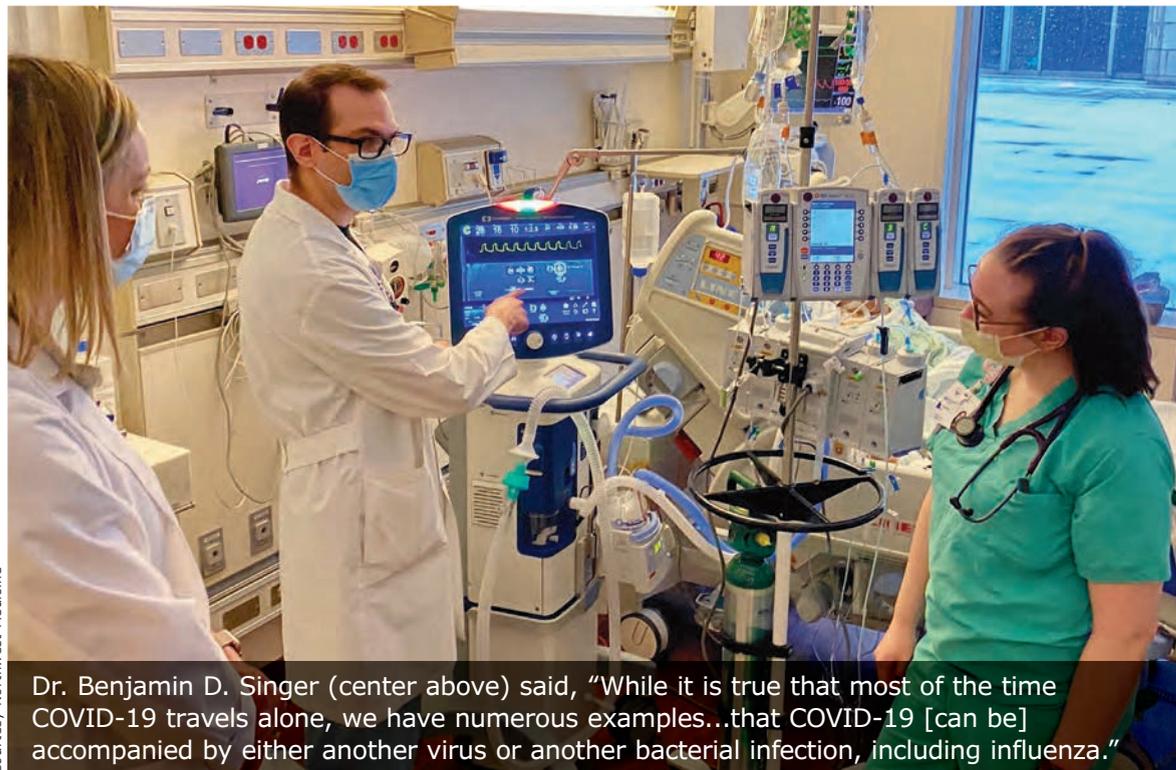




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Courtesy Northwest Medicine

Dr. Benjamin D. Singer (center above) said, "While it is true that most of the time COVID-19 travels alone, we have numerous examples...that COVID-19 [can be] accompanied by either another virus or another bacterial infection, including influenza."

## When viruses collide: Flu season during COVID-19 pandemic

BY RICHARD MARK KIRKNER  
*MDedge News*

The medical community is about to find out how prepared it is for the double whammy of influenza and COVID-19 that has been predicted for the fall of 2020. The complexities of diagnosis, management of vulnerable patients, and overflowing medical centers that have made the COVID-19 crisis so brutal may all be exacerbated by the arrival of seasonal influenza.

Lewis Jay Kaplan, MD, FCCP, a critical care surgeon at the University of Pennsylvania, Philadelphia, has seen his share of critically ill COVID-19 patients in the surgical ICU that

he oversees. He's approaching the upcoming flu season, poised to collide with the ongoing COVID-19 pandemic, ready to listen to each patient's story to distinguish one from the other and determine treatment.

"The patients that have underlying comorbidities all have a story, and it's up to you to figure out which chapter you're in and how far along you happen to be," he said. "It's a very interesting approach to care, medical storytelling."

With flu season closing in, pulmonologists are ruminating about how they'll distinguish symptoms of COVID-19 and traditional influenza and how they'll manage the most vulnerable patients, namely those with underlying respiratory disease

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## NSCLC success story: Mortality down, survival improved

BY PAM HARRISON

Mortality from non-small cell lung cancer (NSCLC) has fallen sharply in the United States over the past few years, and survival following its diagnosis has dramatically improved, the first analysis of its kind indicates.

"This analysis shows for the first time that nationwide mortality rates for the most common category of lung cancer, NSCLC, are declining faster than its incidence, an advance that correlates with the [FDA] approval of several targeted therapies for this cancer in recent years," coauthor Douglas Lowy, MD, deputy director, National Cancer Institute, Bethesda, Md., said in a statement.

"Major improvements have been made in NSCLC treatment with the advent of targeted therapies and immunotherapies," lead author Nadia Howlander, PhD, National Cancer Institute, and colleagues observed.

"The survival benefit for patients with NSCLC treated with targeted therapy has been shown in clinical trials, but our study highlights their possible effect at the population level," they added.

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## NSCLC accounts for 75% of all lung cancers // continued from page 1

In contrast, mortality from SCLC has dropped only in tandem with a decline in the incidence of SCLC, and survival has remained largely unchanged, the same analysis showed.

NSCLC is by far the most common type of lung cancer, accounting for more than 75% of all lung cancer

cases in the United States. SCLC accounts for about 13%.

The study was published online Aug. 12 in the *New England Journal of Medicine*.

“Although overall mortality from lung cancer has been declining in the United States, little is known

about mortality trends according to cancer subtype at the population level because death certificates do not record subtype information,” the authors commented.

“To address this data limitation, the U.S. Surveillance, Epidemiology and End Results (SEER) program

has linked mortality records to incidence cancer cases,” the authors explained. This allowed them to calculate incidence-based mortality among men and women in the United States.

The incidence-based mortality method that the researchers used was

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applied to the SEER data to describe population-level mortality trends in the United States that were attributable to each subtype of lung cancer as well as gender from 2001 to 2016.

Among men, the incidence of NSCLC decreased gradually by 1.9% a year from 2001 to 2008, then more dramatically by 3.1% a year from 2008 to 2016.

Corresponding incidence-based mortality rates among men dropped by 3.2% a year from 2006 to 2013, then again more dramatically by 6.3% a year from 2013 to 2016.

“The 2-year relative survival among patients with lung cancer improved substantially from 26% among men with NSCLC diagnosed in 2001 to 35% among those with

NSCLC diagnosed in 2014,” the researchers added.

Among women, the incidence of NSCLC remained unchanged between 2001 and 2006, after which it began to drop by 1.5% a year from 2006 to 2016.

“In contrast, incidence-based mortality decreased slowly [among women] by 2.3% annually ... from

2006 through 2014 and then at a faster rate of 5.9% annually ... from 2014 through 2016,” the authors noted.

Improvements in survival were also observed for all races and ethnicities, despite concerns that new cancer treatments might increase treatment disparities between races, because they are all so expensive, the authors commented.

Mortality from SCLC declined by 4.3% a year among men, but that decline was entirely due to a similar decrease in the incidence of SCLC. Survival at 2 years for patients with this subtype of lung cancer remained largely unchanged over the same interval.

### Genetic testing

The accelerating decline in NSCLC mortality starting in 2013 corresponds to the period in which clinicians began to routinely test for molecular alterations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), the authors pointed out.

In 2012, the National Comprehensive Cancer Network recommended that all patients with nonsquamous NSCLC undergo genetic testing for EGFR mutations and ALK rearrangements.

At about the same time, the FDA approved a number of targeted therapies for tumors that are sensitive to targeted tyrosine kinase inhibition.

More recently, immunotherapies that act as programmed cell death inhibitors have substantially improved NSCLC outcomes, the authors noted. The first of these was approved for NSCLC in 2015 (pembrolizumab). It was followed by a number of similar agents. It is unlikely that their approval contributed to the observed decline in NSCLC mortality, which started to accelerate in 2013 in the United States, the authors commented.

Another contributing factor is the decline in smoking that has occurred in the United States since the 1960s. This has led to the decrease in the incidence of lung cancer. The faster decrease in the incidence of SCLC, compared with NSCLC can be explained by the higher relative risk of smoking with regard to SCLC compared to NSCLC, they said.

Similarly, the faster decrease in lung cancer incidence in men compared to women can be explained by the relative difference in the prevalence of smoking between men and women, they added.

The authors disclosed no relevant financial relationships.

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# COVID-19 vaccine supply will be limited at first

BY TROY BROWN, RN

**T**wo COVID-19 vaccines are entering phase 3 clinical trials, according to data presented at a virtual meeting of vaccine and infectious disease experts.

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention yesterday held its third meeting this summer to discuss the vaccines and plan how initial vaccines will be allocated, inasmuch as supplies will likely be limited at first. Vaccines are expected to be more available as production ramps up and as more than one vaccine becomes available, but vaccine allocation initially will need to take place in phases.

Considerations include first getting the vaccine to individuals who need it the most, such as health care personnel and essential workers, as well as those at higher risk for severe illness or death, including the elderly, those with underlying conditions, and certain racial and ethnic minorities. Other factors include storage requirements that might be difficult to meet in certain settings and the fact that both vaccines must be given in two doses.

## Vaccine allocation models

The group presented two possible models for allocating initial vaccine supplies. The first population model considers risk status within each age group on the basis of underlying health conditions and occupational group, with priority given to health-care personnel (paid or unpaid) and essential workers. The model considers partial reopening and social distancing, expected vaccine efficacy, prevaccination immunity, mortality, and the direct and indirect benefits of vaccination.

In this model, COVID-19 infections and deaths were reduced when healthcare personnel, essential workers, or adults with underlying conditions were vaccinated. There were smaller differences between the groups with respect to the impact of vaccination. Declines in infections were “more modest” and declines in deaths were greater when adults aged 65 years and older were vaccinated in comparison with other age groups.

