions with explanations decreased accuracy by 9.1%. The decrease in accuracy with systematically biased AI predictions without explanations was mainly attributable to a decrease in the participants' diagnostic specificity, the researchers noted, but the addition of explanations did little to improve it.

Potentially useful but still imperfect

The findings were limited by several factors including the use of a web-based survey, younger-than-average study population, and the focus on the clinicians making treatment decisions vs other clinicians who might have a better understanding of the AI explanations. "In our study, explanations were presented in a way that were considered to be obvious, where the AI model was completely focused on areas of the chest x-rays unrelated to the clinical condition," Ms. Jabbour said. "We hypothesized that if presented with such explanations, the participants in our study would notice the model was behaving incorrectly and not rely on its predictions. This was surprisingly not the case, and the explanations when presented alongside biased AI predictions had seemingly no effect in mitigating clinicians' overreliance on biased AI," she said.

"AI is being developed at an extraordinary rate, and our study shows it has the potential to improve clinical decision-making. At the same time, it could harm clinical decision-making when biased," Ms. Jabbour said. "We must be thoughtful about how to integrate AI into clinical workflows, with the goal of improving clinical care while not introducing systematic errors or harming patients."

Don't overestimate AI

"With the increasing use of AI and machine learning, there has been an interest in exploring how they can be utilized to improve clinical outcomes," said Suman Pal, MD, assistant professor in the division of hospital medicine at the University of New Mexico, Albuquerque. "However, concerns remain regarding the possible harms and ways to mitigate them," said Dr. Pal, who was not involved in the study. "The findings of this study caution against overreliance on AI in clinical decision-making, especially due the risk of exacerbating existing health disparities due to systemic inequities in existing literature," Dr. Pal said.

The study was funded by the National Heart, Lung, and Blood Institute. The researchers had no financial conflicts to disclose. Dr. Pal had no financial conflicts to disclose. ■

SLEEP MEDICINE

Irregular sleep patterns and OSA prompt increased odds of hypertension

BY HEIDI SPLETE

Severe sleep irregularity often occurs with obstructive sleep apnea (OSA), and this combination approximately doubled the odds of hypertension in middle-aged individuals.

OSA has demonstrated an association with hypertension, but data on the impact of sleep irregularity on this relationship are lacking. In the study, researchers used the sleep regularity index (SRI) to determine sleep patterns using a scale of 0-100 (with higher numbers indicating greater regularity) to assess relationships between OSA, sleep patterns, and hypertension in 602 adults with a mean age of 57 years. The study's goal was an assessment of the associations between sleep regularity, OSA, and hypertension in a community sample of adults with

normal circadian patterns.

The odds of OSA were significantly greater for individuals with mildly irregular or severely irregular sleep than for regular sleepers (odds ratios, 1.97 and 2.06, respectively). Individuals with OSA and severely irregular sleep had the highest odds of hypertension compared with individuals with no OSA and regular sleep (OR [OR], 2.34). However, participants with OSA and regular sleep or mildly irregular sleep had no significant increase in hypertension risk. "Irregular sleep may be an important marker of OSA-related sleep disruption and may be an important modifiable health target," the researchers wrote.

Study limitations included that the cross-sectional design prevented conclusions of causality, and the SRI is a nonspecific measure that may

capture a range of phenotypes with one score. Other study limitations included the small sample sizes of sleep regularity groups and the use of actigraphy to collect sleep times.

The study was led by Kelly Sansom, a PhD candidate at the Centre for Sleep Science at the University of Western Australia, Albany. The study was published online in the journal *Sleep* (2024 Jan 5. doi: 10.1093/sleep/zsae001).

The study was supported by an Australian Government Research Training Program Scholarship and the Raine Study PhD Top-up Scholarship; the scholarship is supported by the NHMRC, the Centre for Sleep Science, School of Anatomy, Physiology & Human Biology of the University of Western Australia, and the Lions Eye Institute.

The researchers had no financial conflicts to disclose. ■

Circadian blood pressure shifts earlier in children with moderate to severe OSA

BY HEIDI SPLETE

The time arrived at peak blood pressure (BP) velocity (TAPV) was significantly earlier in children with moderate to severe (MS) obstructive sleep apnea (OSA) than in controls.

In this study, researchers compared 24-hour circadian BP in children with OSA and controls to examine the impact of OSA on circadian BP.

The study population included 219 children aged 5-14 years: 52 with mild OSA, 50 with MS OSA, and 117 controls. Participants underwent 24-hour BP monitoring and actigraphy; models included the times of BP peaks and TAPV.

Severe OSA leads to earlier BP shifts

Children with MS OSA had a TAPV for diastolic BP in the morning, an average of 51 minutes earlier than controls ($P < .001$). Evening

TAPV was significantly earlier in the children with MS OSA than in controls for both systolic BP (SBP) and diastolic BP (DBP) (95 min, $P < .001$ and 28 min, $P = .028$, respectively). Midday SBP and DBP velocity nadirs were significantly earlier in the children with MS OSA than in controls (57 min, $P < .001$ and 38 min, $P < .01$, respectively).

Findings may improve understanding of OSA impact

Overall, children with MS OSA reached most BP values significantly earlier than controls, and both SBP and DBP were significantly elevated in the MS OSA group compared with the control group. “The findings provide an essential puzzle piece in our understanding of the cardiovascular effects of OSA in children,” wrote the authors of an accompanying editorial.

More research is necessary

According to the authors of the accompanying editorial on the study, more research is needed to investigate the potential mechanisms of action, optimize methodology, and investigate circadian biology via actigraphy and biomarkers.

The lead author of the study was Md Tareq Ferdous Khan, MD, of the University of Cincinnati, Cincinnati, Ohio; the authors of the accompanying editorial were Kate Ching-Ching Chan, MD, and Albert Martin Li, MD, of the Chinese University of Hong Kong, China.

The study was published online in the journal *Sleep* (doi: 10.1093/sleep/zsad254) on December 13, 2023, along with the accompanying editorial (doi: 10.1093/sleep/zsad284).

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

Which therapies reduce daytime symptoms of insomnia?

BY KERRY DOOLEY YOUNG

Zolpidem and behavior therapy significantly reduce daytime symptoms of insomnia such as fatigue, functional impairments, and depressive symptoms, data suggested.

In a randomized clinical trial of more than 200 patients with chronic insomnia, behavioral therapy was associated with a 4.7-point reduction in Multidimensional Fatigue Inventory (MFI) score. Zolpidem was associated with a 5.2-point reduction in this score.

“There may be some advantage to starting with behavioral intervention,” said study author Charles Morin, PhD, Canada research chair in sleeping disorders at Laval University in Quebec City. “But by the same token, because it takes a bit more time to produce benefits, some patients quit too quickly. So, even if we want to minimize the use of medications because of potential side effects, there may be times where we need to use it.” The results were published in *JAMA Network Open* (2023 Dec 28. doi: 10.1001/jamanetworkopen.2023.49638).

‘Different treatment options’

The investigators randomly assigned 211 adults with chronic insomnia to behavioral therapy, which included sleep restriction and stimulus control procedures, or zolpidem (5-10 mg nightly) for 6 weeks. Participants who achieved insomnia remission

by that point were followed for 12 months. Participants who did not achieve remission were randomly assigned to a second-stage psychological therapy or medication therapy (zolpidem or trazodone).

The outcome measures were daytime functional outcomes such as mood disturbances, fatigue, functional impairments of insomnia, and physical and mental health. The researchers assessed these outcomes at baseline, 6 weeks, the end of second-stage therapy, and 3- and 12-month follow-up visits.

Both initial treatments were associated with significant and equivalent reductions in depressive symptoms, fatigue, and functional impairments. Mean change in the Beck Depression Inventory-II was -3.5 for patients in the behavioral therapy arm and -4.3 for patients in the zolpidem arm. Mean change in the MFI score was -4.7 among patients who received behavioral therapy and -5.2 among those who received zolpidem. Mean change in the Work and Social Adjustment Scale, which measured functional impairments, was -5.0 for the behavioral therapy arm and -5.1 for the zolpidem arm.

In addition, both treatments were associated with improvements in mental health, as measured by the Short-Form Health Survey (SF-36). Mean change in the mental health subscale of SF-36 was 3.5 points in the behavioral therapy arm and 2.5 points in the zolpidem arm.

Second-stage treatments were associated with further improvements, and these benefits were maintained throughout the 12 months of follow-up. These findings support adding a second treatment of insomnia as part of efforts to address daytime function, the authors wrote. “If the first treatment doesn’t work, we should not stop there. There are different treatment options,” Dr. Morin said.

The study was limited by the lack of a control condition and by relatively small sample sizes for each treatment group, which may reduce the statistical power to detect more significant group differences. Only patients who did not achieve insomnia remission received second-stage therapy, but those who did achieve remission can still have residual daytime impairments that are associated with future relapse.

Compliance needed

Commenting on the findings, Jocelyn Y. Cheng, MD, vice chair of the public safety committee of the American Academy of Sleep Medicine (AASM) and a researcher at the pharmaceutical firm Eisai, said the research was designed well and used established and practical assessment tools. Dr. Cheng did not participate in the study.

In 2020, AASM published a clinical practice guideline on chronic insomnia disorder that recommended cognitive-behavioral therapy (CBT). Some of the guideline’s

authors, such as Dr. Morin, conducted the present study. The current results offer reassurance about cases in which patients may prefer options other than CBT, said Dr. Cheng. Therapy and medication each appear to help reduce daytime outcomes of insomnia such as anxiety, she said. CBT “does require compliance and somebody willing to participate and also somebody able to participate,” Dr. Cheng said. “So, in that case, medication might be the better way to go first line.”

This study was funded by the National Institute of Mental Health. Dr. Morin reported receiving grants and personal fees from Eisai and Idorsia, grants from Lallemand Health, and royalties from Mapi Research Trust outside the submitted work. A coauthor reported receiving grants from Janssen Pharmaceuticals, Axsome Pharmaceuticals, Attune, Harmony, Neurocrine Biosciences, Reveal Biosensors, the Ray and Dagmar Dolby Family Fund, and the National Institutes of Health; personal fees from Axsome Therapeutics, Big Health, Eisai, Evecxia, Harmony Biosciences, Idorsia, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Millenium Pharmaceuticals, Merck, Neurocrine Biosciences, Neurawell, Pernix, Otsuka Pharmaceuticals, Sage, and Takeda; and stock options from Big Health and Neurawell outside the submitted work. Dr. Cheng reported no relevant financial relationships other than her employment by Eisai. ■

Children and preteen use of melatonin increased

BY DAMIAN MCNAMARA, MA

More children and preteens are taking melatonin to help them sleep, a new study found, while experts cautioned parents may be unaware of some risks, particularly with long-term use. The investigators noted some melatonin supplements tested in a separate study contained two to three times the amount of melatonin on the label, and one supplement contained none at all.

