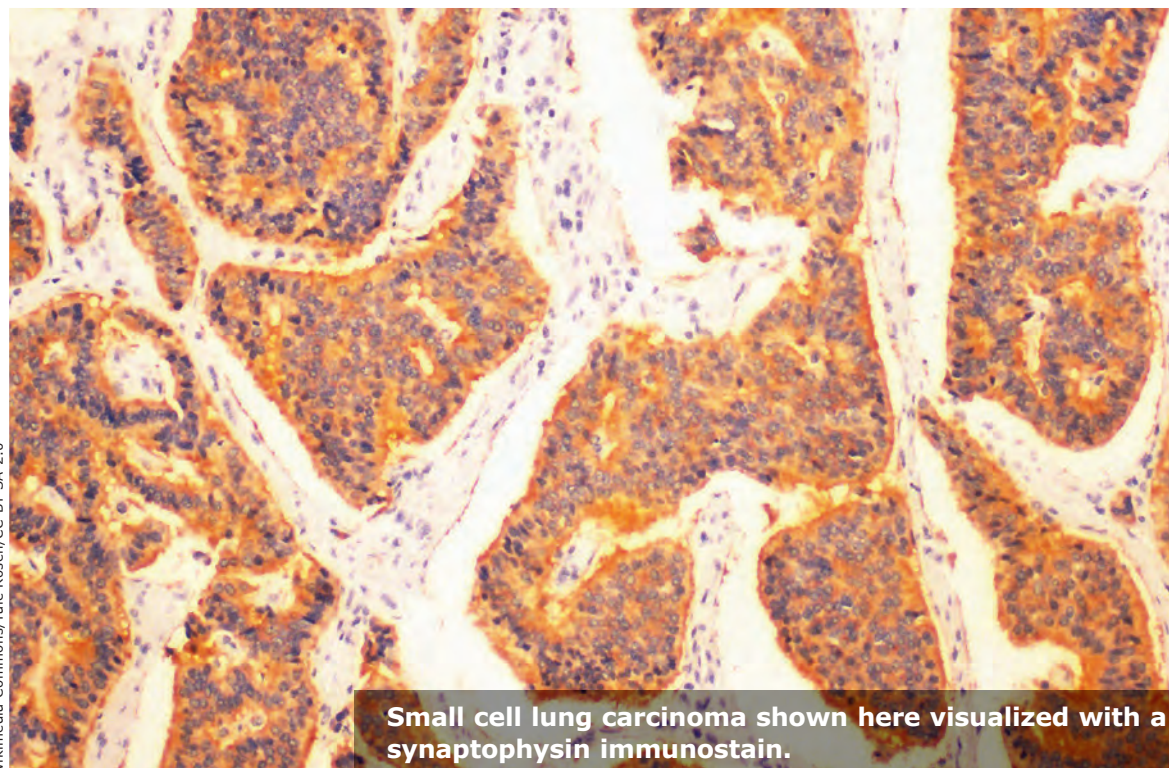


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Small cell lung carcinoma shown here visualized with a synaptophysin immunostain.

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'Unprecedented' 3-year sustained survival with lung cancer tx combo

BY SHARON WORCESTER
MDedge News

The overall survival benefit with durvalumab plus etoposide and cisplatin/carboplatin versus EP alone for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) as demonstrated in the phase 3 CASPIAN trial was sustained beyond 3 years, according to a planned exploratory analysis.

The durable overall survival (OS) benefit and the well-tolerated safety profile of the durvalumab with EP therapy further establishes the combination as the standard of care for the first-line treatment of ES-SCLC, Luis Paz-Ares, MD, reported at the 2021 European Society for Medical Oncology

Congress (abstract LBA61).

At 3 years, there is more than three times the survival in patients with durvalumab and EP versus EP, and at the same time, the adverse-event profile continues to be favorable," said Dr. Paz-Ares of Universidad Complutense & Ciberonc, Madrid.

This is the longest follow-up reported to date for a phase 3 trial of a programmed death–ligand 1 inhibitor and EP in this setting, he said.

The CASPIAN trial included 805 treatment-naïve patients with ES-SCLC who were randomized 1:1:1 to receive 1,500 mg of durvalumab with EP every 3 weeks, 1,500 mg of durvalumab at 75 mg of tremelimumab and EP every 3 weeks, or EP

CANCER TREATMENT COMBO // *continued on page 7*

New COVID-19 pill: 'Game changer' or just one more tool?

BY KATHLEEN DOHENY
MDedge News

Soon after Merck announced that it would ask federal regulators for emergency use authorization (EUA) for its auspicious new COVID-19 pill, the accolades began.

Former Food and Drug Administration chief Scott Gottlieb, MD, told CNBC the drug was "a profound game changer." Top infectious disease expert Anthony S. Fauci, MD, called the early data "impressive." The World Health Organization termed it "certainly good news," while saying it awaits more data.

Merck, partnering with Ridgeback Biotherapeutics on the investigational oral antiviral medicine molnupiravir, plans to submit applications to regulatory agencies worldwide, hoping to deliver the first oral antiviral medication for COVID-19.

Interim clinical trial results show that the drug may slash the risk for hospitalization or death by

COVID-19 PILL // *continued on page 6*

INSIDE HIGHLIGHT



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Once-daily poziotinib shows efficacy in NSCLC

BY WALTER ALEXANDER

MDedge News

Once-daily dosing of poziotinib shows clinically meaningful efficacy for patients with

treatment-naive non-small cell lung cancer (NSCLC) HER2 exon 20 mutations, according to results of the ZENITH20 trial presented at the 2021 European Society for Medical Oncology Congress. Tumor

reductions, stated lead author Robin Cornelissen, PhD, MD, Erasmus University, Rotterdam, the Netherlands, were seen in 88% of patients.

EGFR and HER2 exon 20 insertion mutations are rare subsets

accounting for about 10% each of all mutations and 2%-4% each in NSCLC. “There is no approved therapy for either treatment-naive or previously treated NSCLC with HER2 exon 20 mutations,”

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Dr. Cornelissen said in a virtual oral presentation (abstract LBA46). While chemotherapy agents with or without checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) are currently utilized, none are specific to exon 20 mutations, and historical response rates from mostly small uncontrolled studies vary widely from about 6.9% to 35%, with me-

dian progression-free survival (PFS) ranging from 3 to 7 months.

Dr. Cornelissen presented preliminary safety and efficacy data from the phase 2 ZENITH20, a seven-cohort global clinical trial, specifically from cohort 4 (daily dosing) which included 48 HER2 exon 20 insertion NSCLC patients (median age, 60.5 years; women/men, 26/22) treated

first-line with oral daily poziotinib (16 mg) with an Eastern Cooperative Oncology Group performance status of 1 (65%). The primary endpoint was objective response rate evaluated centrally by an independent image review committee using RECIST 1.1 criteria.

All patients have experienced treatment-related adverse events

(TRAEs) with 10% considered serious, and permanent discontinuation in 13%. About 83% of patients had dose interruptions and 76% had dose reductions. The most common adverse events were diarrhea, rash, stomatitis/mucosal inflammation, and paronychia. Pneumonitis occurred in two patients (4%), with one grade 3 (2%). No grade 4/5 TRAEs were reported.

Discontinuations in 44 patients (92%), Dr. Cornelissen said, are attributed to death (5/10%), disease progression (30/63%), adverse events (1/2%), and other (8/17%), with treatment ongoing in 4 patients (8%).

The rate for the primary endpoint of objective response rate (ORR) was 43.8% (n = 21) (95% confidence interval, 29.5%-58.8%). Tumor reductions have been observed in 42/48 patients (88%) with a median reduction of 35%. One complete response was reported (2.1%), with partial responses in 20 (41.7%), stable disease in 15 (31.3%), progressive disease in 7 (14.6%), and 5 (10.4%) not evaluable. The disease control rate was 75.0%.

Dr. Cornelissen concluded: "Poziotinib shows clinically meaningful efficacy for treatment-naive NSCLC HER2 exon 20 mutations with [daily] dosing." The toxicity profile, he added, is manageable and in line with previous poziotinib studies and other second-generation EGFR TKIs.

Noting that improved tolerability and antitumor activity have been observed in the cohort 5 (8 mg b.i.d.) interim analysis, Dr. Cornelissen said that cohort 4 is ongoing with patients enrolling at 8-mg b.i.d. dosing.

HER2 mutations represents 1.7%-2.2% of NSCLC, with high-sequence homology with EGFR mutation, observed ESMO-appointed discussant Daniel S.W. Tan, PhD, National Cancer Center in Singapore. He pointed out that, while HER2 antibody drug conjugates and TKIs have gained approval in other cancer types (e.g., breast, gastric), currently no HER2 therapies are approved in NSCLC. Reviewing ZENITH20 findings (risk ratio, 43.8%; duration of response (DoR), 5.4 months; PFS, 5.6 months), Dr. Tan stated that poziotinib is an active agent in HER2 mutated NSCLC. "One concern that remains for me is the safety profile that will require further evaluation in order to determine optimal dosing," he said.

The study was funded by Spectrum Pharmaceuticals. Other authors associated with the research disclosed full- or part-time employment with Spectrum.

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50% in those with mild to moderate COVID-19.

When the results were found to be so favorable, the study was halted at the recommendation of an independent data-monitoring committee and in consultation with the FDA.

