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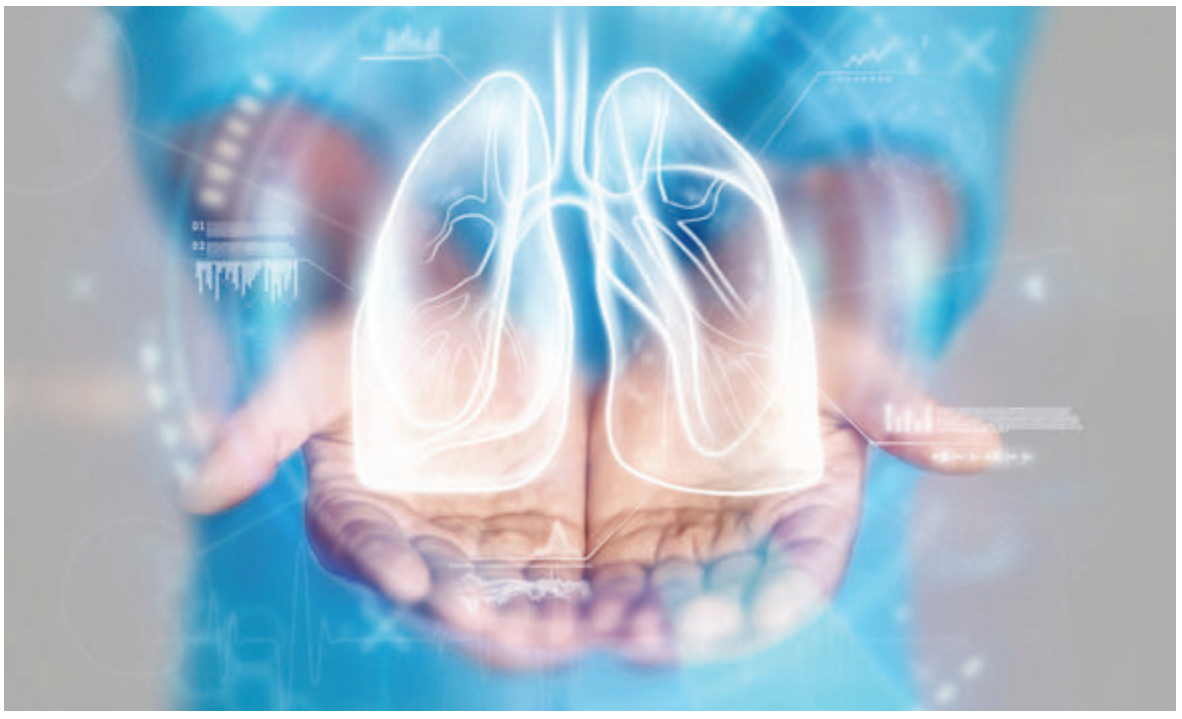

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Can new ideas overcome disparities in lung transplantation?

BY RICHARD MARK KIRKNER

The evidence that white patients with lung disease are disproportionately more likely to get a lung transplant than minority populations hasn't moved much in recent years.

At the same time, while pulmonology transplant experts acknowledge multiple challenges moving toward a more equitable donor lung allocation that overcomes racial, ethnic, and socioeconomic disparities, they noted that nascent widespread efforts to improve lung transplant data collection, preservation of donor lungs, and donor lung distribution could address those inequities.

Data lacking

But getting detailed data on lung transplants and who gets them has been an ongoing challenge, said Holly Keyt, MD, lung transplant director at University of Texas Health San Antonio. "Research in this area is lacking," Dr. Keyt said. "It's something we as the pulmonary community and we as the transplant community need to come together to understand better."

That people at the low end of the socioeconomic spectrum are less likely to get a lung transplant is well known, if not well documented, she said.

Studies have been done in specific patient populations, such as idiopathic pulmonary fibrosis and cystic fibrosis, Dr. Keyt said, "but a lot of referral data are lacking because we don't have a large registry that captures that. A lot of the data we have come from the registry of patients who

TRANSPLANT // *continued on page 7*

Children on Medicaid receive less specialty care for asthma

BY HEIDI SPLETE

Children with asthma who were insured by Medicaid were significantly less likely to receive specialist care over a 1-year period than children with private insurance, based on claims data from nearly 200,000 children.

Primary care clinicians successfully manage many children with asthma, but data on specialist care according to insurance coverage are lacking, wrote Kimberley H. Geissler, PhD, of the University of Massachusetts Chan Medical School–Baystate, Springfield, Massachusetts, and colleagues.

Despite many interventions over time, "low-income children insured by Medicaid, many of whom are from minoritized racial and ethnic groups, continue to have worse outcomes and higher rates of poorly controlled asthma than children who are privately insured," Dr. Geissler said in an interview.

"Because differences in whether a child sees an asthma specialist could contribute to these

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INSIDE HIGHLIGHT

NEWS FROM CHEST

In memory of former CHEST president

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disparities, better understanding specialist use among both groups of kids may help inform potential solutions," she said.

In a study published in *JAMA Network Open*, the researchers identified children with asthma aged 2-17 years using data from the Massachusetts All-Payer Claims Database for the years 2015-2020. The study population included 198,101 children and 432,455 child-year observations from children with asthma during a year when they met at least one of three criteria with any asthma diagnosis: one or more hospital visits, two or more outpatient visits, or at least one outpatient visit and at least one asthma medication.

Outpatient visit outcome

The primary outcome of asthma specialist care was defined as at least one outpatient visit with any asthma diagnosis to a clinician with a code of allergy and immunology, pulmonology, or otolaryngology.

"Perhaps unsurprisingly, children with private insurance were more likely to receive asthma specialist care than children with Medicaid." – Dr. Geissler.

A total of 66.2% of the child-year observations involved Medicaid and 33.8% involved private insurance. Approximately 15% of the children received asthma specialist care. However, nearly twice as many children with private insurance received asthma specialty care compared with those with Medicaid (20.6% vs 11.9%). In a full logistic regression analysis, children with Medicaid insurance were 55% less likely to receive asthma specialist treatment than children with private insurance.

Allergy and immunology was the most common specialty used, and the child-years for this specialty among children with Medicaid were less than half of those among children with private insurance (7.1% vs 15.9%).

Rates of persistent asthma were 20.0% and 16.9% in children with Medicaid and private insurance, respectively. Overall, children with persistent asthma were nearly four times as likely to receive asthma specialist care (adjusted odds ratio, 3.96). However, the difference in odds of receiving specialty care based on insurance type in favor of private insurance was greater among children with persistent asthma than among those without persistent asthma (−24.0 percentage points vs −20.8 percentage points).

The researchers found a similar pattern of difference in asthma specialty care in a sensitivity analysis limiting the results to child-year observations with at least one outpatient visit with any asthma diagnosis in a calendar year, although they also found a slight narrowing of the difference between the groups over time.

"Contrary to expectations, disparities in specialist care by insurance type were even more striking in children with persistent asthma," the researchers wrote in their discussion. Notably, the growth of specialty drugs such as biologics for moderate to severe asthma are mainly prescribed by specialists, and ensuring access to specialists for children with Medicaid may reduce disparities in asthma control for those with severe or poorly controlled disease, they added.

The study findings were limited by several factors including the use of data from only Massachusetts, which may not generalize to other states, and the use of completed specialist visits without data on referrals, the researchers noted. Other limitations included a lack of data on asthma symptom frequency or control and on the setting in which an asthma diagnosis was made.

However, the results suggest a need for more attention to disparities in asthma care by insurance type, and more research is needed to determine whether these disparities persist in subsets of children with asthma, such as those with allergies or chronic medical conditions, they concluded.

Takeaways and next steps

"Perhaps unsurprisingly, children with private insurance were more likely to receive asthma specialist care than children with Medicaid," Dr. Geissler told this news organization. The researchers expected a smaller gap between insurance types among children with persistent asthma, a marker for asthma severity, she said. However, "we found that the gap between those with Medicaid and those with private insurance is actually larger" for children with persistent asthma, she added.

As improved treatments for

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Therapy may offer COPD patients relief, convenience

BY HEIDI SPLETE

The recent Food and Drug Administration (FDA) approval of ensifentrine marks the first new treatment for patients with persistent chronic obstrutive pulmonary disease (COPD) in more than a decade, according to manufacturer Verona Pharma. Ensifentrine offers a new medication and a new delivery method, according to a company press release. Ensifentrine is the first-in-class selective dual inhibitor of both phosphodiesterase 3 (PDE 3) and PDE 4, combining both bronchodilator and nonsteroidal anti-inflammatory effects in a single molecule. The drug is delivered through a standard jet nebulizer.

Disease management made easier

Although currently approved therapies for COPD, such as bronchodilators and inhaled corticosteroids (ICS), have benefited many patients, additional treatment options are still needed to help those who remain symptomatic and suffer from frequent exacerbations, said Diego J. Maselli, MD, FCCP, of the University of Texas Health Science Center, San Antonio, and a member of the *CHEST Physician* Editorial Board.

"Ensifentrine is a new class of medication that inhibits both PDE 3 and PDE 4; this results in both bronchodilation and suppression of the inflammatory response in COPD," said Dr. Maselli, who was not involved in studies of ensifentrine.

"Large phase 3, double-blind, randomized, placebo-controlled studies have demonstrated that ensifentrine improved lung function and reduced the risk of exacerbations in patients with symptomatic moderate to severe COPD," he said. The study participants were on no long-acting maintenance therapy, or they were receiving long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) with or without inhaled corticosteroids, he noted.

"Ensifentrine is a welcome addition to the current armamentarium of therapies for COPD as an option for patients who are symptomatic or who have frequent exacerbations."
– Dr. Maselli

The FDA approval was supported by data from the phase 3 ENHANCE 1 and 2 trials, which included 760 and 789 adults aged 40-80 years with moderate to severe symptomatic COPD, respectively. Participants were randomized to 3 mg ensifentrine delivered via nebulizer or a placebo twice daily. In the studies, ensifentrine significantly improved lung function based on the primary outcome of average forced expiratory volume per second within 0-12 hours of administration compared with placebo in both studies. In ENHANCE 1, ensifentrine significantly improved symptoms and quality of life compared with placebo at 24 weeks. The ENHANCE 2 results showed similar trends in favor of ensifentrine, although the differences were not significant at 24 weeks. However, the effects of ensifentrine vs placebo were consistent overall across all symptom and quality of life endpoints at all assessments during the study period, the researchers wrote. In addition, the inhaled drug was well tolerated, with similar proportions of ensifentrine and placebo patients reporting treatment-emergent adverse events (38.4% and 36.4%, respectively, in ENHANCE 1 and 35.3% and 35.4%, respectively, in ENHANCE 2). The most common treatment-emergent adverse events were nasopharyngitis, hypertension, and back pain, reported in < 3% of the ensifentrine group.

The safety profile of ensifentrine is a plus for patients, Dr. Maselli said. "Ensifentrine was well tolerated in these studies, and the side effect profile was similar to placebo," he said. The "ensifentrine is delivered via nebulizer and dosed every 12 hours. Some patients may still prefer the use of inhalers, while others may feel more comfortable with this mode of delivery," he said.