A matter of timing?

While not completely advising against the sleep supplement, the study researchers pointed out short-term use is likely safer. “We are not saying melatonin is necessarily harmful to children. But much more research needs to be done before we can state with confidence it is safe for kids to be taking long term,” lead study author Lauren Hartstein, PhD, a postdoctoral fellow in the Sleep and Development Lab at the University of Colorado in Boulder, said in a news release.

“If, after weighing potential risks and benefits, melatonin is recommended as the appropriate treatment, [a sleep medicine specialist] can recommend a dose and timing to treat the sleep issue,” said Raj Bhui, MD, a sleep medicine specialist and American Academy of Sleep



TETRA IMAGES/DIGITALVISION/GETTY IMAGES

Medicine spokesperson, who was not involved in the study.

An increasing trend

From 2017 to 2018, only about 1.3% of parents reported their children used melatonin in national data (*MMWR Morb Mortal Wkly Rep.* 2020 Oct 30. doi: 10.15585/mmwr.mm6943a1) looking at supplement use in children and teenagers. In fact, usage more than doubled in this younger population from 2017 to 2020, another study revealed (*JAMA.* 2022 Jul 27. doi: 10.1001/jama.2022.11506). “All of a sudden, in 2022, we started noticing a lot of parents telling us their healthy child was regularly taking melatonin,” Dr. Hartstein said.

She and colleagues surveyed the parents of 993 children, aged 1 to less than 14, from January to April 2023. They found about 20% of these school-aged children and preteens took melatonin as a sleep aid. The findings, published in the journal *JAMA Pediatrics* (2023 Nov 13. doi: 10.1001/jamapediatrics.2023.4749), also suggest some parents routinely give their preschool children melatonin.

They found nearly 6% of preschoolers aged 1-4, 18.5% of children aged 5-9, and 19.4% of kids aged 10-13 had taken melatonin in the previous month.

The researchers also discovered many took melatonin for longer

than a few nights. Preschool children took the supplement for a median of 1 year, grade school children for a median 18 months, and preteens for 21 months.

What's in your supplement?

In a different study published April 25 (*JAMA.* 2023. doi: 10.1001/jama.2023.2296), researchers looked at 25 melatonin gummy products and found that 22 of them contained different amounts of melatonin than listed on the label. In fact, one called Sleep Plus Immune contained more than three times the amount, and with a supplement called Sleep Support, researchers could not detect any melatonin.

There is a general misconception that supplements are natural and therefore safe, Dr. Bhui said. “Multiple investigations of commercially available supplements have shown we cannot assume what is on the label is in the pill or what is in the pill is disclosed on the label. Formal laboratory testing has revealed some supplements to be adulterated with unapproved pharmaceutical ingredients, contaminated with microbes, or even tainted with toxins like arsenic, lead, and mercury.” Choosing a product with the “USP Verified Mark” may give parents some comfort regarding melatonin content and consistency with labeling, Dr. Bhui said. ■

Transcranial electrical stimulation effective for insomnia

BY PAULINE ANDERSON

Transcranial alternating current stimulation (tACS), a noninvasive technique that uses low-intensity electrical currents to modulate brain activity, is an effective intervention for treating chronic insomnia, especially in older people, results of a relatively large study suggested.

The double-blind study included 124 adults with chronic insomnia (difficulty falling asleep or maintaining sleep and early morning awakening occurring at least three times a week over 3 or more months) and mean age about 51 years from two centers in China who were randomized to receive either tACS (active group) or sham tACS (control group). Patients underwent 20 40-minute sessions over 4 weeks. The tACS intervention involved positioning three electrodes on the scalp and applying a current of 15 mA at a frequency of 77.5 Hz, whereas the control group received no stimulation.

Primary outcome measures included total score on the Chinese version of the self-report Pittsburgh Sleep Quality Index (PSQI), sleep onset latency, total sleep time (TST), sleep efficiency,

sleep quality, and daily disturbances (such as fatigue and attention deficits). Secondary outcomes included Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Clinical Global Impression scale (including Clinical Global Impression Severity of Illness [CGI-SI], Clinical Global Impression Global Improvement [CGI-GI], and Clinical Global Impression Efficacy Index [CGI-EI]). As rates of chronic insomnia increase with age, researchers explored the influence of age on treatment benefits by dividing participants into two age groups (< 50 years and ≥ 50 years).

Among the 120 participants who completed the trial, tACS resulted in a statistically significant decrease in insomnia severity compared with the control group (estimated advantage [number of points on PSQI scale], 2.61; 95% CI, 1.47-3.75; $P < .001$). There were statistically significant estimated advantages of tACS for TST (-0.65; 95% CI, -1.06 to -0.24; $P = .002$), sleep efficiency (1.05; 95% CI, 0.48-1.62; $P < .001$), sleep quality (0.82; 95% CI, 0.29-1.34; $P = .003$), and daily disturbances (0.91; 95% CI, 0.58-1.25; $P < .001$). In addition, tACS exhibited significant effects

on CGI-SI (0.84; 95% CI, 0.38-1.30; $P < .001$), CGI-GI (0.74; 95% CI, 0.42-1.06; $P < .001$), and CGI-EI (-0.71; 95% CI, -1.02 to -0.39; $P < .001$) but not on total scores of HAMD and HAMA, possibly because of the relatively low baseline levels of depression and anxiety among study subjects, said the authors. In the older, but not younger, group, tACS treatment had a significant benefit in sleep quality, sleep efficiency, PSQI total score, CGI-SI, CGI-GI, and CGI-EI.

The follow-up period was limited to 8 weeks; longer follow-up studies are needed. Severity of chronic insomnia was limited by using the self-report PSQI, not objective measures of insomnia. The age of study subjects ranged from 22 to 65 years.

The study was conducted by Xiaolin Zhu, Beijing Huilongguan Hospital, Peking University Huilongguan Clinical Medical School, Beijing, China, and colleagues. It was published in the *Journal of Psychiatric Research* (2023 Dec 29. doi: 10.1016/j.jpsychires.2023.12.037). The study was supported by the Beijing Municipal Science and Technology Commission. The authors had no relevant conflicts of interest. ■

Biomarker checklist seeks to expedite NSCLC diagnoses

Drs. Tamer Said Ahmed and Adam Fox receive funding for quality improvement projects in biomarker testing

BY LAURA DIMASI

Senior Specialist, Public Relations and Communications, CHEST

Establishing a systematic biomarker testing program for patients with suspected non-small cell lung cancer (NSCLC) takes both time and collaboration across specialties. To standardize this process, the American College of Chest Physicians (CHEST) created two clinician checklists for use in practice.

The case-by-case checklist helps guide physicians to ensure timely and comprehensive biomarker testing for individual patients, and the programmatic/institutional checklist is for multidisciplinary teams to enable clear expectations and processes across hand-offs to aid in the testing process.

To substantiate best practices for ordering biomarker tests using

the checklists, CHEST issued quality improvement demonstration grants for implementation at two institutions. This year, Tamer Said Ahmed, MD, FCCP, pulmonary and

sleep physician at Toledo Hospital (ProMedica Health System) and Assistant Professor at the University of Toledo, and Adam Fox, MD, MS, Assistant Professor of Medicine at the Medical University of South Carolina, will begin projects to improve biomarker testing.

“Biomarker testing allows for tailored treatment plans that drastically

impact the progression of lung cancer, but every hospital system and practice is following a different procedure for testing,” Dr. Said Ahmed said. “To best serve the patient, our project

“The more streamlined we can make the biomarker testing process, the earlier we will get to an accurate diagnosis, begin treatment, and likely extend the life of a patient.”

—Tamer Said Ahmed, MD, FCCP

aims to streamline the approach to biomarker testing to bridge health care inconsistencies. Given the intense progression of some forms of lung cancer where every week matters, the more streamlined we can make the biomarker testing process, the earlier we will get to an accurate diagnosis, begin treatment, and likely extend the life of a patient.”

Discrepancies in the testing process stem from existing silos between specialties, including pathology, oncology, interventional

radiology, and more. Care is fragmented, leading to delays like repeat biopsies because a large enough sample was not taken the first time.

This is the exact problem that checklist implementation will seek to solve.

“By intent, these checklists help to provide a systematic approach to timely and comprehensive biomarker testing,” said Dr. Fox, who was also part of the team that developed the checklists. “What we need now is to implement them into clinical practice to gain metrics that can be studied, identified, and will lead to the process being widely accepted. To truly impact practice, we need to be able to provide strong evidence for interventions that work for clinicians to implement.”

To learn more and download the checklists, visit CHEST’s Thoracic Oncology Topic Collection online at chestnet.org/thoracic-oncology.

This project is supported in part by AstraZeneca, Sanofi, and Pfizer. ■

This month in the journal CHEST®

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BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

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Obesity and lung disease in the era of GLP-1 agonists

BY KIEFER MESPELT, DO,
AND KIMBERLY FABYAN, MD

Now is the time for pulmonary clinicians to become comfortable counseling patients about and treating obesity. By 2030, half of the US population will have obesity, a quarter of which will be severe (Ward et al. *NEJM*. 2019;2440-2450).

Many pulmonary diseases, including asthma, COPD, and interstitial pulmonary fibrosis (IPF) are linked to and made worse by obesity with increased exacerbations, patient-reported decreased quality of life, and resistance to therapy (Ray et al. *Am Rev Respir Dis*. 1983;501-6). Asthma is even recognized as an obesity-related comorbid condition by both the American Society Metabolic and Bariatric Surgery (ASMBS) and the American Association of Clinical Endocrinologists (AACE) when considering indications for early or more aggressive treatment of obesity (Eisenberg et al. *Obesity Surg*. 2023;3-14) (Garvey et al. *Endocr Pract*. 2016;1-203).

Obesity has multiple negative effects on pulmonary function due to the physical forces of extra weight on the lungs and inflammation related to adipose tissue (see Figure 1) (Zerah et al. *Chest*. 1993;1470-6).

Obesity-related respiratory changes include reduced lung compliance, functional residual capacity (FRC), and expiratory reserve

volume (ERV). These changes lead to peripheral atelectasis and V/Q mismatch and increased metabolic demands placed on the respiratory system (Parameswaran et al. *Can Respir J*. 2006;203-10). The increased weight supported by the thoracic cage alters the equilibrium between the chest wall and lung tissue decreasing FRC and ERV. This reduces lung compliance and increases stiffness by promoting areas of atelectasis and increased alveolar surface tension (Dixon et al. *Expert Rev Respir Med*. 2018;755-67).

