1917 2021 104

RHODE ISLAND MEDICAL JOURNAL

## 20 Years Later: Recollections & Reflections of 9/11/01

See Perspective, page 73

SPECIAL SECTION

# PULMONARY MEDICINE UPDATES 2021

GUEST EDITOR: JAMES SIMMONS, MD

SEPTEMBER 2021 VOLUME 104 • NUMBER 7 ISSN 2327-2228

COVERYS®
REDUCE DISTRACTIONS. IMPROVE OUTCOMES.®


## More means combining insurance protection with unique claims analytics and risk management.

**So providers can reduce distractions and focus on improving outcomes.**

Coverys is rated A (Excellent)* and has over 45+ years' experience protecting healthcare.
**Visit coverys.com.**

*A.M. Best financial rating is held by Medical Professional Mutual Insurance Company and its insurance subsidiaries.

RHODE ISLAND
MEDICAL JOURNAL


James Simmons, MD

SEPTEMBER 2021
VOLUME 104 • NUMBER 7



*RHODE ISLAND MEDICAL JOURNAL* (USPS 464-820), a monthly publication, is owned and published by the Rhode Island Medical Society, 405 Promenade Street, Suite A, Providence RI 02908, 401-331-3207. All rights reserved. ISSN 2327-2228. Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society, unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society.



# RHODE ISLAND MEDICAL JOURNAL

RHODE ISLAND
MEDICAL JOURNAL






RHODE ISLAND
MEDICAL JOURNAL

## IN THE NEWS



## PEOPLE/PLACES















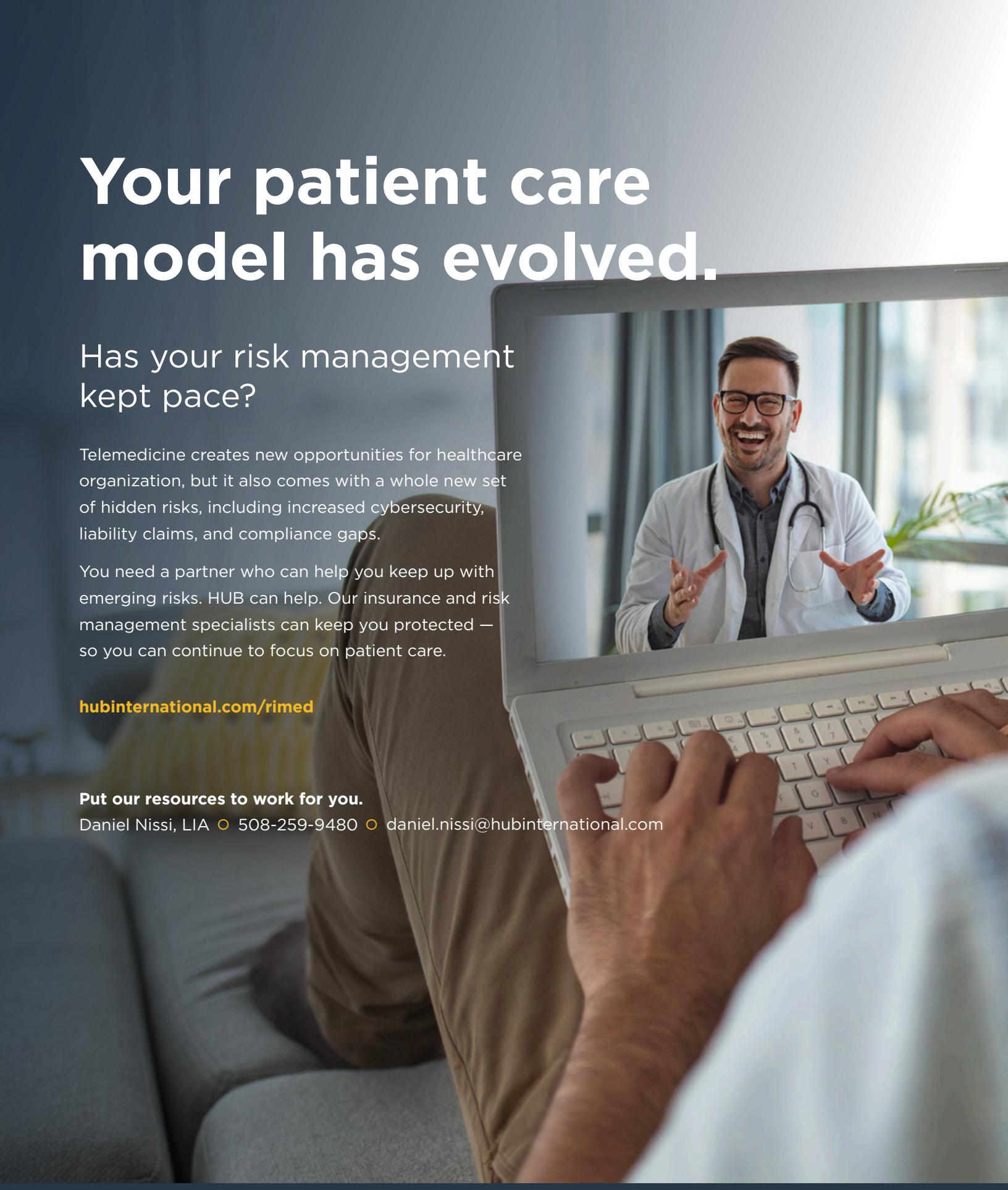
# Your patient care model has evolved.

## Has your risk management kept pace?

Telemedicine creates new opportunities for healthcare organization, but it also comes with a whole new set of hidden risks, including increased cybersecurity, liability claims, and compliance gaps.

You need a partner who can help you keep up with emerging risks. HUB can help. Our insurance and risk management specialists can keep you protected — so you can continue to focus on patient care.

**hubinternational.com/rimed**



**Put our resources to work for you.**

Daniel Nissi, LIA ○ 508-259-9480 ○ daniel.nissi@hubinternational.com

HUB

Risk & Insurance | Employee Benefits | Retirement & Private Wealth

# Updates in Pulmonary Medicine 2021

JAMES SIMMONS, MD
GUEST EDITOR

In the setting of the COVID-19 pandemic, pulmonary medicine has been brought to the forefront in the minds of many medical professionals over the past year. However, COVID-19 is only a small part of the vast array of pulmonary diseases that have affected and continue to impact Rhode Islanders. In this issue of the *Rhode Island Medical Journal*, pulmonologists from Rhode Island will review a variety of important and dynamic issues in pulmonary and sleep medicine, including common disease states with complicated management strategies and rare diseases that many readers are exposed to while practicing in Rhode Island and elsewhere. Our hope is this issue will improve both the specialist's and the general practitioner's ability and confidence in identifying, diagnosing, managing, and appropriately referring patients affected by these topics, so that we may all improve the lives of thousands of Ocean State patients.

## Obstructive Sleep Apnea Syndrome

Obstructive Sleep Apnea Syndrome (OSAS) is a common and underdiagnosed disorder leading to significant morbidity for a variety of patients worldwide. Our knowledge of the risks of OSAS and benefits of therapy have continued to evolve, and **ALICE BONITATI, MD**, the Associate Director of the Lifespan Sleep Disorders Center in Rhode Island, and **PARVATI SINGH, MD**, provide a succinct but comprehensive up-to-date guide to the diagnosis and initial management of this disorder.

## The Clinical Utility of Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is a functional and dynamic way to assess cardiopulmonary function at a patient's personal maximal exercise capacity. In many cases, the plethora of data generated can help differentiate complicated and unclear causes of dyspnea and exercise intolerance when used by experienced clinicians. **EVAN SMITH, MD**, along with **ERIC GARTMAN, MD**, Director of the Cardiopulmonary Exercise Training Laboratory at the Providence Veteran Affairs Medical Center, describe the components of CPET, as well as its varied indications to aid in evidence-based diagnosis, prognosis, and management of cardiopulmonary disease, including, for example, congestive heart failure, preoperative evaluation, and evaluation for organ transplant.

## Updates on Cystic Fibrosis Treatments

Although cystic fibrosis (CF) is a rare disease, it still affects more than 70,000 people worldwide and leads to significant morbidity and mortality of multiple organ systems in many patients. As the therapies to manage CF have advanced and patients' life expectancies have increased, it has become a more chronic but complicated medical problem that can often be managed over decades with the appropriate multidisciplinary care. **DEBASREE BANERJEE, MD**, and **MICHAEL BLUNDIN, MD**, provide such care for many of the cystic fibrosis patients in Rhode Island, and, along with **CHELSEA BOYD, MD**, and **ROGER AUTH, MD**, they offer a review of the exciting recent changes to the management of cystic fibrosis in the age of personalized medicine, including a review of novel therapeutics that modulate the cystic fibrosis transmembrane regulator protein and changes to antibiotic management.

## Diagnosis and Management of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. Definitive diagnosis requires the exclusion of known causes of pulmonary fibrosis, aided by the multidisciplinary discussion involving pulmonologists, radiologists, and pathologists with expertise in the diagnosis of IPF and other forms of interstitial lung disease. **JULIA MUNCHEL, MD**, and **BARRY SHEA, MD**, provide an excellent review of the current recommendations for the diagnosis, prognostication, and management of patients with IPF, which focuses on anti-fibrotic therapy and early referral to lung transplant centers for those who are candidates.

## Diagnosis of Pulmonary Hypertension

Pulmonary hypertension (PH) is a chronic disease of elevated pulmonary artery pressure that can result from pulmonary vascular diseases or complicate left heart and lung disease, while pulmonary arterial hypertension (PAH) is a rare pulmonary artery vasculopathy that leads to progressive right heart failure and death. Timely and accurate diagnosis of PH is paramount given the increased morbidity and mortality, but can be challenging given the nonspecific nature of the presenting symptoms and the many potential causative or contributing conditions. Although right heart catheterization is required for diagnosis and early referral to a PH expert

center, such as the Rhode Island Hospital Pulmonary Hypertension Center, is strongly recommended, it is an important and increasingly common problem for all RI healthcare providers to consider and care for. To that end, **NAVNEET SINGH, MD**, and **CHRISTOPHER MULLIN, MD**, a pulmonary hypertension specialist practicing in RI, provide a review of the complicated workup of PH, based on the current medical knowledge and significant local experience.

### The Evolving Continuum of Diagnosis in the Modern Age of Non-Small Cell Lung Cancer

Although lung cancer is the leading cause of cancer-related death in the United States, there has been significant advancement in the diagnosis and treatment of non-small cell lung cancer (NSCLC) over the past couple of decades. Improvements in diagnostic evaluation and biopsy techniques coupled with advances in targeted therapies with newer drug targets are giving patients and their families more hope in the face of this challenging disease, but this, in turn, leads to new challenges navigating increasingly complex decision-making for the healthcare providers. **DANIEL DUSTIN, DO**, and **DOUG MARTIN, MD**, provide a concise overview of the current best practices for workup and management of NSCLC from the pulmonary viewpoint, while also noting emergent complications based on recent data and their personal experiences caring for patients with lung cancer in RI.

In conclusion, we hope this compilation will enhance your knowledge of and interest in some of the many important pulmonary diseases seen in Rhode Island patients and the world at large.

### Guest Editor

James Simmons, MD, Assistant Professor of Medicine, Alpert Medical School of Brown University; Pulmonary and Critical Care Physician, The Miriam Hospital, Providence, RI.