The second model focused on vaccination of nursing home health care personnel and residents. Vac-

inating nursing home healthcare personnel reduced infections and deaths more than vaccinating nursing home residents.

In settings such as long-term care facilities and correction facilities, where people gather in groups, cases increase first among staff. The vaccine working group suggests that vaccinating staff may also benefit individuals living in those facilities.

The working group expects that from 15 to 45 million doses of vaccine will be available by the end of December, depending on which vaccine is approved by then or whether both are approved.

Supplies won't be nearly enough to vaccinate everyone: There are approximately 17 to 20 million healthcare workers in the United States and 60 to 80 million essential workers who do not work in health care. More than 100 million adults have underlying medical conditions that put them at higher risk for hospitalization and death, such as obesity, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease. And approximately 53 million adults are aged 65 years or older.

The group reviewed promising early data for two vaccines under development. The mRNA-1273 vaccine, made by Moderna with support from two federal agencies, is moving into phase 3 clinical trials – enrollment into the COVID-19 Efficacy and Safety study is ongoing, according to Jacqueline M. Miller, MD, senior vice president and therapeutic area head of infectious diseases. The study's primary objective will be to determine whether two doses can prevent symptomatic COVID-19, according to an National Institutes of Health.

A second mRNA vaccine, BNT 162b2, made by Pfizer and BioNTech, is entering phase 2/3 trials. Nearly 20% of people enrolled are Black or Hispanic persons, and 4% are Asian persons. The team is also trying to recruit Native American participants, Nicholas Kitchin, MD, senior director in Pfizer's vaccine clinical research and development group, said in a presentation to the advisory committee.

The advisory committee will meet again on Sept. 22. At that time, they'll vote on an interim plan for prioritization of the first COVID-19 vaccine.

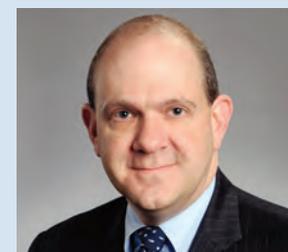
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and children. Influenza kills 12,000-61,000 people a year, according to the Centers for Disease Control, and results in 140,000-810,00 hospitalizations. Having a flu season in the midst of a pandemic of a disease with multiple overlapping symptoms threatens to overwhelm practitioners, hospitals, and the health system.

Dr. Kaplan said each patient's story can point to the correct clinical approach. "Instead of just sharing data when you are on rounds, you're really telling some-



DR. KAPLAN

one's story." It arises from a series of questions about how the disease has impacted them, specifics of their presentation, how their signs and symptoms differ from the usual, and how they responded to treatment. "It also helps you to then take what you're doing, which can seem very, very complicated to individuals who are not medically sophisticated, and then help them to understand why you're doing what you're doing at this point."

That can help get through to a patient with respiratory disease who insists he or she has or doesn't have COVID-19 rather than the flu. "They form a different group that brings with them different fears and concerns, and you have to help them navigate that, too: all of this data and your decision-making around testing and admissions, and what you can omit doing and what you must do help them to navigate their own story," Dr. Kaplan said.

Benjamin D. Singer, MD, a pulmonologist at Northwestern University, Chicago, authored an editorial in *Science Advances* (2020 Jul 29. doi: 10.1126/sciadv.abd0086) that addressed four factors that will determine the scope of flu spread in the upcoming season: rate of transmission; vaccination rates; coinfection rates; and health disparities in minority populations, which are prone to higher rates of flu as well as COVID-19.

### 'Extra importance' of flu vaccine

The convergence of COVID-19 and influenza has the potential to overwhelm the health system, said Daniel A. Solomon, MD, of Brigham and Women's in Boston. He coauthored a JAMA Insights

clinical update on flu season during the COVID-19 pandemic (2020 Aug 14. doi: 10.1001/jama.2020.14661) that lists distinguishing and overlapping signs and symptoms of the two diseases.

The flu vaccine, he said, is "extra important this year," especially in patients with existing respiratory disease, but COVID-19 has thrown up barriers to vaccination. Telemedicine has supplanted office visits. "People may miss that easy-touch opportunity to get the flu vaccine, so we have to be creative about making the flu vaccine highly accessible, maybe in nontraditional ways," Dr. Solomon said. Some ideas he offered are pop-up vaccine fairs at schools and churches.

But just as COVID-19 may hinder flu vaccines, it may also be helping to mitigate flu transmission. "The interesting thing about transmission of the flu is that it's transmitted the same way COVID is, so if we actually know how to decrease



DR. SOLOMON

transmission of COVID, which we do – we've done it – we can actually decrease transmission of influenza as well," Dr. Solomon said. Studies out of Hong Kong and Japan have reported a reduction in influenza cases during COVID-19 outbreaks in those places (*Lancet Public Health*. 2020;5:e279-88; *JAMA*. 2020;323:1969-71).

### Risks of coinfection

About one in four COVID-19 patients have been diagnosed with an additional respiratory infection, including influenza (*JAMA*. 2020;323:2085-6). Pulmonologists must keep that in mind when managing COVID-19 suspects, said Dr. Singer.

"While it is true that most of the time COVID-19 travels alone, we have numerous examples in the literature and in our own experience that COVID-19 [can be] accompanied by either another virus or another bacterial infection, including influenza," Dr. Singer said. "The distinction is important. One is just for diagnostic reasons and public reporting reasons, but also because flu and COVID-19 have different requirements for how you care for patients in terms of the health system."

Clinical suspicion for coinfection should remain high if the com-

munity spread of both COVID-19 and influenza is high, said Megan Conroy, MD, chief pulmonary and critical care fellow at Ohio State University, Columbus. "As the coronavirus first took hold in the United States in March 2020, we were at the tail end of influenza season, so it's hard to predict what the upcoming influenza season will really look like with regards to coinfection."



DR. SINGER

### Distinguishing COVID-19 from flu

Multiple signs and symptoms between COVID-19 and the flu overlap. They include fever, chills, headache, myalgia, cough, and fatigue. Nasal congestion and sore throat are characteristic of the flu; shortness of breath and loss of the sense of smell have been widely reported in COVID-19. "While many upper respiratory infections can result in loss of smell, this may be more prevalent in COVID-19," Dr. Conroy said. Other symptoms unique to COVID-19 are GI symptoms such as diarrhea and skin rashes such as acral ischemia.



DR. CONROY

Testing, however, is the cornerstone of the differential diagnosis. "You can't confidently distinguish between them on symptoms alone," Dr. Conroy added.

"I think the challenge we'll face as clinicians, is caring for people with nonspecific symptoms of a respiratory viral illness, especially in the early phase of the illness," said Dr. Solomon.

But even after that, symptoms can be difficult to distinguish.

"Later in the illness, COVID is more associated with a hypercoagulable state," he said. "It is more associated with viral pneumonia on chest imaging, like the diffuse ground-glass infiltrates that we've all gotten used to seeing – but flu can do both of those things as well. So, without a test, it's impossible to distinguish between the two infections in the clinic."

But testing can have its shortcomings when flu season clashes

with the COVID-19 pandemic. "Getting the test is not the same as getting the test results," Dr. Solomon added. "Though a lot of people can get a test, if it takes 7 or 8 days to get the test result back, the result is useless."

Widespread, rapid testing also depends on having adequate supplies of viral media transport and swabs. "I think that this is what we should be focusing on now: scaling up access to rapid turnaround testing," he said. Distinguishing between the two is also important to preserve hospital resources. COVID-19 has more rigorous standards than flu for personal protective equipment and isolation of patients within the hospital.

Having chronic lung disease isn't necessarily a risk factor for contracting COVID-19 or the flu, or both, Dr. Solomon said. "It's a risk factor for having severe disease." Again, he noted that flu vaccines are still necessary in these patients, as well as patients of advanced age and underlying medical conditions such as heart disease, diabetes, and obesity.

In managing children, it's important to keep in mind that they communicate differently about their illnesses than adults, said Dr. Kaplan. "They may not have the words to tell you the same kind of thing that the adult tells you." That's where family members can help to flesh out the history. "They may present with an initially much milder form, if you will, where they're not as critical up front, but then that small proportion of them comes back with the multi-inflammatory syndrome and then they are profoundly ill."

Younger people make up a larger share of COVID-19 patients now, compared with the initial wave that hit the Northeast in the spring, Dr. Kaplan said. "We don't know if that's because the virus is a little different or the people that are getting sick are a little bit different."

The COVID-19 strain now emerging may be less virulent than the strain that hit in early spring, he said. "That doesn't mean that there aren't still profoundly critical ill people with COVID of many different age ranges, that is true, but there are a lot of people that we now see will test positive, but aren't really as profoundly ill as when it first landed here in the United States."

That may be somewhat welcome as flu season arrives.

The physicians interviewed have no relevant disclosures.

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# Heart damage after COVID-19 'recovery'

BY STEVE STILES

**E**vidence that the heart can take a major hit in patients hospitalized with COVID-19, especially those already with cardiovascular disease or its risk factors, has been sadly apparent from the pandemic's earliest days.

Less clear from case studies and small series to date has been whether SARS-CoV-2 directly attacks the heart and whether acute cardiac effects of the illness may lead to some kind of lingering cardiomyopathy.

The field's grasp of those issues advanced a bit in two new reports published in *JAMA Cardiology* that seem to validate concerns the virus can infect the myocardium, without necessarily causing myocarditis and the possibility that some "recovered" patients may be left with persistent myocardial injury and inflammation that potentially could later manifest as heart failure.



DR. YANCY

## Persistent inflammation by cardiac magnetic resonance

A prospective cohort study (2020 Jul 27. doi: 10.1001/jamacardio.2020.3557) with 100 patients recovered from a recent bout of the disease showed evidence of ventricular dysfunction, greater ventricular mass, and in 78% of the cohort, signs of myocardial inflammation by cardiac magnetic resonance (CMR) imaging. The CMR findings correlated with elevations in troponin T by high-sensitivity assay (hs-TnT).

Two-thirds of the cohort, whose acute COVID-19 severity had "ranged from asymptomatic to minor-to-moderate symptoms," had recovered at home, whereas the remaining "severely unwell patients" had been hospitalized, wrote the authors, led by Valentina O. Püntmann, MD, PhD, University Hospital Frankfurt (Germany).