Another biomechanical cost of obesity on respiratory function is the increased consumption of oxygen to sustain ventilation at rest (Koenig SM, *Am J Med Sci*. 2001;249-79). This can lead to early respiratory muscle fatigue when respiratory rate and tidal volume increase with activity. Patients with obesity are more likely to develop obstructive sleep apnea and obesity hypoventilation syndrome. The resulting alveolar hypoxemia is thought to contribute to the increase in pulmonary hypertension observed in patients with obesity (Shah et al. *Breathe*. 2023;19[1]). In addition to the biomechanical consequences of obesity, increased adipose tissue can lead to chronic, systemic inflammation that can exacerbate or unmask underlying respiratory disease. Increased leptin and downregulation of adiponectin



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have been shown to increase systemic cytokine production (Ray et al. *Am Rev Respir Dis*. 1983;501-6). This inflammatory process contributes to increased airway resistance and an altered response to corticosteroids (inhaled or systemic) in obese patients treated for bronchial hyperresponsiveness. This perhaps reflects the Th2-low phenotype seen in patients with obesity and metabolic syndrome-related asthma (Shah et al. *Breathe*. 2023;19[1]) (Kanwar et al. *Cureus*. 2022 Oct 28. doi: 10.7759/cureus.30812).

Multiple studies have demonstrated weight loss through lifestyle changes, medical therapy, and obesity surgery result in benefits for pulmonary disease (Forno et al. *PloS One*. 2019;14[4]) (Ardila-Gatas et al. *Surg Endosc*. 2019;1952-8). Benefits include decreased exacerbation frequency, improved functional testing, and improved patient-reported quality of life. Pulmonary clinicians should be empowered to address

obesity as a comorbid condition and treat with appropriate referrals for obesity surgery and initiation of medications when indicated.

GLP-1 receptor agonists

In the past year, glucagon-like peptide receptor agonists (GLP-1RAs) have garnered attention in the medical literature and popular news outlets. GLP-1RAs, including semaglutide, liraglutide, and tirzepatide, are currently FDA approved for the treatment of obesity in patients with a body mass index (BMI) greater than or equal to 30 or a BMI greater than or equal to 27 in the setting of an obesity-related comorbidity, including asthma.

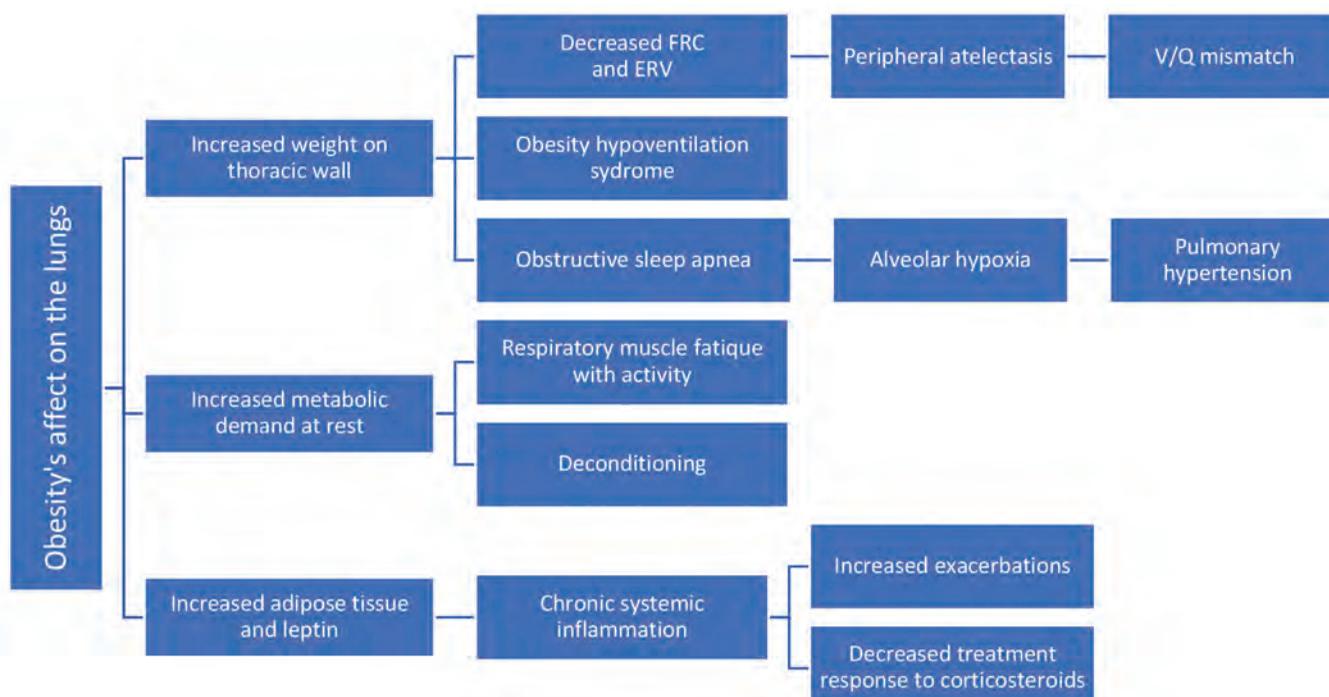
This class of medications acts by increasing the physiologic insulin response to a glucose load, delaying gastric emptying, and reducing production of glucagon. In a phase III study, semaglutide resulted in greater than 15% weight reduction from baseline (Wadden et al. *JAMA*. 2021;1403-13). In clinical trials, these medications have not only resulted in significant, sustained weight loss but also improved lipid profiles, decreased A1c, and reduced major cardiovascular events (Lincoff et al. *N Engl J Med*. 2023;389[23]:2221-32) (Verma et al. *Circulation*. 2018;138[25]:2884-94).

GLP-1RAs and lung disease

GLP-1RAs are associated with ranges of weight loss that lead to symptom improvement. Beyond the anticipated benefits for pulmonary health, there is interest in whether GLP-1RAs may improve specific lung diseases. GLP-1 receptors are found throughout the body (eg, gastrointestinal tract, kidneys, and heart) with the largest proportion located in the lungs (Wu AY and Peebles RS. *Expert Rev Clin Immunol*. 2021;1053-7). In

Figure 1: Multiple ways that obesity impacts pulmonary function.

FRC: functional residual capacity; ERV: expiratory reserve volume; V/Q: ventilation/perfusion



CHEST

AGONISTS continued on following page



APP INTERSECTION

The emergence of postgraduate training programs for APPs in pulmonary and critical care

BY VINCENT DERIENZO AND SARAH TOMASHEFSKI

Postgraduate training for advanced practice providers (APPs) has existed in one form or another since the genesis of the allied professions. They are typically referred to as residencies, fellowships, postgraduate programs, and transition-to-practice.

The desire and necessity for these programs has increased in the past decade with workforce changes; namely the increasing number of nurse practitioners (NPs) graduating with fewer years of experience at the bedside compared with previous eras, a similar decrease in patient contact hours for graduating PAs, the transition of physician colleagues from employers to employees and the subsequent change in priorities in training new graduate APPs, and resident work hour restrictions necessitating more APPs to staff inpatient units and work in various specialties.

The goal of these programs is to provide postgraduate training to physician assistants/associates (PAs) and NPs across myriad medical specialties to both newly graduated APPs and those looking to transition specialties. Current programs exist in family medicine, emergency medicine, urgent care, critical care medicine, pulmonary medicine, oncology, surgery, and various surgical subspecialties, to name a few. Program length is highly variable, though most programs advertise as lasting around 12 months, with varying ratios of clinical and didactic education. Postgraduate APP programs are largely advertised as salaried, benefitted positions, though usually at a rate below that of a so-called “direct hire” due to the protected learning time associated with the postgraduate training year.

Accreditation for these programs is still disjointed, although unifying efforts have been made as of late, and is currently available through the Advanced Practice Provider Fellowship Accreditation, Association of Postgraduate Physician Assistant Programs, ARC-PA, the Accreditation Commission for Education in Nursing, and the Consortium for Advanced Practice Providers. Other organizations, such as

the Association of Post Graduate APRN Programs, host regular conferences to discuss the formulation of postgraduate APP education curricula and program development.

While accreditation offers guidance for fledgling programs, many utilize the standards published by the American College of Graduate Medical Education to ensure that appropriate clinical milestones are being met and that a common language among APPs and physicians who are involved in the evaluation of the postgraduate APP trainee is being used. Programs also seek to utilize other well-established curricula and certification programs published by various national and international organizations. A key distinction from physician postgraduate training is that there is currently no fiscal or legislative support for postgraduate APP programs; these issues have been cited as reasons for the limited scope and number of programs.

When starting APP Fellowship programs, it is important to consider why this would be beneficial to a specific division and health care organization. Usually, fellowship programs develop out of a need to train and retain APPs. It is no secret that turnover and retention of skilled APPs is a nationwide problem associated with significant costs to organizations. The ability to retain fellowship-trained APPs will result in cost savings due to the reduction in onboarding time and orientation costs, as these APP fellows finish their programs ready to be fully productive team members.

Additional considerations for the development of an APP fellowship include improving access to care and increasing the quality of the care provided. Fellowship programs encourage a smoother transition to practice by offering more support through education, closer evaluation, and frequent feedback, which improves competence and confidence of these providers. A supported APP is more likely to practice to the fullest extent of their license and have improved personal and professional satisfaction, leading to employee



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retention and better patient care.

When developing a budget for these types of programs, it is important to include the full-time equivalent (FTE) for the fellow, benefits, onboarding/licensure, simulations, and fellowship faculty costs.

Faculty compensation varies by institution but can include salary support, FTE reduction, and nonclinical appointments. Tracking metrics such as fellow billing, length of stay, and access to care during the fellowship year are helpful to highlight the benefit of these programs to the organization.

Initiating a program like those described may seem like a Herculean feat, but motivated individuals have been able to accomplish similar goals in both adequately and poorly resourced areas. For those aspiring to start a postgraduate APP program at their institution, these authors suggest the following approach.

First, identify your institution's need for such a program. Next, define your curriculum, evaluation process, and expectations. Then, create buy-in from stakeholders, including administrative and clinical personnel. Finally, focus on recruitment. Seeking accreditation may be challenging for new programs, but identifying the accreditation standard you plan to pursue early will pay dividends when the time comes for the program to apply. Those starting down this path should realistically expect an 18- to 24-month period between their first efforts and the start of the first class.

“APP Intersection” is a new quarterly column focusing on areas of interest for the entire chest medicine health care team. ■

AGONISTS *continued from previous page*

addition to their known effect on insulin response, GLP-1RAs are hypothesized to reduce proinflammatory cytokine signaling and alter surfactant production potentially improving both airway resistance and lung compliance (Kanwar et al. *Cureus*. 2022 Oct 28. doi: 10.7759/cureus.30812). Animal models suggest an antifibrotic effect with delay in the endothelial-mesenchymal transition. If further substantiated, this could impact both acute and chronic lung injury.