# Obstructive Sleep Apnea Syndrome – A Review for Primary Care Physicians and Pulmonologists

PARVATI SINGH, MD; ALICE BONITATI, MD


## ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep disorder that leads to excessive daytime sleepiness and poor quality of life. OSAS is characterized by intermittent hypoxia and sleep fragmentation and is associated with increased risk of cardiovascular and neurocognitive disorders. The focus of our article is to discuss the approach to diagnosis and management.


**KEYWORDS:** obstructive sleep apnea, apnea, polysomnography, AHI, positive airway pressure therapy

## EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that is defined by either partial or complete collapse of the airway that interrupts ventilation.[1] These interruptions in breathing during sleep can result in intermittent hypoxia, sleep fragmentation, and lack of restorative sleep.[1] OSAS refers to symptomatic obstructive sleep apnea.

Fatigue, daytime sleepiness, and poor quality of life are hallmark symptoms of OSAS. Other common symptoms include headaches, awakenings with gasping or choking sensation, concentration and memory problems, irritability, and depression.[1] Additionally, OSAS is associated with increased risk of hypertension, atrial fibrillation, myocardial infarction, pulmonary hypertension, insulin resistance, and stroke.[2] This risk is primarily applicable to patients with moderate to severe disease. A 2021 meta-analysis found that OSA was associated with an increased risk for cardiac and all-cause mortality.[3]

There is data suggesting that OSAS increases the risk of developing dementia and cancer.[2] A cohort study found that patients with sleep disordered breathing developed mild cognitive impairment at an earlier age than those who did not have self-reported sleep disordered breathing.[4] In a prospective study of 298 women 65 years or older without dementia, those with OSA were more likely to develop mild cognitive impairment or dementia (45% vs 35%, p=0.02, adj. odds ratio 1.8).[21] With regards to malignancy, the theory is that repetitive hypoxic episodes lead to a change in gene expression for angiogenesis.[2] A study that followed patients from the Wisconsin Sleep Cohort for 22 years found that as the severity of OSA increased the cancer mortality also increased.[5]

It is estimated that more than 1 billion people globally have some degree of OSA.[6] Obesity is a major risk factor, partially explaining the increased prevalence of the disorder in our society. Weight gain of 10% can lead to a six-fold increase in odds of developing OSA.[1] Other risk factors include age, male gender, tonsillar hypertrophy, and craniofacial abnormalities that narrow the upper airway.[7] It is important to note that approximately 25% of patients with OSA in the U.S. are non-obese.[16] Ethnicity is one factor implicated in OSA in non-obese individuals. In addition, non-obese OSA represents its own phenotype, exhibiting some differences in clinical characteristics such as lower arousal threshold and often lesser tolerance of positive pressure therapy.[16]

## DIAGNOSIS

Patients to consider for testing are those with any of the above signs or symptoms. Snoring in conjunction with suggestive OSA symptom(s) or comorbidities is an indication for testing. On exam, patients may have a wide neck, large tongue, large adenoids/tonsils, and a Mallampati score of III-IV.[7] Questionnaires can be helpful in identifying patients who should be screened for OSAS. A score of $\geq$10 on the Epworth Sleepiness Scale and/or a score $\geq$3 on STOP-BANG questionnaire are concerning for possible sleep apnea.[7] The STOP-BANG screening tool that asks yes or no questions about snoring, fatigue, observed apneas, hypertension, BMI, age, neck circumference, and gender has ~90–93% sensitivity for sleep apnea.[1] While useful, this and other screening tools have not been validated in all populations, such as in patients undergoing bariatric surgery, in whom excessive daytime sleepiness may be lacking.[25] OSA is highly prevalent in the bariatric patient population and there is increased risk of peri- and postoperative complications if sleep apnea is not monitored and treated. Therefore, all patients should undergo testing to determine if they have sleep apnea and start treatment if the sleep apnea is found to be significant.

Polysomnography (PSG) or home sleep testing is generally required to diagnose OSAS. An all-night in-laboratory PSG involves use of EEG, EOG (electrooculography), EMG, pressure sensors to detect air flow, EKG, and chest/abdomen belts to detect respiratory effort.[1] Despite PSGs being the gold standard test, there are drawbacks of cost, possible lack of insurance coverage, and lower patient acceptance compared to home testing.

Home sleep apnea testing (HSAT) use has been on the rise, due to benefits of convenience, lower cost, and increased access to evaluation, as well as improved quality of this testing.[8] Compared to PSG, HSAT does not utilize EEG or EMG and therefore actual sleep time is not known.[1] HSAT should be used when there is a high pretest probability for OSA, there are no severe comorbidities and no concern for additional sleep disorders.[1] HSATs can underestimate severity or miss OSA. False negative rate of this test is approximately 17%.[1] Thus, if HSAT is negative then the patient should generally complete a formal PSG.[1]

One ambulatory sleep study device that is gaining traction is the WatchPAT, a peripheral arterial tonometer. The WatchPAT measures apnea or hypopnea by using an algorithm that utilizes data on the changes in peripheral arterial blood volume, desaturations on pulse oximetry, and changes in heart rate.[9] A meta-analysis showed that WatchPAT's respiratory indexes did correlate with scoring from PSGs.[9] The peripheral arterial tonometry has a positive predictive value of 76% and negative predictive value of 83%.[1] Currently however, a PSG or HSAT is required to initiate therapy.

The tests mentioned determine the apnea-hypopnea index (AHI) score and help guide treatment options for OSA.[7] AHI is the number of hypopnea/apnea events per an hour and is used for classification of OSA severity. In adults, AHI 5-14.9 is mild OSA, AHI 15-29.9 is moderate OSA, and AHI $\geq$ 30 is severe OSA. Of note, this classification system does not account for other factors that could contribute to severity of OSA, such as the level of desaturation, degree of sleep fragmentation, or level of sympathetic system activation.[17]

## TREATMENT

### Lifestyle changes and conservative measures

Lifestyle changes can improve OSA and in those with mild disease and symptoms can sometimes be the primary form of management. The following are beneficial:

1. Weight loss lowers severity of OSA,[13] but especially in moderate to severe disease is often not curative.
2. Patients should limit alcohol, opiate, and benzodiazepine use.
3. Smoking cessation may help as well. Nicotine is thought to increase upper airway muscle collapse due to muscle relaxation and increased sleep fragmentation.[13]
4. Many patients have worse AHI scores in the supine position in part due to airway closure due to tongue relaxation. It has been shown that sleeping in the lateral decubitus position can decrease sleepiness and AHI scores.[13] There are many positional devices that can be used to help patients sleep off their back.
5. Treatment of nasal congestion to improve upper airway patency.

### Positive Airway Pressure Therapy (PAP)

The mainstay of OSA treatment is PAP therapy, in which positive pressure is applied to keep the upper airway patent during sleep, thereby reducing apneas and hypopneas. PAP therapy can be either CPAP, APAP (auto-titrating), or BiPAP (bilevel). According to the American Academy of Sleep Medicine (AASM) clinical practice guidelines, PAP therapy is recommended for patients with excessive sleepiness.[10] There have been 38 randomized control trials that have shown that PAP decreases excessive sleepiness with minimal side effects.[10] Effective PAP pressures can be determined during split PSG testing, in which pressures are titrated during the second half of the night. Positive pressure titration in the sleep center is recommended for patients with CHF, COPD, central sleep apnea, and obesity hypoventilation syndrome.[1] Otherwise, APAP can be prescribed. APAP is set over a range of PAP pressures and the unit titrates the pressure to achieve the lowest AHI score. Once the patient is using APAP for a period of time, the patient's sleep medicine provider reviews efficacy of therapy and makes additional adjustments to settings if needed.

Per the AASM guidelines, there is a conditional recommendation of prescribing PAP therapy to patients with diagnosed OSA with HTN or impaired sleep-related quality of life.[10] There have been five randomized control trials showing that PAP therapy can lower blood pressure, though a meta-analysis did not support this.[10] Similarly, in terms of impaired sleep-related quality of life, a meta-analysis did not support the positive benefits seen in 19 randomized control trials.[10]

Additionally, the AASM guidelines list that there is not enough evidence on the use of PAP therapy for asymptomatic OSA patients.[10] There is mixed data regarding whether implementation of PAP therapy reverses the increased risk of cardiovascular disease or mortality. Observational studies have shown a positive response to PAP therapy for cardiovascular outcomes, while four randomized control trials have not confirmed, but have not excluded benefit in this regard.[10] Negative results may be related to exclusion of patients with more significant cardiovascular disease and the relatively low PAP adherence in these randomized trials.[1] A recent study found that the degree of heart rate increase in relation to apneas/hypopneas was a predictor of poor cardiovascular outcomes, and perhaps these patients should be included in future randomized trials.[22] In a recent subgroup analysis of a large RCT, it was found that patients with CAD who used CPAP for more than 4 hours a night had lower rates of cardiovascular or neurovascular events compared to patients who used it for less than 4 hours a night.[24] About 20% of OSA patients have pulmonary hypertension, and small studies have shown that CPAP therapy lowers right ventricular and pulmonary artery pressures.[23]

Adherence to PAP therapy is a significant issue for patients with OSAS. To improve compliance, finding a well-fitting

and comfortable interface and using in-line humidification can be helpful.[10] Despite these adjustments, PAP adherence can still be poor, especially in those who require higher pressures.[12] A ramp function with which the starting pressure is gradually increased can also help with comfort.[12] It has been recently shown that remote electronic monitoring of PAP use by patients and their providers can lead to improved overall compliance with therapy. Over the past one to two decades there have been significant improvements in PAP technology, leading to improved comfort with therapy.

### Other Therapies for OSA

Other therapies for OSAS include oral appliances, upper airway surgery, and hypoglossal nerve stimulation.

Mandibular Advancement Devices are often a good alternative to PAP therapy for mild to moderate OSAS. The mandibular device causes the mandible to jut forward, advancing the tongue and lifting the palate thereby reducing airway collapse.[14] One retrospective study of OSA patients with mild to severe disease found that a mandibular device led to 37% of patients having resolution of their OSA and 64% of patients having their AHI score cut in half.[14] However, the response to the mandibular device was not as profound in patients with severe OSA.[14]

Lastly, various surgeries have been used to treat OSA. The data for this treatment option is mostly limited to case series and a handful of RCTs. There is no RCT comparing PAP therapy against surgical interventions for OSA treatment. Two RCTs have compared upper airway surgery with conservative management in patients who did not tolerate PAP or mandibular advancement devices.[19,20] The SKUP3 RCT trial found that uvolopalatopharyngoplasty (UPPP) reduced AHI on average from 53.3 to 21.1, though a few patients had an increase in AHI after surgery.[19] Similarly, the SAMS RCT trial found that those who had UPPP with radiofrequency ablation to reduce tongue size had average drop in AHI from 47.9 to 20.8.[20] Only 28% of patients had resolution of OSA.[20] Other surgical interventions include tonsillectomy (usually performed with UPPP), genioglossus advancement, and maxillo-mandibular advancement. Generally, in select patients with certain anatomical abnormalities who do not tolerate PAP or mandibular devices, surgical intervention is an option. Surgery can reduce the severity of OSA and in well-selected patients it can sometimes completely treat sleep apnea.