That initial enthusiasm is now tempered with some perspective on the pros and cons. “This anticipated drug has gotten a little more hype than it deserves,” said William Schaffner, MD, professor of preventive medicine and infectious disease specialist at Vanderbilt University Medical Center in Nashville, Tenn. He and others suggest a reality check.

“It’s not exactly a home run, like penicillin for strep throat,” agreed Carl Fichtenbaum, MD, professor of infectious diseases at the University of Cincinnati, who is investigating a similar pill for a rival company, Atea, partnering with Roche.



Dr. Schaffner

“But it is encouraging,” he said. “It will

probably be an incremental improvement on what we have.” The fact that it can be taken at home is a plus.

“The data show in this higher risk group [those who were studied had at least one risk factor for severe COVID-19, such as age or a medical condition], it reduces the risk of advancing to severe disease by 50%,” Dr. Schaffner said. While that’s a clear benefit for half, it of course leaves the other half without benefit, he said.

Others critiqued the predicted cost of the drug. The U.S. government has already agreed to pay about \$700 per patient, according to a new report from Harvard T. H. Chan School of Public Health, Boston, and King’s College Hospital, London. That analysis concluded that the actual cost of production for the 5-day course is \$17.74.

“We fully expect that having an oral treatment that reduces the risk of hospitalizations will be significantly cost effective for society,” Melissa Moody, a Merck spokesperson, told this news organization.

Merck expects to produce 10 million courses of treatment by the end of the year, with additional doses expected to be produced in 2022, according to a company press release. Earlier in 2021, Merck finalized its agreement with the U.S. government

to supply about 1.7 million courses of the drug at the \$700 price, once an EUA or FDA approval is given.

Study details

Details about the study findings came from a Merck press release. In the planned interim analysis, Merck and Ridgeback evaluated data from 775 patients initially enrolled in the phase 3 MOVE-OUT trial.

All adults had lab-confirmed mild to moderate COVID-19, and reported onset of symptoms within 5 days of being randomly assigned to the drug or placebo. All had at least one risk factor linked with poor disease outcome (such as older age or obesity).

The drug is a ribonucleoside and works by creating mutations in the virus’s genome, halting the ability of the virus to replicate.

Through day 29 of the study, the drug reduced the risk of hospitalization or death by about 50%. While 7.3% of those who received the drug either died or were hospitalized by day 29, 14.1% of those on placebo did, a statistically significant difference ($P = .0012$).

Side effects were similar in both groups, with 35% of the drug-treated and 40% of the placebo group reporting some side effect, Merck reported.

Pros, cons, and unknowns

The ability to take the drug orally, and at home, is a definite plus, Dr. Schaffner said, compared with the monoclonal antibody treatment currently approved that must be given intravenously or subcutaneously and in certain locations.

The regimen for molnupiravir is four pills, two times daily, for 5 days, even if symptoms are mild.

The 50% reduction is not as effective as the benefit often quoted for monoclonal antibody treatment. In clinical trials of Regeneron’s monoclonal antibody treatment, the regimen reduced COVID-19–related hospitalization or death in high-risk patients by 70%.

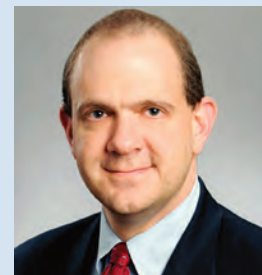
Even so, the new pill could change the pandemic’s course, others say. “I think molnupiravir has the potential to change how we take care of people who have COVID and risk factors for developing severe disease,” said Rajesh Tim Gandhi, MD, an infectious disease physician at Harvard Medical School in Boston.

“What we’ll need to do, however, is make sure that people get tested quickly after they develop symptoms and, if they’re confirmed to have

Continued on following page

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David Schulman, MD, MPH, FCCP, is Editor in Chief of CHEST Physician.

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alone. Patients in the durvalumab arms received four cycles of treatment followed by maintenance durvalumab, and those in the EP-only arm received up to six cycles of EP.

Primary outcomes data from the trial showed a significant overall survival benefit with durvalumab and EP versus EP alone (hazard ratio, 0.73), as did a subsequent analysis after a median follow-up of 25.1 months (HR, 0.75).

At median follow-up of 39.4 months, the durvalumab and EP combination showed sustained improvement in overall survival versus EP alone (HR, 0.71).

Median overall survival was 12.9 versus 10.5 months. OS was 22.9% versus 13.9% at 24 months, and 17.6% versus 5.8% at 36 months with durvalumab with EP versus EP, respectively, Dr. Paz-Ares said.

Durvalumab plus tremelimumab plus EP continued to numerically improve overall survival, compared with EP alone (HR, 0.81). Serious adverse events occurred in 32.5%, 47.4%, and 36.5% of patients in the durvalumab with EP, durvalumab plus tremelimumab plus EP, and EP arms, respectively.

The findings are “really encouraging and unprecedented, frankly,” said session chair Alfredo Addeo, MD, of University Hospital, Geneva.

“They are setting the bar for competitors,” he said, referencing the IMpower 133 trial looking at atezolizumab with chemotherapy in ES-SCLC.

The CASPIAN study was funded by AstraZeneca. Dr. Paz-Ares reported relationships with multiple pharmaceutical companies.

Continued from previous page

COVID, start on the pills within 5 days of developing symptoms,” he said, while warning that more data are needed about the drug and the trial results.

Another concern is that the promise of a pill will stall vaccination rates, with some people figuring why get vaccinated when they can obtain the pill if they do get sick.

Relying on treatment alone won't work, Dr. Schaffner said. “Let's [also] focus on prevention, which is the vaccine. We have to keep working both sides of the street.”

Dr. Gandhi added: “It's important to remember that even though molnupiravir reduced the likelihood of hospitalization and death, a number of people who received the drug still got sick enough to end up in the hospital.” Also unknown, he said, is how severe their disease was and if they will develop long COVID.

The Merck study included only unvaccinated people. Might it work for those vaccinated people who get a breakthrough infection?

“From a purely scientific perspective, there is no reason to believe molnupiravir would not work in people who are vaccinated, but the overall efficacy on top of the vaccine is likely dependent on how well they were able to mount a protective immune response to the vaccine,” Ms. Moody said.

As for the expected cost, Ms. Moody said that the company takes into account a number of factors in setting pricing, “but fundamentally we look at the impact of the disease, the benefits that the drug delivers to patients and to society, and at sup-

porting ongoing drug development.”

On Merck's heels

Pfizer is studying an antiviral pill, PF-07321332, a protease inhibitor that blocks the protease enzymes and halts replication of the virus.

In addition to studying the drug in infected patients at high risk of severe illness and in those at typical risk, Pfizer launched a phase 2-3 study in late September that will enroll people who live in the same household as a person with a confirmed, symptomatic COVID-19 infection to see if the drug can prevent disease in those who have been exposed.

Atea and Roche's COVID pill, AT527, is in phase 3 trials as well. AT527 is an inhibitor of polymerase, an enzyme many viruses have, to stop replications. Atea is evaluating the drug to reduce disease “burden” and for both pre- and postexposure prevention.

Role of COVID-19 pills

It may be necessary to target the coronavirus with more than one antiviral agent, said Dr. Fichtenbaum, a principal investigator for the AT527 trials.

“Sometimes viruses require two or three active agents to control their replication,” he said, citing information gleaned from other viral research, such as HIV. For control of HIV infection, a cocktail or combination of antivirals is often recommended.

That may well be the case for COVID-19, Dr. Fichtenbaum said. The goal would be to attack the virus at more than one pathway.

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D-dimer unreliable for ruling out pulmonary embolism in COVID-19

BY FRAN LOWRY

The plasma D-dimer assay has been used, along with clinical prediction scores, to rule out pulmonary embolism (PE) in critically ill patients for decades, but a new study suggests it may not be the right test to use in hospitalized COVID-19 patients.

The results showed that all hospitalized patients with COVID-19 and radiographic evidence of PE had plasma D-dimer levels of 0.05 mcg/mL or greater, the cutoff point for the diagnosis.

“If using D-dimer to exclude patients with PE, the increased values we found among 92.3% of patients suggest that this assay would be less useful than in the populations in which it was originally validated, among which a minority of patients had increased D-dimer values,” the authors write.

“Setting higher D-dimer thresholds was associated with improved specificity at the cost of an increased false-negative rate that could be associated with an unacceptable patient safety risk,” they added.

“If using D-dimer to exclude patients with PE, the increased values we found among 92.3% of patients suggest that this assay would be less useful than in the populations in which it was originally validated.”

The inclusion of patients with D-dimer and computed tomography pulmonary angiography (CTPA) was necessary to estimate diagnostic performance, they note, but “this may have introduced selection bias by excluding patients unable to undergo CTPA.”

“Nonetheless, given the high pretest probability of PE and low specificity observed in this and other studies, these results suggest that use of D-dimer levels to exclude PE among patients hospitalized with COVID-19 may be inappropriate and have limited clinical utility,” they conclude.

Led by Constantine N. Logothetis, MD, from Morsani College of Medicine, University of South Florida, Tampa, the study was published online Oct. 8 as a Research Letter in JAMA Network Open (2021. doi: 10.1001/jamanetworkopen.2021.28802).

Uncertain utility

The authors note that the availability of D-dimer samples routinely collected from hospitalized COVID-19 patients – as well as the heterogeneity of early, smaller studies – generated uncertainty about the utility of this assay.