In clinical practice, "ensifentrine is a welcome addition to the current armamentarium of therapies for COPD as an option for patients who are symptomatic or who have frequent exacerbations," Dr. Maselli emphasized. Looking ahead, he said, more studies are needed to evaluate ensifentrine in broader populations of COPD patients. For example, ensifentrine could be used as an add-on therapy for patients receiving triple therapy (ICS/LABA/LAMA) and for patients with other obstructive inflammatory diseases such as asthma, bronchiectasis, and cystic fibrosis, he noted. Dr. Maselli disclosed serving as a consultant for GlaxoSmithKline, AstraZeneca, Amgen, and Sanofi/Regeneron. ■

MEDICAID *continued from page 2*

hard-to-control asthma become more available, pediatricians and primary care clinicians should follow the latest clinical guidelines for referring children to specialists for asthma care, Dr. Geissler said. "Additionally, asthma specialists should ensure that their practices are accessible to children with Medicaid, as these families may face higher barriers to care; for example, transportation needs or scheduling challenges," she said. Other strategies to overcome barriers to care might include electronic consultations with specialists or primary care–oriented interdisciplinary asthma clinics, which may be useful for all children with asthma but may particularly benefit those insured by Medicaid, she noted. "Based on data limitations, we could not examine why we observed such big differences in specialist use by insurance type; for example, whether pediatricians were referring to specialists less for Medicaid-insured kids, or whether kids with Medicaid were less likely to see a specialist after a referral was made," Dr. Geissler said. More research is needed to examine not only these factors but also the appropriateness of specialty care based on clinical guidelines to ensure high-quality evidence-based care for children with asthma who are insured by Medicaid, she said.

Dr. Coates

"The burden of asthma differentially affects people of color who are living in lower resourced areas, and it is important in further research to understanding the barriers to helping people get the care they need."

Improve access, analysis

Asthma is a chronic and prevalent disease and requires a comprehensive approach that sometimes calls for specialist care, said Anne Coates, MD, FCCP, a pediatric pulmonologist in Portland, Maine, and a member of the *CHEST Physician* Editorial Board. Dr. Coates said she was surprised by the results of the current study but commended the authors for highlighting its limitations, which illustrate areas for additional research. Notably, "the authors couldn't observe referrals to specialists from primary care physicians; they used completed visits as a proxy," Dr. Coates said. More studies are needed to assess the completion of referral visits regardless of children's insurance in order to better understand and address the barriers to specialty care, she added. The current study is important because of the extent of asthma coupled with the significant number of children across the United States who are insured by Medicaid, especially underserved populations, she said. "The burden of asthma differentially affects people of color who are living in lower resourced areas, and it is important in further research to understanding the barriers to helping people get the care they need," Dr. Coates said. Some alternatives might include telehealth visits or even a hybrid visit to a primary care provider (PCP) who has high-speed internet, and the specialist could then conduct a telehealth visit from the PCP's office, with the PCP acting as on-site eyes and ears, said Dr. Coates, who has used this strategy in her practice in Maine, where many patients live far from specialist care.

The study was supported by the National Heart, Lung, and Blood Institute and the University of Massachusetts Center for Clinical and Translational Science-Biostatistics, Epidemiology & Research Design Component. Dr. Geissler and Dr. Coates had no financial conflicts to disclose. ■

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actually go through the evaluation process."

Dr. Keyt noted that a symposium of transplant experts held before this year's International Society of Heart Lung Transplantation meeting in Prague tackled improving data collection on lung transplantation, possibly even creating a registry. "Hopefully out of that is going to come more work," she said.

Dr. Keyt

"Research in this area is lacking. It's something we as the pulmonary community and we as the transplant community need to come together to understand better."

Nature of disparities unclear

That lack of data has made it difficult to get a clear picture of disparities among lung transplant recipients, Dr. Keyt said. A recent study in *JAMA* (2024;331:1379-1386) identified race and gender disparities in heart transplant, but no parallel study exists for lung transplants.

A 2022 National Academy of Sciences, Engineering, and Medicine (NASEM) report showed that almost 2800 lung transplants were performed in the United States in 2019, increasing more than 50% in the previous decade. At the same time, the number of donor lungs increased by 62%.

The NASEM report "found that the organ transplantation system was demonstrably inequitable," said the report's chair, Kenneth W. Kizer, MD, distinguished professor emeritus in emergency medicine at the University of California Davis School of Medicine in Sacramento.

"Most of the same factors that contribute to inequities or disparities in organ transplantation broadly also contribute to disparities in lung transplantation," Dr. Kizer said.

"These factors include minority race, low socioeconomic status, living in rural or other medically underserved areas, lack of health insurance, intellectual disability, and lack of family or other social support."

Lung transplant disparities may mirror those in other organs

A 2021 study identified sex, race, geographic, and age disparities in both heart and lung transplantation, but did not separate the two (Curr Opin Organ Transplant. 2021:26:521-530). A 2020 study reported on geographic disparities for lung transplant access (Transplantation. 2020;104;e199-e207).

This study found that people with an associate degree or higher were more likely to seek out a high-volume center, but it found no survival difference between patients who stayed at their home hospital and those who went to an alternative institution.

Dr. Kizer

"Most of the same factors that contribute to inequities or disparities in organ transplantation broadly also contribute to disparities in lung transplantation."

Does geographic location matter?

Dr. Keyt noted that a 2021 study of patients with advanced cystic fibrosis lung disease found that those in the United States had a 79% greater risk of death without lung transplant and a 34% lower likelihood of getting a lung transplant than similar patients in Canada (CHEST Infections. 2021;843-853).

Meanwhile, in the United States, overall lung transplant survival rates are stagnant, Dr. Kizer said. The Health Resources and Services Administration Scientific Registry of Transplant Recipients 2021 Annual Data Report found that 85.3% of transplant recipients survive to 1 year, but only a half — 54.3% — make it to 5 years and less than a third — 32.8% — to 10 years. "More recent data are not notably different," Dr. Kizer said.

Continuous distribution

One potential strategy to address disparities in lung transplants is a concept known as continuous distribution, noted Wayne Tsuang, MD, PhD, who specializes in pulmonary, critical care, and transplant medicine at Case Western Reserve University and Cleveland Clinic in Cleveland, and has studied disparities in transplantation. The Organ Procurement & Transplantation Network implemented a lung continuous distribution policy in 2023.

"The goal of the new system is to increase the efficiency of donor lung allocation and reduce the role of geography in matching waitlisted patients with donor lungs," Dr. Tsuang said.

Continuous distribution generates a composite allocation score (CAS) for each waitlisted patient.

"This new score determines where a patient is on the waitlist and includes many attributes which were not accounted for previously, such as biologic characteristics including height or blood type as well as travel distance from donor hospital to recipient hospital."

"These innovations streamline and simplify the care of transplant recipients, and in doing so, enable transplant care to be offered to a broader population, and therefore contribute toward a reduction in disparities."

Dr. Tsuang

Preserving more donor lungs

Other advances have the potential to increase the pool of donor lungs viable for transplantation.

"At present, only about 15%-20% of donor lungs are considered viable for transplantation," Dr. Kizer said. "A number of circumstances may make a donated lung not suitable for transplantation, including the lung's susceptibility to injuries from excess fluid accumulation, bacterial infection, or complications from the donor's pre-terminal medical care."

Technological advances could help close the gap

One such advance Dr. Kizer noted is ex vivo lung perfusion in which the lung is connected to a ventilator, pump, and filters inside a sterile plastic dome which perfuses the organ with an acellular solution containing nutrients, proteins, and a mix of oxygen, carbon dioxide, and nitrogen.

"These combined procedures have been shown to reduce post-transplantation rejection and to improve patient posttransplant survival rates to those comparable to transplants with less physiologically stressed or noncompromised organs," Dr. Kizer said.

At the International Society of Heart Lung Transplantation meeting in April, Pedro A. Catarino, MD, director of aortic surgery at Cedars-Sinai Medical Center in Los Angeles, reported on another technique to increase the number of viable donor lungs. Normothermic regional perfusion (TA-NRP) perfuses blood through a donor's abdomen and chest after the heart has stopped beating for up to 40 minutes to reanimate the heart and ventilate the lungs.

Dr. Catarino presented data showing that the retrieval rate for deceased donor lungs has increased to about 15% with the utilization of TA-NRP. However, some lung experts harbor concerns that lungs are injured during the in situ perfusion process.

Ongoing innovations in technology can also help reduce disparities, Dr. Tsuang said. "Examples include the wider implementation of telehealth for follow-up patient care, or the use of new blood tests which can detect complications after lung transplant instead of having to do a more invasive lung biopsy," he said.

"These innovations streamline and simplify the care of transplant recipients, and in doing so, enable transplant care to be offered to a broader population, and therefore contribute toward a reduction in disparities."

Dr. Keyt, Dr. Kizer, and Dr. Tsuang have no relevant financial relationships to disclose. ■

SLEEP MEDICINE

Light during nighttime linked to diabetes risk

BY CHRISTINA SZALINSKI

A study in *The Lancet* (2024 Jun. doi: 10.1016/j.lanepe.2024.100943) found that people who were exposed to the most light between 12:30 a.m. and 6 a.m. were 1.5 times more likely to develop diabetes than those who remained in darkness during that time frame.

The study builds on growing evidence linking nighttime light exposure to type 2 diabetes risk. But unlike previous large studies that relied on satellite data of outdoor light levels (an indirect measure of light exposure) (Diabetologia. 2023 Feb;66[2]:336-345), the recent study looked at personal light exposure — that is, light measured directly on individuals — as recorded by a wrist-worn sensor.

"Those previous studies likely underestimated the effect," said study author Andrew Phillips, PhD, professor of sleep health at Flinders University in Adelaide, Australia, "since they did not capture indoor light environments." Using data from 85,000 participants from the UK Biobank, the recent study is the largest to date linking diabetes risk to personal light exposure at night.

"This is really a phenomenal study," said Courtney Peterson, PhD, a scientist at the University of Alabama at Birmingham's Diabetes Research Center, who was not involved in the study. "This is the first large-scale study we have looking at people's light exposure patterns and linking it to their long-term health."

What the study showed

The participants wore the light sensors for a week, recording day and night light from all sources — whether from sunlight, lamps, streetlights, or digital screens. The researchers then tracked participants for 8 years.

"About half of the people that we looked at had very dim levels of light at night, so less than 1 lux — that basically means less than candlelight," Dr. Phillips said. "They were the people who were protected against type 2 diabetes." Those exposed to more light at night — defined in the study as 12:30 a.m.–6 a.m. — had a higher risk for type 2 diabetes. The risk went up as a dose response, Dr. Phillips said. The brighter the light exposure, the higher the diabetes risk. Participants in the top 10% of light exposure — who were exposed to about 48 lux , or the equivalent of relatively dim overhead lighting — were 1.5 times more likely to develop diabetes than those in the dark. That's about the risk increase you'd have from a family history of type 2 diabetes, the researchers said.

How light may increase diabetes risk

The results are not entirely surprising, said endocrinologist Susanne Miedlich, MD, a professor at the University of Rochester Medical Center, Rochester, New York, who was not involved in the study. Light at night can disrupt the circadian rhythm, or your body's internal 24-hour cycle. And scientists have long known that circadian rhythm is important for all kinds of biologic processes, including how the body manages blood sugar. One's internal clock regulates food intake, sugar absorption, and the release of insulin. Dysregulation in the circadian rhythm is associated with insulin resistance, a precursor to type 2 diabetes (Nat Rev Endocrinol. 2019 Feb;15[2]:75-89).