Hypoglossal nerve stimulation (HNS) is a newer therapy that stimulates the nerve to act on the genioglossus muscle during sleep to help open the upper airway.[1] A cohort study in 2014 found the hypoglossal nerve stimulator lowered the median AHI score by 68% in 12 months and also decreased level of daytime sleepiness in OSA patients.[15] HNS is considered if the patient fails or doesn't tolerate PAP therapy, does not have concentric collapse of the upper airway on drug-induced sleep endoscopy (DISE), and there is no anatomical obstruction, BMI $\leq$ 35 kg/m$^2$, and AHI is 15–65.[18]

## CONCLUSION

OSAS is a highly prevalent sleep disorder that can negatively affect quality of life and is linked to cardiovascular disorders and neurocognitive abnormalities. Diagnosis is generally made with PSG or home-sleep testing. Primary treatment for symptomatic OSA, especially if moderate or severe, is usually with positive airway pressure therapy, but other therapies are available and evolving. PAP therapy has been shown to improve excessive daytime sleepiness, AHI score, and blood pressure. It is likely that there are benefits for primary and secondary prevention of cardiovascular events including stroke, but results of randomized controlled trials are mixed and there are large ongoing studies examining this topic.

### References


1. Lee JJ, Sundar KM. Evaluation and Management of Adults with Obstructive Sleep Apnea Syndrome. Lung. 2021 Apr;199(2): 87-101.
2. Lim DC, Pack AI. Obstructive Sleep Apnea: Update and Future. Annu Rev Med. 2017 Jan 14;68:99-112.
3. Heilbrunn ES, Ssentongo P, Chinchilli VM, Oh J, Ssentongo AE. Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis. BMJ Open Respir Res. 2021 Jun;8(1):e000656.
4. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ. Alzheimer's Disease Neuroimaging Initiative. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology. 2015 May 12;84(19):1964-71.
5. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 2012 Jul 15;186(2):190-4.
6. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019 Aug;7(8):687-698.
7. Slowik J, Collen J. 2020, Dec 3. Obstructive Sleep Apnea. In: StatPearls [Internet]. Treasure Island (FL): StatPearsl Publishing; 2021 Jan. Available from: Obstructive Sleep Apnea - StatPearls - NCBI Bookshelf (nih.gov)
8. Billings ME, Pendharkar SR. Alternative Care Pathways for Obstructive Sleep Apnea and the Impact on Positive Airway Pressure Adherence: Unraveling the Puzzle of Adherence. Sleep Med Clin. 2021 Mar;16(1):61-74.
9. Yalamanchali S, Farajian V, Hamilton C, Pott TR, Samuelson CG, Friedman M. Diagnosis of obstructive sleep apnea by peripheral arterial tonometry: meta-analysis. JAMA Otolaryngol Head Neck Surg. 2013 Dec;139(12):1343-50.
10. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019 Feb 15;15(2):335-343.
11. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, Mediano O, Masdeu MJ, Alonso ML, Masa JF, Barceló A, de la Peña M, Mayos M, Coloma R, Montserrat JM, Chiner E, Perelló S, Rubinós G, Mínguez O, Pascual L, Cortijo A, Martínez D, Aldomà A, Dalmases M, McEvoy RD, Barbé F; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. Lancet Respir Med. 2020 Apr;8(4):359-367.

12. Killick R, Marshall NS. The Impact of Device Modifications and Pressure Delivery on Adherence. Sleep Med Clin. 2021 Mar;16(1):75-84.
13. Kaleelullah RA, Nagarajan PP. Cultivating Lifestyle Transformations in Obstructive Sleep Apnea. Cureus. 2021 Jan 26;13(1):e12927.
14. Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA. Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. J Clin Sleep Med. 2015 Aug 15;11(8):861-8.
15. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014 Jan 9;370(2):139-49.
16. Gray EL, McKenzie DK, Eckert DJ. Obstructive Sleep Apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype. J Clin Sleep Med. 2017 Jan 15;13(1):81-88.
17. Rapoport DM. POINT: Is the Apnea-Hypopnea Index the Best Way to Quantify the Severity of Sleep-Disordered Breathing? Yes. Chest. 2016 Jan; 149(1):14-6.
18. Steffen A, Heiser C, Galetke W, Herkenrath SD, Maurer JT, Gunther E, Stuck BA, Woehrle H, Lohler J, Randerath W. Hypoglossal nerve stimulation for obstructive sleep apnea: updated position paper of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery. Eur Arch Otorhinolaryngol. 2021 Jun 21.
19. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013 Sep; 68(9): 846-53.
20. MacKay S, Carney As, Catcheside PG, Chai-Coetzer CL, Chia M, Cistulli PA, Hodge JC, Jones A, Kaambwa B, Lewis R, Ooi EH, Pinczel AJ, McArdle N, Rees G, Singh B, Stow N, Weaver EM, Woodman RJ, Woods CM, Yeo A, McEvoy RD. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients with Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. JAMA. 2020 Sep 22;324(12):1168-1179.
21. Yaffe K, et al. JAMA. 2011;306(6):613-619.
22. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, Alex RM, Kim SW, Gottlieb DJ, White DP, Redline S, Wellman A. The Sleep Apnea-Specific Pulse-Rate Response Predicts Cardiovascular Morbidity and Mortality. Am J Respir Crit Care Med. 2021 Jun 15;203(12):1546-1555.
23. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ. 2015 Jun;5(2):220-7.
24. Peker Y, Thunström E, Glantz H, Eulenburg C. Effect of Obstructive Sleep Apnea and CPAP Treatment on Cardiovascular Outcomes in Acute Coronary Syndrome in the RICCADSA Trial. J Clin Med. 2020 Dec 15;9(12):4051.
25. Sharkey K, et al Predicting OSA among women candidates for bariatric surgery. J Women's Health. 2010 19(10):1833-1841.

## Authors

Parvati Singh, MD, Sleep Medicine Fellow, University of Pennsylvania.

Alice Bonitati, MD, Associate Professor of Medicine, Clinician Educator, Division of Pulmonary, Critical Care and Sleep Medicine, Brown University.

## Correspondence

Alice Bonitati, MD
Rhode Island Hospital
Division of Pulmonary, Critical Care and Sleep Medicine
593 Eddy Street (APC 7)
Providence, RI 02903
401-444-2670
Fax 401-444-5493
Abonitati@lifespan.org

# The Clinical Utility of Cardiopulmonary Exercise Testing

EVAN J. SMITH, MD; ERIC J. GARTMAN, MD

**KEYWORDS:** cardiopulmonary exercise testing, physiology, stress testing, oxygen consumption (VO2)

## GLOSSARY

**AT** – Anaerobic threshold, the point at which oxygen delivery to exercising muscle can no longer meet demands and lactic acid begins to accumulate

**VO2** – oxygen consumption per minute, expressed in L/min and mL/kg/min

**$VO2_{peak}$** – Highest VO2 obtained during an exercise test. If a further increase in workload does not lead to further increase in VO2, i.e. there is a plateau in VO2, this is referred to as **$VO2_{max}$**.

**$VO2_{reserve}$** – Difference between resting VO2 and VO2max.

**VCO2** – Carbon dioxide production, L/min

**VE** – Minute ventilation, L/min

**VE/VCO2** – Ratio of minute ventilation to CO2 production (how much one is breathing to ventilate off a given amount of CO2), a measure of ventilatory efficiency

## INTRODUCTION

Cardiopulmonary exercise testing (CPET) can be conducted in several ways, but most commonly is performed as a progressive incremental exercise test that concludes at exhaustion at maximal exercise capacity. For several reasons, the most important being safety, the test generally is done utilizing a cycle ergometer that has the ability to ramp the work rate over time. During the exam, the patient has extensive safety monitoring – including continuous electrocardiogram (ECG), pulse oximetry, and frequent blood pressure recordings. A physician typically is in attendance for the duration of the test. Additionally, the patient has all inhaled and exhaled gas analyzed – with the ability to determine oxygen consumption (VO2), carbon dioxide elimination (VCO2), tidal volumes, and respiratory flow curves. Before and directly after the test serial spirometry is performed to assess baseline pulmonary function and assess for exercise-induced airway disorders, respectively. See **Figure 1** for typical CPET laboratory set-up and equipment.

It is well known that static measures of pulmonary and cardiac function (such as pulmonary function testing (PFT) and echocardiography) do not always relate well to dynamic measures during exertion.[1] While other modalities of stress testing are well-suited for a limited evaluation (e.g. a cardiac stress test for ischemia), the extensive cardiopulmonary data obtained by CPET has the potential to determine the overriding factor or system limiting maximal exercise (e.g. cardiac, ventilatory, systemic vascular, mitochondrial, deconditioning or psychological). Further, given that it does not have artificial test stopping points (e.g. HR endpoints), a full evaluation of the cardiopulmonary system can be obtained. Many of performance measures that are obtained during the test are able to be reported as percent predicted using published equations – such as $VO2_{peak}$, work rate, and certain ventilation parameters.

While overwhelmingly the most common indication for CPET is unexplained dyspnea on exertion, this review

**Figure 1**. Typical CPET laboratory set-up using a cycle ergometer. The monitoring equipment includes continuous ECG, pulse oximetry, sphygmomanometer, flow sensor, and gas analyzer (interface can either be facemask or mouthpiece/noseclip). Also, the equipment has the ability to perform standalone spirometry.

will examine the evidence supporting other valuable uses for CPET, including in heart failure, evaluation for cardiac transplant, and preoperative evaluation (**Table 1**).

**Table 1.** Indications for CPET referral. Adapted from ATS/ACCP Statement, 2001[4]

| Disease state | Indication |
|---|---|
| Dyspnea on Exertion | Unexplained dyspnea |
| Congestive Heart Failure | Guide transplant referral<br>Prognostication<br>Response to medical therapy |
| Pre-operative, general surgery | Predictive of post-operative complications and mortality<br>Guide post-operative level of care<br>Inform shared decision making |
| Pre-operative, lung resection | Identify those who will tolerate resection |
| Lung volume reduction surgery (LVRS) | Identify those most likely to benefit from LVRS<br>Measure functional improvement post-operative |
| Asthma | Identification of exercise-induced bronchospasm<br>Identification of non-ventilatory exercise limitation |
| Cystic Fibrosis | Prognostication |
| COPD | Identification of non-ventilatory exercise limitation<br>Early identification of group 3 pulmonary hypertension |
| Pulmonary Hypertension | Identify Etiology<br>Prognostication<br>Evaluate response to treatment |
| Rehabilitation | Determine safety pre-rehabilitation<br>Determine precise rehabilitation prescription<br>Evaluate response to rehabilitation |

## DYSPNEA EVALUATION

The most common indication for CPET is unexplained dyspnea or dyspnea out of proportion to disease severity demonstrated on other testing. Unexplained dyspnea or exercise intolerance is considered a Class I indication for CPET referral.[2] Unexplained dyspnea is largely divided into two categories – patients with no obvious cause on routine testing and patients with multiple potential causes. It is most often the case that patients are referred for CPET after they have had a fairly significant evaluation that has been unrevealing – including PFTs, radiographic imaging, echocardiography, and/or cardiac stress testing. Common etiologies of symptoms that may be suggested through CPET include limits on ventilation, exercise-induced bronchoconstriction, cardiac ischemia, heart failure, pulmonary hypertension, and peripheral vascular disease. Additionally, CPET can potentially identify non-cardiopulmonary limitations such as pathologic breathing patterns, obesity, and deconditioning.[3] Assuming a maximal test is performed, the comprehensive nature of a CPET can provide reassurance to a patient and potentially limit further diagnostic testing. Likewise, when a defined etiology of exercise limitation is identified, CPET can guide further therapy and investigations – or help determine which system warrants further therapeutic attention or testing in a patient with several known conditions.[4]

CPET also can be helpful in the evaluation of disability due to exertional symptoms. Often, job-related or exertional complaints are out of proportion to routine testing results used for disability determination (such as PFTs or echocardiography), making it difficult for such patients to receive compensation.[5] Maximal CPET can provide an objective measure of work capacity and possesses the ability to differentiate poor volitional effort from a true physiologic impairment – and may be helpful in select workman's compensation cases.1

## CONGESTIVE HEART FAILURE

Outside of the evaluation of dyspnea, CPET has been studied most robustly in the realm of congestive heart failure. There are several roles for comprehensive exercise testing in therapeutic management of heart failure with or without reduced ejection fraction, including prognostication and evaluation for transplant.