This uncertainty prompted them to test the diagnostic accuracy of the D-dimer assay among a sample of 1,541 patients who were

hospitalized with COVID-19 at their institution between January 2020 and February 2021 for a possible PE.

They compared plasma D-dimer concentrations with CTPA, the criterion standard for diagnosing PE, in 287 of those patients.

Overall, 118 patients (41.1%) required care in the ICU, and 27 patients (9.4%) died during hospitalization.

The investigators looked at the ability of plasma D-dimer levels collected on the same day as CTPA to diagnose PE.

Thirty-seven patients (12.9%) had radiographic evidence of PE, and 250 patients (87.1%) did not.

Overall, the vast majority of patients (92.3%; n = 265 patients) had plasma D-dimer levels of 0.05 mcg/mL or more, including all patients with PE and 225 of 250 patients without PE (91.2%).

The median D-dimer values were 1.0 mcg/mL for 250 patients without PE and 6.1 mcg/mL for 37 patients with PE.

D-dimer values ranged from 0.2 mcg/mL to 128 mcg/mL among patients without PE, and from 0.5 mcg/mL to more than 10,000 mcg/mL among patients with PE. Patients without PE had statistically significantly decreased mean D-dimer values (8.7 mcg/mL vs. 1.2 mcg/mL; $P < .001$).

A D-dimer concentration of 0.05 mcg/mL was associated with a sensitivity of 100%, specificity of 8.8%, negative predictive value (NPV) of 100%, positive predictive value (PPV) of 13.9%, and a negative likelihood ratio (NLR) of less than 0.1.

The age-adjusted threshold was associated with a sensitivity of 94.6%, specificity of 22.8%, NPV of 96.6%, PPV of 13.9%, and NLR of 0.24.

The authors note that all hospitalized patients with COVID-19 and radiographic evidence of PE had plasma D-dimer levels of 0.05 mcg/mL or greater.

D-dimer in VTE may not extrapolate to COVID-19

“The D-dimer test, which is a measure of circulating byproducts of blood clot dissolution, has long been incorporated into diagnostic algorithms for venous thromboembolic [VTE] disease, including deep vein thrombosis and pulmonary embolism.

“It is uncertain whether this diagnostic use of D-dimer testing can be extrapolated to the context of COVID-19 – an illness we now understand to be associated itself with intravascular thrombosis and fibrinolysis,” Matthew Tomey, MD, a cardiologist at Mount Sinai Morningside, New York, said in an interview.

“The authors of this study sought to evaluate the test characteristics of the D-dimer assay for diagnosis of pulmonary embolism in a consecutive series of 287 hospitalized patients with COVID-19 who underwent computed tomography pulmonary angiography (CTPA).

“This was a selected group of patients representing less than 20% of the 1,541 patients screened. Exclusion of data on the more than

VIEW ON THE NEWS

Sachin Gupta, MD, FCCP, comments:

As I recall from a project I was involved in during internal medicine residency, applying a Bayesian approach to PE diagnosis truly begins with a clear understanding of the pretest probability of VTE. Retrospective studies are challenging in that we do not know the pretest clinical probability of PE in these cases. That the D-dimer is unreliable in ruling in PE in the setting of infection is not entirely surprising, based on how the D-dimer was designed to be used. The results of this study should remind us of the importance of strongly considering clinical probability before testing for VTE.



80% of screened patients who did not undergo CTPA is a significant limitation of the study,” Dr. Tomey said.

“In the highly selected, small cohort studied, representing a group of patients at high pretest probability of pulmonary embolism, there was no patient with pulmonary embolism who had a D-dimer value less than 0.5 mcg/mL.

“Yet broad ranges of D-dimer values were observed in COVID-19 patients with (0.5 to >10,000 mcg/mL) and without (0.2 to 128 mcg/mL) pulmonary embolism,” he added.

Based on the presented data, it is likely true that very low levels of D-dimer decrease the likelihood of finding a pulmonary embolus on a CTPA, if it is performed, Dr. Tomey noted.

“Yet the data confirm that a wide range of D-dimer values can be observed in COVID-19 patients with or without pulmonary embolism. It is not clear at this time that D-dimer levels should be used as gatekeepers to diagnostic imaging studies such as CTPA when pretest suspicion of pulmonary embolism is high,” according to Dr. Tomey.

“This issue becomes relevant as we consider evolving data on use of anticoagulation in treatment of hospitalized patients with COVID-19. We learned this year that, in critically ill patients hospitalized with COVID-19, routine therapeutic anticoagulation (with heparin) was not beneficial and potentially harmful when compared with usual thromboprophylaxis,” he concluded.

“As we strive to balance competing risks of bleeding and thrombosis, accurate diagnosis of pulmonary embolism is important to guide decision-making about therapeutic anticoagulation, including in COVID-19.”

Dr. Logothetis and Dr. Tomey disclosed that they had no relevant financial relationships.

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Revised sarcoidosis treatment guidelines offer important updates

BY AARON B. HOLLEY, MD

Nothing about sarcoidosis is easy. In the United States, lifetime risk is 2.4% and 0.85% for African American persons and White persons, respectively. Despite study of its genetics and immunopathology, we don't know its cause. Diagnosis is challenging because noncaseating granulomas, the tissue finding associated with sarcoidosis, aren't specific for the disease. With the exception of Löfgren syndrome, a well-described sarcoid presentation that portends an excellent prognosis, initial signs and symptoms are variable and disease course is unpredictable. Alas, because sarcoid affects the lungs in more than 90% of patients, the general pulmonologist is left carrying the bag as the "sarcoidologist."

Within the past 18 months, the ATS and ERS have delivered updated guidelines for diagnosis and treatment. Predictably, neither document issues earth-shattering conclusions.

The inherent heterogeneity of sarcoid makes it challenging to study. The American Thoracic Society (ATS) is one of just a few, premier organizations that creates respiratory medicine guidelines. In 1999, they published a sarcoid consensus statement with the European Respiratory Society (ERS), another outstanding and influential respiratory medicine organization, and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG). For the past 20 years, I've been referring trainees to this document for guidance on managing their patients with sarcoid.

Twenty years later, sarcoid remains frustrating and mysterious, but much has changed. Our methods for evaluating evidence and creating guidelines are now based on the GRADE criteria. Now that we have easy access to advanced

technologies such as endobronchial ultrasound, obtaining tissue for diagnosis is easier. Our study of sarcoid itself has advanced, with large cohorts providing data on phenotyping, new immunosuppressants being used for treatment, and an improved understanding of cardiac sarcoidosis. In short, we're in need of a sarcoidosis guideline for the 21st century.

Within the past 18 months, the ATS and ERS have delivered updated guidelines for diagnosis and treatment. Despite the advancements cited above, sarcoid remains difficult to study. So predictably, neither document issues earth-shattering conclusions. Truth be told, well-done guidelines rarely do. They do provide several important updates that physicians managing patients with sarcoid should note.

The guideline on diagnosis provides recommendations for routine monitoring after diagnosis. Many practicing clinicians took from the 1999 ATS/ERS/WASOG consensus statement that all patients with sarcoid needed to be seen annually. At pulmonary clinics where I've worked, we've defaulted to annual follow-up for everyone, usually with chest radiography, lab testing, electrocardiography, and referral to ophthalmology. Because a majority of patients with sarcoid will remain asymptomatic or experience spontaneous remission, this practice never really seemed cost effective or clinically efficient. The new guidelines are far more proscriptive on what monitoring is required and grade requirements at specific levels of certainty and often advise symptom-based assessments in lieu of reflexive annual testing.

The ERS guideline on treatment provides a thoughtful discussion of corticosteroid indications and dosing, broken down by underlying disease severity (assessed by lung function abnormalities and imaging). It also recognizes that two of the most common sarcoid symptoms are fatigue and dyspnea, which are both inherently nonspecific. In practice, proving these symptoms are directly attributable to sarcoid is challenging. The treatment guideline allows for flexibility in these cases, with shared decision-making and

Sachin Gupta, MD, FCCP, comments:

In my observation, community and academic center practices alike tend to have wide variation in how patients with sarcoidosis are managed and this may be in part due to the large time-gap since the large society guidelines have been updated. Inequities in care may arise as a result. Both the ATS guideline recommendations on diagnosis and the ERS guidelines for treatment of sarcoidosis are must reads for those of us who regularly see patients with sarcoidosis. Though mostly leaning on consensus opinion because of a lack of published data, these recommendations are driven by leading researchers in the field and should help raise the level of care of patients with this disease.

trials of low-dose steroids recommended. This seems an excellent hedge against overtreatment with immunosuppressive medications that have harmful side effects.

The ATS and ERS guidelines are not without controversy. Their approach to cardiac sarcoid differs slightly from that recommended by a commonly cited Heart Rhythm Society consensus statement, and despite discussing treatment options, the section on fatigue is quite limited. These two facts and other limitations largely reflect differing interpretations of the limited data; they do not detract from the overall importance of the ATS and ERS guidelines. Sarcoid remains an enigma, but little by little the academic physicians at the ATS and ERS are providing clarity.

Dr. Holley is program director, pulmonary and critical care medical fellowship, department of medicine, Walter Reed National Military Medical Center, Bethesda, Maryland. He has received a research grant from Fisher-Paykel and income from the American College of Chest Physicians.