Early clinical studies of GLP-1RAs in patients with respiratory diseases have demonstrated improved symptoms and pulmonary function (Kanwar et al. *Cureus*. 2022 Oct 28. doi: 10.7759/cureus.30812). Even modest weight loss (2.5 kg in a year) with GLP-1RAs leads to improved symptoms and a reduction in asthma exacerbations. Other asthma literature shows GLP-1RAs improve symptoms and reduce exacerbations independent of changes in weight, supporting the hypothesis that the benefit of GLP-1RAs may be

more than biomechanical improvement from weight loss alone (Foer et al. *Am J Respir Crit Care Med*. 2021;831-40).

GLP-1RAs reduce the proinflammatory cytokine signaling in both TH2-high and TH2-low asthma phenotypes and alter surfactant production, airway resistance, and perhaps even pulmonary vascular resistance (Altintas Dogan et al. *Int J Chron Obstruct Pulmon Dis*. 2022;405-14). GATA-3 is an ongoing clinical trial examining whether GLP-1RAs reduce

airway inflammation via direct effects on of the respiratory tract (NCT05254314).

Drugs developed to treat one condition are often found to impact others during validation studies or postmarketing observation. Some examples are aspirin, sildenafil, minoxidil, hydroxychloroquine, and SGLT-2 inhibitors. Will GLP-1RAs be the latest medication to affect a broad array of physiologic process and end up improving not just metabolic but also lung health? ■

NETWORKS

Rituximab for ILD and need for high-quality data in interventional pulmonology

DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK Interstitial Lung Disease Section

Updates in Evidence for Rituximab in Interstitial Lung Disease

Interstitial lung diseases (ILD) are a heterogeneous group of fibro-inflammatory disorders that can be progressive despite available therapies. The cornerstones of pharmacologic therapy include immunosuppression and antifibrotics.

Data on the use of rituximab, a B-lymphocyte-depleting monoclonal antibody, often utilized as rescue therapy in progressive and severe ILD, was limited until recently. The RECITAL trial reported the first randomized controlled trial investigating rituximab in severe

or progressive autoimmune ILD. Though rituximab was not superior to cyclophosphamide, both agents improved forced vital capacity (FVC) at 24 weeks and respiratory-related quality of life. Rituximab was associated with less adverse events and lower corticosteroid exposure (Maher et al. *Lancet Respir Med.* 2023;11:45-54). In the DESIRES trial, patients with systemic sclerosis-associated ILD treated with rituximab had preservation of FVC at 24 and 48 weeks compared to placebo (Ebata et al. *Lancet Rheumatol.* 2021;3:e489-97; *Lancet Rheumatol.* 2022;4:e546-55). The EVER-ILD investigators compared mycophenolate mofetil (MMF) alone vs addition of rituximab in patients with autoimmune and idiopathic nonspecific interstitial pneumonia (NSIP). Combination therapy was superior to MMF alone in improving FVC and progression-free survival. Combination regimen was well tolerated though nonserious viral and

bacterial infections were more frequent (Mankikian et al. *Eur Respir J.* 2023;61[6]:2202071).

These findings, primarily in autoimmune ILD, are promising and provide clinicians with evidence for utilizing rituximab in patients with severe and progressive ILD. Nonetheless, they highlight the need for additional research and standardized guidance regarding the target population who stands to most benefit from rituximab.

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Section Chair

explosion of technological advancements in the field of interventional pulmonary (IP) has afforded patients the opportunity to undergo



Dr. Duke

novel, minimally invasive diagnostic and therapeutic procedures. However, these unprecedented technological advances have often been introduced without the support of high-quality research on safety and efficacy, and without evaluating their impact on meaningful patient outcomes. Encouraging and participating in high-quality IP research should remain a top priority for those practicing in the field.

Structured research networks, such as the UK Pleural Society and more recently the Interventional Pulmonary Outcome Group,

NETWORKS *continued on following page*



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Learn More and Apply

New age of CHEST philanthropy to focus on education, impact, community

BY MEGGIE CRAMER

Director of Philanthropy & Advancement,
CHEST

In a time echoing with the constant call for transformation, CHEST delved deep into its essence, questioning its potential for impact. This pivotal introspection led to a crucial inquiry...

Are we harnessing every opportunity to make a difference?

It's a familiar question, yet its resonance urged a deeper evaluation.



Meggie Cramer

Philanthropy has long been entwined in CHEST's identity. Commemorating 25 years of the CHEST Foundation at CHEST 2022 spotlighted our history of generosity. Stories

of transformative community initiatives and pivotal clinical research grants narrated a tale of empowered change and fostering healthier communities worldwide.

However, amid these achievements, more pressing inquiries surfaced:

- What unique role can CHEST play?
- Where do unmet needs persist?
- Which causes deeply resonate within our community?

CHEST's leadership and dedicated staff embarked on a comprehensive review, scrutinizing past triumphs, donor commitments, and the evolving aspirations of our members. Themes of social responsibility, professional diversity, community impact, and expanded partnerships emerged as pivotal points. This extensive process, spanning nearly

a year, resembled a reflective pause amid the rapid cadence of change.

Achieving these aspirations meant reimagining our approach, thereby streamlining efforts for maximal impact by...

- Integrating philanthropy as an integral facet of our mission, and amplifying the culture of giving within CHEST
- Consolidating philanthropic initiatives under CHEST to maximize resources for direct, substantial impact
- Defining clear avenues for giving that deeply resonate with our members

With endorsement from the Board of Regents, the CHEST Foundation seamlessly merged into CHEST, inaugurating a new chapter in our philanthropic endeavors.

Central to this transformative shift is the crystallization of our giving strategy, fortified by four pillars: Clinical Research, Community Impact, Support to the Profession, and Dedication to Education. These pillars encapsulate our commitment to nurturing clinicians, supporting trainees, and enhancing patient care.

Clinical Research emerges as the cornerstone, transcending boundaries to empower researchers in their pursuit of groundbreaking insights. Through strategic grants, we embolden early career investigators to delve into uncharted territories, unraveling mysteries that underpin advancements in chest



medicine. The ripple effect extends beyond labs; it traverses communities, amplifying equitable health care solutions and bridging disparities in patient care. Our commitment to nurturing this pillar springs from the belief that every breakthrough, regardless of scale, is a catalyst for transformative change.

Community Impact extends CHEST's reach far beyond clinical settings, fostering alliances with local organizations. Together, we forge a tapestry of collaboration, weaving essential services and imparting knowledge on crucial lung health issues into the fabric of diverse communities. This engagement not only elevates awareness but also empowers individuals and communities to take charge of their respiratory well-being. It's the grassroots unity that amplifies our impact, creating enduring shifts in local landscapes.

Support of the Profession epitomizes our dedication to fortifying the backbone of pulmonary, critical care, and sleep medicine. By offering unparalleled clinical education and mentorship, we empower emerging clinicians from diverse backgrounds with the latest knowledge and resources. Fueling their professional growth is pivotal to nurturing a robust and inclusive cadre of health care professionals, ensuring comprehensive and culturally sensitive care for patients worldwide.

Dedication to Education isn't just a commitment—it's a bridge spanning the gap between knowledge and application, patient and clinician. Strengthening this connection involves equipping clinicians with tools for effective communication and partnering with patient-centered organizations. Our focus transcends textbooks; it embodies a relentless pursuit to refine patient-clinician interactions, enhancing patient understanding and, ultimately, elevating their quality of life.

CHEST's philanthropic evolution signifies not just growth but a resolute commitment to effecting tangible change in chest medicine and patient care. These pillars stand as guiding beacons, steering us toward a future that mirrors our mission, vision, and values. Each pillar represents a pathway to meaningful, enduring change within chest medicine, ensuring a lasting impact on patient well-being. ■

NETWORKS continued from previous page

have facilitated the transition of IP research from observational case series and single-center experiences to multicenter, randomized controlled trials to generate level I evidence and inform patient care (Laskawiec-Szkonter M, et al. *Br J Hosp Med (Lond)*. 2019 Apr 2;80[4]:186-7) (Maldonado F, et al. *J Bronchology Interv Pulmonol*. 2019 Jul;26(3):150-2). In the bronchoscopy space, important investigator-initiated clinical trial results

anticipated in 2024 include VERITAS (NCT04250194), FROSTBITE2 (NCT05751278), and RELIANT (NCT05705544), among others. These research efforts complement industry-sponsored clinical trials (such as RheSolve, NCT04677465) and aim to emulate the extraordinary track record achieved in the field of pleural disease that has led to recently updated evidence-based guidelines for the management of challenging diseases like malignant pleural effusions, pleural space

infections, and pneumothorax (Davies HE, et al. *JAMA*. 2012 Jun 13;307[22]:2383-9, Mishra EK, et al. *Am J Respir Crit Care Med*. 2018 Feb 15;197[4]:502-8) (Rahman NM, et al. *N Engl J Med*. 2011 Aug 11;365[6]:518-26) (Hallifax RJ, et al. *Lancet*. 2020 Jul 4;396[10243]:39-49).

Ultimately, the rapidly evolving technological advancements in interventional pulmonology must be supported by research based on high-quality clinical trials, which

will be contingent on appropriate trial funding requiring partnership with industry and federal funding agencies. Only through such collaboration can researchers design robust clinical trials based on complex methodology, which will advance patient care and lead to improved patient outcomes. ■

– Jennifer D. Duke, MD
Section Fellow-in-Training
– Fabien Maldonado, MD,
MSc, FCCP
Section Member

CDC: Condition has caused thousands of US deaths

BY LISA RAPAPORT

While COVID has now claimed more than 1 million lives in the United States alone, these aren't the only fatalities caused at least in part by the virus. A small but growing number of Americans are surviving acute infections only to succumb months later to the lingering health problems caused by long COVID.

Much of the attention on long COVID has centered on the sometimes debilitating symptoms that strike people with the condition, with no formal diagnostic tests or standard treatments available, and the effect it has on quality of life. But new figures from the US Centers for Disease Control and Prevention (CDC) show that long COVID can also be deadly.

More than 5000 Americans have died from long COVID since the start of the pandemic, according to new estimates from the CDC. This total, based on death certificate data collected by the CDC, includes a preliminary tally of 1491 long COVID deaths in 2023 in addition to 3544 fatalities previously reported from January 2020 through June 2022.

Guidance issued in 2023 on how to formally report long COVID as a cause of death on death certificates should help get a more accurate count of these fatalities going forward, said Robert Anderson, PhD, chief mortality statistician for the CDC, Atlanta, Georgia.

"We hope that the guidance will help cause of death certifiers be more aware of the impact of long COVID and more likely to report long COVID as a cause of death when appropriate," Dr. Anderson said. "That said, we do not expect that this guidance will have a dramatic impact on the trend."

There's no standard definition or diagnostic test for long COVID. It's typically diagnosed when people have symptoms at least 3 months after an acute infection that weren't present before they got sick. As of the end of last year, about 7% of American adults had experienced long COVID at some point, the CDC estimated in September 2023.