CPET has been studied extensively in the evaluation for eligibility for cardiac transplantation. Using CPET to evaluate patients prior to transplant is considered a class IA indication[2], with $VO2_{peak}$ being the variable most often utilized. In one prospective study of patients referred for cardiac transplant, $VO2_{peak}$ of 14cc/kg/minute was used as a cut-off for transplant surgery. Those who were referred for cardiac transplant with $VO2_{peak}$ > 14cc/kg/min who did not receive a transplant had a similar 1- and 2-year survival (94% and 84% respectively) to those who underwent transplant. Those with $VO2_{peak}$ less than that cut-off who did not receive a transplant due to non-cardiac reasons had a significantly lower survival at 1 and 2 years (47% and 32%).[6] While this landmark study was not randomized, and there is a question of conditions that prohibited transplant as contributing to mortality, in practice a cut-off of 14cc/kg/min $VO2_{peak}$ is used to determine the eligibility for cardiac transplant. Further, those who are re-evaluated while awaiting their transplant who are able to increase their $VO2_{peak}$ by at least 2cc/kg/min to at least 12cc/kg/minute are able to be safely removed from the transplant list and show excellent survival (85–100% at 2 years).[7]

It follows that those with higher levels of fitness, as measured by $VO2_{peak}$, are more likely to have better outcomes. This variable has been studied in prognosticating heart failure with both preserved and reduced ejection fraction. Using an outcome of transplant and mechanical support-free

survival, patients can be stratified into groups based on their $VO2_{peak,}$ corresponding to Weber class, a functional class analogous to NYHA class. The most fit (defined as >20cc/kg/min) exhibited a 3-year survival of 97%, which was similar to those in the next highest quartile (16–20cc/kg/min). Three-year survival decreased further as $VO2_{peak}$ declined (83% with a $VO2_{peak}$ of 10–16 cc/kg/min and 64% for those <10cc/kg/min 8) (**Table 2**).

Similar to what has been seen in those awaiting heart transplant, patients with systolic heart failure are able to improve their risk of mortality and hospitalization by undergoing exercise training programs. In the large HF-ACTION trial, those undergoing a supervised exercise program were able to increase their $VO2_{peak}$ an average of 4%[9]; with other studies demonstrating that formalized exercise programs can increase $VO2_{peak}$ by 10%–18%.[10,11] In the HF-ACTION trial, $VO2_{peak}$, percent predicted $VO2_{peak}$, and exercise duration had the strongest associations with mortality in both systolic and diastolic heart failure.[9]

**Table 2.** Survival in Congestive Heart Failure stratified by $VO2_{peak}$. Adapted from Luiz, et al[8]

| $VO2_{peak}$ | 3-year event free survival |
|---|---|
| >20cc/kg/min (Weber Class A) | 97% |
| 16–20cc/kg/min (Weber Class B) | 94% |
| 10–16cc/kg/min (Weber Class C) | 83% |
| <10cc/kg/min (Weber Class D) | 64% |

## PREOPERATIVE USE OF CPET IN GENERAL SURGERY

The use of CPET in preoperative risk stratification has been extensively studied. However, unlike in heart failure, the studies in preoperative risk assessment are more heterogenous given the different outcome measures used and the variability inherent in various surgical populations (**Table 3**).

Many studies have demonstrated that low $VO2_{peak}$, early anaerobic threshold, and elevated ratio of maximal ventilation to CO2 production during exercise (VE/VCO2) can predict operative complications and mortality.[12,13,14] Identifying those at higher operative risk via the objective outcomes from CPET can provide valuable information for appropriate patient selection for surgery and when discussing operative risk with patients.

A large systematic review[15] of 37 studies, encompassing 7852 patients, identified which variables were most predictive of poor outcomes relative to a given operation. For hepatic transplant or resection, early anaerobic threshold was most predictive of mortality with a value < 9.9cc/kg/minute predicting 30-day mortality, and < 9.0cc/kg/min predicting 90-day mortality.[16,17,18,19,20,21] In elective abdominal aortic aneurysm (AAA) repair, increased 30- and 90-day mortality was associated with VE/VCO2>42.[22,23,24,25] In elective colorectal surgery, early anaerobic threshold (<11cc/kg/min) and low $VO2_{peak}$ (<10.6cc/kg/min) were both associated with increased 30-day, 90-day and 2-year mortality, as well as increased postoperative length of stay.[26,27,28] In pancreatic surgery, the predictive value of early anaerobic threshold was not as strong, but similar to AAA surgery an increased VE/VCO2 portended an increased mortality.[29,30,31] In studies of other surgical procedures (e.g. upper gastrointestinal, renal transplant, bariatric surgery), the data supporting CPET's prognostic ability for operative risk is not as strong – potentially resulting from lesser inherent operative risk and population differences to the other major surgeries discussed above (i.e. the patients undergoing these procedures may be younger and with less medical comorbidity).[14]

While many small studies have found associations between CPET results and operative complications and mortality, the largest study to date evaluating CPET as a preoperative risk assessment tool, the METS study (Measurement of Exercise Tolerance before Surgery), shows more nuanced results beyond mortality prediction alone. The METS study was a multicenter prospective cohort study evaluating 1,401 patients undergoing non-cardiac surgery. Patients with low $VO2_{peak}$ and earlier anaerobic threshold had increased post-operative complications, including surgical site infections, respiratory failure, ICU length of stay and need for re-operation. Notably, this was in the absence of an increase in postoperative cardiac events.[32]

**Table 3.** Utility of CPET parameters in predicting post-operative complications and survival. Adapted from Moran, et al[15]

| | AT | $VO2_{peak}$ | VE/VCO2 |
|---|---|---|---|
| Hepatic | **Strong Association** | Equivocal | No association |
| AAA | Equivocal | Equivocal | Limited Association |
| Colorectal | **Strong Association** | **Strong Association** | Equivocal |
| Pancreatic | Limited association | Equivocal | **Strong Association** |
| Bariatric/Upper GI | No association | No association | No association |
| Renal Transplant | No association | No association | No association |

## LUNG RESECTION

Pulmonary function testing performs well in identifying those at low risk for postoperative complications from anatomic lung resection (e.g. lobectomy). However, for those with marginal lung function, the use of CPET in the preoperative evaluation is suggested to help determine appropriate patients for surgery.[33,34] Multiple studies have demonstrated that postoperative mortality was best predicted by $VO2_{peak.}$[35] For example, in one cohort, those with $VO2_{peak}$ > 20cc/kg/min had no post-resection deaths, and those with $VO2_{peak}$ < 10cc/kg/min had highest rates of death (29%) and complications (43%).[36] In another small cohort,

those with $VO2_{peak}$ > 15cc/kg/min but FEV1 < 33% had no fatalities after resection, supporting the use of CPET in those with otherwise prohibitively low FEV1.[37]

## LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) has been shown to be effective in upper lobe predominant emphysema patients. In carefully selected patients, LVRS may improve mortality, quality of life, and exercise capacity.[38] In the National Emphysema Treatment Trial, over 1,000 patients were randomized to LVRS or maximum medical therapy. CPET was used to identify those who may benefit most from resection, and found that impaired peak work rate was the best predictor of who would have the most clinical benefit[39] (cut-off <25 W in women and <40 W in men). In follow-up studies after surgery, those who undergo LVRS have been shown to have improvements in $VO2_{peak}$, work-load achieved, and VE/VCO2.[40]

## PULMONARY DISEASE

### Asthma

An obvious utility of CPET is the identification of exercise-induced bronchoconstriction. While a specific protocol can be used (rapid increase to 90% of peak predicted HR for 6 minutes while breathing dry air[41]), usually patients are being evaluated as part of a general dyspnea work-up. As such, evaluating for declines in serial post-exercise spirometries at multiple intervals can be helpful in this determination. CPET can also determine other etiologies of exercise intolerance that are common in asthma and not related to bronchospasm. Asthmatic patients can develop steroid myopathies, deconditioning and primary hyperventilation, all of which can influence exercise tolerance.[42] Identification of non-bronchospastic causes of dyspnea may serve to limit further steroids and step-ups in therapy.[43] Similar to other cardio-pulmonary conditions, CPET can be used to assess objective responses to therapy, such as an increase in $VO2_{peak}$ and reduction in dynamic hyperinflation with exercise.[44]

### Cystic fibrosis (CF)

Cardiopulmonary exercise testing can provide valuable prognostic information in CF. One longitudinal study of CF patients over an 8-year period found that $VO2_{peak}$ correlated well with overall survival., When stratified into tertiles based on pulmonary function, the 8-year survival was 83%, 51%, and 28% from highest to lowest functional group, respectively.[45]

### Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD often possess multiple other comorbid conditions that can affect exercise tolerance (e.g. coronary disease, heart failure, pulmonary hypertension, anemia, depression) and it can be difficult to ascertain which etiology one should focus additional therapy.[46] CPET may be able to discriminate the factor most responsible for exercise intolerance and enable the clinician to better direct therapy and guidance to their patient.[47] For example, in COPD patients with similar FEV1, CPET was shown to have the ability to detect COPD-CHF overlap, suggested by an elevated VE/VCO2 slope and nadir, as well as a decreased end-tidal CO2.[48]

CPET may also provide a non-invasive early measure of World Health Organization group 3 pulmonary hypertension (PH), a type of pulmonary hypertension due to primary lung pathology. In a retrospective analysis of COPD patients with available right heart catheterization and CPET data, a more significantly elevated VE/VCO2 slope and VE/VCO2 nadir suggested co-morbid PH in those with COPD compared to those with COPD alone, and exertional hypoxemia was more common in those with PH.[49] In another study of outpatient COPD patients without a diagnosis of CHF, exertional hypoxemia and elevated VE/VCO2 were significantly associated with a later finding of PH.[50]

However, in practice, there can be a large overlap in CPET findings between those with COPD alone and COPD associated with comorbidities, and as such it is recommended that CPET utilization should be determined on a case-by-case basis for COPD patients with dyspnea.[51]

### Pulmonary Hypertension

While hemodynamic studies generally define the etiology of PH, certain patterns on CPET may prove helpful when uncertainty exists. Pulmonary hypertension due to left heart disease (group 2 PH) is common but it can occasionally be difficult to discriminate from pulmonary arterial hypertension (PAH; group 1 PH). On CPET, it has been demonstrated that patients with PAH have higher VE/VCO2 slope and lower end-tidal CO2 than those with PH due to left ventricular (LV) dysfunction.[52] Additionally, patients with PAH are more likely to develop exertional hypoxemia during CPET than those with LV failure and those with LV failure may also exhibit a unique pattern of oscillatory ventilation during exercise that will not be present in PAH patients.[53]

Prognosis in patients with PAH and chronic thromboembolic PH (CTEPH) is associated with CPET parameters. In a study of 86 patients with group 1 PH, peak BP below 120mmHg at maximal exercise and $VO2_{peak}$ < 10.4cc/kg/min were associated with 1-year mortality. Survival was highest in those with neither parameter (97%), worse in those with both (23%), and intermediate if only one of the two applied (79%).[54] In a study of patients with PAH or CTEPH, low $VO2_{peak}$ (< 11.2cc/kg/min) predicted significantly lower 1-, 3- and 4-year survival.[55] In another study conducted with PAH and CTEPH patients, a significantly elevated VE/VCO2 slope (>60) and VE/VCO2 nadir >55 were associated with a high risk of death at 2 years.[56]