LUNG CANCER

COVID especially dangerous for those with mesothelioma

BY M. ALEXANDER OTTO

MDedge News

Clinicians should pay particular attention to malignant pleural mesothelioma patients with COVID-19. Among people with thoracic malignancies, they have an especially high risk of bad outcomes, according to Susana Cedres, MD, PhD, a thoracic medical oncologist at Vall d'Hebron University Hospital, Barcelona.

At the annual World Conference on Lung Cancer, she reported on her institution's experience during the first year of the pandemic before widespread vaccine rollouts. Among 38 malig-

nant pleural mesothelioma (MPM) patients, 7 (18%) patients were diagnosed with COVID-19 and of these, 3 patients were asymptomatic, 4 (57%) died of complications including bilateral pneumonia within a median of less than half a month after diagnosis, and a 5th patient died from MPM progression.

The findings confirm the particular risk of COVID in MPM. According to researchers reporting in *Scientific Reports* (2021 Feb 4. doi: 10.1038/s41598-021-82384-0), mesothelioma was the only cancer linked to significantly worse outcomes. Other risks included tuberculosis, drug use, hepatitis, HIV/AIDS, cardiomyopathy, and diabetes.

"There really is a need for more inclusion of MPM patients in international [COVID] registries" to better characterize the course of infection and improve outcomes, said study discussant Francoise Galateau-Salle, MD, PhD, of the Cancer Center Leon Berard in Lyon, France. Among the seven positive cases in Barcelona, almost all had comorbidities, with the most common being cardiovascular disease in four patients (57%).

Dr. Cedres is an adviser and/or reported travel expenses from a number of companies, including Merck, Pfizer, and Bristol-Myers Squibb. Dr. Galateau-Salle had no disclosures.

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Cardiogenic shock teams again tied to lower mortality

BY PATRICE WENDLING

A large multicenter study provides further evidence supporting the rationale for multidisciplinary teams for cardiogenic shock, one of the most lethal diseases in cardiovascular medicine.

The analysis of 24 critical care ICUs in the Critical Care Cardiology Trials Network showed that the presence of a shock team was independently associated with a 28% lower risk for CICU mortality (23% vs. 29%; odds ratio, 0.72; $P = .016$).

Patients treated by a shock team also had significantly shorter CICU stays and less need for mechanical ventilation or renal replacement

determine the severity of the lesion and the phenotype, Dr. Papolos observed.

A 2018 study showed PAC use was tied to increased survival among patients with acute myocardial infarction cardiogenic shock (AMI-CS) supported with the Impella (Abiomed) device (Am Heart J. 2018 Aug;202:33-8). Additionally, a 2021 study by the Cardiogenic Shock Working Group demonstrated a dose-dependent survival response based on the completeness of hemodynamic assessment by PAC prior to initiating mechanical circulatory support (MCS).

A third factor might be that a structured, team-based evaluation

balloon pumps, and that's what we saw here."

The study involved 6,872 consecutive medical admissions at 24 level 1 CICU centers during an annual 2-month period from 2017 to 2019. Of these, 1,242 admissions were for cardiogenic shock and 546 (44%) were treated at 1 of 10 centers with a shock team.

Shock team centers had higher-acuity patients than centers without a shock team (Sequential Organ Failure Assessment score, 4 vs. 3) but a similar proportion of patients with AMI-CS (27% vs. 28%).

Among all admissions, CICU mortality was not significantly different between centers with and without a shock team.

For cardiogenic shock patients treated at centers with and without a shock team, the median CICU stay was 4.0 and 5.1 days, respectively, mechanical ventilation was used in 41% and 52%, respectively, and new renal replacement therapy in 11% and 19%, respectively ($P < .001$ for all).

Shock team centers used significantly more PACs for AMI-CS and non-AMI-CS admissions; advanced MCS therapy was also greater in the AMI-CS subgroup.

Lower CICU mortality at shock team centers persisted among patients with non-AMI-CS (adjusted OR, 0.67; $P = .017$) and AMI-CS (adjusted OR, 0.79; $P = .344$).

"This analysis supports that all AHA level 1 cardiac ICUs should strongly consider having a shock team," Dr. Papolos said.

Evidence from single centers and the National Cardiogenic Shock Initiative has shown improved survival with a cardiogenic shock algorithm (J Am Coll Cardiol. 2019 Apr;73[13]:1659-69), but this is the first report specifically comparing no shock teams with shock teams, Perwaiz Meraj, MD, Northwell Health, Manhasset, N.Y., told this news organization.

"People may say that it's just another paper that's saying, 'shock teams, shock teams, rah, rah, rah,' but it's important for all of us to really take a close look under the covers and see how are we best managing these patients, what teams are we putting together, and to create systems of care, where if you're at a center that really doesn't have the capabilities of doing this, then you should partner up with a center that does," he said.

Notably, the 10 shock teams were present only in medium or large ur-

ban, academic medical centers with more than 500 beds. Although they followed individual protocols, survey results show service-line representation, structure, and operations were similar across centers.

They all had a centralized way to activate the shock team, the service was 24/7, and members came from areas such as critical care cardiology (100%), cardiac surgery (100%), interventional cardiology (90%), advanced heart failure (80%), and extracorporeal membrane oxygenation service (70%).

Limitations of the study include the possibility of residual confounding, the fact that the registry did not capture patients with cardiogenic shock managed outside the CICU or the time of onset of cardiogenic shock, and data were limited on inotropic strategies, sedation practices, and ventilator management, the authors wrote.

"Although many critics will continue to discuss the lack of randomized controlled trials in cardiogenic shock, this paper supports the process previously outlined of a multidisciplinary team-based approach improving survival," Dr. Meraj and William W. O'Neill, MD, director of the Center for Structural Heart Disease and Henry Ford Health System, Detroit, and the force behind the National Cardiogenic Shock Initiative, wrote in an accompanying editorial (J Am Coll Cardiol. 2021 Sep;78[13]:1318-20).

They point out that the report doesn't address the escalation of care based on invasive hemodynamics in the CICU and the protocols to prevent acute vascular/limb complications (ALI) that can arise from the use of MCS.

"Many procedural techniques and novel CICU models exist to mitigate the risk of ALI in CS patients with MCS," they wrote. "Finally, escalation of care and support is vital to the continued success of any shock team and center."

One coauthor has served as a consultant to Abbott. Another has served as a consultant to the Abiomed critical care advisory board. All other authors reported having no relevant financial relationships.

Dr. Meraj has received research and grant funding from Abiomed, Medtronic, CSI, and Boston Scientific. Dr. O'Neill has received consulting/speaker honoraria from Abiomed, Boston Scientific, and Abbott.



"This paper supports the process previously outlined of a multidisciplinary team-based approach improving survival."

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therapy, as reported in the Journal of the American College of Cardiology (2021 Sep;78[13]:1309-17).

"It's observational, but the association that we're seeing here, just because of our sample size, is the strongest that's been published yet," lead author Alexander Papolos, MD, MedStar Washington Hospital Center, said in an interview.

Although a causal relationship cannot be drawn, the authors suggest several factors that could explain the findings, including a shock team's ability to rapidly diagnose and treat cardiogenic shock before multiorgan dysfunction occurs.

Centers with shock teams also used significantly more pulmonary artery catheters (60% vs. 49%; adjusted OR, 1.86; $P < .001$) and placed them earlier (0.3 vs. 0.66 days; $P = .019$).

Pulmonary artery catheter (PAC) use has declined after earlier trials like ESCAPE showed little or no benefit in other acutely ill patient groups, but positive results have been reported recently in cardiogenic shock, where a PAC is needed to

can facilitate timely and optimal MCS device selection, deployment, and management, suggested Dr. Papolos.

Centers with shock teams used more advanced types of MCS – defined as Impella, TandemHeart (LivaNova), extracorporeal membrane oxygenation, and temporary or durable surgical ventricular assist devices – than those without a shock team (53% vs. 43%; adjusted OR, 1.73; $P = .005$) and did so more often as the initial device (42% vs. 28%; $P = .002$).

Overall MCS use was lower at shock team centers (35% vs. 43%), driven by less frequent use of intra-aortic balloon pumps (58% vs. 72%).

"The standard, basic MCS has always been the balloon pump because it's something that's easy to put in at the cath lab or at the bedside," Dr. Papolos said.

"So, if you take away having all of the information and having the right people at the table to discuss what the best level of support is, then you're going to end up with

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Pandemic adds more weight to the increasing burden of obesity in children

BY KATE JOHNSON

MDedge News

American children gained a lot of weight in the last year, setting a dangerous trajectory toward metabolic disease that requires urgent policy change, according to a new report from the Robert Wood Johnson Foundation.

“Our nation’s safety net is fragile, outdated, and out of reach for millions of eligible kids and caregivers,” said Jamie Bussel, senior program officer at the RWJF, and senior author of the report. She added that the pandemic further fractured an already broken system that disproportionately overlooks “children of color and those who live farthest from economic opportunity.”

Think ‘bigger and better’

Ms. Bussel said, during a press conference, that congress responded to the pandemic with “an array of policy solutions,” but it’s now time to think “bigger and better.”

“There have been huge flexibilities

deployed across the safety net program and these have been really important reliefs, but the fact is many of them are temporary emergency relief measures,” she explained.

For the past 3 years, the RWJF’s annual State of Childhood Obesity report has drawn national and state obesity data from large surveys including the National Survey of Children’s Health, the Youth Risk Behavior Surveillance System, the WIC Participant and Program Characteristics Survey, and the National Health and Nutrition Examination Survey.