None of the patients had a history of heart failure or cardiomyopathy, although some had hypertension, diabetes, or evidence of coronary disease.

"Our findings demonstrate that participants with a relative paucity of preexisting cardiovascular condition and with mostly home-based recovery had frequent cardiac inflammatory involvement, which was

similar to the hospitalized subgroup with regards to severity and extent," the group noted.

"There is a considerable ongoing myocardial inflammation in the heart muscle weeks after recovery from COVID-19 illness. This finding is important because it may herald a considerable burden of heart failure in a few years down the line," Dr. Püntmann said in an interview.

Early diagnosis would offer "a good chance that early treatment could reduce the relentless course of inflammatory damage or even halt it," she said.

"The relatively clear onset of COVID-19 illness provides an opportunity, which we often do not have with other conditions, to take a proactive action and to look for heart involvement early, within a few weeks of recovery."

The study's CMR evidence of inflammation edema, scarring, and pericardial effusion are among "the major diagnostic criteria for inflammatory and viral myocarditis," observed Biykem Bozkurt, MD, PhD, from Baylor College of Medicine, Houston, who wasn't part of either new study.

The findings suggest – consistent with previous evidence – that some patients with recent COVID-19 may be left with ongoing myocardial inflammation, and this study further adds that it could potentially become subacute or even chronic and in some may not be totally reversible, she said in an interview. How long the effects are likely to persist "remains to be determined. We need longer-term outcomes data."

## Viral presence without myocarditis

The accompanying report (2020 Jul 27. doi: 10.1001/jamacardio.2020.3551) featured a post-mortem analysis of hearts from 39 patients with mostly severe COVID-19 that pointed to a significant SARS-CoV-2 presence and signs that the virus vigorously replicated in the myocardium.

There was no evidence, however, that the infection led to fulminant myocarditis. Rather, the virus had apparently infiltrated the heart by localizing in interstitial cells or in macrophages that took up in the myocardium without actually entering myocytes, concluded the report's authors, led by Diana Lindner, PhD, from the University Heart and Vascular Centre Hamburg (Germany).

The findings suggest "that the pres-

## VIEW ON THE NEWS

**G. Hossein Almassi, MD, FCCP, comments:** These two reports from Germany suggest two different types of cardiac involvement by SAR-CoV-2 virus. The Frankfurt study confirmed myocardial involvement with ventricular dysfunction and evidence of myocardial inflammation and myocarditis on cardiac MRI long after recovery from COVID-19 illness (60-90 days) in a relatively young group of patients (median age 49) and volunteers, while the second report from Hamburg on autopsy findings in 39 elderly patients (median age 85), 15 patients negative for COVID, indicates a different type of cardiac involvement with viral replication in the interstitial cells but no myocyte infiltration or necrosis.

Could the age difference between the two studies partially explain this divergent finding? Maybe!

The real concern is the long-term impact of myocarditis and myocardial fibrosis on cardiac function and the possibility for future congestive heart failure. Sound preventive measures against COVID-19 to reduce the number of COVID cases, and careful long-term follow-up of patients recovered from this disease would help identify that group of patients with persistent myocarditis at an earlier stage.



ence of SARS-CoV-2 in cardiac tissue does not necessarily cause an inflammatory reaction consistent with clinical myocarditis," the group wrote.

No evidence of the virus was seen in 15 cases, about 61% of the group. In 16 of the remaining 24 hearts, the viral load exceeded 1,000 copies per mcg of RNA, a substantial presence. Those 16 showed increased expression of inflammatory cytokines but no inflammatory cell infiltrates or changes in leukocyte counts, the researchers noted.



DR. BOZKURT

"Findings of suggested viral replication in the cases with a very high viral load are showing that we need to do more studies to find out long-term consequences, which we do not know right now," senior author Dirk Westermann, MD, also from the University Heart and Vascular Centre Hamburg, said.

## Implications for heart failure

The postmortem findings from Dr. Lindner and associates "provide intriguing evidence that COVID-19 is associated with at least some component of myocardial injury, perhaps as the result of direct viral infection of the heart," wrote Clyde W. Yancy, MD, MSc, from Northwestern University, Chicago, and Gregg C. Fonarow, MD, from

the University of California, Los Angeles, in an editorial accompanying both reports (2020 Jul 27. doi: 10.1001/jamacardio.2020.3575).

The CMR study from Dr. Püntmann and colleagues – on the backdrop of earlier COVID-19 observations – suggests the potential for "residual left ventricular dysfunction and ongoing inflammation" in the months following a COVID-19 diagnosis. Both developments may be "of sufficient concern to represent a nidus for new-onset heart failure and other cardiovascular complications," contend Dr. Yancy and Dr. Fonarow.

"When added to the postmortem pathological findings from Lindner et al., we see the plot thickening and we are inclined to raise a new and very evident concern that cardiomyopathy and heart failure related to COVID-19 may potentially evolve as the natural history of this infection becomes clearer," they wrote.

Some patients, having recovered from the acute illness, may be left with a chronic inflammatory state that probably puts them at increased risk for future heart failure, agreed Dr. Bozkurt when interviewed.

"They could show further decline in cardiac function, and their recovery might take longer than with the usual viral illnesses that we see," she said.

Dr. Püntmann had no disclosures; statements of potential conflict for the other authors are in the report.

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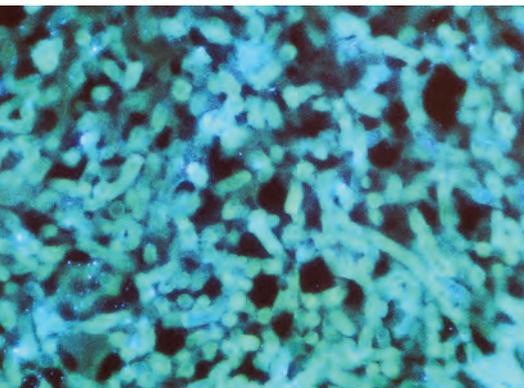
# COVID-linked aspergillosis increased 30-day mortality

BY NEIL OSTERWEIL

MDedge News

Researchers are beginning to make some inroads in identifying the role of secondary infections in the course and outcomes of COVID-19.

Patients who are on ventilatory support for severe COVID-19 in-



Aspergillus

fections appear to be at high risk for invasive pulmonary aspergillosis, which in a small prospective study was associated with a more than threefold risk for 30-day mortality. The findings were published online in *Clinical Infectious Diseases*.

Among 108 patients with COVID-19 on mechanical ventilation in one of three intensive care units, 30 (27.7%) were diagnosed with coronavirus-associated pulmonary aspergillosis (CAPA) based on consensus definitions similar to those used to diagnose influenza-associated pulmonary aspergillosis (IAPA).

Of the patients with CAPA, 44% died within 30 days of ICU admission, compared with 19% of patients who did not meet the criteria for aspergillosis ( $P = .002$ ). This difference translated into an odds ratio for death with CAPA of 3.55 ( $P = .014$ ), reported Michele Bartoletti, MD, PhD, of the infectious diseases unit at Sant'Orsola Malpighi Hospital in Bologna, Italy, and colleagues.

When the investigators applied a proposed definition of putative invasive pulmonary aspergillosis, or "PIPA" to the same patients, the 30-day mortality rate jumped to 74% vs. 26% for patients without PIPA ( $P < .001$ ), with an OR of 11.60 ( $P < .001$ ). "We found a high incidence of CAPA among critically ill COVID-19 patients and that its occurrence seems to change the natural history of disease," they wrote.

## Diagnosis challenging

At the best of times, the diagnosis of pulmonary aspergillosis is difficult, subject to both false-positive and false-negative results, said a critical care specialist who was not involved in the study.

"Critically ill patients are susceptible to having aspergillus, so in reading the article, my only concerns are that I don't know how accurate the testing is, and I don't know if their population is truly different from a general population of patients in the ICU," Daniel R. Ouellette, MD, FCCP, associate director of medical critical care at Henry Ford Hospital in Detroit, said in an interview.

As seen in ICU patients with severe influenza or other viral infections, patients with severe COVID-19 disease are susceptible to secondary infections, he said, making it difficult to know whether the worse outcomes seen in patients with COVID-19 and presumed aspergillosis are a reflection of their being more critically ill or whether the secondary infections themselves account for the difference in mortality.

## Aspergillosis linked with 30-day mortality

Dr. Bartoletti and colleagues conducted a study on all adult patients with microbiologically confirmed COVID-19 receiving mechanical ventilation in three ICUs in Bologna.

All patients included in the study were screened for invasive pulmonary aspergillosis with bronchoalveolar lavage and galactomannan detection and cultures. The lavage was performed on ICU admission, one day from the first day of mechanical ventilation, and if patients had evidence of clinical disease progression.

Samples that tested positive for galactomannan, a component of the aspergillus cell wall, were stored and later analyzed with a commercial quantitative real-time polymerase chain reaction assay for aspergillus; these results were not reported to clinicians on the patient floors.

The investigators defined invasive pulmonary aspergillosis according to a recently proposed definition for CAPA. This definition applies to COVID-19-positive patients admitted to an ICU with pulmonary infiltrates and at least one of the following:

- A serum galactomannan  $> 0.5$ .
- Bronchoalveolar lavage galactomannan  $> 1.0$ .
- Positive aspergillus bronchoalveolar

lavage culture or cavitating infiltrate not attributed to another cause in the area of the pulmonary infiltrate.

They compared the CAPA diagnostic criteria with those of PIPA criteria as described by Stijn J. Blot, PhD, and colleagues in study published in the *American Journal of Respiratory and Critical Care Medicine* (2012 Jul 1;186[1]:56-64).

A total of 108 patients were screened for aspergillosis. The majority of patients (78%) were male. The median age-adjusted Charlson Comorbidity Index was 2.5 (range 1-4). The median Sequential Organ Failure Assessment (SOFA) score at



DR. OUELLETTE

ICU admission was 4 (range, 3-5).

As noted, probable aspergillosis by CAPA criteria was diagnosed in 30 patients (27.7%), with the diagnosis made after a median of 4 days after intubation and a median of 14 days from onset of COVID-19 symptoms.