Dr. Phillips speculated that the sleep hormone melatonin also plays a role. "Melatonin does a lot of things, but one of the things that it does is it manages our glucose and our insulin responses," Dr. Phillips said. "So if you're chronically getting light exposure at night, that's reducing a level of melatonin that, in the long term, could lead to poor metabolic outcomes."

Previous studies have explored melatonin supplementation to help manage diabetes. "However, while melatonin clearly regulates circadian rhythms, its utility as a drug to prevent diabetes has not really panned out thus far [Clin Nutr. 2021 Jul;40(7):4595-4605]," Dr. Miedlich said.

Interventional studies are needed to confirm whether strategies like powering down screens, turning off lights, or using blackout curtains could reduce diabetes risk. ■

INFECTIOUS DISEASE

TB medication management may be no sweat

BY HEIDI SPLETE

Analysis of finger sweat detected isoniazid in adults with tuberculosis (TB) for ≤ 6 hours after administration, based on new study data.

Risk factors for TB treatment failure include poor medication compliance and insufficient exposure to medications, but measurement of drugs in samples of blood, saliva, or sweat can help assess adherence and inform dose adjustments, Katherine Longman, a PhD student at the University of Surrey, Guildford, England, and colleagues wrote.

Although TB is treatable, "it is well known that insufficient drug dosing leads to treatment failure and drug resistance, and so ensuring that patients have sufficient drug exposure is important," said corresponding author Melanie J. Bailey, PhD, also of the University of Surrey.

"This can be carried out using blood, but blood is painful to collect and difficult to transport. Finger sweat offers a completely noninvasive way to sample patients," but its use to determine medication adherence has not been examined, she said.

In a pilot study published in the *International Journal of Antimicrobial Agents* (2024 Jun 25. doi: 10.1016/j.ijantimicag.2024.107231), the researchers reviewed data from 10 adults with TB who provided finger sweat, blood, and saliva samples at several time points ≤ 6 hours after receiving a controlled dose of isoniazid (median of 300 mg daily). They used liquid chromatography–mass spectrometry to examine the samples. Overall, "isoniazid and acetyl isoniazid were detected in at least one finger sweat sample from all patients," with detection rates of 96% and 77%, respectively, the researchers wrote. Given the short half-life of isoniazid, they used a window of 1-6 hours after administration. Isoniazid was consistently detected between 1 and 6 hours after administration, while acetyl isoniazid had a noticeably higher detection rate at 6 hours.

The researchers also examined creatinine to account for variability in volume of sweat samples, and found that finger sweat was significantly correlated to isoniazid concentration. The maximum isoniazid to creatinine ratio in finger sweat occurred mainly in the first hour after drug administration, and the activity of isoniazid in finger sweat over time reflected isoniazid concentration in serum more closely after normalization to creatinine, they said. The Pearson's correlation coefficient (r) was 0.98 ($P < .001$; one-tailed), with normalization to creatinine, compared with r = 0.52 without normalization ($P = .051$).

The study findings were limited by several factors including the lack of knowledge of the last drug dose and lack of confirmation testing with an established method of analysis, the researchers noted. However, the results support the potential of the finger sweat test as a screening tool to indicate patients' nonadherence or to identify patients at risk of low medication exposure.

"We were surprised that we were able to detect the drug in so many patient samples because the sample volume is so low, and so detection is challenging," Dr. Bailey said. "We were also surprised that fingerprint and drug levels correlated so well after normalizing to creatinine. This is exciting as it unlocks the possibility to test drug levels, as well as providing a yes/no test."

In practice, the finger sweat technique could reduce the burden on clinics by offering a completely noninvasive way to test a patient's medication adherence. In future, more research is needed to explore whether creatinine normalization is widely applicable, such as whether it works for patients with abnormal kidney function, she added.

Noninvasive option

The current study presents a strategy that might address current limitations in TB management, said Krishna Thavarajah, MD, a pulmonologist and director of the interstitial lung disease program at Henry Ford Hospital, Detroit, Michigan, in an interview.

Both self-administered treatment and directly observed therapy (DOT) for TB have limitations, including adherence as low as 50% for TB regimens, she said. In addition, "DOT availability and efficacy can be limited by cost, personnel availability from an administration perspective, and by distrust of those being treated."

SWEAT *continued on following page*

Cold or flu virus may trigger long COVID relapse

BY TINKER READY

People who have recovered from long COVID can suffer relapses or flare-ups from new viral infections — not just from COVID but from cold, flu, and other viral pathogens, researchers have found.

In some cases, they may be experiencing what researchers call viral interference (Emerg Infect Dis. 2022 Feb;28[2]:273-281), something also experienced by people with HIV and other infections associated with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Clinical studies on the issue are limited, but patients, doctors, and researchers report many people who previously had long COVID have developed recurring symptoms after consequent viral infections. Viral persistence — where bits of virus linger in the body — and viral reactivation remain two of the leading suspects for Yale researchers. Viral activation occurs when the immune system responds to an infection by triggering a dormant virus.

Anecdotally, these flare-ups occur more commonly in patients with long COVID with autonomic dysfunction — severe dizziness when standing up — and other symptoms of ME/CFS, said Alba Azola, MD, a Johns Hopkins Medicine rehabilitation specialist in Baltimore, Maryland, who works with patients with long COVID and other "fatiguing illnesses."

At last count, about 18% of those surveyed by the Centers for Disease Control and Prevention said they had experienced long COVID. Nearly 60% of those surveyed said they had contracted COVID-19 at least once.

Dr. Azola said that very afternoon she had seen a patient with the flu and a recurrence of previous long COVID symptoms. Not much data exist about cases like this. "I can't say there is a specific study looking at this, but anecdotally, we see it all the time," Dr. Azola said. She has not seen completely different symptoms; more commonly, she sees a flare-up of previously existing symptoms.

David Putrino, PhD, is director of rehabilitation innovation for the Mount Sinai Health System in New York City. He treats and studies patients with long COVID and echoes what others have seen.

Patients can "recover (or feel recovered) from long COVID until the next immune challenge — another COVID infection, flu infection, pregnancy, food poisoning (all examples we have seen in the clinic) — and experience a significant flare-up of your initial COVID infection," he said.

"Relapse" is a better term than reinfection, said Jeffrey Parsonnet, MD, an infectious diseases specialist and director of the Dartmouth Hitchcock Post-Acute COVID Syndrome Clinic, Lebanon, New Hampshire. "We see patients who had COVID-19 followed by long COVID who then get better — either completely or mostly better. Then they've gotten COVID again, and this is followed by recurrence of long COVID symptoms," he said.

VIRUS *continued on following page*

SWEAT *continued from previous page*

In the current study, "I was struck by the correlation between the sweat and serum values of [isoniazid] and by the level of sophistication of noninvasive testing, being able to normalize for creatinine to account for different volumes of sweat," Dr. Thavarajah said. In clinical practice, finger sweat isoniazid could potentially serve as an adjunct or alternative to DOT in patients with TB.

Although adherence to the sampling protocol and possible patient distrust of the process (such as concerns over what else is being collected in their sweat) might be barriers to the use of a finger sweat strategy in the clinical setting, appropriate patient selection, patient training, and encouraging clinicians to incorporate this testing into practice could overcome these barriers, Dr. Thavarajah said.

More research is needed to study the finger sweat strategy in larger, real-world samples and to study accuracy and treatment adherence with monitoring in a population undergoing DOT, she said.

The study was supported by the Engineering & Physical Sciences Research Council and by Santander PhD Mobility Awards 2019. The researchers had no financial conflicts to disclose. Dr. Thavarajah had no financial conflicts to disclose. ■

Mixed messages on COVID and asthma in peds

BY TED BOSWORTH

In one of several recent studies on the relationship between COVID-19 infection and asthma, asthma symptoms in children declined as the proportion of the US population vaccinated against COVID-19 increased, according to data from the National Survey of Children's Health (NSCH). The inverse correlation between symptoms and vaccination was strong and statistically significant, according to investigators led by Matthew M. Davis, MD, physician in chief and chief scientific officer, Nemours Children's Health, Wilmington, Delaware. "With each increase of 10% in COVID-19 vaccination coverage, the parent-reported child asthma symptom prevalence decreased by 0.36% ($P < .05$)," as reported in a research letter published in *JAMA Network Open* (2024 Jul 1. doi: 10.1001/jamanetworkopen.2024.19979).

COVID and asthma relationship

This is just one of several recently published studies exploring the interaction between COVID-19 infection and asthma, but two studies that posed the same question did not reach the same conclusion. In one, COVID-19 infection in children was not found to be a trigger for new-onset asthma, while the second found that it was. In a third study, the preponderance of evidence from a meta-analysis found patients with asthma — whether children or adults — did not necessarily experience a more severe course of COVID-19 infection than in those without asthma. The NSCH database study calculated state-level change in scores for patient-reported childhood asthma symptoms in the pre-pandemic years 2018-2019, and the years 2020-2021, when the pandemic began. The hypothesis was that the proportion of the population 5 years of age or older who completed the COVID-19 primary vaccination would be inversely related to asthma symptom prevalence. Relative to the 2018-2019 years, the mean rate of parent-reported asthma symptoms was 0.85% lower (6.93% vs 7.77%; $P < .001$) in 2020-2021, when the mean primary series COVID-19 vaccination rate was 72.3%. The study was not able to evaluate the impact of COVID-19 vaccination specifically in children with asthma, because history of asthma is not captured in the NSCH data, but Dr. Davis contended the reduction in symptomatic asthma among children with increased vaccination offers validation for the state-level findings.

Protection from respiratory viruses

Dr. Davis reported that these data are consistent with previous evidence that immunization against influenza also reduces risk of asthma symptoms. In a meta-analysis published in 2017, it was estimated that live vaccines reduced risk of influenza by 81% and prevented 59%-72% of asthma attacks leading to hospitalizations or emergency room visits (Clin Infect Dis. 2017 Oct 15;65[8]:1388-1395. doi: 10.1093/cid/cix524). "The similarity of our findings regarding COVID-19 vaccination to prior data regarding influenza vaccination underscores the importance of preventing viral illnesses in individuals with a history of asthma," Dr. Davis said. It is not yet clear if this is true of RSV.

While vaccination appears to reduce asthmatic symptoms related to COVID-19 infection, one study suggests that COVID-19 does not trigger new-onset asthma. In a retrospective study published in *Pediatrics* (2024 May 1;153[5]:e2023064615. doi: 10.1542/peds.2023-064615), no association between COVID-19 infection and new-onset asthma could be made in an analysis of 27,423 children (ages, 1-16 years) from the Children's Hospital of Philadelphia (CHOP) Care Network.

Across all the pediatric age groups evaluated, the consistent finding was "SARS-CoV-2 positivity does not confer an additional risk for asthma diagnosis at least within the first 18 months after a [polymerase chain reaction] test," concluded the investigators, led by David A. Hill, MD, PhD, Division of Allergy and Immunology, CHOP, Philadelphia, Pennsylvania.