The new death tally indicates long COVID remains a significant public health threat and is likely to grow in the years ahead, even though the pandemic may no longer be considered a global

health crisis, experts said.

For example, the death certificate figures indicate:

COVID-19 was the third leading cause of American deaths in 2020 and 2021, and the fourth leading cause of death in the United States in 2023.

Nearly 1% of the more than 1 million deaths related to COVID-19 since the start of the pandemic have been attributed to long COVID, according to data released by the CDC.

Nearly 1% of the more than 1 million deaths related to COVID-19 since the start of the pandemic have been attributed to long COVID.

The proportion of COVID-related deaths from long COVID peaked in June 2021 at 1.2% and again in April 2022 at 3.8%, according to the CDC. Both of these peaks coincided with periods of declining fatalities from acute infections.

"I do expect that deaths associated with long COVID will make up an increasingly larger proportion of total deaths associated with COVID-19," said Mark Czeisler, PhD, a researcher at Harvard Medical School, Boston, Massachusetts, who has studied long COVID fatalities.

Months and even years after an acute infection, long COVID can contribute to serious and potentially life-threatening conditions that impact nearly every major system in the body, according to the CDC guidelines for identifying the condition on death certificates.

This means long COVID may often be listed as an underlying cause of death when people with this condition die of issues related to their heart, lungs, brain, or kidneys, the CDC guidelines noted.

The risk for long COVID fatalities remains elevated for at least 6 months for people with milder acute infections and for at least 2 years in severe cases that require hospitalization, some previous research suggested.

As happens with other acute infections, certain people are more at risk for fatal case of long

COVID. Age, race, and ethnicity have all been cited as risk factors by researchers who have been tracking the condition since the start of the pandemic.

Half of long COVID fatalities from July 2021 to June 2022 occurred in people aged 65 years and older, and another 23% were recorded among people aged 50-64 years old, according a report from CDC.

Long COVID death rates also varied by race and ethnicity, from a high of 14.1 cases per million among American Indian and Alaskan natives to a low of 1.5 cases per million among Asian people, the CDC found. Death rates per million were 6.7 for White individuals, 6.4 for Black people, and 4.7 for Hispanic people.

The disproportionate share of Black and Hispanic people who developed and died from severe acute infections may have left fewer survivors to develop long COVID, limiting long COVID fatalities among these groups, the CDC report concluded.

It's also possible that long COVID fatalities were undercounted in these populations because they faced challenges accessing health care or seeing providers who could recognize the hallmark symptoms of long COVID.

It's also difficult to distinguish between how many deaths related to the virus ultimately occur as a result of long COVID rather than acute infections. That's because it may depend on a variety of factors, including how consistently medical examiners follow the CDC guidelines, said Ziyad Al-Aly, MD, chief of research at the Veterans Affairs, St. Louis Health Care System and a senior clinical epidemiologist at Washington University in St. Louis, Missouri.

"Long COVID remains massively underdiagnosed, and death in people with long COVID is misattributed to other things," Dr. Al-Aly said.

An accurate test for long COVID could help lead to a more accurate count of these fatalities, Dr. Czeisler said. Some preliminary research suggests that it might one day be possible to diagnose long COVID with a blood test.

"The timeline for such a test and the extent to which it would be widely applied is uncertain," Dr. Czeisler noted, "though that would certainly be a gamechanger." ■

SMOKING

WHO: Quitting tobacco reduces risk of type 2 diabetes

BY NANCY A. MELVILLE

Tobacco users who quit smoking reduce their risk of developing type 2 diabetes by as much as 30%-40%, and quitting even after one has developed type 2 diabetes is important in preventing a worsening of the disease's many serious comorbidities, according to a policy brief jointly issued by the World Health Organization (WHO), the International Diabetes Federation (IDF), and the University of Newcastle, Callaghan, Australia.

With type 2 diabetes representing one of the most prevalent chronic diseases worldwide and

the ninth cause of death globally, the potential to reduce the risk and worsening of the disease by quitting smoking adds to the urgency of smoking cessation as a public health interest. The policy brief summarizes the evidence on the health impacts of type 2 diabetes, tobacco smoking, and the pathophysiology of tobacco use and its role in the development of type 2 diabetes.

Impact of vaping, smokeless tobacco

The brief also describes the latest data on newer products that target smokers or potential smokers, including smokeless tobacco, new nicotine

and tobacco products, and their relationship with type 2 diabetes. For instance, evidence suggests that even with smokeless tobacco, heavy use or high consumption increases the risk of developing type 2 diabetes, as the products often contain nicotine, known to contribute to the development of type 2 diabetes and related health conditions. Evidence on the effectiveness of tobacco control interventions among those with type 2 diabetes is also summarized, including discussion of a systematic review of six studies suggesting that interventions focusing on education and the

T2DM continued on following page

Challenges to smoking cessation in Black patients

BY BRITTANY VARGAS

Black Americans attempt to quit smoking more often than their White counterparts but are less likely to succeed, and they pay the health consequences. This knowledge has driven Kevin Choi, MD, acting scientific director of the National Institute on Minority Health and Health Disparities in Bethesda, Md., to dedicate his career to studying the patterns and disparities of smoking among these patients.

Dr. Choi wants primary care clinicians to know not just that they have the potential to educate patients on the harms of smoking — most patients already know smoking is unhealthy — but that aiding them will likely necessitate more assertive follow-up.

To do so, “we need to understand the bigger backdrop of racial and sociological stress experienced by the Black population, which stems from both interpersonal and structural racism,” Dr. Choi said.

Not only are Black smokers more likely to try to quit, but they also tend to smoke fewer cigarettes per day than other racial groups. Yet they experience higher rates of smoking-related mortality.

The reasons behind the attempts

Multiple factors play into Black smokers’ lower rates of successful quitting attempts than Asian, Hispanic, White, and Native American individuals.

One reason: An estimated 85% of Black smokers smoke highly addictive menthol cigarettes. According

to Dr. Choi and other experts, the tobacco industry engages in targeted marketing of menthols by sponsoring community events in predominantly Black neighborhoods and colleges with historically Black populations and by using Black culture in advertising. “The built



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environment really drives a change in behavior, and we have seen that chronically in the African American population being overly targeted and now being overly addicted to nicotine,” said Daniel Kortsch, MD, a family medicine physician and chair of the Tobacco Cessation Workgroup at Denver Health.

Menthol cigarettes are more addictive than traditional cigarettes, in part because they provide a less harsh feeling in the respiratory system, owing to anti-tussive, anti-irritant, and cooling properties that act as a cough suppressant and mask irritation and pain. “You do not feel like you’re smoking that much

or that it’s dangerous, and that’s exactly the reason why it’s harder to quit,” said Julia Adamian, MD, section chief of general internal medicine and clinical innovation at NYU Langone Tisch Hospital.

In addition, menthol cigarettes interact with the body in complex

ways that make quitting harder, according to a study published in *Nicotine & Tobacco Research* (2019 Dec 23. doi: 10.1093/ntr/ntz239). Menthol increases the amount of nicotine that the body absorbs and thus increases the risk of dependence on the drug.

According to Dr. Choi, rates of cigar and cigarillo use are higher among Black Americans, compared with other races, and these products are often left out of cessation programs. Smokers, regardless of race, may have a misguided belief that cigars and cigarillos are less harmful than cigarettes.

Research published in 2021 found

that Black cigar smokers who were interested in cessation had not been asked by their health care provider if they smoked cigars, and those who were asked reported a lack of support for cessation.

Primary care providers should work to remove any misconceptions a patient has regarding the safety of cigarillos and cigars, Dr. Choi said.

These smokers are also at a disadvantage regarding cessation success because of the neighborhoods they may live in, according to Dr. Choi. Black Americans are more likely to earn less and to live in neighborhoods with lower housing values than other racial groups. Areas with more low-income households tend to have a higher density of tobacco outlets.

“If you’re trying to quit smoking, but you walk by three, four, or five gas stations, convenience stores, and other tobacco outlets with signs that advertise sales, it’s not going to make quitting easy,” Dr. Choi said.

Tailoring treatment to Black smokers

Considering the unique challenges Black patients may face in quitting, clinicians should provide more follow-up and consistent support, according to Dr. Adamian. The higher risk of tobacco-related death among Black smokers means clinicians need to be more aggressive in recommending every treatment possible if one treatment fails.

Pharmacotherapy, nicotine replacement therapy, and counseling are evidence-based options to help patients stop smoking.

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T2DM *continued from previous page*

involvement of health care professionals and pharmacists can be beneficial for people with type 2 diabetes.

Smoking exacerbates the known serious complications of diabetic neuropathy and foot ulcers with type 2 diabetes, while further impeding wound healing. Smoking also causes damage to retinal blood vessels already at risk with type 2 diabetes, increasing the risk of diabetic retinopathy and vision loss. Quitting tobacco use can help prevent those and other major health complications already linked to diabetes, including kidney failure and cardiovascular events. Studies show that key misconceptions among smokers with type 2 diabetes that can prevent cessation include concerns about postcessation weight gain, the influence of peers who smoke, and the psychological aspect of addiction. Clinicians are urged to provide advice on how to stop smoking

to all tobacco users during the course of a routine consultation or interaction, which can be accomplished in only a few minutes.

Role of clinicians in smoking cessation

“Health professionals play a vital role in motivating and guiding individuals with type 2 diabetes in their journey to quit tobacco,” Ruediger Krech, MD, director of the Department of Health Promotion at the World Health Organization in Geneva, Switzerland, said in a press statement on the policy brief.

Government’s potential role in deterring smoking

“Simultaneously, governments must take the crucial step of ensuring all indoor public places, workplaces, and public transport are completely smoke-free. These interventions are essential safeguards against the onset and progression

of this and many other chronic diseases,” he emphasized.

The policy brief was jointly developed by the World Health Organization, the International Diabetes Federation, and the University of Newcastle. The detailed policy brief can be downloaded on the IDF website.

Research gaps on tobacco control

Research remains limited on some issues, including the effectiveness of tobacco control interventions and smoking cessation methods for people with type 2 diabetes.

Likewise, specific guidelines for smoking cessation in the type 2 diabetes population are lacking. However, the general approaches of building patient motivation, behavioral interventions, and pharmacological treatments are advised.

The authors reported no relevant financial relationships. ■

Monitoring program finds fivefold increase in vaping during pregnancies in adolescents

BY JAKE REMALY

Among adolescent pregnancies in the United States, the prevalence of e-cigarette use during the third trimester increased from 0.8% in 2016 to 4.1% in 2021, according to research published online on December 13, 2023, in *JAMA Network Open*.

Researchers analyzed data from the 2016-2021 Pregnancy Risk Assessment Monitoring System. They focused on 10,428 adolescents aged 10-19 years who had had a singleton birth and provided information about their use of e-cigarettes or cigarettes.