A comparison of clinical characteristics of patients with and without probable CAPA showed that only chronic steroid therapy at  $\geq 16$  mg/day prednisone for at least 15 days was significantly associated with risk for CAPA ( $P = .02$ ).

At a median follow-up of 31 days, 54 patients (50%) had been discharged, 44 (41%) had died, and the remaining patients were still on follow-up. The mortality rate with 30 days of ICU admission was 44% for patients with probable CAPA vs. 19% for patients without. Among patients deemed to have PIPA, 74% died within 30 days of admission, compared with 26% without PIPA.

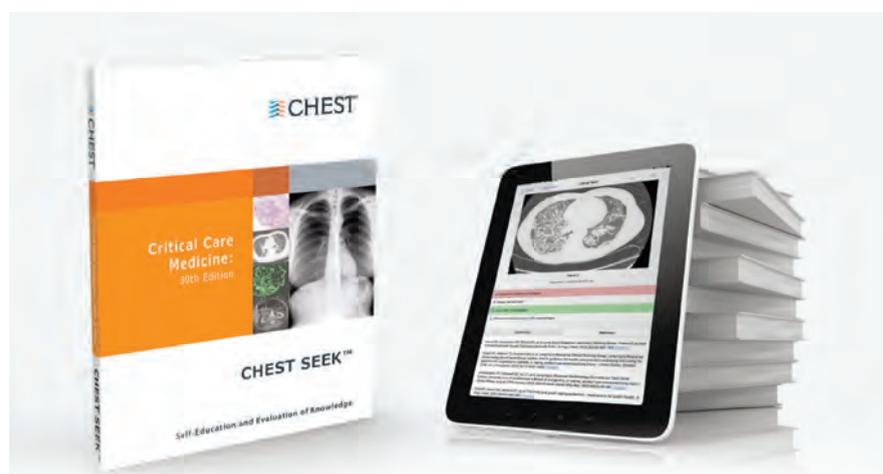
In a logistic regression model, the association of CAPA with increased risk for 30-day mortality remained even after adjustment for the need for renal replacement therapy (OR 3.02;  $P = .015$ ) and SOFA score at ICU admission (OR 1.38;  $P = .004$ ).

In a logistic regression using the PIPA rather than CAPA definition, the OR for 30-day mortality was 11.60 ( $P = .001$ ).

The study was performed without external funding. The authors and Dr. Ouellette reported no conflicts of interest.

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**SOURCE:** Bartoletti M et al. *Clin Infect Dis*. 2020 Jul 28. doi: 10.1093/cid/ciaa1065.



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# 'Long sleep' in middle age doubles Alzheimer's risk

BY PAULINE ANDERSON

**M**iddle-aged individuals who have sleep apnea or who get 9 or more hours of sleep at night have more than double the risk

of developing Alzheimer's disease within about 6 years, new research suggests. A U.K. Biobank study of more than 500,000 individuals also showed that excessive daytime sleepiness was associated with increased

risk for Alzheimer's disease.

"Addressing sleep problems in middle-age may play a role in improving brain health," said lead author Lei Gao, MD, assistant professor of anesthesia at Harvard Medical School

and associate scientist in the division of sleep and circadian disorders at Brigham and Women's Hospital, both in Boston. The findings were presented at the virtual annual meeting of the Alzheimer's Association International Conference 2020.

## Intricately linked

Sleep disturbances are common and on the rise around the world. In recent years, researchers have become increasingly aware of the intricate link between sleep health and brain health, Dr. Gao noted.

The current study included 502,538 individuals from the U.K. Biobank (mean age, 57 years) who were free from Alzheimer's disease at baseline. They were followed for up to 12 years. The participants self-reported sleep traits, including hours of nighttime sleep, daytime sleepiness, sleep apnea diagnosis, snoring, and napping. Researchers determined Alzheimer's disease diagnoses from hospital admissions and from death registries.

In addition to adjusting for age, sex, education, and ethnicity, the full model adjusted for socioeconomic status, body mass index, physical activity, smoking and alcohol use, cardiovascular diseases and risk factors, neurological diseases, respiratory diseases, depression/anxiety, and medication use. Over the course of a mean follow-up of 6.4 years, 932 participants developed Alzheimer's disease.

## Complex disorder

Compared with those who got an average of 6-9 hours of sleep per night, those getting more than 9 hours had a higher risk for Alzheimer's disease (hazard ratio, 2.04; 95% confidence interval, 1.56-2.67;  $P < .001$ ). Having sleep apnea also raised the risk significantly (HR, 2.05; 95% CI, 1.23-3.42;  $P = .006$ ), as did daytime sleepiness (HR, 1.56; 95% CI, 1.18-2.03;  $P = .001$ ).

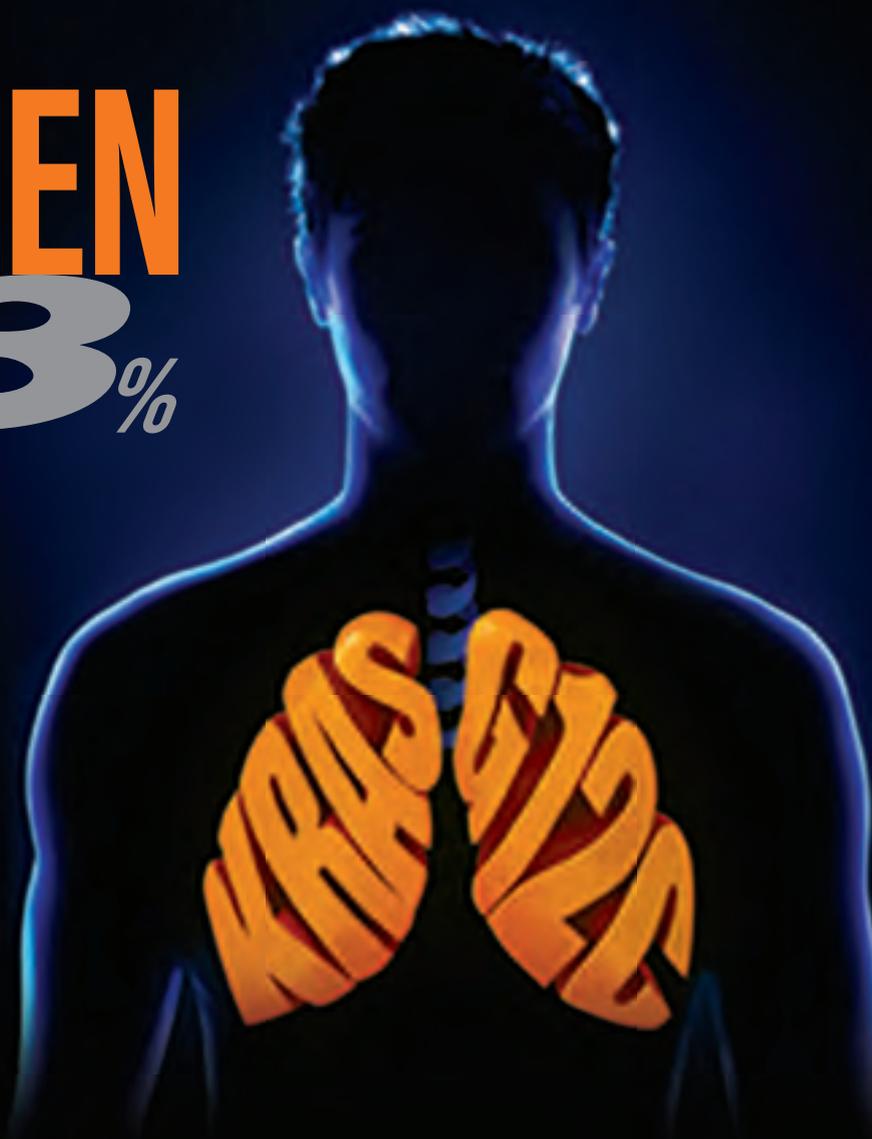
Dr. Gao noted that daytime sleepiness and sleep apnea remained predictive after controlling for sleep duration. "In fact, all three sleep traits remained associated with Alzheimer's disease within the same model, suggesting some degree of independence."

Interestingly, snoring, which is a common symptom of sleep ap-



DR. GAO

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EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

References: 1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198.  
2. Ahmadzadeh T, et al. *J Clin Med.* 2018;7:153.

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Oncology

nea, was not linked to Alzheimer's disease risk. The "vast majority" of people who snore don't meet criteria for a diagnosis of sleep apnea, which was particularly true for this large cohort of relatively healthy study participants, Dr. Gao noted.

"Sleep apnea is a complex, multisystemic sleep disorder associated with obesity, high blood pressure, and often other heart problems," he said.

He added that, as an anesthesiologist, he is particularly wary if patients have this condition, "given their increased risk for airway difficulties, adverse cardiac events, postoperative respiratory complications, and confusion or delirium, which is also associated with higher risk for eventual Alzheimer's disease and death."

These multisystemic factors may be driving the link to Alzheimer's disease. "We certainly need to address this better as the population ages and obesity rates rise," Dr. Gao said.

### No association with napping

Unlike another of Dr. Gao's studies that was conducted in a much older population, napping was not a risk factor for Alzheimer's disease in the current study's younger participants. It could be that the impacts of different sleep traits on health outcome change with age, Dr. Gao said, or this could represent a limitation of using self-reported sleep measures as opposed to objective and/or quantitative measures, such as actigraphy. The reasons for napping, which differ around the world with the habit being common in certain parts, may also help explain differences in observed associations.

Although the investigators tried to control for comorbidities and medication use, there "most certainly" could be a reverse causation at work. For example, sleeping too much could be both a cause and a symptom of dementia. Dr. Gao noted that sleep disturbances often become more prevalent with dementia, and sleeping too much or complaining of daytime sleepiness may be a result of preclinical Alzheimer's disease. Even if there is a reverse causation, however, the average time to Alzheimer's disease diagnosis was over 6 years in this study. "This may be a significant window of time to intervene," he said.