Risk of asthma doubled after COVID-19

However, the opposite conclusion was reached by investigators evaluating data from two cohorts of children ages 5-18 drawn from the TriNetX database, a global health research network with data on more than 250 million individuals (Infection. 2024 Jun 21. doi: 10.1007/s15010-024-02329-3). Cohort 1 included more than 250,000 children who had never received COVID-19 vaccination. The 50,000 patients in cohort 2 had all received COVID-19 vaccination. For the impact of COVID-19 infection on new-onset asthma, the patients who were infected with COVID-19 were compared with those who were not infected after propensity score matching over 18 months of follow-up. In cohort 1, the rate of new-onset asthma was more than twofold greater among those with COVID-19 infection (4.7% vs 2.0%). The hazard ratio (HR) of 2.25 had tight confidence intervals (95% CI, 2.158-2.367). In cohort 2, the risk of new-onset asthma at 18 months among those who had a COVID-19 infection relative to those without was even greater (8.3% vs 3.1%). The relative risk approached a threefold increase (HR 2.745; 95% CI, 2.521-2.99).

In another recent study from *Environmental Health Insights* (2024 Jan 3. doi: 10.1177/11786302231221925), the goal of a meta-analysis was to determine if patients with asthma relative to those without asthma face a higher risk of serious disease from COVID-19 infection. The meta-analysis included studies of children and adults. The answer, according an in-depth analysis of 21 articles in a "scoping review," was a qualified no. Of the 21 articles, 4 concluded that asthma is a risk factor for serious COVID-19 infection, but 17 did not, according to Chukwudi S. Ubah, PhD, Department of Public Health, Brody School of Medicine, East Caroline University, Greenville, North Carolina.

None of these questions are fully resolved

Overall, the data do not support a major interaction between asthma and COVID-19, even if the data are not conclusive. Each of the senior authors of these studies called for larger and better investigations to further explore whether COVID-19 infection and preexisting asthma interact. So far, the data indicate that if COVID-19 infection poses a risk of precipitating new-onset asthma or inducing a more severe infection in children with asthma, it is low, but the degree of risk, if any, remains unresolved in subgroups defined by asthma treatment or asthma severity.

Dr. Davis, Dr. Hill, and Dr. Ubah reported no potential conflicts of interest. None of these studies received funding from commercial interests. ■

VIRUS *continued from previous page*

"Every patient looks different in terms of what gets better and how quickly. And again, some patients are not better (or even minimally so) after a couple of years," he said.

Patients tell their stories

On the COVID-19 Long Haulers Support Facebook group, many of the 100,000 followers ask about viral reactivation. Delainne "Laney" Bond, RN, who has battled postinfection chronic illness herself, runs the Facebook group. From what she sees, "each time a person is infected or reinfected with SARS-CoV-2, they have a risk of developing long COVID or experiencing worse long COVID. Multiple infections can lead to progressive health complications."

The posts on her site include many queries about reinfections. A post from December 2023 included nearly 80 comments with people describing the full range of symptoms. Some stories relayed how the reinfection symptoms were short lived. Some report returning to their baseline — not completely symptom free but improved.

Doctors and patients say long COVID comes and goes — relapsing-remitting — and shares many features with other complex multisystem chronic conditions, according to a new National Academy of Sciences report. Those include ME/CFS and the Epstein-Barr virus.

As far as how to treat, Dr. Putrino is one of the clinical researchers testing antivirals (Am J Med. 2024 May 10. doi: 10.1016/j.amjmed.2024.04.030). One is Paxlovid; the others are drugs developed for the AIDS virus.

"A plausible mechanism for long COVID is persistence of the SARS-CoV-2 virus in tissue and/or the reactivation of latent pathogens [Nat Immunol. 2023 Oct;24(10):1616-1627]," according to an explanation of the research on the PolyBio Institute website, which is involved with the research. In the meantime, "long COVID appears to be a chronic condition with few patients achieving full remission," according to a new Academy of Sciences report. The report concludes that long COVID recovery can plateau at 6-12 months. They also note that 18%-22% of people who have long COVID symptoms at 5 months are still ill at 1 year. ■

New trials: Could your patients benefit?

BY HELEN LEASK

Medscape Composite: Dreamstime

Several new studies in lung cancer have opened their doors recently. Is one of your patients eligible to participate?

Resected stage II, IIIA, or IIIB with nodal involvement non–small cell lung cancer (NSCLC). Adult patients with this type of cancer can join a randomized, controlled, phase 3 study assessing whether an investigational drug called V940 added to pembrolizumab (Keytruda) delays cancer recurrence better than pembrolizumab alone.

V940 is an individualized neoantigen therapy designed to generate T-cell antitumor responses targeted to a patient's specific mutation profile. V940 plus pembrolizumab showed a trend toward longer recurrence-free survival vs pembrolizumab alone in a recent phase 2 study in melanoma (hazard ratio, 0.561; $P = .053$).

In the current trial, one group of participants will receive intramuscular injections of V940 every 3 weeks plus intravenous (IV) pembrolizumab every 6 weeks for up to approximately 1 year or until disease recurrence or unacceptable toxicity, whichever happens first. The other people in the trial will be on the same schedule, with a placebo replacing V940.

Centers in Florida, Georgia, Kentucky, Montana, New Jersey, New York, North Dakota, and six other countries started recruiting for the trial's 868 participants in December 2023. Disease-free survival is the primary endpoint. Overall survival over approximately 12 years and quality of life (QoL) are secondary endpoints. More details are at clinicaltrials.gov.

Metastatic NSCLC with a programmed cell death ligand 1 (PD-L1)–tumor proportion score of > 50%. Adults in this clinical situation are eligible for a randomized, open-label, phase 3 trial to determine whether an experimental antibody-drug conjugate called MK-2870 added to standard pembrolizumab prolongs survival.

MK-2870 delivers a cytotoxin to cancer cells by binding to trophoblast cell-surface antigen 2, known to promote tumor cell growth and metastasis. For up to 2 years, half of participants will receive MK-2870 by IV every 2 weeks plus IV pembrolizumab every 6 weeks. The other group will receive only pembrolizumab.

In December 2023, study sites in Georgia, Minnesota, Mississippi, Nevada, Oregon, Australia, Denmark, Taiwan, and Turkey started seeking the trial's 614 participants. Overall survival over approximately 4 years is the primary endpoint; QoL is a secondary endpoint. More details are at clinicaltrials.gov.

Untreated locally advanced or metastatic NSCLC with *KRAS* G12C mutations. Individuals with this type of lung cancer may be interested in a randomized, controlled, phase 3 study examining whether an experimental oral *KRAS* G12C inhibitor called LY3537982 boosts the effectiveness of standard treatment and patients can tolerate the combination. Currently approved

TRIALS *continued on following page*

Cessation boosts life expectancy at any age

EDITED BY SHRABASTI BHATTACHARYA AND LISA GILLESPIE

Quitting smoking at any age increases life expectancy, with the most significant increases observed in younger individuals, a new study finds. However, people who quit over age 65 can still extend life expectancy.

Impact of smoking cessation

In the study, researchers analyzed the detrimental effects of smoking and the positive impacts of cessation on life expectancy in individuals aged 35-75 years. Age-specific death rates by smoking status were calculated using the relative risks for all-cause mortality derived from the Cancer Prevention Study II data, 2018 National Health Interview Survey smoking prevalence data, and 2018 all-cause mortality rates.

Researchers contructed life tables to obtain information on the life expectancies of people who never smoked, those who currently smoked, and those who previously smoked but quit at various ages. Finally, the estimates of years lost due to smoking and years gained by quitting smoking were calculated for people starting at age 35 and over 10-year increments.

Gaining years of life expectancy

According to the study analysis, those who smoked at ages 35, 45, 55, 65, and 75 years and continued smoking throughout their lives would

AndreyPopov/IStock/Getty Images

lose 9.1, 8.3, 7.3, 5.9, and 4.4 years, respectively, compared with people who never smoked. Even people who quit smoking at ages 35, 45, 55, 65, and 75 years would have life expectancies that are shorter by 1.2, 2.7, 3.9, 4.2, and 3.7 years, respectively, than those of same-age individuals who never smoked.

On the positive side, those who quit smokig at various ages can likely expect to gain years on their potential lifetime. Individuals who quit smoking at ages 35, 45, 55, 65, and 75 years would experience an additional 8.0, 5.6, 3.4, 1.7, and 0.7 years of life expectancy compared with those who continued smoking. People who quit at ages 65 and 75 years would have a 23.4% and 14.2% chance of gaining at least 1 additional year of life.

Motivating patients to stop smoking

"This cessation benefit is not limited to young- and middle-aged adults who smoke; this study demonstrates its applicability to seniors as well. These findings may be valuable for clinicians seeking scientific evidence to motivate their patients who smoke to quit," the authors wrote.

Smoking intensity not measured

Study limitations included that the study's estimates were according to data from 2018 and may not reflect current trends. The estimates also did not account for variability in smoking intensity among individuals.

The study was led by Thuy T.T. Le, PhD, from the Department of Health Management and Policy at the University of Michigan School of Public Health in Ann Arbor and published online in the *American Journal of Preventive Medicine* (2024 Jun 25. doi: 10.1016/j.amepre.2024.06.020).

The study was supported by grants from the National Cancer Institute of the US National Institutes of Health and the US Food and Drug Administration Center for Tobacco Products. The authors declared that they had no conflicts of interest.

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TRIALS *continued from previous page*

KRAS G12C inhibitors sotorasib (Lumakras, Lumykras) and adagrasib (Krazati) are indicated for second-line treatment; this trial may lead to a first-line approval for newcomer LY3537982.

The trial has three parts: dose optimization, safety, and efficacy. During dose optimization, each participant will take one of two oral doses of LY3537982 and receive IV pembrolizumab every 3 weeks. In the safety phase, all participants will receive oral LY3537982 at the chosen dose plus standard therapy of 3-times-weekly IV pembrolizumab, pemetrexed, and a platinum therapy (cisplatin or carboplatin). In the experimental phase, for up to about 1 year, participants will receive one of these four options: pembrolizumab plus LY3537982, pembrolizumab plus a placebo, standard therapy plus LY3537982, or standard therapy plus a placebo.

The study, which is planning to recruit 1016 participants, opened across 16 US states and 12 countries worldwide in December 2023. Sites in 11 more US states, the District of Columbia, Brazil, Canada, China, India, and 11 more European countries are gearing up. Adverse events and progression-free survival are the primary endpoints. Overall survival over approximately 3 years and QoL are secondary endpoints. More details are at clinicaltrials.gov.

Unresectable, untreated locally advanced or metastatic nonsquamous NSCLC with human epidermal growth factor receptor 2 (HER2) mutations. People with this diagnosis who have HER2 mutations instead of *KRAS* G12C mutations can participate in a phase 3 study comparing an investigational oral first-line treatment with standard IV therapy. The drug in this study, zongertinib, is a HER2 tyrosine kinase inhibitor.

For up to approximately 4 years, one group of participants will take oral zongertinib only, and the other individuals will receive IV pembrolizumab, pemetrexed, and a platinum agent (cisplatin or carboplatin). Study sites in California, Missouri, South Carolina, Australia, China, Japan, South Korea, and Singapore opened in January ready to welcome 270 participants. Progression-free survival is the primary outcome. Overall survival over 53 months and QoL are secondary endpoints. More details are at clinicaltrials.gov.