Rates of vaping up

Whereas the researchers found a roughly fivefold increase in the exclusive use of e-cigarettes, the percentage of patients using only cigarettes decreased from 9.2% in 2017 to 3.2% in 2021. The percentage of patients who both vaped and smoked fluctuated between 0.6% and 1.6%.

The rate of small-for-gestational-age (SGA) births for adolescents who did not smoke or vape (12.9%) did not differ significantly from that among adolescents who exclusively used



be interpreted with caution given the low prevalence of use and the limited sample size," the study authors wrote.

Potential for underreporting

Study limitations include that participants may have underreported their use of e-cigarettes and cigarettes because of fears of social stigma. The researchers lacked information about vaping in the first and second trimesters, exposure to secondhand smoke, cannabis use, and diet.

Research support

Xiaozhong Wen, MD, PhD, with the Jacobs School of Medicine and Biomedical Sciences at the State University of New York at Buffalo, was the corresponding author of

the study.

The research was supported by the National Institute on Drug Abuse; the Food and Drug Administration Center for Tobacco Products; the National Heart, Lung, and Blood Institute; and the American Heart Association. A study coauthor has received grants from Pfizer and personal fees from Johnson & Johnson, the World Health Organization, and the Campaign for Tobacco-Free Kids. ■

e-cigarettes (16.8%) or those who used both cigarettes and e-cigarettes (17.6%). The researchers found use of cigarettes only was associated with a significantly higher rate of SGA births: 24.6%.

Low sample size

"Exclusive e-cigarette use and dual use of cigarettes and e-cigarettes did not seem to be statistically significantly associated with SGA birth in our analysis, but this finding should

CESSATION *continued from previous page*

Dr. Kortsch considers pharmacotherapy to be the most effective and evidence-based treatment for nicotine addiction. However, Black Americans are less likely than White smokers to try smoking cessation medications, and they express more suspicion about efficacy and potential addiction to the tools.

"African American populations simply do not use pharmacotherapy to the extent that other populations do to help them quit smoking; this is a problem," Dr. Kortsch said.

Dr. Kortsch recommends the use of varenicline for all patients with nicotine addiction. He recommends varenicline in combination with tobacco replacement products such as lozenges, patches, gums, or inhalers if the patient is a heavy smoker as opposed to someone who has a few cigarettes on the weekends.

If a patient has anxiety or depression, Dr. Adamian advises initiating a pharmacologic treatment such as bupropion or varenicline more quickly, because mood disorders can hinder cessation.

Cessation counseling is another option, but clinicians may need to more thoroughly explain what it entails. According to Dr. Choi,

Black patients may be more reluctant to try cessation counseling because of the negative stigma associated with the term "counseling." But this treatment is not therapy — it involves identifying and coming up with strategies to manage smoking triggers and providing encouragement. Clinicians can eliminate any confusion patients may have between psychological therapy and cessation counseling. "'Counseling' tends to have a somewhat negative connotation among racial minority populations, like you go to counseling because you're crazy," Dr. Choi said. "That needs to change."

Clinicians also must clarify how each cessation tool works. For example, some patients may not realize that the nicotine patch isn't an instant fix for a craving and that hours may pass before the user feels its effects, according to Dr. Choi.

Move past the "advise" stage

While recommending to patients various forms of cessation, clinicians should be mindful of the US Preventive Services Task Force's guidelines for providers who treat patients who smoke. Those guidelines include a five-step process:

Ask, Advise, Assess, Assist, and Arrange.

Dr. Choi said most providers stop at the "Advise" stage. In steps one and two, providers ask patients whether they smoke, then advise them to quit. Stage three involves asking whether or not a patient is ready to quit and where they are in their journey.

Clinicians shouldn't give up when patients say they do not currently plan to quit. Instead, they can use the conversation to create an ongoing dialogue about the patient's readiness to quit in future visits. Follow-up phone calls or text messages should be made 2-4 weeks after a patient makes an attempt to quit and at the same interval thereafter, Dr. Adamian advised.

"It takes a concerted effort on behalf of all people to be successful, and it is really uncommon for someone to be successful with only one attempt," Dr. Kortsch said.

In a recent study published in the *Journal of the American Medical Association* (2023 Sep 20. doi: 10.1001/jamanetworkopen.2023.34695), researchers identified three key factors that influence a Black smoker's ability to stop smoking in early attempts. These factors have been shown to increase

the chances of long-term cessation: fewer cigarettes per day, nonuse of other tobacco products, and lower levels of cotinine (a nicotine metabolite) at baseline.

"Using these predictors of early treatment response could allow providers to anticipate which smokers may benefit from a minimal, low-cost intervention and who may benefit from more intensive treatment," said Eleanor Leavens, PhD, assistant professor in the department of population health at the University of Kansas School of Medicine, Kansas City, who led the study.

Dr. Leavens' research also confirmed that early abstinence predicts long-term cessation success. Smokers who were able to forgo cigarettes within 2 weeks of their quit date were almost four times more likely to remain abstinent over the long term.

A quick phone call or message from the clinician or a staff member can help patients achieve early progress, enable changes in approach to quitting, and build a relationship with the patient, Dr. Adamian said. "Have more empathy for what Black patients are going through," Dr. Choi said. "Continue to cheer them on and to be a supporter of their smoking cessation journey." ■

Researchers making strides to better understand RA-associated ILD

BY DOUG BRUNK

Clinically significant interstitial lung disease (ILD) is believed to occur in 5%-10% of patients with rheumatoid arthritis (RA), but robust data are lacking on how to best predict which patients face the highest risk for RA-associated ILD. However, the results of several studies presented at the American College of Rheumatology (ACR) annual meeting indicate researchers are making strides in this field of care.

Adding genetic factors improves ILD risk prediction

In the realm of risk stratification, Austin M. Wheeler, MD, a rheumatology fellow at the University of

For the current study, Dr. Wheeler and colleagues drew from 2386 participants in the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a multicenter, prospective cohort of US veterans with rheumatologist-diagnosed RA and who fulfilled the 1987 ACR classification criteria. The researchers validated ILD through a systematic review of medical records, including clinical diagnosis of ILD plus either imaging or lung biopsy findings, and collected whole-genome data that included 12 single nucleotide polymorphisms (SNPs) previously identified to be associated with risk for RA-ILD. They then used a meta-analytic approach to create pooled associations for each of those



Dr. Wheeler

“This study demonstrates the potential utility of genetic risk scores in RA-ILD identification and supports further investigation into individual risk stratification and screening.”

—Austin M. Wheeler, MD

Nebraska Medical Center, Omaha, discussed the development and validation of a combined clinical and genetic risk score for ILD.

“There is clear and well documented phenotypic and genetic overlap of ILD with idiopathic pulmonary fibrosis [IPF],” Dr. Wheeler said. “A number of clinical risk factors have been described for RA-ILD, including older age, male sex, smoking history, higher disease activity, and seropositivity. There are also well-documented genetic risk factors for RA-ILD. The MUC5B genetic variant is the strongest risk factor for IPF, and it’s been described in RA-ILD as well.”

A recently published study indicated a genetic risk score without the MUC5B variant improved predictive ability for IPF and interstitial lung abnormalities better than using the MUC5B variant alone (*Am J Respir Crit Care.* 2023;208[7]:791-801. doi: 10.1164/rccm.202212-2257OC), “but no prior attempts have been made at developing a composite genetic risk score in RA-ILD” using both genetic and clinical risk factors, he said.

respective SNPs using data from the VARA registry participants as well as participants from the past study where the SNPs were first identified.

“Those pooled associations were what we used for our effects size within the genetic risk score,” which ended up using five of the SNPs, Dr. Wheeler explained. Next, he and his colleagues combined the genetic risk score with clinical risk factors including age, sex, smoking history, disease activity, and rheumatoid factor (RF) positivity to create their combined risk score.

The mean age of the cohort was 70 years, 89% were male, 78% had a smoking history, and 78% were anti-cyclic citrullinated peptide (CCP) antibody positive. Of the 2386 participants, 224 (9.4%) had RA-ILD. The full composite risk score had the highest area under the receiver operating curve (AUC) of 0.67, compared with an AUC of 0.623 using the clinical factors alone, 0.651 using the clinical factors plus only the MUC5B variant, and 0.654 using the composite score minus only the MUC5B variant.

RA-ILD continued on following page



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These AUCs show that “the combined risk score performs better than clinical factors even without the inclusion of the MUC5B variant in the score, which is notable because it supports the importance of further investigation into polygenic risk scores in RA-ILD as there is clearly more at play in a patient’s overall genetic risk,” Dr. Wheeler said.

As an example of the composite score’s ability to discriminate between people with and without RA-ILD, a cutpoint of 0.05 gave a sensitivity of 90.2% and would have eliminated about 25% of the cohort from unnecessary high-resolution CT scans and pulmonary function tests, he said.

“This study demonstrates the potential utility of genetic risk scores in RA-ILD identification and supports further investigation into individual risk stratification and screening,” he concluded. “This isn’t ready for clinical applicability by any means, but I think it serves as a proof of concept of the idea of a genetic risk score in RA-ILD.”

Biomarker score investigated

In a separate abstract, Brent Luedders, MD, assistant professor of rheumatology and immunology at



Dr. Luedders

the University of Nebraska Medical Center, and colleagues set out to determine if a previously derived biomarker score is associated with prevalent and incident ILD in the same VARA registry cohort. An abstract presented at the ACR 2022 annual meeting found that a panel derived from IPF peripheral biomarkers was significantly associated with RA-ILD, including matrix metalloproteinase (MMP)-2, -7, and -9, eotaxin, macrophage-derived chemokine (MDC), monocyte chemoattractant protein-1 (MCP-1), fms-like tyrosine kinase 3 ligand (Flt3L), and interleukin-8 (IL-8). For the current analysis, Dr. Luedders and colleagues measured the concentrations of seven biomarkers (MMP-7, MMP-9, eotaxin, MDC, MCP-1, Flt3L, IL-8) from serum/plasma samples collected from

VARA’s participants at enrollment to develop a score based on the concentrations of each biomarker.

Baseline characteristics were similar between the groups, although those with prevalent RA-ILD were slightly older than those without ILD, and those who developed incident ILD during follow-up had slightly higher RA disease activity at the time of enrollment. When the researchers examined the association of the biomarker score with prevalent RA-ILD as a continuous measure, they found an adjusted odds ratio of 1.08 for prevalent RA-ILD for each 1-point increase in the biomarker score.

“When this was divided into quartiles, we found that the highest quartile of the biomarker score was associated with an adjusted odds ratio of 2.31 for prevalent RA-ILD,” Dr. Luedders said.

“We saw a significant *P* for trend of < .001, suggesting a dose-response relationship, in which higher scores had higher risk.” Similar associations were observed for incident RA-ILD, in which participants with the highest quartile had an adjusted hazard ratio of 2.26 for incident RA-ILD.