Few therapeutic trials have used CPET variables as outcome measures, instead preferring to use the submaximal 6MWT for its ease of use. However, several small studies have shown that various PAH treatments improve $VO2_{peak}$.[57,58] Importantly, improvements following treatment in multiple CPET parameters have been shown to correlate with improvements in RV function and survival – including increases in $VO2_{peak}$, peak heart rate, and oxygen pulse (a surrogate for stroke volume).[59]

### Rehabilitation

Exercise training is an integral part of pulmonary and cardiac rehabilitation programs. When available, CPET can play a role in ensuring safety prior to beginning an exercise program and can determine an appropriate training intensity leading to a more personalized exercise prescription.[60] Optimal improvement in cardiopulmonary function during a rehabilitation program occurs when consistently targeting a VO2 of 40–80% predicted VO2.[61] In healthy adults, $VO2_{reserve}$ correlates well with heart rate reserve (i.e. amount of VO2 or HR remaining from maximal, respectively) and an objective determination of $VO2_{reserve}$ would not be necessary to guide a rehabilitation prescription.[62] However, in those with congestive heart failure, objective determination of $VO2_{peak}$ and $VO2_{reserve}$ need to be determined, as it has been shown that heart rate reserve and $VO2_{reserve}$ do not correlate well in this population. Objective determination of $VO2_{reserve}$ and the HR at which this occurs enables those undergoing cardiac rehabilitation to exercise at an intensity that will more reliably lead to improvement in cardiovascular fitness and achievement of rehabilitation goals.

In attempt to improve outcomes following an intervention, there is also an emerging role for "pre-habilitation" prior to major surgery. We have discussed elsewhere in this review the association between CPET performance and surgical outcomes. If a patient is able to objectively improve their cardiopulmonary fitness as evidenced by higher $VO2_{peak}$, improved anaerobic threshold, or improved ventilatory efficiency, they may be able to improve their candidacy for surgery and reduce the likelihood of postoperative complications and mortality.[63]

## CONCLUSIONS

The comprehensive physiologic information provided by cardiopulmonary exercise testing enables a clinician to gain unique insights into the factors limiting a given patient's maximal exercise and fitness. It is invaluable and most commonly utilized in the assessment of dyspnea, but also holds prognostic information in the longitudinal assessment of cardiac and pulmonary pathologies, as well as guidance regarding appropriateness for a given surgery and risks of postoperative complications. Despite the wide breadth of physiologic information gleaned from this testing, it remains under-utilized and should be considered more often in the care of our patients.

### References


1. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis 1992;146:935–940.
2. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Postgrad Med J. 2007;83(985):675-682.
3. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest. 1994 Jan;105(1):168-74.
4. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003 Jan 15;167(2):211-77.
5. Smith DD. Pulmonary impairment/disability evaluation: controversies and criticisms. Clin Pulm Med 1995;2:334–343.
6. Mancini D, Eisen H, Kussmaul W, Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778–786
7. Stevenson LW, Steimle AE, Fonarow G, Kermani M, Kermani D, Hamilton MA, Moriguchi JD, Walden J, Tillisch JH, Drinkwater DC, et al. Improvement in exercise capacity of candidates awaiting heart transplantation. J Am Coll Cardiol. 1995 Jan;25(1): 163-70.
8. Luiz E. Ritt, Jonathan Myers, Ricardo Stein, Ross Arena, Marco Guazzi, Paul Chase, Daniel Bensimhon, Euan Ashley, Lawrence P. Cahalin, Daniel E. Forman, Additive prognostic value of a cardiopulmonary exercise test score in patients with heart failure and intermediate risk, International Journal of Cardiology, Volume 178, 2015, Pages 262-264
9. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009 Apr 8;301(14):1439-50
10. McKelvie RS. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. Heart Fail Rev. 2008;13(1):3-1117960476
11. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation. 1999;99(9):1173–1182
12. Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. Chest. 2009;135(5):1260–7.
13. Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. Ann Surg. 2013;257(6):999–1004.
14. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. Br J Surg. 2007;94(8):966–9.
15. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016 Feb;116(2):177-91.
16. Prentis JM, Manas DM, Trenell MI, Hudson M, Jones DJ, Snowden CP. Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation. Liver Transpl 2012; 18: 152–9 14.
17. Junejo MA, Mason JM, Sheen AJ, et al. Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection. Br J Surg 2012; 99: 1097–104 13.

18. Bernal W, Martin-Mateos R, Lipcsey M, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transpl 2014; 20: 54–62
19. Kaibori M, Ishizaki M, Matsui K, et al. Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy. BMC Gastroenterol 2013; 13: 119
20. Neviere R, Edme JL, Montaigne D, Boleslawski E, Pruvot FR, Dharancy S. Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation. Am J Transplant 2014; 14: 88–95 17.
21. Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. Liver Transpl 2004; 10: 418–24
22. Grant SW, Hickey GL, Wisely NA, et al. Cardiopulmonary exercise testing and survival after elective abdominal aortic aneurysm repair. Br J Anaesth 2015; 114: 430–6 21.
23. Nugent AM, Riley M, Megarry J, O'Reilly MJG, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the preoperative assessment of patients for repair of abdominal aortic aneurysm. Irish J Med Sci 1998; 167: 238–41 20.
24. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. Br J Surg 2007; 94: 966–9
25. Hartley RA, Pichel AC, Grant SW, et al. Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair. Br J Surg 2012; 99: 1539–46 22.
26. West MA, Parry MG, Lythgoe D, et al. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. Br J Surg 2014; 101: 1166–72)
27. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, McGarrity L, Jack S, Grocott MP; Perioperative Exercise Testing and Training Society. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg. 2016 May;103(6):744-752
28. Lai CW, Minto G, Challand CP, et al. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. Br J Anaesth 2013; 111: 607–11 25.
29. Chandrabalan VV, McMillan DC, Carter R, et al. Pre-operative cardiopulmonary exercise testing predicts adverse postoperative events and non-progression to adjuvant therapy after major pancreatic surgery. HPB (Oxford) 2013; 15: 899–907
30. Ausania F, Vallance AE, Manas DM, et al. Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome. Ann R Coll Surg Eng 2012; 94: 563–8

References 31–63

## Authors

Evan J. Smith, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Rhode Island Hospital and The Miriam Hospital; Providence VA Medical Center; Alpert Medical School of Brown University.

Eric J. Gartman, MD, Director of Pulmonary Function Testing Laboratory, Director of Cardiopulmonary Exercise Testing Laboratory, Providence VA Medical Center; Associate Professor of Medicine, Alpert Medical School of Brown University.

## Disclosure

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

## Correspondence

Eric_gartman@brown.edu

# Updates on the Management of Cystic Fibrosis: Development of Modulators and Advancement of Antibiotic Therapies

CHELSEA BOYD, MD; ROGER D. AUTH, MD; MICHAEL BLUNDIN, MD; DEBASREE BANERJEE, MD, MS

**KEYWORDS:** cystic fibrosis, CFTR, modulator therapy, suppressive antibiotics

## INTRODUCTION

Cystic fibrosis (CF) is a rare autosomal recessive, multi-organ disease that affects over seventy thousand people worldwide. While CF is the most common heritable disease in Caucasians, improvements in newborn screening and wider availability of genetic testing have shed light on the increasing incidence in non-Caucasian individuals.[1] In decades past, CF was a disease of childhood that was often fatal before adulthood. However, utilization of dedicated multidisciplinary care centers and advances in therapeutics have led to dramatic improvements in lifespan and quality of life. The median life expectancy for persons with cystic fibrosis (PwCF) is now approaching fifty years in many countries.[1]

CF was first characterized in 1938 after the discovery of pancreatic fibrosis in individuals with steatorrhea and nutritional deficiencies previously attributed to celiac disease.[2] Several decades later the discovery of increased sweat salinity in this population led to the development of the preferred diagnostic study, the sweat chloride test.[3,4] While CF was believed to be caused by a recessive genetic defect as early as the 1940s, the cystic fibrosis transmembrane regulator (CFTR) gene was not discovered until 1989.[5,6] The genetic hallmark of CF is absent or impaired function of the CFTR protein and over 2,000 pathogenic variants of the CFTR gene have been described.[7] The most common pathogenic mutation is the deletion of phenylalanine in position 508 (F508del), which results in misfolding of the CFTR protein.[8]

CFTR is present on epithelial membranes in the lungs, gastrointestinal tract, and exocrine pancreas, and is responsible for the chloride transport vital to normal mucus production, function, and clearance. CFTR also has an important role in bicarbonate transport and regulation of the epithelial sodium channel (ENaC), two major determinants of mucosal pH and fluid movement across the cellular membrane. In PwCF, decreased or absent CFTR leads to thick mucus, impaired ciliary function, and altered mucosal pH, ultimately resulting in decreased ability to clear respiratory secretions, recurrent respiratory infections and inflammation, nutrient malabsorption, and exocrine pancreas dysfunction. Research has also demonstrated direct and indirect effects of the dysfunctional CFTR protein on the innate and adaptive immune systems, further predisposing to recurrent lung infections, bronchiectasis, and reduced lung function. These injuries ultimately lead to respiratory failure, the major cause of mortality in PwCF.

The last decade has brought tremendous progress to the treatment of CF. Novel therapeutics, particularly medications designed to improve the production of functional CFTR, collectively termed modulators, have the capacity to improve lung function, decrease pulmonary infections, and improve quality of life. This article will review the development and validation of modulator therapies, as well as discuss updates on the state of antibiotic therapies, two mainstays of modern CF care.

## NOVEL THERAPEUTICS: MODULATORS

Production of functional CFTR protein is a multistep process that includes transcription of deoxyribonucleic acid (DNA) into messenger ribonucleic acid (mRNA), translation into a sequence of amino acids, processing to fold and transport the resultant protein to the cell membrane and maintaining proper gating and stability to allow sufficient ion conductance. Mutations in the CFTR gene that prevent any of these processes from occurring correctly can result in functional protein deficiency and serve as potential therapeutic targets. CFTR mutations are classified into six categories based on their primary downstream effect, though one mutation may cause defects in multiple classes.

Class I, II, and III mutations involve premature termination codons, protein processing mutations, and gating mutations, respectively, leading to minimal or no CFTR activity and severe clinical phenotypes. These mutations are classified as minimal function (MF) mutations and are often not amenable to targeted therapies. Class IV mutations affect ion conductance, class V mutations blunt CFTR protein production, and class VI mutations cause instability at the cell surface. Class IV, V, and VI mutations are classified as residual function (RF) mutations because some functional CFTR is formed, typically generating less severe clinical phenotypes.[9] These mutations have become some of the first therapeutic targets for modulator therapies (**Figures 1 and 2**).