Completely resected stage IIB, IIIA, or select IIIB, PD-L1–positive NSCLC. Adults with this type of lung cancer who have received adjuvant platinum-based chemotherapy may be eligible for a randomized, controlled, phase 3 study to assess whether two immune checkpoint inhibitors are better than one at delaying cancer recurrence. In this trial, tiragolumab will be added to the approved PD-L1 inhibitor atezolizumab (Tecentriq).

A recent study, however, found that tiragolumab did not confer an additional benefit when added to atezolizumab, carboplatin, and etoposide in untreated extensive-stage small cell lung cancer.

In the current trial, one group of participants will receive IV atezolizumab and tiragolumab, while the other people will receive a placebo instead of tiragolumab. Centers in California, Georgia, Illinois, New Mexico, Australia, China, South Korea, and Taiwan started recruiting for the trial's 1150 participants in March 2024. Disease-free survival is the primary endpoint. Overall survival over approximately 15 years and QoL are secondary outcomes. More details are at clinicaltrials.gov.

Previously treated metastatic or non-operable non-squamous NSCLC. Adults in this position who have received no more than one platinum-based chemotherapy and one anti–PD-L1 drug are sought for a randomized, open-label, phase 3 trial comparing second-line standard docetaxel with experimental antibody-drug conjugate sigvotatug vedotin. Patients who have tumors with certain treatable genomic alterations must have received at least one drug targeted to that alteration, as well as a platinum-based agent.

Approximately half the participants will receive sigvotatug vedotin by IV every 2 weeks, and the other half will receive IV docetaxel every 3 weeks. The study opened in March across 13 US states, France, Hungary, Poland, and Spain seeking 600 people eligible to participate. The primary outcomes are overall survival over approximately 5 years and objective response rate. QoL is a secondary outcome. More details are at clinicaltrials.gov.

All trial information is from the National Institutes of Health US National Library of Medicine (online at clinicaltrials.gov).

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

In memoriam: Dr. James E. Dalen

CHEST was recently informed of the death of former CHEST President, James E. Dalen, MD, MPH, Master FCCP. He served as CHEST President from 1985 to 1986.

Dr. Dalen was a graduate of Washington State University. (His undergraduate education was temporarily interrupted when he served as a Corpsman in the Navy and Marines.) He held a master's degree from the University of Michigan, an MD from the University of Washington, an MPH from Harvard University, and an honorary Doctor of Science degree from the University of Massachusetts. He was internationally recognized as a medical visionary and esteemed cardiologist.

Dr. Dalen

Dr. Dalen's academic career spanned 3 medical schools. During the time he spent at each, he achieved great things and nurtured great ideas that helped transform medicine. From 1967 to 1975, he was on the faculty of Harvard Medical School (and the Peter Bent Brigham Hospital). From 1975 to 1988, he was a faculty member at the University of Massachusetts Medical School where he served as Chairman of Cardiovascular Medicine from 1975 to 1977 and as Chairman of Medicine from 1977 to 1988. From 1986 to 1987, he served as Interim Chancellor of the University of Massachusetts at the Worcester Campus. Dr. Dalen left Massachusetts in 1988 to become the Dean of the University of Arizona College of Medicine.

During his tenure as Dean and Vice-President at the University of Arizona, Dr. Dalen oversaw the establishment of the Zuckerman College of Public Health, the Arizona Center for Integrative Medicine, and the Arizona Telemedicine Program. Successful fundraising under his leadership led to the establishment of new research facilities, including the Children's Research Center, the Sarver Heart Center, the Arizona Arthritis Center, and a major expansion of the Arizona Cancer Center. While at the University of Arizona College of Medicine, Dr. Dalen recognized the importance of integrative medicine and the need to promote integrative medicine in the academic environment. With the active participation of Dr. Andrew Weil, this led to the creation of the Academic Consortium for Integrative Medicine and Health and the Arizona Center for Integrative Medicine.

Dr. Dalen received many teaching awards. In 1987, he received the Distinguished Public Service Award from the University of Massachusetts. In 1988, he was named the University of Washington Distinguished Medical Alumnus of the Year and received the Alumni Achievement Award from Washington State University. In 2000, he received the College Medal from CHEST and was named a Master Fellow. In 2010, he was awarded the Harvard School of Public Health's highest honor for its alumni: the 2010 Alumni Award of Merit. In 2012, he was named a Master Fellow of the American College of Physicians and was awarded an honorary Doctor of Science degree by the University of Massachusetts in 2013. In 2015, he received the Bravewell Distinguished Service Award from the Academic Consortium for Integrative Medicine and Health for his role as one of the founders of the consortium and as one of the founders of the Arizona Center for Integrative Medicine at the University of Arizona.

In his spare time, he enjoyed reading, gardening, sailing, art, and music and was a lifelong student with a passion for the pursuit of knowledge. Dr. Dalen enjoyed watching basketball, particularly the Arizona Wildcats. His favorite place to spend time was by the ocean in Coronado, California. Dr. Dalen was an advocate for public health, social justice, and health care reform throughout his life and career. He mentored thousands of medical students and championed access to health care for populations who were underserved. He touched many lives as a leading physician and caring friend.

Dr. Dalen is survived by his devoted wife, Priscilla M. Dalen (Dunton); loving children, James E. Dalen, Jr, and Angela M. Snodgrass (Dalen); daughter-in-law, Suzan M. Dalen; son-in-law, Daniel N. Snodgrass; and many step-grandchildren. We remember our colleague and extend our sincere condolences. ■

Top reads from the CHEST journal portfolio

Studying endotypes in sleep apnea, diagnostic testing in ILD, and inhaled corticosteroid use in children

Journal *CHEST*®

Differences in Physiologic Endotypes Between Nonpositional and Positional OSA: Results From the Shanghai Sleep Health Study Cohort

By Xiaoting Wang, MM, and colleagues

This study from the Shanghai Sleep Health Study cohort enhances our understanding of physiologic endotypes in sleep apnea—nonpositional OSA (NPOSA) and positional OSA (POSA). The study found that nonanatomic traits play a more significant role in POSA severity. Patients with POSA exhibited lower arousal thresholds and greater ventilatory compensation, while anatomical abnormalities were more prominent in NPOSA. This research underscores the need for personalized treatment strategies based on specific endotypes, especially with the increasing emergence of alternatives to CPAP therapy, such as mandibular advancement therapy and hypoglossal nerve stimulation. Patients with obesity with NPOSA were found to have elevated loop gain, which is known to be impacted by weight loss. This is particularly relevant in light of recent studies showing that new GLP-1 agonists can dramatically reduce sleep apnea severity. Future research should focus on refining these personalized approaches and integrating alternative treatments to provide a more individualized approach to managing sleep apnea.

– Commentary by Shyam Subramanian, MD, FCCP, Member of the *CHEST Physician* Editorial Board

CHEST® Pulmonary

Employment of the Envisia Genomic Classifier in Conjunction With Cryobiopsy in Patients With Undiagnosed Interstitial Lung Disease

By Fayez Kheir, MD, and colleagues

The novel mRNA genomic array, Envisia Genomic Classifier (EGC), used in this study has been shown to be highly specific for a histopathologic diagnosis of usual interstitial pneumonia (UIP). A diagnosis of UIP carries significant prognostic import as patients exhibit a higher risk for progressive fibrosis and death compared with other interstitial lung diseases (ILDs). In this retrospective study, the combination of bronchoscopic lung cryobiopsy and EGC testing was associated with a significant change in clinical management of those living with an indeterminate ILD. Participants were more likely to be started on antifibrotic therapy following this intervention. This study emphasizes the need for prospective trials on the diagnostic yield of molecular phenotyping with bronchoscopic lung biopsy compared with the traditional surgical approach for the undifferentiated ILD.

– Commentary by Michael Marll, MD, Member of the *CHEST Physician* Editorial Board

CHEST® Critical Care

Inhaled Corticosteroids Use Before Hospitalization May Be Protective in Children With Direct Lung Injury

By Elizabeth Landzberg, MD, and colleagues

Respiratory illness is the most common reason for both hospitalization and ICU admission in children. Studies suggest inhaled corticosteroids (ICSs) may protect adults with direct lung injury (DLI) from developing respiratory failure. However, there is a paucity of literature on this therapeutic intervention within the pediatric population. This retrospective, large, single-center study identified children seeking treatment at the emergency department (ED) with DLI before hospitalization. ICS use before hospitalization was associated with one-half the odds of escalation to intubation and noninvasive respiratory support (NRS) in pediatric patients seeking treatment in the ED with DLI. The protective effect was greatest in patients with a history of asthma. According to the authors, this is the first study to assess ICS exposure before hospitalization and progression to respiratory failure in all-cause pediatric DLI. It highlights the need for future studies to evaluate whether a role exists for early prophylactic ICS use in pediatric DLI without status asthmaticus, stratified by history of asthma.

– Commentary by Anne C. Coates, MD, FCCP, Member of the *CHEST Physician* Editorial Board

Improving ILD diagnosis in primary care settings

BY KATLYN CAMPBELL
Communications Specialist, CHEST

Interstitial lung diseases (ILDs), with their many ubiquitous symptoms, are often hard to diagnose in patients. That's why Amirahwaty Abdullah, MBBS, and Kavitha Selvan, MD, see value in educating clinicians on how to identify and diagnose ILD.

Both Dr. Abdullah and Dr. Selvan received quality improvement grants from CHEST in October 2023 to do just that. Their projects put the ILD Clinician Toolkit into practice, created as a part of CHEST's Bridging Specialties™: Timely Diagnosis for ILD initiative aimed at shortening the time to diagnosis.

Recently, CHEST caught up with the two grant recipients to see how their projects were progressing.

Combating the prevalence of ILDs in West Virginia

Dr. Abdullah and Co-Principal Investigator, Haroon Ahmed, MD, are two of the staff members supporting West Virginia University ILD Clinic, where the ILD Clinician Toolkit is being utilized.

"ILD is so prevalent here, so we thought it would be an excellent opportunity to do the quality improvement project here because we really do need the resources to improve the care of our [patients with ILD]," Dr. Abdullah said. "For the entire state of West Virginia, we're the only ILD center."

In West Virginia, many factors are at play making ILD prevalent, with a recent study showing that the state has the second highest rate of interstitial pulmonary fibrosis, Dr. Abdullah said. This is all due to the economy of the state, the rurality of the population, and the occupational hazards with common jobs like coal mining and farming.

"This topic about bridging the gap and early diagnosis really resonated with us because we see all these patients who end up seeing us after they've been on oxygen for years, when they can't do anything else," Dr. Ahmed said. "There was a big gap here, and we saw that every day in our clinical practice."

Since implementing the ILD Clinician Toolkit into their program, the two have started providing these resources to primary care physicians in an effort to help expedite their workups when they see patients with common ILD symptoms. This was done through grand rounds and educational conferences for those practicing in family medicine, internal medicine, and pediatric medicine. And more education is planned for the future.

They have also created working relationships with these departments and have encouraged them to send patients to the ILD Clinic, so patients don't have to be referred to multiple different physicians.

The next step for the project is to implement telemedicine capabilities, which will allow the team to roll out the patient questionnaire from the toolkit. The questionnaire helps physicians gather a detailed history about their patients, including their past and current medications, surgeries, occupational and environmental exposures, and known comorbidities.