Similar to in past years, this year’s data show that rates of obesity and overweight have remained relatively steady and have been highest among minority and low-income populations. For example, data from the 2019-2020 National Survey of Children’s Health, along with an analysis conducted by the Health Resources and Services Administration’s Maternal and Child Health Bureau, show that one in six – or 16.2% – of youth aged 10-17 years have obesity.

VIEW ON THE NEWS

Mary Cataletto, MD, FCCP, comments: As children return to school, overweight and obesity are major concerns. Obesity is a significant risk factor for obstructive breathing disorders from snoring to apnea and has been associated with daytime symptoms of poor memory and focus, which impact learning. This is further compounded by recent supply chain issues and labor shortages that impact the quality and availability of nutritious options in school lunch programs. Substituting or supplementing with fast foods (which are generally high calorie) brought from home or purchased outside of school can further increase the obesity epidemic.



ed toward stabilization – but these numbers blow that out of the water ... COVID has escalated the rates,” she said in an interview.

“Unfortunately, these two crises – the COVID pandemic, the childhood obesity epidemic – in so many ways have exacerbated one another,” said Ms. Bussel. “It’s not a huge surprise that we’re seeing an increase in childhood obesity rates given the complete and utter disruption of every single system that circumscribes our lives.”

Digging deeper

Other studies included in this year’s report were specifically designed to measure the impact of the pandemic, and show a distinct rise in overweight and obesity, especially in younger children. For example, a retrospective cohort study using data from Kaiser Permanente Southern California (JAMA. 2021;326[14]:1434-6) showed the rate of overweight and obesity in children aged 5-11 years rose to 45.7% between March 2020 and January 2021, up from 36.2% before the pandemic.

Another of these studies, which was based on national electronic health records of more than 430,000 children, showed the obesity rate crept from 19.3% to 22.4% between August 2019 and August 2020 (Morb Mortal Wkly Rep. 2021;70:1278-83).

“The lid we had been trying desperately to put on the obesity epidemic has come off again,” said Sandra G. Hassink, MD, MSc, who is medical director of the American Academy of Pediatrics Institute for Healthy Childhood Weight.

“In the absence of COVID we had been seeing slow upticks in the numbers – and in some groups we’d been thinking maybe we were head-

The systems that feed obesity

Addressing childhood obesity requires targeting far beyond healthy eating and physical activity, Ms. Bussel said.

“As important is whether that child has a safe place to call home.



Addressing childhood obesity requires targeting far beyond healthy eating.

MS. BUSSEL

Does mom or dad or their care provider have a stable income? Is there reliable transportation? Is their access to health insurance? Is there access to high-quality health care? ... All of those factors influence the child and the family’s opportunities to live well, be healthy, and be at a healthy weight,” she said.

The report includes a list of five main policy recommendations.

- Making free, universal school meal programs permanent.
- Extending eligibility for WIC, the Special Supplemental Nutrition Program for Women, Infants, and

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- Children, to postpartum mothers and to children through age 6.
- Extending and expanding other programs, such as the Child Tax Credit.
- Closing the Medicaid coverage gap.
- Developing a consistent approach to collecting obesity data organized by race, ethnicity, and income level.

“Collectively, over at least the course of the last generation or two, our policy approach to obesity prevention has not been sufficient. But that doesn’t mean all of our policy approaches have been failures,” Ms. Bussel said during an interview.

“Policy change does not always need to be dramatic to have a real impact on families.”

“In the absence of COVID we had been seeing slow upticks in the numbers – and in some groups we’d been thinking maybe we were headed toward stabilization – but these numbers blow that out of the water.”

Fighting complacency

For Dr. Hassink, one of the barriers to change is society’s level of acceptance. She said an identifiable explanation for pandemic weight gain doesn’t mean society should simply shrug it off.

“If we regarded childhood obesity as the population level catastrophe that it is for chronic disease maybe people would be activated around these policy changes,” she said.

“We’re accepting a disease process that wreaks havoc on people,” noted Dr. Hassink, who was not involved in the new report.

“I think it’s hard for people to realize the magnitude of the disease burden that we’re seeing. If you’re in a weight-management clinic or any pediatrician’s office you would see it – you would see kids coming in with liver disease, 9-year-olds on [continuous positive airway pressure] for sleep apnea, kids needing their hips pinned because they had a hip fracture because of obesity.

“So, those of us that see the disease burden see what’s behind those numbers. The sadness of what we’re talking about is we know a lot about what could push the dial and help reduce this epidemic and we’re not doing what we already know,” added Dr. Hassink.

Ms. Bussel and Dr. Hassink reported that they had no conflicts.



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Age, C-reactive protein linked to death risk in diabetes

BY MIRIAM E. TUCKER

Both high C-reactive protein (CRP) and older age predict mortality from COVID-19 in patients with diabetes, according

to data from the retrospective AC-CREDIT cohort study, presented at the virtual annual meeting of the European Association for the Study of Diabetes (EASD 2021) by Daniel Kevin Llanera, MD, of the Imperial

College, London.

The combination of older age and high levels of the inflammatory marker CRP were linked to a tripled risk for death by day 7 after hospitalization for COVID-19

among people with diabetes. But, in contrast to other studies, recent A1c and body mass index did not predict COVID-19 outcomes.

The study, conducted involved 1,004 patients with diabetes admitted

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with COVID-19 to seven hospitals in northwest England from Jan. 1 through June 30, 2020. The patients were a mean age of 74.1 years, 60.7% were male, and 45% were in the most deprived quintile based on the U.K. government deprivation index.

The primary outcome, death within 7 days of admission, occurred in 24%. By day 30, 33% had died.

These rates are higher than the rate found in previous studies, possibly because of greater socioeconomic deprivation and older age of the population, Dr. Llanera speculated.

A total of 7.5% of patients received intensive care by day 7 and 9.8% required intravenous insulin infusions. On univariate analysis, insulin infusion was found to be

protective, with those receiving it half as likely to die as those who didn't need IV insulin (odds ratio [OR], 0.5).

In contrast, chronic kidney disease in people younger than 70 years increased the risk of death more than twofold (OR, 2.74), as did type 2 diabetes compared with other diabetes types (OR, 2.52).

In multivariate analysis, CRP and age emerged as the most significant predictors of the primary outcome, with those deemed high risk by a logistic regression model having an OR of 3.44 for death by day 7 compared with those at lower risk based on the two factors.

Dr. Llanera reported having no relevant financial relationships.

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SLEEP STRATEGIES

The apnea-hypopnea index: Limitations and future directions

BY WISSAM MANSOUR, MD,
AND
CHRISTINE H. J. WON, MD,
MS

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse resulting in intermittent hypoxemia

and hypercapnia, large intrathoracic pressure swings, and cortical arousals. The rate of apneas and hypopneas observed during sleep,

the apnea-hypopnea index (AHI), has been used for decades to diagnose OSA and to classify its severity. Despite the wide acceptance of this metric by the sleep medicine community, clinical research has found poor correlations between the AHI- and OSA-related complications or symptoms. We have come to learn that the AHI is an oversimplification of a complex and diverse disease process. (Punjabi. *Chest*. 2016;149[1]:16-9).

The most important features of a disease metric are reliability, and the



Dr. Mansour



Dr. Won

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ability to predict clinically relevant outcomes. The reliability of the AHI has been in question due to substantial night-to-night variability that can lead to missed diagnosis and disease severity misclassification (Dzierzewski et al. *J Clin Sleep Med*. 2020;16[4]:539-44). Furthermore, the AHI fails to reflect some important physiologic derangements resulting from respiratory events. Apart from imperfectly set thresholds for scoring, it disregards the depth and the duration of ventilatory disturbances. For example, a hypopnea lasting 30 seconds and resulting in a decrease of 10% in oxyhemoglobin saturation is considered equivalent to a hypopnea lasting 10 seconds and resulting in a decrease of 4% in oxyhemoglobin saturation. The AHI also assumes that apneas and hypopneas are equal in their biological effects regardless of when they occur during sleep (NREM vs REM), despite reports suggesting that the sequelae of OSA are sleep-stage dependent (Varga, Mokhlesi. *Sleep Breath*. 2019;23[2]:413-23). This is further complicated by the varying hypopnea definitions and the difficulties in differentiating obstructive vs central hypopneas. It is doubtful that these events, which differ in mechanism, would result in similar outcomes.

Over the past decade, our understanding of the different pathophysiological mechanisms leading to OSA

has grown substantially, suggesting the need for a phenotype-specific treatment approach (Zinchuk, Yaggi. *Chest*. 2020;157[2]:403-20). The reliance on a single metric that does not capture this heterogeneity may prove detrimental to our therapeutic efforts. One extremely important dimension that is missed by the AHI is the patient. Individual response to airway obstruction varies with age, genetics, gender, and comorbidities, among other things. This may explain the difference in symptoms and outcomes experienced by patients with the same AHI. During the era of precision medicine, the concept of defining a clinical condition by a single test result, without regard to patient characteristics, is antiquated.