It's also important to have sleep apnea treated. "While more studies are needed, it's generally believed that addressing the pauses in breathing, the apnea episodes, will help reduce cardiovascular health risks such as obesity, high blood pressure and heart failure. All are known to be strongly linked to dementia risk," Dr. Gao said.

Results from an assessment of 100,000 actigraphy records from a

subset of the same population are expected soon and will add objective confirmation of these self-reported results, he added.

### Unique, powerful

Commenting on the findings, Alberto Ramos, MD, associate professor of clinical neurology and research director of the sleep medicine program

at the University of Miami, called the study "unique" because of its prospective design and large sample size.

"Another strength of the study was that it included a population-based sample as opposed to one from a memory or sleep clinic where people already have symptoms or are already sick," said Dr. Ramos, who was not involved with the research.

While most studies that have linked sleep disturbances with dementia risk have been in older adults, this study's population was middle-aged to start out, he noted.

Dr. Gao and Dr. Ramos reported no relevant financial relationships.

*A version of this article originally appeared on Medscape.com.*

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# Proposed rule – 2021 Physician Fee Schedule

BY DENISE MERLINO AND  
MICHAEL NELSON, MD, FCCP

The Centers for Medicare and Medicaid Services (CMS) released the proposed rule for the 2021 Physician Fee Schedule (PFS) on August 4th and it contains a number of changes of interest to pulmonary, critical care and sleep physicians (<http://federalregister.gov/d/2020-17127>). This is a “proposed rule” and CMS will accept comments from the public and societies until October 5th with the final rule published around December 1st. This is an opportunity to make one’s opinion known so please take advantage of it. The two items of particular interest include the drop in the conversion factor and the acceptance of the changes to office evaluation and management (E/M) Current Procedural Terminology (CPT) codes.

The PFS conversion factor is the reimbursement level set by CMS for one relative value unit (RVU) and changes each year, usually in a positive way. Since the repeal of the sustainable growth rate in 2015, healthcare providers have counted on relative stability in the conversion factor. In 2021, however, the conversion factor will go from \$36.09 to \$32.26, a 10.61% reduction absent congressional action or other legal authorities identified by the white house. CMS predicts a \$10.2 billion dollar increase in spending in certain areas and budget neutrality requires this be offset by reductions in other areas. Approximately half of the reduction is necessary to pay for the increase in the RVUs related to the revaluing of the office E/M CPT codes and the remainder for other programs and services.

The impact on physician practices varies by specialty. Those practices that rely on inpatient and proce-

dural services will see the greatest reduction in reimbursement while office-based practices will actually see an increase in reimbursement.

The increase in reimbursement for office E/M visits did not apply to the visits that are bundled into global surgery codes and is, therefore, partly responsible for the drop in reimbursement for surgical specialties.

In the CY 2021 proposed rule CMS has also accepted the RUC recommended changes in code descriptors and levels of reimbursement for office based E/M codes 99202-99215. The level of these codes will now be determined using medical decision making or time. Recall that the CPT code 99201 has been eliminated effective January 1, 2021. Additionally, as noted in the 2020 final rule, CMS finalized a new E/M add-on code (GPC1X Visit complexity inherent to evaluation and management associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient’s single, serious, or complex chronic condition. (Add-on code, list separately in addition to office/outpatient evaluation and management visit, new or established)) to describe visit complexity. CMS states that this service is distinct from other preventive or care management codes because “GPC1X reflects the time, intensity, and PE when practitioners furnish services that enable them to build longitudinal relationships with all patients (that is, not only those patients who have a chronic condition or single-high risk disease) and to address the majority of patients’ health care needs with consistency and continuity over longer periods of time.” CMS assumes that the specialties which predominantly furnish E/M

associated with medical care services that are part of ongoing care related to a patient’s single, serious, or complex condition will bill the add-on code with every E/M visit. Total utilization for the code across all specialties is estimated to be \$181M.

In response to concerns from commenters that the code is unclear, CMS is soliciting more specific information about how the definition of GPC1X is unclear, how CMS might address those concerns and how the utilization assumptions for the code can be refined.

CPT code 99XXX represents a prolonged service code that should be used when one uses time to determine the level of a code and exceeds the time of codes 99205 and 99215. While CMS accepted the RVU values of the 99XXX code, it also changed the time elements for reporting.

One can see that there is a significant increase in the RVU values of the E/M codes at the higher levels and, as noted above, this increase is responsible for about 8% of the 10% reduction in the conversion factor.

| CPT code | 2020 time | 2020 RVU | Proposed 2021 time | Proposed 2021 RVU |
|----------|-----------|----------|--------------------|-------------------|
| 99201    | 17        | 0.48     | NA                 | NA                |
| 99202    | 22        | 0.93     | 22                 | 0.93              |
| 99203    | 29        | 1.42     | 40                 | 1.6               |
| 99204    | 45        | 2.43     | 60                 | 2.6               |
| 99205    | 67        | 3.17     | 85                 | 3.5               |
| 99211    | 7         | 0.18     | 7                  | 0.18              |
| 99212    | 16        | 0.48     | 18                 | 0.70              |
| 99213    | 23        | 0.97     | 30                 | 1.30              |
| 99214    | 40        | 1.50     | 49                 | 1.92              |
| 99215    | 55        | 2.11     | 70                 | 2.8               |
| 99XXX    | NA        | NA       | 15                 | 0.61              |

| New Patient Office/Outpatient E/M Visit (Total Practitioner Time, When Time is Used to Select Code Level)         | CPT code   |
|---|--|
| 60-74 minutes   | 99205  |
| 89-103 minutes  | 99205 x1 and 99XXX x1  |
| 104-118 minutes   | 99205 x1 and 99XXX x2  |
| 119 or more minutes   | 99205 x1 and 99XXX x3 or more for each additional 15 minutes |
| Established Patient Office/Outpatient E/M Visit (Total Practitioner Time, When Time is Used to Select Code Level) | CPT code   |
| 40-54 minutes   | 99215  |
| 69-83 minutes   | 99215 x1 and 99XXX x1  |
| 84-98 minutes   | 99215 x1 and 99XXX x2  |
| 99 or more minutes  | 99215 x1 and 99XXX x3 or more for each additional 15 minutes |
| 99 or more minutes  | 99215 x1 and 99XXX x3 or more for each additional 15 minutes |

## Proposed RVUs and National Unadjusted PFS Rates for Office/Outpatient E/M Visits

| Specialty              | Change in 2021 Reimbursement |
|------------------------|------------------------------|
| Pulmonary Medicine     | + 1%                         |
| Critical Care Medicine | - 8%                         |
| Cardiology             | + 1%                         |
| Thoracic Surgery       | - 8%                         |
| Cardiac Surgery        | - 9%                         |
| Internal Medicine      | + 4%                         |
| Family Practice        | + 13%                        |

| HPCS Code | Work | Non-Facility PE | Facility PE | Mal-practice | Total Non-Facility | Total Facility | Non-facility Rate | Facility Rate |
|-----------|------|-----------------|-------------|--------------|--------------------|----------------|-------------------|---------------|
| 99202     | 0.93 | 1.12            | 0.41        | 0.09         | 2.14               | 1.43           | \$69.04           | \$46.13       |
| 99203     | 1.60 | 1.54            | 0.67        | 0.15         | 3.29               | 2.42           | \$106.14          | \$78.07       |
| 99204     | 2.60 | 2.10            | 1.12        | 0.24         | 4.94               | 3.96           | \$159.37          | \$127.75      |
| 99205     | 3.50 | 2.71            | 1.57        | 0.32         | 6.53               | 5.39           | \$210.66          | \$173.88      |
| 99211     | 0.18 | 0.50            | 0.08        | 0.01         | 0.69               | 0.27           | \$22.26           | \$8.71        |
| 99212     | 0.70 | 0.91            | 0.29        | 0.07         | 1.68               | 1.06           | \$54.20           | \$34.20       |
| 99213     | 1.30 | 1.29            | 0.56        | 0.10         | 2.69               | 1.96           | \$86.78           | \$63.23       |
| 99214     | 1.92 | 1.76            | 0.84        | 0.13         | 3.81               | 2.89           | \$122.91          | \$93.23       |
| 99215     | 2.80 | 2.33            | 1.26        | 0.21         | 5.34               | 4.27           | \$172.27          | \$137.75      |
| 99XXX     | 0.61 | 0.31            | 0.28        | 0.05         | 0.97               | 0.94           | \$31.29           | \$30.32       |
| GPC1X     | 0.33 | 0.14            | 0.14        | 0.02         | 0.49               | 0.49           | \$15.81           | \$15.81       |

## FROM CHEST PRESIDENT-ELECT

## Steven Q. Simpson, MD, FCCP

**C**HEST President-Elect Steven Q. Simpson, MD, FCCP, is Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Kansas. He is also senior advisor to the Solving Sepsis initiative of the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services.

As we greet our new incoming CHEST President, we asked him for a few thoughts about his upcoming presidential year. He kindly offered these responses:

#### What would you like to accomplish as President of CHEST?

This is an interesting question, because a global pandemic and other developments in our world dictate that our organizational goals must adapt to a landscape that has shifted in recent months. My goals as President are somewhat different from what I stated when I ran for the office.

**1** First, I will build on the efforts of my predecessors to ensure that CHEST is an inclusive and anti-racist organization. All CHEST members must have equal opportunities within our organization to advance their lives and their careers, regardless of race, ethnicity, sex, or gender. My goal is to examine our structures for participation and advancement to positions of leadership in the organization and to evaluate our educational and research offerings, all with the purpose of discovering and remedying places where we have been blind to our own systematic bias. Further, CHEST must advocate for and lead others to advocate for equality, for equal access to medical care, and for policies that promote them. We must be leaders in this arena, through both our voice and our actions.

**2** We will build on CHEST's new initiative to support the wellness of our members and to help us all perform at our best, day in and day out. I hope for our newly established Wellness Center (<https://tinyurl.com/y4eflecw>) to become a frequent stop for all CHEST members, myself included, to help us to sustain ourselves through the pandemic and beyond.