**Figure 1.** CFTR Mutation Classification

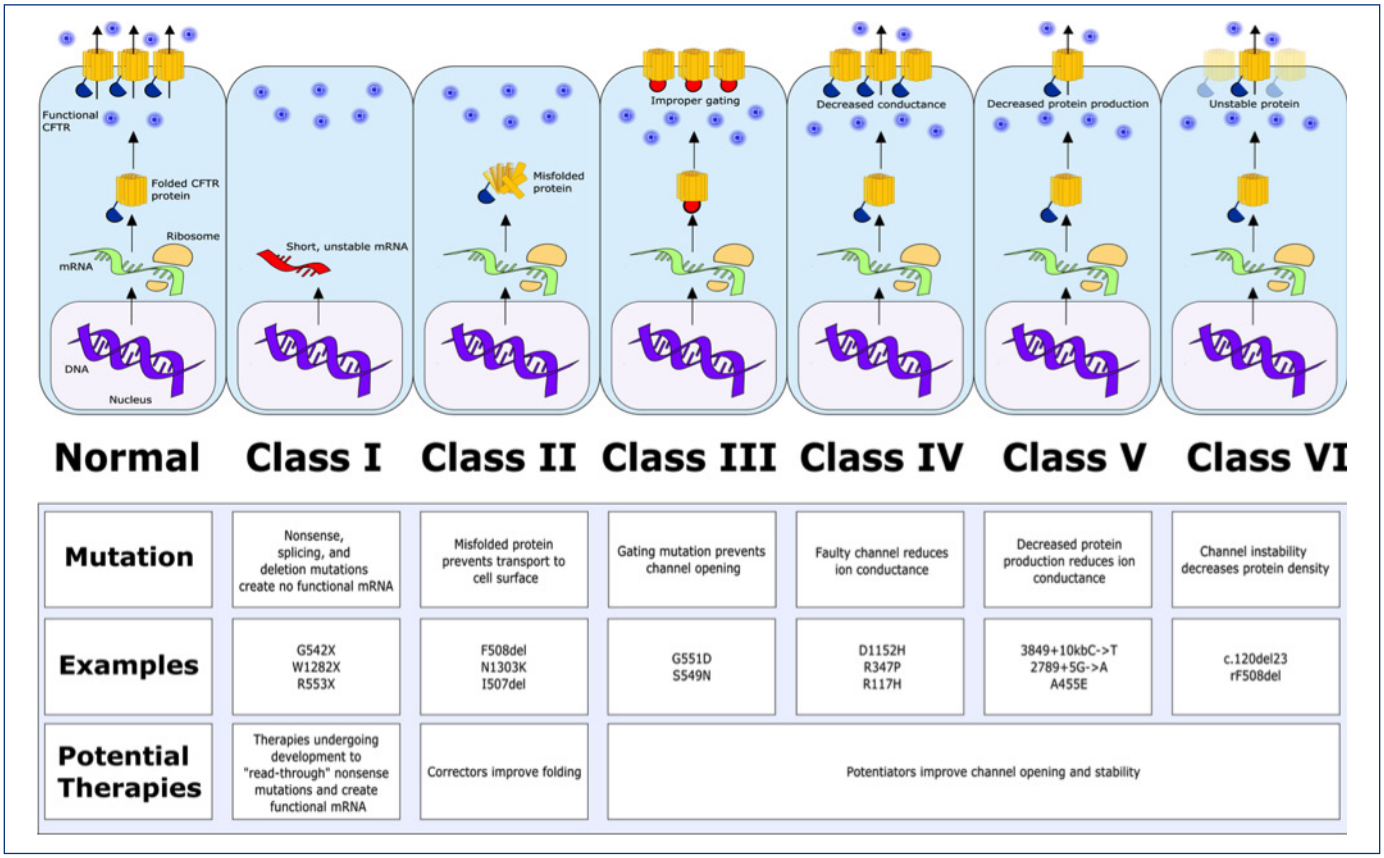
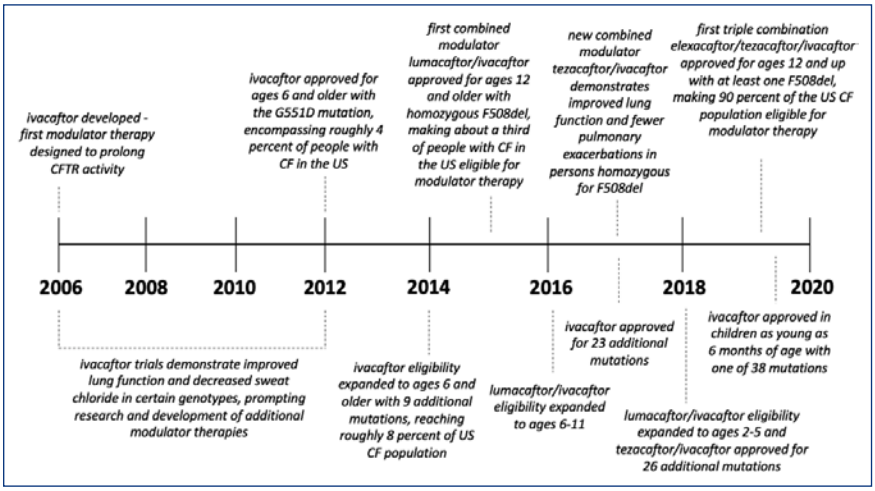



**Figure 2.** Timeline of Modulator Therapy Development and Approval




## Ivacaftor

In 2006, ivacaftor (Kalydeco®) was developed and became the first modulator to enter clinical trials. Ivacaftor acts on CFTR gating, prolonging the duration of CFTR opening. This type of therapy is known as a "potentiator," because it prolongs the activity of CFTR already present at the cell surface. In 2007, a pilot clinical trial demonstrated significant improvement in clinical outcomes with ivacaftor including an 8.7 percent increase in percent predicted forced expiratory volume in one second (ppFEV1) and median decrease in sweat chloride by –59.5 mmol/L.[10] Ivacaftor became available in the United States (US) in 2012 for patients six years and older with one specific CF mutation (G551D). Despite the drug's limited eligibility, this landmark discovery demonstrated clinically meaningful improvements in lung function and laid the groundwork for future study. Additionally, a recent observational study that followed US patients starting ivacaftor within the first years of commercial availability provided evidence that the benefits of ivacaftor extend well beyond improved lung function. This study demonstrated that in the subsequent three years, patients taking ivacaftor experienced significantly lower risk of death, transplantation, hospitalization, pulmonary exacerbations, CF-related diabetes, bone or joint complications, and cultures involving methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and Aspergillus species.[11]

Throughout the decade following its initial approval, the FDA progressively expanded approval for ivacaftor to ultimately include patients four months of age and older with 38 RF mutations.[9] Still, by 2014 only approximately eight percent of the US CF population qualified for ivacaftor based on their mutations.

### Lumacaftor

The next modulator to be developed was lumacaftor, the first member of a class of "correctors." Correctors are named for their ability to restore the shape of poorly processed CFTR protein, thereby improving successful transit to and activity in the cell membrane. Although in vitro studies suggested that lumacaftor increases the density of functional CFTR at the cell surface, phase II clinical trials in patients with homozygous F508del mutations were only able to demonstrate a dose-dependent decrease in sweat chloride levels. There was no improvement in clinically relevant endpoints such as lung function or patient-reported outcomes.[12] However, when combined with the potentiator ivacaftor, the combination lumacaftor/ivacaftor (known as Orkambi®) was shown in phase II and III clinical trials to improve ppFEV1 by 2.6–4.0 percentage points, decrease pulmonary exacerbations by 30–39 percent, and decrease events leading to hospitalization and use of intravenous antibiotics when compared with placebo.[13,14] As a result, in 2015 the FDA approved lumacaftor/ivacaftor for patients ages 12 and older who are homozygous for the F508del mutation, expanding availability of modulator therapy to approximately one third of US PwCF. Subsequently, studies demonstrated reduced pulmonary exacerbations to approximately 0.6 exacerbations per patient per year with lumacaftor/ivacaftor when compared with placebo.[15] Another study demonstrated sustained benefit in slowing ppFEV1 decline over an extended study period of 96 weeks, and two additional clinical trials redemonstrated efficacy and safety in younger populations.[16-18] Together, trials supporting lumacaftor/ivacaftor led to FDA approval for patients aged two and older by 2018.

### Tezacaftor

In 2017, another corrector called tezacaftor was developed, with a similar structure to lumacaftor but improved pharmacokinetics and fewer respiratory side effects.[9] It was tested alone in phase II clinical trials and in combination with ivacaftor in phase II and III trials, both in patients homozygous for F508del and in patients with one F508del mutation and another RF mutation. Phase II clinical trials demonstrated decreased sweat chloride levels in higher-dose tezacaftor and in most tezacaftor/ivacaftor groups compared with placebo, but increased ppFEV1 only in tezacaftor/ivacaftor combination groups.[19] Combination tezacaftor/ivacaftor (Symdeko®) was found to increase ppFEV1 in patients homozygous and heterozygous for F508del with an additional RF mutation.[19,20] Phase III clinical trials demonstrated four percent absolute increase in ppFEV1 and 35 percent decrease in pulmonary exacerbations with tezacaftor/ivacaftor compared to placebo.[21] In 2018, the FDA approved tezacaftor/ivacaftor for patients 12 years and older homozygous for F508del or heterozygous F508del with a second RF mutation. This again markedly increased the pool of PwCF eligible for modulator therapy. Following publication of a phase III clinical trial that demonstrated a similar safety profile with tezacaftor/ivacaftor in patients ages six through 11, FDA approval was extended to this age group in 2019.[22]

### Elexacaftor

Nearly a decade after the introduction of ivacaftor, new modulators and combinations were undergoing development and preclinical trials. Although major advancements had been made, improvements in lung function with available modulator treatments remained limited and there were minimal options for patients with certain mutations, particularly MF mutations.[9] However, 2019 proved to be another landmark year for the CF community when a triple therapy containing two correctors, elexacaftor and tezacaftor, and potentiator ivacaftor was released for patients 12 years and older with at least one F508del mutation. This extended availability of modulator therapy to nearly 90 percent of PwCF. Further, phase III clinical trials demonstrated marked improvement with 41.8mmol/L decrease in sweat chloride, 14.3 percent increase in ppFEV1 over 24 weeks, 63.0 percent decrease in pulmonary exacerbations, and a 20.2 point increase in the Cystic-Fibrosis Questionnaire-Revised score indicating improved quality of life with elexacaftor/tezacaftor/ivacaftor (Trikafta®) compared with placebo.[23] Studies are underway evaluating the safety and efficacy of elexacaftor/tezacaftor/ivacaftor long-term and in younger populations. Additionally, an ongoing observational study entitled PROMISE aims to assess for broader systemic improvements with triple therapy.

There are several treatments designed to restore CFTR function that are currently undergoing phase II clinical trials including correctors, potentiators, and a compound designed to target premature termination mutations. Others are currently in phase I clinical trials, including a potentiator and an inhaled therapy designed to deliver CFTR mRNA to the lungs.

## UPDATES ON ANTIBIOTIC THERAPIES

PwCF are chronically colonized with bacteria that alter the lung microbiome.[24] Common pathogens include *Staph aureus* and *Hemophilus influenzae* in early disease with progression to resistant organisms that can form biofilms such as *Pseudomonas aeruginosa* and *Burkholderia cepacia.* Colonization with *Pseudomonas aeruginosa* and *Burkholderia cepacia* is correlated with worsening lung function and as such, suppressive therapy with inhaled antibiotics is a cornerstone of CF management.[25,26] There is also increased susceptibility in PwCF for chronic infections with opportunistic

pathogens such as mycobacterium avium complex (MAC). There are ongoing efforts to develop alternative anti-infective therapies for chronic use, especially for the resistant and diverse pathogens now recognized to colonize the CF lung. Additionally, acute CF exacerbations are repeatedly treated with short-term oral or intravenous antibiotics. There are ongoing investigations to optimize acute antibiotic treatment to minimize exposure and toxicities.