Several studies have attempted to propose complementary metrics that may better characterize OSA and predict outcomes. The hypoxic burden has gained a lot of attention as it is generally felt that hypoxemia is a major factor contributing to the pathogenesis of OSA-related comorbidities. Azarbarzin, et al. reported a hypoxic burden metric by measuring the area under the oxygen desaturation curve during a respiratory event (Azarbarzin et al. *Eur Heart J*. 2019;40[14]:1149-57). It factors the length and depth of the desaturations into a single value that expresses the average desaturation burden per hour of sleep time. The hypoxic burden was independently predictive of cardiovascular mortality in two large cohorts. Interestingly, the AHI did not have such an association. Similarly, another novel proposed parameter, the oxygen desaturation rate (ODR), outperformed the AHI in predicting cardiovascular outcomes in severe OSA patients (Wang et al. *J Clin Sleep Med*. 2020;16[7]:1055-62). The ODR measures the speed of an oxygen desaturation during an apnea event. Subjects with a faster ODR were found to have higher blood pressure values and variability. The authors hypothesized that slower desaturations generate hypoxemia-conditioning that may protect from exaggerated hemodynamic changes. These findings of novel hypoxemia metrics, albeit having their own limitations, recapitulate the need to move beyond the AHI to characterize OSA.

The apnea-hypopnea event duration is another overlooked feature that may impact OSA outcomes. Butler, et al. demonstrated that shorter event duration predicted a higher all-cause mortality over

and beyond that predicted by AHI (Butler et al. *Am J Respir Crit Care Med*. 2019;199[7]:903-12). These results contrast views that early arousals in response to respiratory events may improve outcomes as they reflect a protective mechanism to prevent further hypoxemia and

sympatho-excitation. For example, Ma, et al. found that higher percentage of total sleep time spent in apnea/hypopnea (AHT%) predicted worse daytime sleepiness to a higher degree than standard AHI (Ma et al. *Sci Rep*. 2021;11[1]:4702). However, shorter event duration may

represent lower arousal thresholds (increased excitability), and ventilatory control instability (higher loop gain), predisposing patients to augmented sympathetic activity. Along similar lines, the intensity of respiratory-related arousals (as mea-

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Finding your passion in fellowship

BY KEVIN SWIATEK, DO

(This post is part of *Our Life as a Fellow* blog post series. This series includes “fellow life lessons” from current trainees in leadership with CHEST.)

Finding your passion in fellowship is an integral part of career development and has a profound impact on a young professional’s personal satisfaction. This can be a difficult task, but it can be accomplished by finding a mentor, thinking about long-term career goals, and considering what re-energizes you.

Entering fellowship, some may have a preconceived idea of who they would like to be upon completion of training: An asthma specialist, a physician-scientist, a critical care junkie, etc. For most of us, fellowship is a black box of opportunity with endless paths and permu-

tations. It can be difficult to navigate this landscape, as the path may meander and a few initial interests may develop into true passions.

During my fellowship, I have been fortunate to have had many great teachers and experiences caring for patients with pulmonary hypertension, my current primary focus. Here are a few steps I have taken in pursuit of finding my passion over the past several years of post-graduate medical education. ***Disclaimer: I am still a work in progress.***

First, find a mentor. For me it was easy – I remember interviewing for fellowship with my mentor and thinking: “That is who I want to be.” I think this is hugely important. Use the insights, mistakes, and successes of someone you admire (from near or far) to help guide you. Initially, while getting to know my mentor,

Passion // Continued on following page

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sured by EEG wavelet transformation) was found to be independent of preceding respiratory stimulus, with higher arousal intensity levels correlating with higher respiratory and heart rate responses (Amatoury et al. *Sleep*. 2016;39[12]:2091-100). The contribution of arousals to OSA morbidity is of particular importance for women in whom long-term outcomes of elevated AHI are poorly understood. Bearing in mind the differences in the metrics used, these results underscore the role of event duration and arousability in the pathogenesis of OSA-related morbidity.

The AHI is certainly an important piece of data that is informative and somewhat predictive. However, when used as a sole disease-defining metric, it has yielded disappointing results, especially after OSA treatment trials failed to show cardiovascular benefits despite therapies achieving a low residual AHI. As we aim to achieve a more personalized approach for diagnosing and treating OSA, we need to explore beyond the concept of a single metric to define a heterogeneous and complex disorder. Instead of relying on the frequency of respiratory events, it is time to use complementary polysomnographic data that better reflect the origin and systemic effects of these

disturbances. Machine-learning methods may offer sophisticated approaches to identifying polysomnographic patterns for future research. Clinical characteristics will also likely need to be considered in OSA severity scales. The identification of symptom subtypes or blood biomarkers may help identify patient groups who may be impacted differently by OSA, and consequently have a different treatment response (Malhotra et al. *Sleep*. 2021;44[7]:zsab030).

Almost half a century has lapsed since the original descriptions of OSA. Since then, our understanding of the disorder has improved greatly, with much still to be discovered, but our method of disease capture is unwavering. Future research requires a focus on novel measures aimed at identifying OSA endophenotypes, which will transform our understanding of disease traits and propel us into personalized therapies.

Dr. Mansour is Assistant Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University School of Medicine, Durham, North Carolina. Dr. Won is Associate Professor of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine; and VA Connecticut Healthcare System, West Haven, Connecticut.

Passion // Continued from previous page

it was more comfortable to follow from a safe distance without making an official commitment. This was a slow process that allowed me to explore multiple clinical and research interests simultaneously.

Once your mind is set, stating your professional interests in a concise way helps you and your mentor define and differentiate hobbies from passions.

The practice of medicine is still very much an apprenticeship, so having someone to act as a sounding board remains important.

Mentorship is also critical for networking, which is important for professional growth and life beyond fellowship. Our community is small, and “people know people.”

What happens if you can't find a perfect mentor? Don't worry! Try out as many mentors as you can find. You can learn from every conversation and every relationship. Sometimes the path taken is just as important as the destination.

Second, think about your 5- or 10-year plan. Ultimately, when training is over, we will graduate from fellowship and be released into the wild.

The skills we have obtained in training are going to be the foun-

ation for the rest of our careers. Where would you like to be a few years post-training? In a lab? Private practice? Rural medicine? Teaching?

Does the energy you are spending in fellowship to develop your passion extend beyond fellowship? Part of the excitement of pursuing a passion is envisioning how it may develop over the period of coming years. I envision honing my skills as a master general pulmonary clinician and then narrowing my focus to create a pulmonary hypertension care center of excellence.

I think these are important points to consider while you have the protected headspace of fellowship to experiment and explore, and while you are not constrained by contractual obligations.

Third, think about what personally and professionally energizes you. Especially in the context of an ongoing global pandemic, burnout and physician dissatisfaction are at an all-time high. Acknowledge that your job is tough, and try to identify the things that will keep the engine running.

This sounds straightforward, but you have to decide what recharges you and acknowledge those things that don't. The importance of determining things that energize me

did not occur to me until I started searching for my first job. This forced me to make a list of things that contributed to my happiness and dissatisfaction. Most future employers are skilled at asking about these qualities. A happy employee is productive and effective at his or her job!

If you are in training, take some time to get creative and answer the questions above. Doodle, make lists, or journal—find a moment to reflect on your hard work and on the promise of your future.

Dr. Swiatek is a third-year Chief Fellow in the Division of Pulmonary and Critical Care Medicine at Virginia Commonwealth University in Richmond, Virginia. Dr. Swiatek is a member of the CHEST Trainee Work Group. His clinical interests include general pulmonary medicine, care of patients with pulmonary hypertension, and using point-of-care ultrasound (POCUS) as a diagnostic tool in the medical intensive care unit. His scholarly interests include implementation of fellowship medical education, teaching POCUS, and clinical and diagnostic assessment of patients with pulmonary hypertension.

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BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief



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How We Do It: Managing Cough in Idiopathic Pulmonary Fibrosis.

By Dr. J. Swigris, et al.

Executive Summary: Optimal Noninvasive Ventilation Medicare Access Promotion (ONMAP).

By Dr. P. Gay, et al.

Screening for Lung Cancer: CHEST Guideline and Expert Panel Report – Executive Summary.

By Dr. P. J. Mazzone, et al.



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CHEST in the news

BY LAURA DIMASI

CHEST PR and Communications Specialist

Creating a stronger voice for CHEST members in pulmonary, critical care, and sleep medicine, CHEST works to provide opportunities for members to serve as expert sources for both mainstream and trade media.

Below are a few highlights of media coverage from the past few months that work to expand awareness of CHEST and to promote the expertise of CHEST members in the media.

The New York Times covers the Philips recall

In August, a *New York Times* article quoted incoming CHEST President, David Schulman, MD, MPH, FCCP. The article covered the recent Philips recall and its impact on the COVID-19 pandemic.

Dr. Schulman is quoted saying, “Because the number of people coming into the hospital with severe respiratory symptoms has increased as a result of COVID-19, the demand for these devices has also increased, which is problematic since available supply has decreased as a result of the Philips recall.”

The full article, *Breathing Machine Recall Over Possible Cancer Risk Leaves Millions Scrambling for Substitutes*, can be found on the New York Times website.

Technical expert panel on coverage determinations

Peter Gay, MD, FCCP, was quoted in an article by *McKnight's Long-Term Care News* on the recent technical expert panel recommendations for national coverage determinations for optimal noninvasive ventilation.

“Centers for Medicare & Medicaid Services was wanting rigorous scientific support necessary to clarify the ‘reasonable and necessary’ role of these new mechanical therapeutic modalities where there was none in order to move forward,” said Dr. Gay. “What we have done is create a pathway to simplify the maze of regulation and perhaps most importantly, remove the obstacles that currently exist.”