**3** We must maintain both the quality and the feel of our educational and research offerings during this time when we cannot come together in person. My goal for us is that we use this time to



Dr. Simpson

embrace remote and nontemporally synchronous education, ie, web-based education, to make CHEST's offerings the best anywhere. In the remainder of the 21st century, digital transformation of teaching and learning will advance tremendously, and our creative use of technology will become a norm. I hope that we never abandon in-person meetings, but using technology to improve information transfer and augmenting our members' continuing education are clearly here to stay. My goal for us is that we maintain an atmosphere to both our in-person meetings and our remotely delivered meetings that makes generating new knowledge and learning what we generate enjoyable, even fun. I believe our digital transformation will make some interesting things possible over time.

**4** My overall goal for CHEST in the coming year is not that we "make it through" the current pandemic, but that we emerge stronger, smarter, and better for the experience, and prepared for the next challenge(s).

Before COVID-19, I had goals for my presidency, and these issues have not disappeared. CHEST needs to be user-friendly for our members, from our website, to the ways in which we deliver education, to the type of research we develop and promote. On the research side, our members have long been interested in clinical research that informs and improves our patient care. My goal is to double down on promoting, supporting, and presenting research that serves exactly this purpose. We are growing our team-based education, and I have a special goal for CHEST to become the home for pulmonary, critical care, and sleep advanced practice providers. I care tremen-

*Continued on following page*

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dously about our international members, and I will promote both international growth and catering of CHEST's offerings to benefit our international members.

### What do you consider to be the greatest strength of CHEST, and how will you build upon this during your Presidency?

There is zero doubt that CHEST's greatest strength is the people who gravitate to our organization. From pure clinicians to academicians; from clinical researchers to clinical educators to outcomes mavens—all levels of the health-care team. At every level of this organization are members who all want to be better at what we do, who want to figure out the ways for doing that, who want to explore the boundaries of what that means, and who want to help others to do the same. That goes, as well, for the professional staff who support the members, and who have adopted the motto, "CRUSH lung disease," because they share our mission and are here to help us do it better.

The absolutely most enjoyable thing about leadership is having the opportunity to survey the landscape

and see who's looking for opportunity, who's a rising star, who's looking for people to mentor, then matching those people with opportunities and with jobs to do. Good people who are motivated by the right principles rise to the occasion. My job as President is to help ensure that the organization via the CHEST Board of Regents is addressing the correct problems with the right vision, to identify the right talented and dedicated members for the jobs, and then to support and stay out of their way as they make the vision a reality.

### What are some challenges facing CHEST, and how will you address these challenges?

The major immediate challenges facing CHEST are pandemic-related, in terms of helping to ensure the well-being of our members, and in helping them to address the inequities and disparities in care for our patients of color, who have been hardest hit by the emergence of SARS-CoV-2. I addressed these with my goals, above. To be more specific, though, our board will be using various techniques, including dialogue with our members of color, to understand and address

our own implicit biases, so that we can achieve the correct vision and tone of inclusion for all of our members. Also addressed in my goals is the isolation from one another that we are all experiencing because of the pandemic. This situation makes it difficult for us to maintain the style and tone of live learning experiences that our CHEST members are accustomed to. The challenge is to develop materials that can be interactive at a distance, and this likely includes gamification of educational content and employing virtual reality. CHEST Innovations is already working in this arena, and it will be our job as member volunteers to support those efforts. The isolation affects our international members, as well, and our ability to travel to maintain relationships. The nice thing is that web conferencing works just as well for international meetings as for meetings in the US, although somebody often has to go to bed very late or get up very early in the morning to make them work! The efforts are worth our time. Again, we will be working in various arenas to maintain and grow our international relationships.

### And finally, what is your charge to the members and new Fellows (FCCPs) of CHEST?

We do not yet see clearly whether to expect a massive winter surge of COVID-19 infections. However, it is a reasonably likely possibility. My charge to our members and our new Fellows is first to stay safe, yourself, and to take care of your mental and physical well-being, so that you can be present and functioning at peak levels for your patients.

Make sure your family is, likewise, being safe. Secondly, keep doing what you do, which is excellent patient care, excellent teaching, excellent research to push the boundaries of our knowledge. And finally, you've seen my ideas of the challenges facing CHEST. I want you to survey, yourself, and tell me what you think our challenges, goals, and responsibilities should be. And if anything I've said resonates with you, volunteer to help us address our challenges and keep CHEST the professional home that you deserve and that you will never want to leave.

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## Occupational and environmental health

### Occupations at risk for COVID-19

As the COVID-19 pandemic has not yet ended, some occupational risks are faced day-to-day. Individuals have been practicing social distancing by working from home in recent months. While this arrangement can be a great way to reduce one's exposure to COVID-19, it's a luxury that's available to just 29% of Americans. The situation for the remaining 71% is uncertain. The individuals on the front lines, whether they're taking care of patients or stocking grocery shelves, may face a high risk of potential exposure to the virus (Baker et al. *PLoS One*. 2020; 15[4]:e0232452. doi: 10.1371/journal.pone.0232452). The high risk of the occupations lies in the close contact with people, such as pulmonologists, dentists, and ENT doctors and nurses using tools to lavage during aerosol-generating procedures (She et al. *Clin Transl Med*. 2020;9(1):19. doi: 10.1186/s40169-020-00271-z). Also, barbers, teachers, beauticians, fitness coaches, stewardesses, kindergarten teachers, chefs, waiters, etc, are required to be in contact with others facing the threat of infection.

Raising awareness of the issues will help avoid occupational transmission of COVID-19. Medical masks, N95 respirators, and hand hygiene are evidenced for high-risk, aerosol or non-aerosol-generating procedures offer protection against viral respiratory infection exposure in the pandemic (She et al. and Bartoszko et al. *Influenza Other Respir Viruses*. 2020;14(4):365. doi: 10.1111/irv.12745). In addition, using datasets to allow us to assign a more quantitative figure to each occupation's level of risk to develop a protection strategy is imperative.

Mary Beth Scholand, MD, FCCP  
Vice-Chair  
Jun She, MD, PhD  
Steering Committee Member

## Palliative and end-of-life care

### Palliative care and critical care mutualism: innovative support during the COVID-19 pandemic

The ICU is the epitome of a complex adaptive system (CAS), a highly organized and structured system

that nonetheless is constantly evolving and adapting to changing needs and circumstances (Waldrom. *Complexity: The Emerging Science at the Edge of Order and Chaos*. Simon & Schuster, New York. 1992). This has never been more apparent than during the current novel coronavirus pandemic. Previously, medical advances and quality improvement projects were carefully vetted, slowly designed, willingly implemented. Today, health systems and society must take rapid and radical leaps to iterate policies and procedures in real time. Deeply embedding and consulting specialized palliative care teams early and often for hospitalized COVID-19 patients is a best practice strategy that benefits patients, families, and staff, and allows critical care teams to function at the top of their expertise. As one of our critical care physician colleagues noted, "Palliative care needs rise with critical care needs – we must help each other innovate practices."

Beyond complex symptom management and relief of suffering, palliative care's foundation is providing support during times of uncertainty and ambiguity. This proficiency is now an imperative. Here are some highly relevant examples of current palliative care initiatives within the ICU:

- Encouraging values assessment and goals of care for alignment of treatment plans.
- Advanced care planning with identification of primary and secondary health-care proxies in the setting of potential concurrent infections within families.
- Facilitating multidisciplinary video family meetings and clinical updates.
- Supporting ICU staff to alleviate moral distress and fatigue.
- Developing and distributing bereavement programs and remembrance rituals.
- Training and education on COVID-specific communication tools.
- Expanding outreach to patients/families through telehealth volunteer programs.

This is an opportunity to strengthen the multidisciplinary model of care in the ICU. It may appear that there is an abyss at the edge of chaos, but palliative care is helping engineer and build

enduring bridges to help us all cross safely to the other side (Bilder and Knudsen. *Front Psychol*. 2014 Sep 30. doi: 10.3389/fpsyg.2014.01104).

Tara Coles, MD  
Hunter Groninger, MD, Vice Chair  
Cheryl Hughes, LICSW  
Rachel Adams, MD

## Respiratory care

### Strategies and technology for safer mechanical ventilation

Clinicians often focus on safe practice as "vigilance in the moment" while interacting with patients and the health-care team and rightly so, especially with mechanical ventilation. New strategies for increasing safety include a more pre-emptive, technology-assisted approach. Alarm fatigue/flooding are serious concerns, and the ECRI found less than 15% of clinical alarms studied (including mechanical ventilation) were



DR. WALSH

"clinically relevant" (eg, requiring some form of action) (ECRI Institute 2018; Plymouth Meeting, PA). Most alarms in health care are set to an "average" patient but as with tailored treatment in precision medicine, it is possible to tune alarm parameters to individual characteristics, including using patient trend data.

An excessive amount of alarms in a clinical environment is thought to be the largest contributing factor to alarm-related adverse events with rates sometimes exceeding 900 alarms per day (Graham et al. *Am J Crit Care*. 2010;19(1):28-34; quiz 35. doi: 10.4037/ajcc2010651). Human response to stimuli suggests response to alarms is closely matched to the perceived reliability of the alarm system. Instead of alarms based upon single physiological variables, the next generation of smart alarms is integrating much more information than previously possible to reduce false alarms and give more useful alerts. Trend data can better guide interpretation and activation of immediate alarm triggers. For example, a composite ventilation alarm could be created

from the integration of trends of respiratory frequency, minute volume, oxygen saturation of hemoglobin, and end-tidal CO<sub>2</sub>. Fewer nonactionable alarms can result in greater attention when alarms do occur.

Integrated monitoring of patient data trends can also prompt clinicians when a different ventilation mode or

setting combination should be considered, especially when indicated by consensus guidelines. The human factor of no-fault, peer audits can improve alarm policy compliance and guide the refinement of alarm policies. Most ventilator manufacturers are developing smart, precise patient monitoring and alarms, and their potential needs to be converted to practice as quickly as possible.