The AUC of 0.653 that was obtained with clinical factors did not significantly improve with inclusion of the biomarker score, rising

*“We found that the highest quartile of the biomarker score was associated with an adjusted odds ratio of 2.31 for prevalent RA-ILD. We saw a significant *P* for trend of < .001, suggesting a dose-response relationship, in which higher scores had higher risk.”*

—Brent Luedders, MD

to only 0.669. “In receiver operating characteristic analysis, the addition of the biomarker score to clinical variables (age, sex, race, smoking status, anti-CCP positivity, and RA disease activity by DAS28) did not lead to a significant increase in the area under the curve. Therefore, further work is needed to identify combinations of clinical, biomarker, and other factors to accurately predict which people with RA will develop ILD,” he said.

Dr. Luedders acknowledged certain limitations of the results, including the fact that MMP-2 was not measured in this cohort and thus not included in the score. “This was an observational study with usual care; therefore, the absence of systemic evaluation for ILD may miss early or mild RA-ILD cases,” he added. “Similarly, a male

predominance may limit the generalizability, and we have limited information on the RA-ILD pattern.” He concluded that the study results “support the shared pathogenesis of IPF and RA-ILD. However, we found that this score has limited discriminative performance, compared to clinical risk factors alone.”

Drilling down on ILD subtypes

In a poster abstract presentation at the meeting, Gregory Campbell McDermott, MD, MPH, a rheumatologist at Brigham and



Dr. McDermott

Women’s Hospital, Boston, Massachusetts, highlighted results from a study that investigated differences in demographic, serologic, and lifestyle factors for RA-ILD and the major subtypes of RA-ILD: usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). “Historically, RA-ILD has been studied as a single entity, even though we increasingly recognized that there are lots of different subtypes that fall under the umbrella of RA-ILD,” Dr. McDermott said in an interview.

“We are also learning that the different subtypes probably have both prognostic and potentially therapeutic implications. For example, the UIP subtype, which is the most fibrotic subtype, has the worst prognosis but also may be a potential target for antifibrotic therapies. We’ve been trying to see if we can identify factors that are associated with specific subtypes, in particular the UIP subtype which has the worst prognosis.”

He and his colleagues examined 208 patients with RA-ILD with a mean age of 51 years and 547 patients with RA but no ILD with a mean age of 49 years from two RA cohorts comprising 3328 patients: the Mass General Brigham Biobank RA Cohort and the Brigham RA Sequential Study (BRASS). Of the 208 RA-ILD cases, nearly half (48%) were RA-UIP, 18% were RA-NSIP, 8% were organizing pneumonia, 3% were respiratory bronchiolitis-ILD, and 23% were other/indeterminate. After conducting multivariable adjusted analyses, the researchers

found that RA-ILD was associated with male sex (OR, 1.58; 95% CI, 1.09-2.23), seropositivity for RF and/or anti-CCP (OR, 2.22; 95% CI, 1.51-3.24), and being an ever smoker (OR, 1.70; 95% CI, 1.13-2.54). Having all three of these risk factors was strongly associated with RA-ILD (OR, 6.04; 95% CI, 2.92-12.47) and with RA-UIP in particular (OR, 7.1).

“We found that a lot of the traditional RA-ILD risk factors like male sex, history of smoking, and seropositive status were most strongly associated with a UIP pattern,” Dr. McDermott said. “We think this is

“Historically, RA-ILD has been studied as a single entity, even though we increasingly recognized that there are lots of different subtypes that fall under the umbrella of RA-ILD.”

—Gregory Campbell McDermott, MD, MPH

a first step in trying to understand how these different ILD subtypes may have different risk factors, pathogenesis, and potentially different treatments, prevention, and screening strategies.”

While clinicians wait for guidelines on systemic autoimmune rheumatic disease-associated ILD that are expected to be published by the ACR in 2024, he added that “we probably shouldn’t screen every single person with RA for ILD, but we need to identify people who have symptoms or findings on clinical exam. This study wasn’t designed to look specifically at who is at high risk, but I think we are moving toward that question: Who is high risk, and who’s asymptomatic [but] may need more screening?”

He pointed out limitations of the study, including its retrospective design and the fact that imaging was done for clinical purposes, “so it’s probably a higher risk group to begin with than the whole RA population,” he said. “We also didn’t have data on RA disease activity or erosions, some of these other measures that we think are important for understanding the full RA disease phenotype in these patients.”

Dr. Wheeler reported having no disclosures. Dr. Luedders reported that his study was supported by the VA, the Rheumatology Research Foundation, and the University of Nebraska Medical Center Mentored Scholars Program. Dr. McDermott reported that his study was supported by the Rheumatology Research Foundation. ■

What's the disease burden from plastic exposure?

BY LIAM DAVENPORT

Exposure to endocrine-disrupting chemicals (EDCs) via daily use of plastics is a major contributor to the overall disease burden in the United States, and the associated costs to society amount to more than 1% of the gross domestic product, revealed a large-scale analysis.

The research, published in the *Journal of the Endocrine Society* (2024 Jan 11. doi: 10.1210/jendso/bvad163), indicated that taken together the disease burden attributable to EDCs used in the manufacture of plastics added up to almost \$250 billion in 2018 alone.

"The diseases due to plastics run the entire life course from preterm birth to obesity, heart disease, and cancers," commented lead author Leonardo Trasande, MD, MPP, the Jim G. Hendrick, MD Professor of Pediatrics, Department of Pediatrics, NYU Langone Medical Center, New York, in a release.

"Our study drives home the need to address chemicals used in plastic materials" through global treaties and other policy initiatives, he said, so as to "reduce these costs" in line with reductions in exposure to the chemicals.

Co-author Michael Belliveau, Executive Director at Defend Our Health in Portland, Maine, agreed, saying: "We can reduce these health costs and the prevalence of chronic endocrine diseases such as diabetes and obesity if governments and companies enact policies that minimize exposure to EDCs to protect public health and the environment."

Plastics may contain any one of a number of EDCs, such as polybrominated diphenylethers in flame-retardant additives, phthalates in food packaging, bisphenols in can linings, and perfluoroalkyl and polyfluoroalkyl substances (PFAS) in nonstick cooking utensils.

These chemicals have been shown to leach and disturb the body's hormone systems, increasing the risk for cancer, diabetes, reproductive disorders, neurological impairments in developing fetuses and children, and even death.

In March 2022, the United Nations Environment Assembly committed to a global plastics treaty to "end plastic pollution and forge an international legally binding agreement by 2024" that "addresses the full life cycle of plastic, including its production, design and disposal."

"The diseases due to plastics run the entire life course from preterm birth to obesity, heart disease, and cancers. Our study drives home the need to address chemicals used in plastic materials."

—Leonardo Trasande,
MD, MPP

Minimizing EDC exposure

But what can doctors tell their patients today to help them reduce their exposure to EDCs?

"There are safe and simple steps that people can take to limit their exposure to the chemicals of greatest concern," Dr. Trasande told this news organization. This can be partly achieved by reducing plastic use down to its essentials. "To use an example, when you are flying, fill up a stainless steel container after clearing security.

At home, use glass or stainless steel" rather than plastic bottles or containers.

In particular, "avoiding microwaving plastic is important," Dr. Trasande said, "even if a container says it's microwave-safe."

He warned that "many chemicals used in plastic are not covalently bound, and heat facilitates leaching into food. Microscopic contaminants can also get into food when you microwave plastic." Dr. Trasande also suggests limiting canned food consumption and avoiding cleaning plastic food containers in machine dishwashers.

Calculating the disease burden

To accurately assess the "the tradeoffs involved in the ongoing reliance on plastic production as a source of economic productivity," the current

researchers calculated the attributable disease burden and cost related to EDCs used in plastic materials in the United States in 2018.

Building on previously published analyses, they used industry reports, publications by national and international governing bodies, and peer-reviewed publications to determine the usage of each type of EDC and its attributable disease and disability burden.

This plastic-related fraction (PRF) of disease burden was then used to calculate an updated cost estimate for each EDC, based on the assumption that the disease burden is directly proportional to its exposure.

They found that for bisphenol A, 97.5% of its use, and therefore its estimated PRF of disease burden, was related to the manufacture of plastics, while this figure was 98%-100% for phthalates. For PDBE, 98% of its use was in plastics vs 93% for PFAS.

Measure of plastics' disease burden

The researchers then estimated the total plastic-attributable disease burden in the United States in 2018 cost the nation \$249 billion, or 1.22% of the gross domestic product.

Of this, \$159 billion was linked to PDBE exposure, which is associated with diseases such as cancer.

Moreover, \$1.02 billion plastic-attributable disease burden was associated with bisphenol A exposure, which can have potentially harmful health effects on the immune system; followed by \$66.7 billion due to phthalates, which are linked to preterm birth, reduced sperm count, and childhood obesity; and \$22.4 billion due to PFAS, which are associated with kidney failure and gestational diabetes.

The study was supported by the National Institutes of Health and the Passport Foundation.

Dr. Trasande declared relationships with Audible, Houghton Mifflin, Paidos, and Kobunsha, none of which relate to the present manuscript. No other financial relationships were declared. ■

BUSINESS OF MEDICINE

Are you sure your patient is alive?

BY F. PERRY WILSON, MD, MSCE

Much of my research focuses on what is known as clinical decision support — prompts and messages to providers to help them make good decisions for their patients. I know that these things can be annoying, which is exactly why I study them — to figure out which ones actually help.

When I got started on this about 10 years ago, we were learning a lot about how best to message providers about their patients. My team had developed a simple alert for acute

kidney injury (AKI). We knew that providers often missed the diagnosis, so maybe letting them know would improve patient outcomes.

As we tested the alert, we got feedback, and I have kept an email from an ICU doctor from those early days. It read:

*Dear Dr. Wilson,
Thank you for the automated alert informing me that my patient had AKI. Regrettably, the alert fired about an hour after the patient had died. I feel that the information is less than actionable at this time.*

Sincerely,

Our early system had neglected

to add a conditional flag ensuring that the patient was still alive at the time it sent the alert message. A small oversight, but one that had very large implications. Future studies would show that "false positive" alerts like this seriously degrade physician confidence in the system. And why wouldn't they?

Knowing whether a patient is alive or dead seems like it should be trivial. But, as it turns out, in



Dr. Wilson is associate professor of medicine and public health and director of the Clinical and Translational Research Accelerator at Yale University, New Haven, Connecticut. He has disclosed no relevant financial relationships.

our modern balkanized health care system, it can be quite difficult. Not knowing the vital status of a patient

ALIVE continued on following page

Yes, patients are getting more complex

BY F. PERRY WILSON, MD, MSCE

The first time I saw a patient in the hospital was in 2004, twenty years ago, when I was a third-year med student. I mean, look at that guy. The things I could tell him.