The full article, *Panel on Non-Invasive Ventilation Seeks to Simplify ‘Maze’ of Regulation for Device Coverage*, can be found on the *McKnight's Long-Term Care News* website.

Asthma and HRT

Originally appearing in *Health-*

Day, *U.S. News and World Report* covered a recent journal CHEST® publication *Hormone Replacement Therapy and Development of New Asthma* by Erik Soeren Halvard Hansen, MD, et al.

The study included about 34,500 women who were diagnosed with

asthma between 1995 and 2018, when they were 40 to 65 years of age. Each was then compared with 10 asthma-free women.

Based on that comparison, HRT use was associated with a 63% higher risk for developing asthma, according to the study.

The full article, *HRT Could Raise Odds for Asthma*, can be found on the *U.S. News & World Report* website.

Pediatric ICU admission and COVID-19

Healio Pulmonology covered a re-



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Daniel Ryan, MD

Royal College of Surgeons Ireland, Dublin, Ireland

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease

Miguel Divo, MD

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Stephen Milne, MBBS

Woolcock Institute of Medical Research
Vancouver, BC, Canada

CHEST Foundation Research Grant in Critical Care

Jacqueline Stocking, PhD

University of California, Davis, Davis, CA

CHEST Foundation and the Alpha-1 Foundation
Research Grant in Alpha-1 Antitrypsin Deficiency

John Charles Rotondo, PhD

University of Ferrara, Ferrara, Italy

CHEST Foundation Research Grant
in Nontuberculous Mycobacteria Diseases

Edward Chan, MD

Rocky Mountain Regional Veterans Affairs
Medical Center, Denver, CO

CHEST Foundation Research Grant in Cystic Fibrosis

Shahid Sheikh, MD, FCCP

Nationwide Children's Hospital, Columbus, OH

John R. Addrizzo, MD, FCCP Research Grant in Sarcoidosis

Maneesh Bhargava, MD, PhD, FCCP

Minneapolis VA Health Care System
Minneapolis, MN

CHEST Foundation Research Grant in Severe Asthma

Felix Reyes, MD

Montefiore Medical Center, Bronx, NY

CHEST Foundation Research Grant in Pulmonary Fibrosis

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Janelle Pugashetti, MD

University of California, Davis, Davis, CA

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Canada

CHEST Foundation and APCCMPD Research
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NYU School of Medicine, New York, NY

CHEST Foundation Research Grant in COVID-19

Marlene Cano, MD, PhD

Washington University, St. Louis, MO

Brandon Walsh, MD

New York University, New York, NY

CHEST Foundation and ATS Research Grant
in COVID-19 and Diversity

Navitha Ramesh, MD, FCCP

UPMC Harrisburg, Harrisburg, PA

Inderjit Singh, MBBCh

Yale University, New Haven, CT

cent journal *CHEST* publication, *Changes in Pediatric ICU Utilization and Clinical Trends During the Coronavirus Pandemic*, by Janine E. Zee-Cheng, MD, et al.

“Severe infections, traumatic injuries, perioperative conditions and acute exacerbations of chronic illnesses such as asthma and diabetes are among the most common causes of admission to a pediatric ICU;

thus, the epidemiology of pediatric critical illness was likely sensitive to the indirect effects of COVID-19,” Janine E. Zee-Cheng, MD, adjunct clinical assistant professor of pediatrics in the department of pediatrics at Indiana University School of Medicine, Indianapolis, and colleagues wrote.

The full article, *Pediatric ICU admissions significantly decreased during*

COVID-19 pandemic, can be found on the *Healio* website.

CHEST news

CHEST also recently issued a handful of statements and press releases on a variety of topics including the spread of misinformation, support of mandatory vaccinations for health care workers, and a statement advocating for broader coverage of

supplemental oxygen use.

For all recent CHEST News, including these statements, visit the CHEST Newsroom on the CHEST website (<https://www.chestnet.org/Newsroom>) and follow the hashtag #CHESTNews on Twitter.

If you have been included in a recent news article and would like it to be featured, send the coverage to media@chestnet.org.

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CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP

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Panagis Galiatsatos, MD, MPH

John Hopkins University, Baltimore, MD

Patricia George, MD

National Jewish Health, Denver, CO

Nishant Gupta, MD, MS

University of Cincinnati, Cincinnati, OH

Syed Naqvi, MD, MBBS

Hoag Hospital Newport Beach
Newport Beach, CA

To learn about the projects from this year's research and community grant recipients, please visit chestnet.org/grants.

CHEST FOUNDATION DIVERSITY GRANT RECIPIENTS

The CHEST Foundation is pleased to announce the recipients of the 2021 Diversity Grant. Diversity Grants are awarded to those who represent underrepresented minorities, outstanding trainees, and early-career clinicians (completed training within previous 5 years).

These individuals were nominated by a member of leadership and will receive complimentary registration to the CHEST 2021 Annual Meeting.

Aparna Balasubramanian, MD, MHS

Dhishna Chaudhary, MD

Jeremy Courtney, MD

Aunie Danyalian, MD

Meghana Dasyam, MBBS

Akash Dodia, MBBS, DTCD

Ahmed El Maghraby, MD, MBBCh

Sangeetha Isaac, MD

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Musaib Ahmed Syed, MD, MBBS

Muhammad Khyzar Hayat Syed, MBBS

Jaleesa Watkins

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Nadia Yimer, MD



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In memoriam

Ronald B. George, MD, Master FCCP

Past President (1993-1994) of the American College of Chest Physicians, Dr. Ronald Baylis George died July 19, 2021, in Shreveport, Louisiana. He was an active and respected leader for the College for many years. Dr. George was



Dr. Ronald B. George

Professor Emeritus of Medicine and former Chairman of the Department of Medicine, School of Medicine, Louisiana State University, Shreveport. He founded the Pulmonary and Critical Care Division at LSU and then served as Chief for many years. Dr. George was an outstanding clinician and a nationally recognized leader in the field of pulmonary diseases. He had a special gift for diagnosing difficult lung disease cases and was constantly sought out by residents, staff, and physicians for his help with patients. He was a visiting professor at many academic institutions throughout the country. As a prolific writer, Dr. George authored over 200 manuscripts, books, and book chapters, including one of the most successful, longstanding pulmonary textbooks, *Chest Medicine*, now in its 5th edition. CHEST extends heartfelt condolences to the George family.

Wearable sensors detect viral infections before symptoms

BY PAM HARRISON

A simple wristband containing biometric monitoring sensors is able to pick up early infection from both influenza and the common cold before symptoms develop. Moreover, it can predict the severity of the illness once it becomes symptomatic, new research shows.

“Prior to the development of symptoms, people are still infectious and can potentially infect others,” senior author Jessilyn Dunn, PhD, Duke University, Durham, N.C., told this news organization.

“That’s why it’s so important to be able to detect infection even when a person doesn’t feel symptomatic, as this would help prevent the spread of pathogens that occur before somebody knows they are sick – and which is why it is important from a public health perspective,” she added.

The study was published online Sept. 29, 2021, in JAMA Network Open (doi: 10.1001/jamanetworkopen.2021.28534).

Two challenge studies

The study involved 31 participants who were inoculated with the H1N1 influenza virus and 18 others who were inoculated with rhinovirus. The rhinovirus challenge study was conducted in 2015, and the H1N1 challenge study was carried out in 2018. Both groups of patients were inoculated via intranasal drops of either the diluted H1N1 virus or the diluted rhinovirus strain type 16.

Participants in both challenge studies wore the E4 wristband (Empatica). Those in the influenza study wore the wristband 1 day before and 11 days after being inoculated, and those in the rhinovirus study wore the wristband for 4 days before and 5 days after inoculation. The E4 wristband measures heart rate, skin temperature, electrodermal activity, and movement.

Symptoms were typical of each infection and were classified as both observable events, such as runny nose, cough, and wheezy chest, or unobservable events, such as muscle soreness and fatigue. Infection status was classified as asymptomatic or noninfectious (AON), mild, or moderate.

The biosensors contained within the wristband were able to detect the presence or absence of H1N1 infection with an accuracy of 79% within 12 hours after participants had been inoculated and an accuracy of 92%

within 24 hours of being inoculated, the authors report. Thus, “we could assess whether or not a participant was infected with H1N1 between 24 and 36 hours before symptom onset,” the investigators noted.

The median time for symptom onset following the rhinovirus challenge was 36 hours after inoculation. The biosensors predicted the presence or absence of rhinovirus infection with an accuracy

of 88%, the authors wrote. And when both viral challenges were combined, models predicting infection had an accuracy of 76% at 24 hours after participants being inoculated.

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Prediction of severity

Twelve hours after participants were inoculated, the technology was also able to predict the development of either AON or moderate H1N1 infection with 83% accuracy. For rhinovirus, the predictive accuracy of distinguishing AON versus moderate infection was slightly higher at 92% whereas for both viruses com-

bined, the technology predicted the development of AON versus moderate infection with 84% accuracy rate.

As the authors pointed out, the ability to identify individuals during the early critical stage of viral infection could have wide-ranging effects. "In the midst of the global SARS-CoV-2 pandemic, the need for novel approaches like this has never been

more apparent," they suggested.