### Chronic suppression

Inhaled antibiotics are the primary treatment for chronic Pseudomonas infection. Inhaled tobramycin and inhaled aztreonam became available in 1997 and 2010 respectively, after studies demonstrated improved lung function, decreased Pseudomonas burden in sputum, improved respiratory symptom scores, and decreased risk of pulmonary exacerbations and hospitalizations with chronic therapy.[27-31] Inhaled antibiotics are typically cycled every 28 days to reduce selective pressure for antibiotic resistance.[29] It is worthwhile to note that oral azithromycin is also approved for chronic pseudomonas suppression after studies demonstrated improved lung function and decreased risk of exacerbations. However, recent studies suggest oral azithromycin may decrease the efficacy of tobramycin and therefore should be used with caution.[32-34]

In 2018, inhaled liposomal amikacin became the first therapy approved under the FDA Limited Population Pathway for Antibacterial and Antifungal Drugs designed to accelerate development of medications for serious infections affecting small populations. It was approved for treatment-refractory mycobacterium avium complex in adults, although notably the primary study leading to its approval excluded PwCF.[35] Recent studies have also suggested inhaled amikacin liposomal suspension to be non-inferior to inhaled tobramycin for treatment of chronic Pseudomonas, although results of a phase III clinical trial evaluating this have not yet been published and it is not FDA-approved for this indication.[36]

Multiple studies have evaluated the efficacy and safety of inhaled levofloxacin, including phase II clinical trials demonstrating decreased sputum Pseudomonas density, dose-dependent improvements in lung function, and reduced need for other inhaled or systemic antipseudomonal antibiotics compared with placebo.[37] However, phase III clinical trials failed to demonstrate a difference in pulmonary exacerbations between inhaled levofloxacin and placebo.[38] Inhaled levofloxacin is not FDA approved in the US, although it is available in the European Union and Canada.

Studies are ongoing to address the diagnosis and treatment of other pathogens that colonize the CF lung. For example, an ongoing prospective study aims to evaluate a standardized approach for diagnosis and management of nontuberculous mycobacteria. Additionally, inhaled vancomycin recently underwent phase III clinical trials for chronic MRSA, however it did not improve lung function or reduce pulmonary exacerbations and is not currently undergoing further development.

There are also several innovative treatments designed to combat chronic infections undergoing phase II trials including intravenous gallium, bacteriophage therapy, and intravenous nitrous oxide. Gallium is thought to inhibit iron-dependent processes and may kill antibiotic-resistant Pseudomonas.[39] Bacteriophage therapy utilizes viruses targeted to kill specific bacterial sources, and has been shown to eliminate more than 80 percent of Pseudomonas strains in PwCF.[40] Nitrous oxide may help eliminate biofilms and nontuberculous mycobacteria.[41] Many other anti-infective therapies are in phase I trials or pre-clinical development.

### Acute exacerbations

Treatment with oral or intravenous antibiotics during pulmonary exacerbations has long been a pillar of CF management. However, the optimal antibiotic selection and duration for acute exacerbations remains unknown.

Due to the recurrent need for antibiotics and increasing prevalence of antibiotic resistance, standard practice for selecting antibiotics during acute CF exacerbations relies on in vitro antimicrobial susceptibility testing (AST). However, a 2019 systematic review demonstrated that 11 out of 13 studies evaluating AST for acute exacerbations demonstrated no relationship between AST and clinical response to treatment, calling the utility of this practice into question.[42] As opposed to isolated monomicrobic infections in otherwise healthy patients, AST may not accurately capture the heterogeneous microbiology of the CF lung or predict clinical response to treatment and thus, may not be effective in guiding treatment decisions.

Additionally, the recurrent need for nephrotoxic and ototoxic antibiotics raises the question of minimum effective dosing regimens. A 2017 Cochrane review found once daily dosing of aminoglycosides equally as effective as three times daily dosing with no difference in lung function or time to next exacerbation requiring intravenous antibiotics. There was a lower risk of nephrotoxicity in children with once daily dosing.[43] Additionally, an ongoing randomized controlled trial entitled STOP2 aims to evaluate the efficacy and safety of 10-day, 14-day, and 21-day intravenous antibiotic regimens during acute exacerbations by comparing improvements in lung function and respiratory symptom scores. Altogether, it may be possible in the near future to decrease the frequency and duration of intravenous antibiotics administered during acute exacerbations, an important step in minimizing total lifetime antibiotic exposure and toxicity.

## CONCLUSIONS

The development of modulator therapies that target the underlying pathophysiology of CF has revolutionized care for PwCF. Still, ongoing research and development promises

upcoming advances in both combination and novel modulator therapies as well as innovative agents for those with mutations not currently served by existing therapies. Further, optimization of both acute and chronic antibiotic treatments will provide more efficient regimens that maximize efficacy and minimize toxicity.

While substantial progress has been made, there remains ample opportunity to improve care for PwCF. Anticipating increased longevity, considerations for ongoing CF care must be prioritized to optimize quality of life. Efforts include, but are not to limited to, improving screening and management of CF-related chronic illnesses as well improving opportunities for family planning. Day-to-day quality of life can be improved by working to minimize the burden of CF care. To this end, an ongoing study entitled SIMPLIFY will examine the outcomes of withdrawing adjunctive therapies for those on modulator therapy.

With recent advancements and continued efforts toward safer, more efficacious, and streamlined treatments, individuals born with CF in 2021 will enjoy quality life years well beyond that of their predecessors.

## References


1. Bell, S.C., et al. *The future of cystic fibrosis care: a global perspective.* The Lancet Respiratory Medicine, 2020. **8**(1): p. 65-124.
2. Andersen, D.H. *Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study.* American journal of Diseases of Children, 1938. **56**(2): p. 344-399.
3. di Sant'Agnese, P.A., et al. *Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas: clinical significance and relationship to the disease.* Pediatrics, 1953. **12**(5): p. 549-563.
4. Gibson, L.E. and R.E. Cooke. *A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis.* Pediatrics, 1959. **23**(3): p. 545-549.
5. Tsui, L.-C. and Dorfman R. *The cystic fibrosis gene: a molecular genetic perspective.* Cold Spring Harbor perspectives in medicine, 2013. **3**(2): p. a009472.
6. Rommens, J.M., et al. *Identification of the cystic fibrosis gene: chromosome walking and jumping.* Science, 1989. **245**(4922): p. 1059-1065.
7. Boyle, M.P. and K. De Boeck. *A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect.* The Lancet Respiratory Medicine, 2013. **1**(2): p. 158-163.
8. Balch, W.E., D.M. Roth, and D.M. Hutt. *Emergent properties of proteostasis in managing cystic fibrosis.* Cold Spring Harbor perspectives in biology, 2011. **3**(2): p. a004499.
9. Bardin, E., et al. *Modulators of CFTR. Updates on clinical development and future directions.* European journal of medicinal chemistry, 2021: p. 113195.
10. Accurso, F.J., et al. *Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation.* New England Journal of Medicine, 2010. **363**(21): p. 1991-2003.
11. Bessonova, L., et al. *Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor.* Thorax, 2018. **73**(8): p. 731-740.
12. Clancy, J., et al. *Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation.* Thorax, 2012. **67**(1): p. 12-18.
13. Boyle, M.P., et al. *A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial.* The lancet Respiratory medicine, 2014. **2**(7): p. 527-538.
14. Wainwright, C.E., et al. *Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR.* New England Journal of Medicine, 2015. **373**(3): p. 220-231.
15. McColley, S.A., et al. *Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1.* Journal of Cystic Fibrosis, 2019. **18**(1): p. 94-101.
16. Konstan, M.W., et al. *Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.* The Lancet Respiratory Medicine, 2017. **5**(2): p. 107-118.
17. Milla, C.E., et al. *Lumacaftor/ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR.* American journal of respiratory and critical care medicine, 2017. **195**(7): p. 912-920.
18. Ratjen, F., et al. *Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial.* The Lancet Respiratory medicine, 2017. **5**(7): p. 557-567.
19. Donaldson, S.H., et al. *Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR.* American journal of respiratory and critical care medicine, 2018. **197**(2): p. 214-224.
20. Rowe, S.M., et al. *Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis.* New England Journal of Medicine, 2017. **377**(21): p. 2024-2035.
21. Taylor-Cousar, J.L., et al. *Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del.* New england journal of medicine, 2017. **377**(21): p. 2013-2023.
22. Walker, S., et al. *A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis.* Journal of Cystic Fibrosis, 2019. **18**(5): p. 708-713.
23. Middleton, P.G., et al. *Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele.* New England Journal of Medicine, 2019. **381**(19): p. 1809-1819.
24. Surette, M.G. *The cystic fibrosis lung microbiome.* Annals of the American Thoracic Society, 2014. **11**(Supplement 1): p. S61-S65.
25. Folescu, T.W., et al. *Burkholderia cepacia complex: clinical course in cystic fibrosis patients.* BMC pulmonary medicine, 2015. **15**(1): p. 1-6.
26. Kosorok, M.R., et al. *Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition.* Pediatric pulmonology, 2001. **32**(4): p. 277-287.
27. Assael, B.M., et al. *Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial.* Journal of Cystic fibrosis, 2013. **12**(2): p. 130-140.
28. McCoy, K.S., et al. *Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis.* American journal of respiratory and critical care medicine, 2008. **178**(9): p. 921-928.
29. Nichols, D.P., et al. *Developing inhaled antibiotics in cystic fibrosis: current challenges and opportunities.* Annals of the American Thoracic Society, 2019. **16**(5): p. 534-539.
30. Ramsey, B.W., et al. *Intermittent administration of inhaled tobramycin in patients with cystic fibrosis.* New England Journal of Medicine, 1999. **340**(1): p. 23-30.
31. Retsch-Bogart, G.Z., et al. *Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis.* Chest, 2009. **135**(5): p. 1223-1232.
32. Nick, J.A., et al. *Azithromycin may antagonize inhaled tobramycin when targeting Pseudomonas aeruginosa in cystic fibrosis.* Annals of the American Thoracic Society, 2014. **11**(3): p. 342-350.
33. Saiman, L., et al. *Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial.* Jama, 2003. **290**(13): p. 1749-1756.

34. Nichols, D.P., et al. *Impact of azithromycin on the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis.* Journal of Cystic Fibrosis, 2017. **16**(3): p. 358-366.
35. Griffith, D.E., et al. *Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study.* American journal of respiratory and critical care medicine, 2018. **198**(12): p. 1559-1569.
36. Bilton, D., et al. *Amikacin liposome inhalation suspension for chronic Pseudomonas aeruginosa infection in cystic fibrosis.* Journal of Cystic Fibrosis, 2020. **19**(2): p. 284-291.
37. Geller, D.E., et al. *Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa.* American journal of respiratory and critical care medicine, 2011. **183**(11): p. 1510-1516.
38. Flume, P.A., et al. *A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients.* Journal of Cystic Fibrosis, 2016. **15**(4): p. 495-502.
39. Goss, C.H., et al. *Gallium disrupts bacterial iron metabolism and has therapeutic effects in mice and humans with lung infections.* Science translational medicine, 2018. **10**(460).
40. Holger, D., et al. *Clinical Pharmacology of Bacteriophage Therapy: A Focus on Multidrug-Resistant Pseudomonas aeruginosa Infections.* Antibiotics, 2021. **10**(5): p. 556.
41. Laudone, T.W., et al. *Novel therapies for treatment of resistant and refractory nontuberculous mycobacterial infections in patients with cystic fibrosis.* Pediatric Pulmonology, 2021. **56**: p. S55-S68.
42. Somayaji, R., et al. *Antimicrobial susceptibility testing (AST) and associated clinical outcomes in individuals with cystic fibrosis: a systematic review.* Journal of Cystic Fibrosis, 2019. **18**(2): p. 236-243.
43. Bhatt, J., N. Jahnke, and A.R. Smyth. *Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis.* Cochrane Database of Systematic Reviews, 2019(9).