Since that time, I have spent countless hours in the hospital as a resident, a renal fellow, and finally as an attending. And I'm sure many of you in the medical community feel the same thing I do, which is that patients are much more complicated now than they used to be. I'll listen to an intern present a new case on rounds and she'll have an assessment and plan that encompasses a dozen individual medical problems. Sometimes I have to literally be like, "Wait, why is this patient here again?"

But until now, I had no data to convince myself that this feeling was

real — that hospitalized patients are getting more and more complicated, or that they only seem more complicated because I'm getting older. Maybe I was better able to keep track of things when I was an intern rather than now as an attending, spending just a couple months of the year in the hospital. I mean,

Given the increased complexity, you might expect that the outcomes for these patients are worse than years ago, but the data do not bear that out.

after all, if patients were getting more complicated, surely hospitals would know this and allocate more resources to patient care, right? Right?

It's not an illusion. At least not according to this paper, "Population-based trends in complexity of hospital inpatients," appearing in *JAMA Internal Medicine*, which examines about 15 years of inpatient hospital admissions in British Columbia.

I like Canada for this study for two reasons: First, their electronic health record system is province-wide, so they don't have issues of getting data from hospital A vs

hospital B. All the data are there — in this case, more than 3 million nonelective hospital admissions from British Columbia. Second, there is universal health care. We don't have to worry about insurance companies changing, or the start of a new program like the Affordable Care Act. It's just a cleaner set-up.

Of course, complexity is hard to

define, and the authors here decide to look at a variety of metrics I think we can agree are tied into complexity. These include things like patient age, comorbidities, medications, frequency of hospitalization, and so on. They also looked at outcomes associated with hospitalization: Did the patient

COMPLEX *continued on following page*

ALIVE *continued from previous page*

can have major consequences.

Health systems send messages to their patients all the time: reminders of appointments, reminders for preventive care, reminders for vaccinations, and so on.

But what if the patient being reminded has died? It's a waste of resources, of course, but more than that, it can be painful for their families and reflects poorly on the health care system. Of all the people who should know whether someone is alive or dead, shouldn't their doctor be at the top of the list?

A new study in *JAMA Internal Medicine* quantifies this very phenomenon.

Researchers examined 11,658 primary care patients in their health system who met the criteria of being "seriously ill" and followed them for 2 years. During that period of time, 25% were recorded as deceased in the electronic health record. But 30.8% had died. That left 676 patients who had died, but were not known to have died, left in the system.

And those 676 were not left to rest in peace. They received 221 telephone and 338 health portal messages not related to death, and 920 letters reminding them about unmet primary care metrics like flu shots and cancer screening. Orders were entered into the health record for things like vaccines and routine screenings for 158 patients, and 310 future appointments — destined to be no-shows — were still on the books. One can only imagine the frustration of families checking their mail and finding yet another letter reminding their deceased loved one to get a mammogram.

How did the researchers figure out who had died? It turns out it's not

that hard. California keeps a record of all deaths in the state; they simply had to search it. Like all state death records, they tend to lag a bit so it's not clinically terribly useful, but it works. California and most other states also have a very accurate and up-to-date death file, which can be used only by law enforcement to investigate criminal activity and fraud; health care is left in the lurch.

Nationwide, there is the real-time fact of death service, supported by the National Association for Public Health Statistics and Information Systems. This allows employers to verify, in real time, whether the person applying for a job is alive. Health care systems are not allowed to use it.

Let's also remember that very few

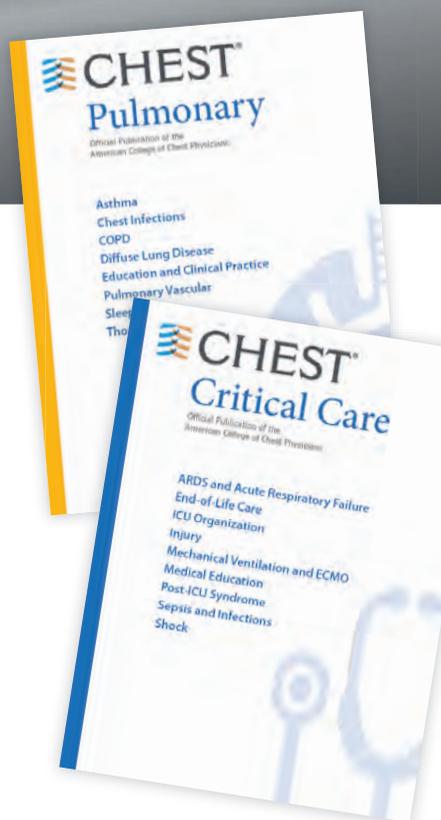
people die in this country without some health care agency knowing about it and recording it. But sharing of medical information is so poor in the United States that your patient could die in a hospital one city away from you and you might not find out until you're calling them to see why they missed a scheduled follow-up appointment.

These events — the embarrassing lack of knowledge about the very vital status of our patients — highlight a huge problem with health care in our country. The fragmented health care system is terrible at data sharing, in part because of poor protocols, in part because of unfounded concerns about patient privacy, and in part because of a tendency to hoard data that might be valuable in the future. It has to stop. We need to know how our patients are doing even when they are not sitting in front of us. When it comes to life and death, the knowledge is out there; we just can't access it. Seems like a pretty easy fix. ■

Most states have a very accurate and up-to-date death file, which can be used only by law enforcement to investigate criminal activity and fraud; health care is left in the lurch.

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10% of US physicians work for UnitedHealth. Is that a problem?

BY STEPH WEBER

UnitedHealth Group, the parent company of the nation's largest private insurer, UnitedHealthcare (UHC), is now affiliated with or employs approximately 10% of the US physician workforce, raising anti-trust and noncompete concerns as more payers and private equity firms pursue medical practice acquisitions.

Health care mergers and consolidations have become more common as physician groups struggle to stay afloat amid dwindling payer reimbursements.

The company added 20,000 physicians in the last year alone, including a previously physician-owned multispecialty group practice of 400 doctors in New York. They join the growing web of doctors — about 90,000 of the 950,000 active US physicians — working for the UnitedHealth Group subsidiary, Optum Health, providing primary, specialty, urgent, and surgical care. Amar Desai, MD, chief executive officer of Optum Health, shared the updated workforce numbers during the health care conglomerate's annual investor conference.

Health care mergers and consolidations have become more common as physician groups struggle to stay afloat amid dwindling payer reimbursements. Although private equity and health systems often acquire practices, payers like UHC are increasingly doing so as part of their model to advance value-based care.

Yashaswini Singh, PhD, health care economist and assistant professor of health services, policy, and practice at Brown University, says such

moves mirror the broader trend in corporate consolidation of physician practices. She said in an interview that the integrated models could possibly enhance care coordination and improve outcomes, but the impact of payer-led consolidation has not been extensively studied.

Meanwhile, evidence considering private equity ownership is just emerging. In a 2022 study published in *JAMA Health Forum*, with Dr. Singh as lead author, findings showed that private equity involvement increased health care spending through higher prices and utilization.

Consolidation can also raise anti-trust concerns. "If payers incentivize referral patterns of their employed physicians to favor other physicians employed by the payer, it can reduce competition by restricting consumer choice," Dr. Singh said.

The Biden Administration has sought to strengthen anti-trust statutes to prevent industry monopolies and consumer harm, and the US Department of Justice and Federal Trade Commission have proposed new merger guidelines that have yet to be finalized.

According to Dr. Singh, some of Optum's medical practice purchases may bypass anti-trust statutes since most prospective mergers and acquisitions are reviewed only if they exceed a specific value (\$101 million for 2023). Limited transparency in ownership structures further complicates matters. Plus, Dr. Singh said instances where physicians are hired instead of acquired through mergers would not be subject to current anti-trust laws.

The "corporatization" of health care is not good for patients or physicians, said Robert McNamara, MD, chief medical officer of the American Academy of Emergency Medicine Physician Group and cofounder of Take Medicine Back, a physician group advocating to remove

corporate interests from health care.

"If you ask a physician what causes them the most moral conflict, they'll tell you it's the insurance companies denying something they want to do for their patients," he said. "To have the doctors now working for the insurance industry conflicts with a physician's duty to put the patient first."

Dr. McNamara, chair of emergency medicine at Temple University's Katz School of Medicine, said in an interview that more than half the states in the United States have laws or court rulings that support protecting physician autonomy from corporate interests. Still, he hopes a federal prohibition on private equity's involvement in health care can soon gain traction. In November, Take Medicine Back raised a resolution at the American Medical Association's interim House of Delegates meeting, which he said was subsequently referred to a committee.

Emergency medicine was among the first specialties to succumb to private equity firms, but Dr. McNamara said that all types of health care providers and entities — from cardiology and urology to addiction treatment centers and nursing homes — are being swallowed up by larger organizations, including payers.

UHC was named in a class action suit recently for allegedly shirking doctors' orders and relying on a flawed algorithm to determine the length of skilled nursing facility stays for Medicare Advantage policyholders.

At the investor meeting, Dr. Desai reiterated Optum's desire to continue expanding care delivery options, especially in its pharmacy and behavioral health business lines, and focus on adopting value-based care. He credited the rapid growth to developing strong relationships with providers and standardizing technology and clinical systems. ■

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require the ICU? Did they survive? Were they readmitted?

And the tale of the tape is as clear as that British Columbian air: Over the past 15 years, your average hospitalized patient is about 3 years older, is twice as likely to have kidney disease, is 70% more likely to have diabetes, is on more medications (particularly anticoagulants), and is much more likely to be admitted through the emergency room. They've also spent more time in the hospital in the past year.

Given the increased complexity, you might expect that the outcomes for these patients are worse than years ago, but the data do not bear that out. In fact, inpatient mortality is lower now than it was 15 years ago, although 30-day postdischarge mortality is higher. Put those together and it turns out that death



rates are pretty stable: 9% of people admitted for nonelective reasons to the hospital will die within 30 days. It's just that nowadays, we tend to discharge them before that happens.

Why are our patients getting more

complex? Some of it is demographics; the population is aging, after all. Some of it relates to the increasing burden of comorbidities like diabetes and kidney disease, which are associated with the obesity epidemic. But in some ways, we're a

victim of our own success. We have the ability to keep people alive today who would not have survived 15 years ago. We have better treatments for metastatic cancer, less-invasive therapies for heart disease, better protocolized ICU care.

Given all that, does it make any sense that many of our hospitals are at skeleton-crew staffing levels? That hospitalists report taking care of more patients than they ever have before?

There's been so much talk about burnout in the health professions lately. Maybe something people need to start acknowledging — particularly those who haven't practiced on the front lines for a decade or two — is that the job is, quite simply, harder now. As patients become more complex, we need more resources, human and otherwise, to care for them. ■

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