And in point of fact, in a not-yet peer-reviewed study using a real-time smartwatch-based alerting system again designed to detect aberrant physiologic and activity signals associated with early infection (medRxiv. 2021 Jun 21. doi: 10.1101/2021.06.13.21258795), Stanford (Calif.) University investigators

found that alerts were generated for presymptomatic and asymptomatic COVID-19 infections in 78% of cases in over 3,200 participants tested at a median of 3 days prior to symptom onset.

The authors also noted that their system is scalable to millions of users, thus offering a personal health

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monitoring system that can operate in real time.

In a comment, Steven Steinhubl, MD, a research scientist and formerly the director of digital medicine at Scripps Research's Translational Institute, La Jolla, Calif., told this news organization that he personally has a lot of faith in

this type of technology.

"Unfortunately, COVID-19 has changed our perspective about respiratory infections but if you think of the bad flu seasons we've had in the past, people do die from influenza, so I think there is a lot of value [in this technology], although the degree of value depends on the severity of the infec-

tion," Dr. Steinhubl said.

For example, if people actually ever go back into work together, early recognition that an employee might have influenza or another highly contagious infection could alert them to the necessity to stay home and self-isolate.

"We have a bit to go before we get there," Dr. Steinhubl acknowledged,

"but you could have a really big impact on the spread of any infectious disease that would be better for everybody."

Dr. Dunn has disclosed no relevant financial relationships. Dr. Steinhubl is chief medical officer at physIQ, a company involved in the development of personalized analytics.

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Remdesivir may lower COVID hospitalization risk

BY MARCIA FRELLICK

Treatment with remdesivir (Veklury, Gilead) was found to reduce some COVID-19 patients' risk of hospitalization by

87% in a phase 3 trial, the drug's manufacturer announced in a press release.

The randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of a 3-day

course of intravenous remdesivir in an analysis of 562 nonhospitalized patients who were at high risk for COVID-19 disease progression.

Remdesivir demonstrated a

statistically significant 87% reduction in risk for COVID-19-related hospitalization or all-cause death by day 28 (0.7% [2/279]) compared with placebo

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(5.3% [15/283]) $P = .008$. Participants were assigned 1:1 to remdesivir or the placebo group.

Researchers also found an 81% reduction in risk for the composite secondary endpoint – medical visits due to COVID-19 or all-cause death by day 28. Only 1.6% had COVID-19 medical visits (4/246)

compared with those in the placebo group (8.3% [21/252]) $P = .002$. No deaths were observed in either arm by day 28.

“These latest data show remdesivir’s potential to help high-risk patients recover before they get sick and stay out of the hospital altogether,” coauthor Robert L. Gottlieb, MD, PhD, from Baylor University

Medical Center, Houston, said in the press release.

Remdesivir is the only drug approved by the U.S. Food and Drug Administration for hospitalized COVID-19 patients at least 12 years old.

Its treatment of nonhospitalized patients with 3 days of dosing is still investigational,

and the safety and the efficacy for this use and dosing duration have not been established or approved by any regulatory agency, according to the Gilead press release.

The patients in this study were considered high risk for disease progression based on comorbidities – commonly obesity, hyper-

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tension, and diabetes – and age, but had not recently had hospitalizations due to COVID-19.

A third of the participants were at least 60 years old. All of the participants in the study must have received a positive diagnosis within 4 days of starting treatment and experienced symptoms for 7 days or less in order to be included.

Use of remdesivir controversial

Results from the Adaptive COVID-19 Treatment Trial (ACTT-1) showed remdesivir was superior to placebo in shortening time to recovery in adults hospitalized with COVID-19 with evidence of lower respiratory tract infection.

However, a large trial of more

than 11,000 people in 30 countries, sponsored by the World Health Organization, did not show any benefit for the drug in reducing COVID deaths.

The WHO has conditionally recommended against using remdesivir in hospitalized patients, regardless of disease severity, “as there is currently no evidence that remdesivir

improves survival and other outcomes in these patients,” the organization indicated.

The drug also is given intravenously, and this study tested three infusions over 3 days, a difficult treatment for nonhospitalized patients.

The study results were released ahead of IDWeek.

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Portal use gives patients access, doctors headaches

BY KEN TERRY

The use of patient portals that provide access to electronic health records has dramatically increased in the past several

years, and patients whose health care practitioner encouraged them to use their online portal accessed them at a higher rate than those who were not encouraged to do so. These were among the top-line

results of a national survey of U.S. adults conducted by the National Institutes of Health from January 2020 to April 2020. Although the COVID-19 pandemic hit the United States in the middle of that

period, a report on the survey by the Office of the National Coordinator for Health IT stated, "These findings largely reflect prepandemic rates of individuals being offered and subsequently using their online medical record, also known as a patient portal."

But with more patient access can come additional work for physicians and other health care practitioners, ranging from an onslaught of patient communications to managing data sent to them by patients.

According to the report, 59% of individuals were offered access to their patient portal, and 38% accessed their record at least once in 2020. By comparison, in 2014, just 42% were offered access to their portal, and 25% used it. But these percentages hardly changed from 2019 to 2020.

But with more patient access can come additional work for physicians and other health care practitioners, ranging from an onslaught of patient communications to managing data sent to them by patients.

The increase in the percentage of people who accessed portals reflects the fact that more people were offered access. In addition, there were signs of rising activity among portal users.

Among patients offered access to their patient portal, 64% accessed it at least once in 2020 – 11 percentage points more than in 2017. Twenty-seven percent of those who had access to a portal used it once or twice; 20% accessed it three to five times; and 18% used it six or more times. The latter two percentages were significantly higher than in 2017.

Of the respondents who were offered access to portals but didn't use them, 69% said they didn't access the portal because they preferred to speak with their health care practitioner directly. Sixty-three percent said they didn't see a need to use their online medical record. This was similar to the percentage 3 years earlier. Other reasons included respondents' concerns about the privacy/security of online medical records (24%), their lack of comfort with computers (20%), and their lack of Internet access (13%).

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The pros and cons of patient portals, greater access

Among portal users who accessed their records through a mobile health app, 51% used the app to facilitate discussions with their health care practitioner in 2020, an 8–percentage point increase from 2017. Fifty-percent of the mobile health app users utilized it to make a decision about how to treat an illness or condition, up from 45% in 2017. And 71% of these individuals used their app to track progress on a health-related goal, just a bit more than in 2017.

Individuals who were encouraged by their health care practitioner to use their patient portal viewed clinical notes and exchanged secure messages with their practitioner at higher rates than those who had not been encouraged. This is not surprising, but it reflects an unintended result of patient portals that many physicians have found burdensome, especially during the pandemic: overflowing electronic in-boxes.

Robert Wachter, MD, chairman of the department of medicine at the University of California, San Francisco, recently tweeted, “We’re seeing huge uptick in in-box messages for MDs during COVID – now seems like biggest driver of MD burnout. The fundamental problem: We turned on 24/7/365 access for patients (who of course like it) with no operational or business model to handle it. Crucial that we fix this.”

Steven Waldren, MD, vice president and chief medical informatics officer at the American Academy of Family Physicians, told this news organization that he agrees that this is a major challenge. “In-box management is a burden on physicians and practices,” he said. “However, it can be done better, either through a team in-box or through better use of technology.”

The team in-box he refers to is a mechanism for triaging patient messages. For example, a triage nurse can look at the messages and decide which ones can be handled by staff and which ones the doctor needs to see. Or physicians and front office staff can see the messages at the same time; a nurse can triage some messages according to protocols,

and the physician can respond to any message, depending on what he or she knows about the patient.

Technology can also be enlisted in the effort, he suggested, perhaps by automating the triaging of messages such as prescription refill requests or using artificial intelligence to sort messages by content.

Making patient records portable

Nearly 40% of portal users accessed it using a smartphone app (17%) or with both their smartphone app and their computer (22%). Sixty-one percent of users relied exclusively on computers to access their portals.

About a third of patient portal users downloaded their online medical records in 2020. This proportion has nearly doubled from 17% since 2017, the ONC report noted.

Although the survey didn’t ask about multiple downloads, it appears that most people had to download their records separately from the patient portal of each practitioner who cared for them. Although the Apple Health app allows people to download records to their iPhones from multiple portals using a standard application programming interface, the ONC report says that only 5% of respondents transmitted their records to a service or app, up slightly from 3% in 2017.

Dr. Waldren hopes most patients will have the ability to download and integrate records from multiple practitioners in a few years, but he wouldn’t bet on it.

“A fair amount of work needs to be done on the business side and on figuring out how the data get con-

nected together,” he said. “And there are still privacy concerns with apps.”

Overall, 21% of portal users transmitted their data to at least one outside party in 2020, compared with 14% in 2017. Seventeen percent of them sent their records to another health care practitioner, up from 10% in 2017. Five percent of the users transmitted their records to a caregiver, slightly more than in 2017.

Managing data is a challenge

Asked how physicians feel about portal users adding information to their record or correcting inaccurate information, Dr. Waldren says, “Doctors are already comfortable

with patient-generated data. The challenge is managing it. If the patient provides data that’s not easy to put in the EHR, that’s going to add work, and they don’t want to see 100 blood pressure readings.

“You’d be hard-pressed to find a doctor who doesn’t welcome additional information about the patient’s health, but it can be onerous and can take time to enter the data,” Dr. Waldren said.

Overall, he said, “Giving patients the ability to take more ownership of their health and participate in their own care is good and can help us move forward. How this will be integrated into patient care is another question.”

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