Brian Walsh, PhD, RRT  
NetWork Member  
Jonathan Waugh, PhD, RRT  
Steering Committee Member



DR. WAUGH

## Sleep medicine

### Treatment-emergent central apnea may be a frequent cause of PAP nonadherence

Treatment-emergent central apnea (TECSA) refers to new onset central-disordered breathing events after initiating treatment of obstructive sleep apnea (OSA), such as with positive airway pressure (PAP) therapy. The nature of the phenomenon is uncertain, but some theorize that in patients with ventilatory instability, CPAP intermittently lowers the partial pressure of P<sub>c</sub>CO<sub>2</sub> below apneic threshold, causing a central apnea event (Gilmartin et al. *Curr Opin Pulm Med*. 2005;11[6]:485).

TECSA develops in 3.5% to 19.8% of patients starting PAP therapy for OSA. Risk factors include high baseline apnea or arousal index, higher CPAP pressure, older age, male sex, low BMI, and presence of heart failure or ischemic heart disease (Moro et al. *Nat Sci Sleep*. 2016;8:259; Nigam et al. *Ann Thorac Med*. 2016;11[3]:202). Most cases

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## SLEEP STRATEGIES

## An update on the pharmacologic treatment of hypersomnia

BY SHIH YEEM ARIE TAN  
GIPSON, MD, AND KEVIN  
GIPSON, MD

The hypersomnias are an etiologically diverse group of disorders of wakefulness and sleep, characterized principally by excessive daytime sleepiness (EDS), often despite sufficient or even long total sleep durations. Hypersomnolence may be severely disabling and isolating for patients, is associated with decreased quality of life and economic disadvantage, and, in some cases, may pose a personal and public health danger through drowsy driving. Though historically, management of these patients has been principally supportive and aimed at reducing daytime functional impairment, new and evolving treatments are quickly changing management paradigms in this population. This brief review highlights some of the newest pharmacotherapeutic advances in this dynamic field.

Hypersomnolence is a common presenting concern primary care and sleep clinics, with an estimated prevalence of EDS in the general adult population of as high as 6%.<sup>1</sup> The initial diagnosis of hypersomnia is, broadly, a clinical one, with careful consideration to the patient's report of daytime sleepiness and functional impairment, sleep/wake cycle, and any medical comorbidities. The primary hypersomnias include narcolepsy type 1 (narcolepsy with cataplexy, NT1) and narcolepsy type 2 (without cataplexy, NT2), Kleine-Levin Syndrome (KLS), and idiopathic hypersomnia. Secondary hypersomnia disorders are more commonly encountered in clinical practice and include hypersomnia attributable to another medical con-



DR. SHIH YEE-MARIE TAN  
GIPSON



DR. KEVIN  
GIPSON

dition (including psychiatric and neurologic disorders), hypersomnia related to medication effects, and EDS related to behaviorally insufficient sleep. Distinguishing primary and secondary etiologies, when possible, is important as treatment pathways may vary considerably between hypersomnias.

Generally, overnight in-lab polysomnography is warranted to exclude untreated or sub-optimally treated sleep-disordered breathing or movement disorders which may undermine sleep quality. In the absence of any such findings, this is usually followed by daytime multiple sleep latency testing (MSLT). The MSLT is comprised of four to five scheduled daytime naps in the sleep lab and is designed to quan-

tify a patient's propensity to sleep during the day and to identify architectural sleep abnormalities which indicate narcolepsy. Specifically, narcolepsy is identified by MSLT when a patient exhibits a sleep onset latency of  $\leq 8$  minutes and at least two sleep-onset REM periods (SOREMPs), or, one SOREMP on MSLT with a second noted on the preceding night's PSG. Actigraphy or sleep logs may be helpful in quantifying a patient's total sleep time in their home environment. Adjunctive laboratory tests for narcolepsy including HLA typing and CSF hypocretin testing may sometimes be indicated.

General hypersomnia management usually consists of the use of wakefulness promoting agents, such as stimulants (eg, dexamethylphenidate) and dopamine-modulating agents (eg, modafinil, armodafinil), and adjunctive supportive strategies, including planned daytime naps and elimination of modifiable second-

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resolve in weeks to months; however, an estimated 14.3% to 46.2% evolve into treatment persistent central sleep apnea. Up to 4.2% of patients develop delayed TECSA (D-TECSA) or the emergence of central events after at least a month of PAP therapy (Nigam et al. *Ann Thorac Med.* 2018;13[2]:86).



DR. DUPUY-MCCAULEY

TECSA can lead to PAP

intolerance (discomfort, gasping, fragmented sleep), lower usage of PAP, and increased likelihood of discontinuing PAP therapy in the first 90 days (Liu et al. *Chest.* 2017;152[4]:751). When a patient presents with initial or delayed PAP intolerance or persistent symptoms, sleep providers should consider TECSA as a potential etiology. The diagnosis may be made by reviewing data from the patient's PAP device, or by repeat testing. When encountering persistent TECSA, one can consider lowering the PAP pressure, or performing polysomnography with the goal of titrating

the patient to an alternative PAP modality, such as bilevel ST or Adapto Servo Ventilation, which can stabilize breathing in patients with compromised ventilatory control (Morgensthaler et al. *Sleep.* 2014;37[5]:927).



DR. OKORIE

Kara Dupuy-McCauley, MD  
Fellow-in-Training Member  
Caroline Okorie, MD, MPH  
Steering Committee Member

### Thoracic oncology Times, they are a-changing: Lung cancer outcomes improve and the time for nihilism is past

The American Cancer Society 2020 Facts and Figures reported the largest single year drop in overall cancer mortality ever: 2.2% from 2016 to 2017. This record decrease was driven by the decline in lung cancer deaths thanks to treatment advances such as immunotherapy and targeted drugs for specific lung cancer mutations, combined with declining smoking rates. Lung cancer 5-year survival rates are 19% now and should continue rising, especially if

screening rates increase. Immunotherapy has shown a 5-fold increase in survival for advanced non-small cell lung cancer (NSCLC) compared with chemotherapy (13.4% vs 2.6%) and half of metastatic NSCLC patients treated with first-line pembrolizumab were alive after 2 years (vs 34% of chemotherapy patients). Targeted therapies (eg, crizotinib) are similarly encouraging with half of stage IV, ALK-positive NSCLC patients diagnosed after 2009 alive 6.8 years later, compared with just 2% of those diagnosed between 1995 and 2001. Pulmonologists have an important role to play in early detection (screening) and identification of candidates for targeted therapy (ordering mutational analysis on diagnostic specimens).



DR. BEGNAUD

Exciting treatment advances compel us to more aggressively diagnose lung cancer with early detection and offer diagnostic procedures, even for patients presenting with advanced disease. In fact, improving outcomes are opening the door to curative-intent

treatment of oligometastatic lung cancer. In addition to improved disease outcomes, most new therapies are much better tolerated by patients than traditional cytotoxic chemotherapy. No longer is the appropriate response to an ugly-looking lung mass to "get your affairs in order."

Abbie Begnaud, MD  
Steering Committee Member

### Reading list

Pacheco JM, Gao D, Smith D, et al. Natural history and factors associated with overall survival in stage IV ALK-rearranged non-small cell lung cancer. *J Thorac Oncol.* 2019;14(4):691. doi: 10.1016/j.jtho.2018.12.014.

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Stephens SJ, Moravan MJ, Salama JK. Managing patients with oligometastatic non-small-cell lung cancer. *J Oncol Pract.* 2018;14(1):23. doi: 10.1200/JOP.2017.026500.

Studies report prolonged long-term survival with immunotherapy vs chemotherapy in advanced NSCLC. *ASCO Post* October 10, 2019.

## CHEST & FFF Virtual Event Series

Sip some wine, play your royal flush, or answer that trivia question right in the nick of time this September with the CHEST Foundation virtual event series! Join us and the Feldman Family Foundation (FFF) as we continue our virtual events through CHEST 2020. And you won't want to miss the CHEST 2020 Foundation Reception on October 18!

For more info and event dates, visit our news and event page or contact us directly at [aperillo@chestnet.org](mailto:aperillo@chestnet.org).

All event proceeds benefit the Buy-A-Mask, Give-A-Mask campaign.



*Continued from previous page*

ary causes. In those patients with hypersomnolence associated with depression or anxiety, the use of antidepressants, including SSRI, SNRI, and DNRI, is often effective, and these medications can also improve cataplexy symptoms in narcoleptics. KLS may respond to treatment with lithium, shortening the duration of the striking hypersomnolent episodes characteristic of this rare syndrome, and there is some indication that ketamine may also be a helpful adjunctive in some cases. In treatment-refractory cases of hypersomnolence associated with GABA-A receptor potentiation, drugs such as flumazenil and clarithromycin appear to improve subjective measures of hypersomnolence.<sup>2,3</sup> In patients with narcolepsy, sodium oxybate (available as Xyrem and, more recently, as a generic medication) has proven to be clinically very useful, reducing EDS and the frequency and severity of cataplexy and sleep disturbance associated with this condition. In July 2020, the FDA approved a new, low-sodium formulation of sodium oxybate (Xywav) for patients 7 years of age and older with a diagnosis of narcolepsy, a helpful option in those patients with cardiovascular and renal disease.

Despite this broadening armamentarium, in many cases daytime sleepiness and functional impairment is refractory to typical pharmacotherapy. In this context, we would like to highlight two newer pharmacotherapeutic options, solriamfetol and pitolisant.

### Solriamfetol

Solriamfetol (Sunosi) is a Schedule IV FDA-approved medication indicated for treatment of EDS in adults with narcolepsy or obstructive sleep apnea. The precise mechanism of action is unknown, but this medication is believed to inhibit both dopamine and norepinephrine reuptake in the brain, similar to the widely-prescribed NDRI bupropion. In a 12-week RCT study on its effects on narcolepsy in adults, solriamfetol improved important measures of wakefulness and sleepiness, without associated polysomnographic evidence of significant sleep disruption.<sup>4</sup> In another 12-week RCT study of solriamfetol in adult patients with EDS related to OSA, there was a dose-dependent improvement in measures of wakefulness.<sup>5</sup> Some notable side-effects seen with this medication include anxiety and elevated mood, as well as increases in blood pressure. A subsequent study

of this medication found that it was efficacious at maintenance of improvements at 6 months.<sup>6</sup> Given the theorized mechanism of action as an NDRI, future observation and studies could provide insights on its effect on depression, as well.