"We definitely want to reach out via telemedicine to patients because, at this point in time, some of our patients travel 3, 4 hours one way just to come see us. So, if we can make it more accessible, we will," Dr. Abdullah said.

Their plan is to provide iPads that are equipped with the questionnaire and other toolkit resources to the providers. Through this method, the team will be able to see how often the questionnaire is used.

"We are very thankful for this grant because I do think we are saving lives," Dr. Abdullah said. "Any little thing that we can do to improve the outcomes of these patients who have a rare but difficult-to-treat disease—it's crucial. This gives us the ability to reach out and help patients who are out of our physical bounds."

Diagnosing ILD among underrepresented minority populations in Chicago

Dr. Kavitha Selvan is conducting her quality improvement research project at the University of Chicago, alongside her team.

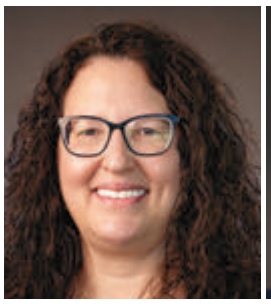
"The community we serve in South Chicago houses a significant number of underrepresented [minority populations]," she said.

"We know that Black patients with ILD experience higher rates of hospitalization, compared with White patients," she said. "And they are hospitalized, require lung transplants, and die at a younger age too."

ILD *continued on following page*


Dr. Adrish


Dr. Surani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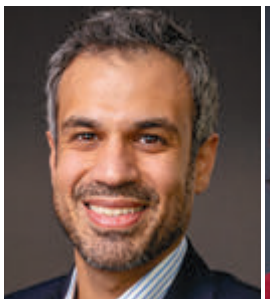
Dr. Chaaban


Dr. Lal


Dr. Ouellette

CHEST 2024: A glimpse into sessions and offerings

The CHEST Annual Meeting, happening October 6 to 9 in Boston, is just around the corner. So we connected with members of the Scientific Program Committee to see what the most-anticipated topics covered in each specialty would be. The sessions at CHEST 2024 will run the gamut of chest medicine — from artificial intelligence and practice-changing guidelines to disparities in care and breakthrough therapies. Here's what they're looking forward to most.

Muhammad Adrish, MD, MBA, FCCP

Chair of the Airways Disease Curriculum Group and Airways Disorders Network

"We're going to have a lot of multidisciplinary discussions where we have experts from all different fields coming in and discussing different topics of importance in airways."

What to expect at CHEST 2024:

- Artificial intelligence in imaging
- Precision medicine therapies
- Biologics guidelines in asthma

Salim Surani, MD, MSc, FCCP

Chair of the Chest Infections/Disaster Medicine/Systemic Disease Curriculum Group and Chest Infections and Disaster Response Network

"There are so many sessions happening every hour at CHEST 2024, I can bet you will have two, three, or even four sessions you want to attend."

What to expect at CHEST 2024:

- Artificial intelligence in diagnosis and treatment
- The intersection of infections and antibiotics
- Reacting to and preparing for disasters

Jean Elwing, MD, FCCP

Chair of the Cardiovascular and Pulmonary Vascular Disease Curriculum Group and Pulmonary Vascular and Cardiovascular Network

"The sessions are designed to appeal to every learner. We're using lecture formats, audience response systems, interactive sessions, master classes, and live learning."

What to expect at CHEST 2024:

- Mock pulmonary embolism response team interactive session
- New guidelines on heart failure with preserved ejection fraction

Jason Akulian, MD, FCCP

Chair of the Lung Cancer/Interventional Pulmonary/Radiology Curriculum Group

"Whether you're a physician or an RT or a PA or nurse or a fellow, you're going to get something from every talk."

What to expect at CHEST 2024:

- Pulmonary nodule management and artificial intelligence
- Biomarkers for lung nodule risk stratification
- Peripheral nodule diagnostics

Said Chaaban, MD, FCCP

Chair of the Interstitial Lung Disease/Transplant Curriculum Group and Diffuse Lung Disease and Lung Transplant Network

"If I had the chance to attend 80% or more of these sessions, I'd be very lucky. I've been out of training for 7 years, but we're students for life."

What to expect at CHEST 2024:

- Multidisciplinary lung transplant teams
- Respiratory assist devices beyond ECMO

Chitra Lal, MD, MBBS, FCCP

Chair of the Sleep Medicine Curriculum Group

"This is a wonderful opportunity not only to learn about the latest advances in sleep medicine but also to develop some wonderful relationships with colleagues and potential mentors in the field."

What to expect at CHEST 2024:

- Sleep apnea
- PAP devices
- Phrenic and hypoglossal nerve stimulation
- Noninvasive ventilation

Daniel R. Ouellette, MD, FCCP

Chair, Critical Care Curriculum Group and Critical Care Network

"Coming to CHEST 2024 will allow attendees to learn what the latest advancements are and the best evidence-based guidance."

What to expect at CHEST 2024:

- Updated guidelines for mechanical ventilation
- Identifying and addressing disparities of care
- Developing ways to avoid burnout
- Digging into newer data on ECMO
- New transfusion guidelines
- The ICU's impact on the climate

ILD *continued from previous page*

In clinical practice, Dr. Selvan has noticed a trend of patients being referred for evaluation of possible ILD later and later. In some cases, several years go by before the appropriate work for ILD is initiated, and that valuable time lost leads to irreversible loss of lung function.

Dr. Selvan's plan is to partner with primary care providers who are seeing these patients first in order to expedite the work-up and referral of ILD when appropriate and, ultimately, reduce the amount of time that passes between symptom onset and definitive diagnosis.

"To me, this grant and the resources it provided represented an important opportunity to improve outcomes in the high-risk patients we care for through early disease recognition and treatment," she said.

Dr. Selvan's project began with educating members of the Primary Care Group at UChicago on risk factors and exam findings that may suggest ILD in patients coming to clinic with nonspecific respiratory complaints. Then they had to equip providers with the ILD Clinician Toolkit and reach patients by handing out the patient questionnaire in primary care clinic.

The next step for this project is going to be dissecting the answers to a postintervention survey that was sent out to understand the practices and comfort of primary care providers in evaluating suspected ILD and the utility of the additional resources created by Dr. Selvan's team.

"My hope is that we can utilize this partnership with the Primary Care Group to provide the education that's needed both on the patient side and the provider side, like knowing not to ignore respiratory symptoms, knowing which patients warrant ILD-specific testing, and knowing what the appropriate tests are. In doing so, we can get patients into ILD clinic earlier, confirm their diagnosis, and get them initiated on the appropriate therapies sooner," she said.

Dr. Selvan credits the quality improvement grant as being fundamental in her success as a fellow at UChicago and believes that this project has created a culture of awareness that wouldn't have been possible without funding.

"I truly believe that early detection and risk factor modification is the most critical aspect of interstitial lung disease care and the mechanism for how we're going to actually improve patient outcomes in our community," Dr. Selvan said. "Building the infrastructure to accomplish that requires time, resources, and support from institutions and philanthropic foundations that believe in that mission too." ■

NETWORKS

Choosing medications in acute critical care, trauma epidemiology, and atypical pulmonary cysts

THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK

Lung Cancer Section

Since the American College of Radiology (ACR) updated its Lung CT Screening Reporting & Data System (Lung-RADS) to include atypical pulmonary cysts in 2022, there has been little discussion among chest physicians regarding the significance of pulmonary cysts and why these changes were made.

Dr. Geringer

Lung-RADS 2022 defined atypical pulmonary cysts as single, unilocular cysts with a wall thickness greater than 2 mm or any multilocular cysts. These can be uniform, asymmetric, or have a focal nodularity. This change was prompted by data derived from multiple studies. First, a finding that 3.6% of lung cancers were associated with cysts at baseline. This was followed by a reanalysis of the NELSON trial's missed cancers showing 22% of those overlooked during initial screening had findings of cystic disease, reaffirming the significance of atypical pulmonary cysts. Though the number is low, we now know 1.1% of all cancers present as an atypical cyst, with 4.7% of them being malignant.

Based on these studies, cysts are a baseline Lung-RADS 4A—a finding that correlates to a higher risk and needs to be followed with a short-term CT scan in 3 months vs a PET. ACR does recommend reserving PET scans for wall thickness > 8 mm. If the repeat CT scan is stable, then the Lung-RADS designation is dropped to a 3 for follow-up.

All references available online at chestphysician.org.

– Rage Geringer, MD
Fellow-in-Training

CHEST INFECTIONS AND DISASTER RESPONSE NETWORK

Disaster Response and Global Health Section

Patients who are injured do better when treated at trauma centers.

During CHEST 2023 in Honolulu last year, the Disaster Response and Global Health Section hosted a presentation to a packed audience highlighting the history of the trauma model system in America. Attendees learned about the emergence of trauma systems in the US and the survival advantages that trauma centers offer to patients who are injured.

Inception of the first "trauma manual" was during President Lincoln's term to address the need for a process to care for patients who were injured during the Civil War.

Dr. Agapian

By the time World War II occurred, hospitals had established the idea of emergency departments, and the foundations for an emergency medical system (EMS) emerged on the world scene. Eventually, the Hill-Burton Act of 1946 required hospitals to have emergency departments by incentivizing them with federal funding.

The Committee on Trauma was founded in the 1950s as an adaptation of the American College of Surgeons' 1922 Committee on Fractures. Then, in 1966, the National Highway Traffic Safety Administration rolled out a federal initiative for all states to develop EMS programs. Additionally, the National Academy of Sciences published Accidental Death and Disability: The Neglected Disease of Modern Society, paving the way for the Emergency Medical Services Systems Act of 1973, along with the Wedworth-Townsend Paramedic Act in California.

The concept of today's trauma centers started in 1966 at Cook County Hospital in Chicago and Shock Trauma Center in Baltimore.

– John Agapian, MD, FCCP
Section Vice-Chair

CRITICAL CARE NETWORK

Palliative and End-of-Life Care Section

As critical care medicine continues to advance understanding of ICU survivorship, thoughtful selection of medications in the acute setting can potentially mitigate long-term cognitive, physical, and affective effects.

As of yet, no significant studies have linked opioid use in critical care to new diagnoses of opioid use disorder, but the opioid epidemic has taught us that profligate use of opioids can have devastating effects despite best intentions. Continuous infusions of full agonist opioids for sedation remain an important tool in management of sedation. For acute pain, buprenorphine represents an attractive alternative for patients who are both intubated and nonintubated. It provides equal pain relief as full agonist opioids while causing less respiratory depression, less delirium, less nausea, less constipation, less euphoria, and less misuse potential. Its unique partial mu-opioid agonism is responsible for the improved nausea, constipation, and respiratory depression, while the kappa and delta receptor antagonisms are responsible for antidepressant effects as well as lessened opioid craving, sedation, and dysphoria. Given the variety of doses and routes for buprenorphine, palliative medicine consults can help navigate preventing precipitated withdrawal in patients who are opioid-tolerant and the variety of available dosing and routes.

Dr. Wichmann

It is a testament to the growth of critical care medicine that we now have the privilege and responsibility to account for long-term sequelae of our lifesaving interventions, rather than the old model of "prevent death at all costs." Continued integration of high-quality symptom management into critical care offers an opportunity to better balance life-prolonging treatment and optimize quality of life.