### Pitolisant

Histaminergic neurons within the CNS play an important role in the promotion of wakefulness. Pitolisant (Wakix) is an interesting wakefulness-promoting agent for adult patients with narcolepsy. It acts as an inverse agonist and antagonist of histamine H3 receptors, resulting in a reduction of the usual feedback inhibition effected through the H3 receptor, thereby enhancing CNS release of histamine and other neurotransmitters. This medication was approved by the FDA in August 2019 and is currently indicated for adult patients with narcolepsy. The HARMONY I trial comparing pitolisant with both placebo and modafinil in adults with narcolepsy and EDS demonstrated improvement in measures of sleepiness and maintenance of wakefulness over placebo, and noninferiority to modafinil.<sup>7</sup> In addition, pitolisant had a favorable side-effect profile compared with modafinil. Subsequent studies have reaffirmed the safety profile of pitolisant, including its minimal abuse potential. In one recent placebo-controlled trial of the use of pitolisant in a population of 268 adults with positive airway pressure (PAP) non-adherence, pitolisant was found to improve measures of EDS and related patient-reported measurements in patients with OSA who were CPAP nonadherent.<sup>8</sup> Though generally well-tolerated by patients, in initial clinical trials pitolisant was associated with increased headache, insomnia, and nausea relative to placebo, among other less commonly reported adverse effects. Pitolisant is QT interval-prolonging, so caution must be taken when using this medication in combination other medications which may induce QT interval prolongation, including SSRIs.

### Future directions

Greater awareness of the hypersomnias and their management has led to improved outcomes and access to care for these patients, yet these disorders remain burdensome and the treatments imperfect. Looking forward, novel pharmacotherapies that target underlying mechanisms

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# This month in the journal *CHEST*<sup>®</sup>: Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

**The burden of community-acquired pneumonia requiring admission to an intensive care unit in the United States.**

By Dr. R. Cavallazzi, et al.

**Practical considerations for the diagnosis and treatment of fibrotic interstitial lung disease during the COVID-19 pandemic.**

By Dr. C. J. Ryerson, et al.



**Pulmonary hypertension by the method of Paul Wood.**

By Dr. J. Newman.

**Patient vs clinician perspectives on communication about results of lung cancer screening: A Qualitative Study.**

By Dr. R. Wiener, et al.

**The Use of Bronchoscopy During the COVID-19 Pandemic: CHEST/AABIP Guideline and Expert Panel Report.**

By Dr. M. Wahidi, et al.

Continued from previous page

rather than symptom palliation will allow for more precise treatments. Ongoing investigations of hypocretin receptor agonists seek to target one critical central mediator of wakefulness. Recent studies have highlighted the association of dysautonomia with hypersomnia, offering interesting insight into possible future targets to improve the function and quality of life of these patients.<sup>9</sup> Similarly, understanding of the interplay between psychiatric disorders and primary and secondary hypersomnias may offer new therapeutic pathways.

As treatment plans targeting hypersomnia become more comprehensive and holistic, with an increased emphasis on self-care, sleep hygiene, and mental health awareness, in addition to mechanism-specific treatments, we hope they will ultimately provide improved symptom and burden relief for our patients.

*Dr. Shih Yee-Marie Tan Gipson is a psychiatrist and Dr. Kevin Gipson is a sleep medicine specialist, both with Massachusetts General Hospital, Boston.*

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# News from your CHEST Foundation



As the NetWorks Challenge draws to a close, CHEST Foundation staff want to thank every member who donated to support this year's drive for our COVID-19 Community Grants. When the fund was established in April, we started with a pool of \$60,000 to award to patient support groups and small community organizations providing resources and interventions for those most vulnerable to develop severe complications from COVID-19 – Americans living with chronic lung disease. Within 2 months, we'd awarded all available funds to 25 organizations and had several others still seeking funding. The lion's share of these groups were providing direct service to medically fragile and isolated patients – purchasing PPE, cleaning supplies, pulse oximeters, and even groceries to patients who otherwise wouldn't have access to these critical supplies.

Because of YOUR support of the NetWorks Challenge, we are proud

to share that we are providing an additional \$43,850 in support of COVID-19 Community Grants. Because of you – we can continue to provide vital funding to support group members whose lives you've changed forever.

“Receiving the CHEST Foundation grant for COVID-19 support was a real boost to all of our spirits. Our staff have been working tirelessly to care for our residents 24/7, and there have been some trying and exhausting moments. When we received the community-based grant, it reminded us that there are still people in our community cheering us on, and it's an acknowledgment that our clients matter just as much to the community as they do to us, personally.”

*Katherine A. Brown  
St. Coletta's of Illinois*

## CHEST annual meeting 2020

Greetings,

As the Program Chair of CHEST Annual Meeting 2020, I'm excited to finally share the good news with all of you – our premiere educational event, CHEST 2020, will be taking place October 18-21! As you might have guessed, we're migrating the meeting onto a virtual platform - not only will this change ensure your safety, it will enable so many more of you to attend. Colleagues who may have been excluded due to geographical restrictions in the past will now have the opportunity to experience all that we have to offer!

As always, we'll be bringing you the latest, most relevant clinical topics in pulmonary, critical care, and sleep medicine. From COVID-19 to cultural diversity, we've carefully curated sessions to explore the issues that you want to learn about. Not to mention, our speakers are all experts in their field – at the forefront of the pandemic – and will bring a level of knowledge and insight to the meeting that is truly unparalleled. After all, that's what our annual meeting is known for. Regardless of where or how it is taking place, it's still “the very best of CHEST.”

Other highlights will include over 88 live sessions, including panel and case-based discussions, original investigation presentations with new, unpublished research, and CHEST Games.

Of course, we will have several networking opportunities where you will be able to connect with so many more of your colleagues because of the virtual nature of the meeting. While you may be sitting worlds apart, you'll be socializing in an intimate online space.

While this isn't exactly what we imagined for our meeting, it's what we had to reimagine. Sometimes being pushed out of your comfort zone can lead to something extraordinary, and, in this instance, we think it did.

In closing, I'd like to acknowledge how challenging these past several months have been. For all the long hours, the time spent away from family, and the stress that continues to pile on – this is your chance to unplug and unwind.

We all need an event to look forward to right now, and at CHEST, we've worked hard to bring you one. I hope you'll visit [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org) to register for CHEST 2020.

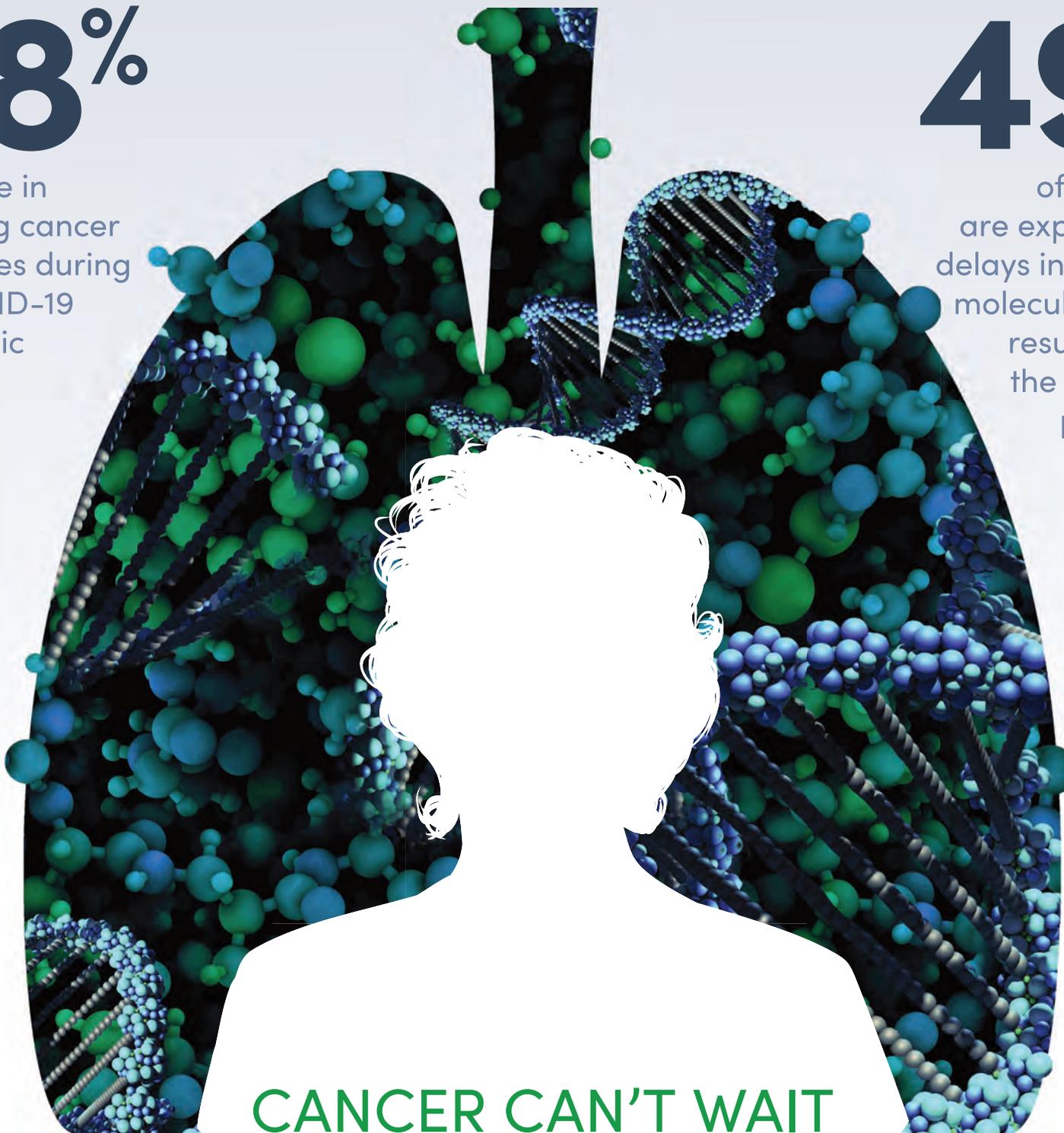
Best,  
*Victor Test, MD, FCCP*

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