All references available online at chestphysician.org.

– Alexandra Wichmann, MD
Section Member

SLEEP STRATEGIES

On 5 Ps: PSG, PM, PPG, PulseOx, and PAT

BY ANOOSHA TAUQUIR, MD, AND OCTAVIAN C. IOACHIMESCU, MD, PHD, MBA

OSA is a very prevalent condition in the general population, but still many patients remain undiagnosed and untreated. Prolonged, untreated OSA is an independent risk factor for major cardiovascular morbidity and mortality. Therefore, timely diagnosis and treatment are required.

Polysomnography (PSG) remains to this day the gold standard for diagnosing sleep apnea. A standard PSG (type I) is performed in a sleep laboratory in the presence of specialized sleep technicians and utilizes EEG, electrooculogram (EOG), and electromyogram (EMG) to determine sleep stages, oronasal thermal and pressure transducer sensors to monitor airflow, respiratory inductance plethysmography to record respiratory effort, EMG for limb movements, pulse oximetry (PulseOx), ECG, and video or body sensor devices to confirm body position. Rising rates of sleep testing have created demand for an alternative to cumbersome, costly, and resource-intensive in-lab PSGs. As such, home sleep apnea testing (HSAT) has emerged as a simpler, more accessible, and cost-effective alternative diagnostic tool.

In 2007, the American Academy of Sleep Medicine (AASM) endorsed Portable Monitoring (PM) as an alternative to standard PSG, with the caveat that it should be used only in patients with a high pretest probability of sleep apnea, without respiratory or cardiovascular disorders and comorbid sleep disorders. All HSAT devices (type II-IV) are required to have a minimum of an oronasal thermal sensor/nasal pressure transducer, respiratory inductance plethysmography, and PulseOx. A major limitation of most HSAT devices is the lack of EEG, preventing detection of cortical arousals and wake time, forcing the use of total recording time as a surrogate for total sleep time.

Peripheral arterial tonometry (PAT)-based HSAT devices are unique in this respect, as their proprietary algorithms allow estimates of total sleep time by monitoring changes in peripheral vascular tone. Anyone who has seen a PAT-based HSAT may have noticed very different outputs from traditional HSATs.

PAT is based on the concept that airflow obstruction may lead to a surge in sympathetic tone, causing vasoconstriction and reduced blood volume in the peripheral vascular bed. A PAT-based device measures relative changes in blood volume and combines this information with actigraphy signals, PulseOx, and heart rate to diagnose the presence of respiratory events. Sleep apnea severity stratification is accomplished by the use of pAHI or pRDI (PAT-based apnea-hypopnea index and respiratory disturbance index, respectively).

PAT-based technology was first approved by the FDA in 2001 as a diagnostic tool for sleep apnea. The 2 best-known medical devices are WatchPAT® and NightOwl®, both of which have been FDA-approved and studied against PSG. To obtain an accurate and sustainable PAT signal, WatchPAT has a pneumo-optic finger probe designed to generate a uniform, subdiastolic pressure on the finger that minimizes venous blood pooling, prevents uncontrolled venous backflow, and effectively unloads the arterial wall tension without blocking digital arterial flow. NightOwl is a smaller device, with a single fingertip sensor that acquires actigraphy and PPG data to measure heart rate, Pulse Ox, and PAT.

The physiological basis of PAT relies on photoplethysmography (PPG), a noninvasive optical monitoring technique that generates a waveform, which ultimately correlates with the circulatory volume of the respective tissue. The PPG technology relies on the fact that when a specific tissue is exposed to light signal of a specific wavelength, its absorbance by tissue fluctuates with arterial pulsations. Pulse oximetry represents the most used application of PPG. Recent advances in PPG signal analysis have fueled its use in clinical and consumer sleep technologies and allowed new capabilities, including capturing heart rate and rhythm, pulse rate variability, arterial stiffness, and even—with somewhat less accuracy—energy expenditure, maximum O2 consumption, and blood pressure. Combining actigraphy monitoring with PPG technology took both consumer and medical-grade sleep technologies further, allowing the estimation of parameters such as sleep stages, sleep times, and respiratory events. With myriad new sleep trackers claiming to assess total sleep time, wake time, light or deep sleep, and even respiratory events, the obvious clinical question is centered on their comparative accuracy, as well against more traditional PM and the gold standard PSG.

Numerous studies have evaluated the efficacy of PAT-based devices for diagnosing sleep apnea, with variable findings. Many have shown good correlations between mean AHI and pAHI. Others have highlighted significant discrepancies in the measurements between PSG and PAT, questioning the reliability of PAT-based devices in the diagnosis and severity stratification of OSA. One meta-analysis of 14 studies showed a high degree of correlation between pAHI and AHI. Another study reported a concordance of 80% between PAT-based testing and consecutive PSG, with an increase to 86% at a higher AHI (>15/h). A subsequent meta-analysis showed that PAT was significantly less sensitive for diagnosing OSA than PSG, particularly for mild or moderate severity disease, emphasizing the need for further confirmation with PSG when faced with inconclusive or negative results. A large sleep clinic-based cohort study of 500 patients with OSA showed that WatchPAT devices misclassify OSA in a sizeable proportion of patients (30%-50%), leading to both over- and under-estimation of severity. Van Pee, et al, found that their PAT-based HSAT NightOwl performed better, using both the 3% and 4% hypopnea scoring rules and a novel near-border zone labeling.

Some of the discordance in AHI between PAT and PSG appears to be related to age and sex. In our large sample comparing PAT to PSG, we found that using PAT-based data in concert with demographic (age, gender) and anthropometric (neck circumference, body mass index) variables improved the diagnostic accuracy of PAT-based testing. Another study concluded that manual scoring of WatchPAT automated results improved concordance with PSG, particularly in older participants and women. Several studies on WatchPAT recordings have demonstrated significant artifacts and inaccuracies in the PulseOx data. Although WatchPAT employs automated algorithms to remove erroneous data, a thorough visual inspection and manual correction of study data is still essential to derive accurate results.

Dr. Tauquir is with the Medical College of Wisconsin, Milwaukee, and Clement J. Zablocki Veteran Affairs Medical Center, Milwaukee. Dr. Ioachimescu is with the Medical College of Wisconsin, Milwaukee; Clement J. Zablocki Veteran Affairs Medical Center, Milwaukee; and Clinical and Translational Science Institute of Southeast Wisconsin, Milwaukee.

Recent studies have found that PAT-based tests can also differentiate between central and obstructive respiratory events by using pulse signal upstroke variations caused by changes in intrathoracic pressure and respiratory/chest wall movement recorded by body position sensors, but large-scale studies are needed to confirm these findings. Korkalainen, et al, recently employed a deep-learning model to perform sleep staging on the PPG PulseOx signals from nearly 900 PSGs in patients with suspected OSA. The deep learning approach enabled the differentiation of sleep stages and accurate estimation of the total sleep time. Going forward, this could easily enhance the diagnostic yield of PM recordings and enable cost-efficient, long-term monitoring of sleep.

Although PAT-based home sleep tests have emerged as a simple and convenient option for the evaluation of sleep apnea, several studies have highlighted their limited sensitivity as a screening tool for mild and moderate cases of sleep apnea. Furthermore, the scope of these tests remains limited, rendering them rather unsuitable for assessment of more complex sleep disorders like narcolepsy or restless leg syndrome. Therefore, when OSA is suspected, the PAT-based sleep study is a good screening tool, but negative tests should not preclude further investigation. Where a high probability of sleep apnea exists but PAT-based testing shows no or mild OSA, an in-lab sleep study should be performed. ■

All references available online at chestphysician.org.

APP INTERSECTION

APPs and POCUS: Overcoming credentialing challenges

BY RHEA VOTIPKA, AG-ACNP, ACCNS-AG

Advanced practice providers (APPs) play an integral role in the care and management of patients both in the ICU and across the spectrum of health care. Due to reduced residency hours and the coming physician shortage, APPs are playing, and will continue to play, a greater role in the care and management of critically ill patients.

Ms. Votipka

Point of care ultrasound (POCUS) is a key diagnostic modality that promotes rapid diagnosis, shortens time to key interventions, and allows for interval reassessment. However, the benefit relies heavily on operator skill to obtain good quality images, interpret this within the context of the patient, and know what interventions, if any, to make. It is imperative that APPs, given their role within critical care, become not only familiar with POCUS but demonstrate proficiency in practice.

Before this can become standard, there are a number of challenges to overcome. Educational institutions are behind on integrating POCUS into the APP curriculum. Additionally, APPs have few opportunities to develop these skills as residencies and fellowships are not required prior to entering the workforce. Instead, for a majority of APPs, POCUS training relies on nonstandardized on-the-job training or an (typically expensive) off-site training, for which they may not receive reimbursement. Other barriers include cultural practices that limit POCUS use by APPs; inability to upload and document images obtained; lack of willing, skilled mentors with time to provide feedback and assess for clinical competence; and even accessibility of ultrasound machines.

Despite these challenges, the clinical benefits of utilizing ultrasound in practice necessitates overcoming these barriers. Institutionally, when APPs perform POCUS, it can lead to more rapid diagnosis and triage of patients, provide billing opportunities, and may reduce overall costs of care. From an APP perspective, having formalized training and credentialing can lead to more consistent POCUS assessment between providers, comprehensive patient care, security in one's skills and knowledge base, and a tangible way of communicating one's credibility between institutions.

While some institutions have overcome these barriers and APPs are trained and credentialed in POCUS, this is not always the norm. For this to come to fruition, we need educators to incorporate this into curriculum, colleagues who are willing to mentor learners, cultural changes to allow APPs to develop and utilize necessary skills for practice, clear structure for obtaining and maintaining competency, physicians to champion these efforts, and institutions to credential skilled APPs. Until then, it is important that we as APPs seek to facilitate these institutional changes and continue to set and maintain high quality standards for ourselves. ■

All references available online at chestphysician.org.

CHEST 2024 is for APPs too

With more than 300 educational sessions on the CHEST 2024 program, it can be overwhelming to figure out which ones you should put on your schedule. That's why CHEST asked Danielle McCamey, DNP, CRNP, ACNP-BC, FCCP, and LaDonna Brown, DNP, CRNA, of DNPs of Color, as well as Corinne Young, MSN, FNP-C, FCCP, of the Association of Pulmonary Advanced Practice Providers, for their recommendations on sessions that advanced practice providers shouldn't miss. Visit **chestnet.org/annual-meeting-apps** for all of their recommendations.

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Changing the tumor board conversation: Immunotherapy in resectable NSCLC

BY NICHOLAS SCHLUND, DO, AND JESSE SHERRATT, DO

Without a doubt, immunotherapy has transformed the treatment landscape of non-small cell lung cancer (NSCLC) and enhanced survival rates across the different stages of disease. High recurrence rates following complete surgical resection prompted the study of immune checkpoint inhibitors (ICI) in earlier, operable stages of disease. This shift toward early application of ICI reflects the larger trend toward merging precision oncology with lung cancer staging. The resulting complexity in treatment and decision making creates systemic and logistical challenges that will require health care systems to adapt and improve.

Adjuvant immunotherapy for NSCLC

Prior to recent approvals for adjuvant immunotherapy, it was standard to give chemotherapy following resection of stage IB-IIIA disease, which offered a statistically nonsignificant survival gain. Recurrence in these patients is believed to be related to postsurgical micrometastasis. The utilization of alternative mechanisms to prevent recurrence is increasingly more common.

Atezolizumab, a PD-L1 inhibitor, is currently approved as first-line adjuvant treatment following chemotherapy in post-NSCLC resection patients with PD-L1 scores ≥1%. This category one recommendation by the National Comprehensive Cancer Network (NCCN) is based on results from the IMpower010 trial, which randomized patients to Atezolizumab vs best supportive care. All were early-stage NSCLC, stage IB-IIIA, who underwent resection followed by platinum-based chemotherapy. Statistically significant benefits were found in disease-free survival (DFS) with a trend toward overall survival.

The PEARLS/KEYNOTE-091 trial evaluated another PD-L1 inhibitor, Pembrolizumab, as adjuvant therapy. Its design largely mirrored the IMPower010 study, but it differed in that the ICI was administered with or without chemotherapy following resection in patients with stage IB-IIIA NSCLC. Improvements in DFS were found in the overall population, leading to FDA approval for adjuvant therapy in 2023.

These approvals require changes to the management of operable NSCLC. Until recently, it was not routine to send surgical specimens for additional testing because adjuvant treatment meant chemotherapy only. However, it is now essential that all surgically resected malignant tissue be sent for genomic sequencing and PD-L1 testing. Selecting the next form of therapy, whether it is an ICI or targeted drug therapy, depends on it.

From a surgical perspective, quality surgery with accurate nodal staging is crucial. The surgical findings can determine and identify those who are candidates for adjuvant immunotherapy. For these same reasons, it is helpful to advise surgeons preoperatively that targeted adjuvant therapy is being considered after resection.

Neoadjuvant immunotherapy for NSCLC

Dr. Schlund

Dr. Sherratt

ICIs have also been used as neoadjuvant treatment for operable NSCLC. In 2021, the Checkmate-816 trial evaluated Nivolumab with platinum doublet chemotherapy prior to resection of stage IB-IIIa NSCLC. When compared with chemotherapy alone, there were significant improvements in EFS, MPR, and time to death or distant metastasis (TTDM) out to 3 years. At a median follow-up time of 41.4 months, only 28% in the nivolumab group had recurrence postsurgery compared with 42% in the chemotherapy-alone group. As a result, certain patients who are likely to receive adjuvant chemotherapy may additionally receive neoadjuvant immunotherapy with chemotherapy before surgical resection. In 2023, the KEYNOTE-671 study demonstrated that neoadjuvant Pembrolizumab and chemotherapy in patients with resectable stage II-IIIb (N2 stage) NSCLC improved EFS. At a median follow-up of 25.2 months, the EFS was 62.4% in the Pembrolizumab group vs 40.6% in the placebo group ($P < .001$).

Such changes in treatment options mean patients should be discussed first and simultaneous referrals to oncology and surgery should occur in early-stage NSCLC. Up-front genomic phenotyping and PD-L1 testing may assist in decision making. High PD-L1 levels correlate better with response.

When an ICI-chemotherapy combination is given up front for newly diagnosed NSCLC, there is the potential for large reductions in

NSCLC *continued on following page*

Immune checkpoint inhibitors in first-line setting for NSCLC

Stage	Preferred first-line Immune Checkpoint Inhibitors
Stage IB	Neoadjuvant: **Nivolumab** + chemo before surgery Adjuvant: **Pembrolizumab** after surgery
Stage II	Neoadjuvant: **Nivolumab** + chemotherapy before surgery Adjuvant: **Atezolizumab** (PDL-1 ≥1%) after surgery and chemoradiation **Pembrolizumab** after surgery
Stage IIIA	Nonoperable: **Durvalumab** (if not progressed) after chemoradiation – category 1 Operable: **Nivolumab** + Chemo, then surgery **Pembrolizumab** after surgery **Atezolizumab** (PDL-1≥1%) after surgery and chemoradiation If not a surgical candidate: Monotherapy with **Pembrolizumab** (PDL-1≥1%) or **Cemiplimab** (PDL-1≥50%)
Stage IIIB	Non-operable: **Durvalumab** (if not progressed) after chemoradiation – category 1 **Pembrolizumab** monotherapy (PDL-1 ≥1%) or **Cemiplimab** monotherapy (PDL-1 ≥50%) Operable: **Atezolizumab** (PDL-1 ≥1%) after surgery and chemoradiation **Only T3,N2
Stage IV	Monotherapy: **Pembrolizumab** (PD-L1 ≥50%) – category 1, **Atezolizumab** (PD-L1 ≥50%) – category 1 **Cemiplimab-rwlc** (PD-L1≥50%) – category 1 Combination Therapy: **Pembrolizumab** + chemo (regardless of PD-L1) – category 1 **Cemiplimab-rwlc** + chemo (regardless of PD-L1) – category 1

*This table was adapted from the National Comprehensive Cancer Network guidelines.

**Does not include all other recommended therapies, recommended therapy after disease progression on chemotherapy, or therapies in the presence of targetable mutations.

Confronting health care misinformation on social media

EDITED BY BENEDETTA PAGNI

More than 90% of internet users are active on social media, which had 4.76 billion users worldwide in January 2023. The digital revolution has reshaped the news landscape and changed how users interact with information. Social media has fostered the ability to interact directly with the content presented. It also has augmented media's ability to reach a large audience with tight deadlines.

These developments suggest that social media can be a useful tool in everyday medical practice for professionals and patients. But social media also can spread misinformation. This is the focus of the latest research by Fabiana Zollo, a computer science professor at Ca' Foscari University of Venice, Italy, and coordinator of the Data Science for Society laboratory. The research was published in *The BMJ*. Ms. Zollo's research group aims to assess the effect of social media on misinformation and consequent behaviors related to health. "The study results focus primarily on two topics, the COVID-19 pandemic and vaccinations, but can also be applied to other health-related behaviors such as smoking and diet," Ms. Zollo told Univadis Italy.

Social media has become an important tool for public health organizations to inform and educate citizens. Institutions can use it to monitor choices and understand which topics are being discussed most at a given time, thus comprehending how the topics evolve and take shape in public discourse. "This could lead to the emergence of people's perceptions, allowing us to understand, among other things, what the population's needs might be, including informational needs," Ms. Zollo said.

Tenuous causal link

While social media offers public health organizations the opportunity to inform and engage the public, it also raises concerns about misinformation and the difficulty of measuring its effect on health behavior. Although some studies have observed correlations between exposure to misinformation on social media and levels of adherence to vaccination campaigns, establishing a causal link is complex. As the authors emphasize, "despite the importance of the effect of social media and misinformation on people's behavior and the broad hypotheses within public and political debates, the current state of the art cannot provide definitive conclusions on a clear causal association between social media and health behaviors." Establishing a clear causal link between information obtained from social media and offline behavior is challenging because of methodologic limitations and the complexity of connections between online and offline behaviors. Studies often rely on self-reported data, which may not accurately reflect real behaviors, and struggle to isolate the effect of social media from other external influences. Moreover, many studies primarily focus on Western countries, limiting the generalizability of the results to other cultural and geographical conditions.

Another issue highlighted by Ms. Zollo and colleagues is the lack of complete and representative data. Studies often lack detailed information about participants, such as demographic or geolocation data, and rely on limited samples. This lack makes it difficult to assess the effect of misinformation on different segments of the population and in different geographic areas.

"The main methodologic difficulty concerns behavior, which is difficult to measure because it would require tracking a person's actions over time and having a shared methodology to do so. We need to understand whether online stated intentions do or do not translate into actual behaviors," Ms. Zollo said. Therefore, despite the recognized importance of the effect of social media and misinformation on people's general behavior and the broad hypotheses expressed within public and political debates, the current state of the art cannot provide definitive conclusions on a causal association between social media and health behaviors.

Institutions' role

Social media is a fertile ground for the formation of echo chambers (where users find themselves communicating with like-minded people, forming a distorted impression of the real prevalence of that opinion) and for reinforcing polarized positions around certain topics. "We know that on certain topics, especially those related to health, there is a lot of misinformation circulating precisely because it is easy to leverage factors such as fear and beliefs, even the difficulties in understanding the technical aspects of a message," Ms. Zollo said. Moreover, institutions have not always provided timely information during the pandemic. "Often, when there is a gap in response to a specific informational need, people turn elsewhere, where those questions find answers. And even if the response is not of high quality, it sometimes confirms the idea that the user had already created in their mind."

The article published in *The BMJ* aims primarily to provide information and evaluation insights to institutions rather than professionals or health care workers. "We would like to spark the interest of institutions and ministries that can analyze this type of data and integrate it into their monitoring system. Social monitoring (the observation of what happens on social media) is a practice that the World Health Organization is also evaluating and trying to integrate with more traditional tools, such as questionnaires. The aim is to understand as well as possible what a population thinks about a particular health measure, such as a vaccine: Through data obtained from social monitoring, a more realistic and comprehensive view of the problem could be achieved," Ms. Zollo said.

A doctor's role

And this is where the doctor comes in: All the information thus obtained allows for identifying the needs that the population expresses and that "could push a patient to turn elsewhere." The doctor can enter this landscape by trying to understand, what needs the patients are trying to fill and what drives them to look for a reference community that offers the relevant confirmations.

From the doctor's perspective, it can be useful to understand how these dynamics arise and evolve because they could help improve interactions with patients. At the institutional level, social monitoring would be an excellent tool for providing services to doctors who, in turn, offer a service to patients. If it were possible to identify areas where a disinformation narrative is developing, both the doctor and the institutions would benefit.

Misinformation vs disinformation

The rapid spread of false or misleading information on social media can undermine trust in health care institutions and negatively influence health-related behaviors. Ms. Zollo and colleagues, in fact, speak of misinformation in their discussion, not disinformation.

Ms. Zollo is mainly interested in understanding how the end user interacts with content, not the purposes for which that content was created. "This allows us to focus on users and the relationships that are created on various social platforms," Ms. Zollo said, "thus bypassing the author of that information and focusing on how misinformation arises and evolves so that it can be effectively combated before it translates into action." ■

This story utilized several editorial tools, including AI, as part of the process. Human editors reviewed this content before publication.

NSCLC *continued from previous page*

tumor size and lymph node burden. Although the NCCN does not recommend ICIs to induce resectability, a patient originally deemed inoperable could theoretically become a surgical candidate with neoadjuvant ICI treatment. There is also the potential for toxicity, which could increase the risk of surgery when it does occur. Such scenarios will require frequent tumor board discussions so plans can be adjusted in real time to optimize outcomes as clinical circumstances change.

Perioperative immunotherapy for NSCLC

It is clear that both neoadjuvant and adjuvant immunotherapy can improve outcomes for patients with resectable NSCLC. The combination of neoadjuvant with adjuvant immunotherapy/chemotherapy is currently being studied. Two recent phase III clinical trials, NEOTORCH and AEGAEN, have found statistical improvements in EFS and MPR with this approach. These studies have not found their way into the NCCN guidelines yet but are sure to be considered in future iterations. Once adopted, the tumor board at each institution will have more options to choose from but many more decisions to make. ■

All references available online at chestphysician.org.

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