## Authors

Chelsea Boyd, MD, Department of Internal Medicine-Pediatrics, Alpert Medical School of Brown University, Providence, RI.

Roger D. Auth, MD, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Michael Blundin, MD, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Debasree Banerjee, MD, MS, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

## Correspondence

Debasree Banerjee, MD, MS
Division of Pulmonary, Critical Care and Sleep Medicine
Rhode Island Hospital
593 Eddy Street, POB Suite 224
Providence, RI 02903
401-444-4191
Fax 401-444-0094
debasree_banerjee@brown.edu

# Diagnosis and Management of Idiopathic Pulmonary Fibrosis

JULIA K. MUNCHEL, MD; BARRY S. SHEA, MD


## ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. Its signs and symptoms are relatively non-specific, and patients often present with chronic cough, progressive dyspnea, resting or exertional hypoxemia, and inspiratory crackles on lung auscultation. Definitive diagnosis requires the exclusion of known causes of pulmonary fibrosis and identification of the usual interstitial pneumonia (UIP) pattern of disease either on high-resolution computed tomography (HRCT) scan of the chest or on surgical lung biopsy. Multidisciplinary discussion involving pulmonologists, radiologists, and pathologists with expertise in the diagnosis of IPF and other forms of interstitial lung disease is recommended and often required. Management focuses on anti-fibrotic therapy and early referral to lung transplant centers for those who are candidates. This review will discuss the current recommendations for the diagnosis, prognostication, and management of patients with IPF.


**KEYWORDS:** idiopathic pulmonary fibrosis (IPF), cryptogenic fibrosing alveolitis, usual interstitial pneumonia (UIP), interstitial lung disease (ILD), idiopathic interstitial pneumonia (IIP), diffuse parenchymal lung diseases (DPLD)

## INTRODUCTION

### History, Epidemiology, and Pathogenesis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial lung disease of an uncertain etiology and a poorly understood pathogenesis.[1] It is the most common of the idiopathic interstitial pneumonias (IIPs) and accounts for 20% of all interstitial lung disease (ILD).[2,3] IPF was first described in the modern literature in 1935 as "fulminating diffuse interstitial fibrosis of the lungs" by Louis Hamman and Arnold Rich and was subsequently coined "Hamman-Rich Syndrome."[4] By the 1960s the term IPF was increasingly being used, but it was not until 1998 when Katzenstein and Myers proposed a classification scheme of IIPs that the diagnosis of IPF was exclusively reserved for those individuals with the usual interstitial pneumonia (UIP) pattern on lung biopsy.[5] This classification scheme was formally adopted by international societies in 1999, resulting in publication of the first international consensus statement on the diagnosis and management of IPF.[6]

Precise estimates of the incidence and prevalence of IPF are difficult to determine, but appear to vary considerably between countries and regions for reasons that remain unclear.[1,7] In the U.S., recent estimates suggest an incidence of 7–17 per 100,000 person years and incidence and mortality rates appear to be increasing over time worldwide.[7,8]

IPF is more common in men, current or former cigarette smokers, and in occupations with a high level of inorganic dust exposure.[1,8] Aging, however, is by far the greatest risk factor.[8] Although some individuals can be diagnosed as young as 50 years old, the median age at the time of diagnosis is 66 years old and incidence, prevalence, and mortality all increase with increasing age.[7-9] Genetic factors also appear to play an important role, as both common and rare genetic variants have been associated with the development of IPF, and up to 20% of cases may in fact be familial.[10] Indeed, IPF is increasingly thought of as the result of a complex interplay between aging, host susceptibility (i.e. genetics and epigenetics), and environmental factors.[11] The specific relationships between these factors have not been fully elucidated, but the end result appears to be the development of an aberrant, or over-exuberant, wound healing response to repetitive microscopic lung injuries.[12,13] Many possible causes of microscopic injury have been theorized and include viral infections, gastroesophageal reflux, inhaled particulates, or other environmental exposures.[12,13]

## DIAGNOSIS

The presentation of patients with IPF is relatively non-specific with insidious onset of dyspnea on exertion, non-productive cough, and inspiratory crackles on lung exam.[2,12,14] Systemic symptoms that would indicate a multisystem disease are not common and if present should raise suspicion for an alternative diagnosis.[15] Clubbing may be present but has only been reported in 25–50% of patients.[2,12] On pulmonary function testing patients are most commonly found to have restriction with a reduced diffusion capacity, but these changes can at times be mild, particularly in early disease.[1] In contrast, virtually all patients have abnormal chest

imaging on presentation.[15] Conventional chest x-ray (CXR) shows reticulonodular opacities that are typically bilateral, symmetric, and lower lung zone predominant. Occasionally the disease can be asymmetric or unilateral or can lack the typical apico-basilar gradient.[15]

Definitive diagnosis first requires the exclusion of any known causes of ILD such as connective tissue disease, drug toxicity, or environmental exposures.[14] Careful history taking is critical with special attention paid to exposures, co-morbidities, medication use, environmental exposures, and family history in order to exclude other etiologies as mentioned above.[1,15] Laboratory findings are generally non-specific, but can be helpful in ruling out alternative diagnoses such as connective tissue diseases.[15] High resolution computed tomography (HRCT) of the chest plays a central role in the diagnosis of IPF. The characteristic pattern on HRCT consists of bilateral, lower lung zone predominant reticular opacities and honeycombing.[1] Honeycombing refers to aggregates of subpleural, thick-walled cysts typically <1 cm in diameter.[1,14] Architectural distortion with traction bronchiectasis and bronchiolectasis is also frequently seen.[14] When this typical pattern is seen on HRCT it is 90–100% specific for histologic UIP and in these cases a lung biopsy is generally not required to confirm the diagnosis.[14] However, in cases where the HRCT lacks honeycombing and/or contains features that are not characteristic of UIP, a histologic diagnosis may be required. A surgical lung biopsy – either via thoracotomy or, more commonly, video-assisted thoracoscopic surgery (VATS) – has historically been required for a histologic diagnosis. Bronchoscopic transbronchial forceps biopsies are currently not recommended because the small size of tissue samples obtained does not allow for adequate assessment of the heterogenous changes seen in UIP.[2,15] The emerging technique of bronchoscopic cryobiopsy may provide a diagnosis of UIP in some cases, but the exact role of this technique in the diagnostic algorithm for IPF remains unclear.[16] If a biopsy is obtained, the typical UIP pattern consists of patchy fibrosis in a predominantly subpleural/paraseptal distribution along with areas of microscopic honeycombing and fibroblastic foci.[14] Fibroblastic foci are aggregates of proliferating fibroblasts and active myofibroblasts which are felt to be indicative of ongoing lung injury and repair that represent the "leading edge" of fibrosis development.[14] Just as with HRCT, lung biopsy specimens may not show all of the typical features of UIP and/or may show features suggestive of an alternative diagnosis. Accordingly, multidisciplinary discussion is recommended between pulmonologists, radiologists, and pathologists to determine whether or not a diagnosis of IPF can be confirmed based on the combination of clinical features, HRCT, and lung biopsy findings if obtained.[1,14]

## PROGNOSIS

IPF is a progressive disease characterized by gradually worsening shortness of breath and, in most cases, the eventual development of respiratory failure.[1] The average survival is only 3–5 years following diagnosis.[13,17,18] At the same time, it is a clinically heterogenous disease process with considerable variability in the pace of disease progression between both different individuals with the disease and within any given individual over time.[19] Some patients suffer from rapidly progressive disease with a precipitous decline in lung function, while others may experience only slow, steady decline over many years.[20] Accordingly, predicting disease progression can be challenging and there is great interest in identifying characteristics that can predict an individual's disease course.[19] Although some imaging findings, such as presence of traction bronchiectasis, have been found to independently predict mortality, changes in pulmonary function tests over time have been found to be among the most robust predictors.[2] A decline as small as 5% in percent predicted FVC over the course of 6 months was found to be associated with more than a two-fold increase in risk of death over the subsequent 12 months.[19] Not surprisingly, older age and recent respiratory hospitalizations, including acute exacerbations of IPF, have also been found to portend poorer outcomes.[19]

Acute exacerbations of IPF (AE-IPF) can occur and often lead to hospitalization for respiratory failure with a precipitous decline in lung function. The proposed definition of AE-IPF requires: 1) a preexisting or concurrent diagnosis of IPF, 2) acute worsening of symptoms (typically <1 month), 3) imaging findings of bilateral ground-glass opacification and/or consolidation superimposed on a background pattern consistent with UIP, and 4) determination that the deterioration is not fully explained by congestive heart failure or volume overload.[21] On histology, although biopsy is not required for diagnosis, a pattern of diffuse alveolar damage or organizing pneumonia can be seen superimposed on a background of UIP.[1] The mortality of hospitalized cases of AE-IPF is approximately 50%.[2,22] Even patients who survive hospitalization for AE-IPF continue to have a poor prognosis, and approximately half of all IPF related mortality occurs after a nonelective respiratory hospitalization.[19] Currently there are no known risk factors for the development of acute exacerbations, other than lower FVC and DLCO at baseline, and these events can occur at any point in the disease course regardless of underlying disease severity.[2,21] Unfortunately, there are no effective treatments for AE-IPF other than supportive care.[21] High-dose steroids are currently recommended and are commonly prescribed for AE-IPF, but there have been no randomized controlled trials performed to support this practice.[1]

## TREATMENT

Initially, therapeutics for IPF were focused on modulating the inflammatory response on the supposition that fibrosis was the end stage manifestation of chronic inflammation in the lung. However, over the last decade this treatment paradigm has shifted due to several studies that demonstrated not only a lack of benefit with immunosuppression, but also the possibility for harm.[23,24] The most notable of these was the PANTHER study published in 2012, which was a randomized, placebo-controlled trial of combination therapy with prednisone, azathioprine, and N-acetylcysteine (NAC) for the treatment of IPF.[23] This study was halted early due to an increase in all-cause mortality, hospitalizations, and treatment-related serious adverse events.[23] It has been hypothesized that prior observational data supporting the use of immunosuppression for IPF may have been skewed by the inclusion of other forms of IIPs that respond more favorably to anti-inflammatory therapy and have more favorable prognoses.[15]

Along with the recognition that anti-inflammatory therapy was ineffective in IPF, there was also growing acceptance that IPF was a disease characterized by abnormal wound healing responses in the lung.[12] Therefore, more recent clinical trials have focused on drugs that target these wound healing responses rather than inflammation. In 2014 the U.S. Food and Drug Administration (FDA) approved two antifibrotic medications, nintedanib and pirfenidone, for the treatment of IPF based on large clinical trials showing that both agents slow the decline in lung function by about 50% per year.[25,26] Pirfenidone is a pyridine molecule with an unknown mechanism of action, but that is thought to have a multitude of anti-fibrotic, anti-inflammatory, and anti-oxidant effects.[15] It has been shown *in vitro* to block growth factor simulated collagen synthesis, extracellular matrix (ECM) secretion, and fibroblast proliferation.[13,15] Nintedanib is a small molecule inhibitor of several receptor tyrosine kinases, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) receptors, and it also appears to inhibit fibroblast activation and ECM synthesis.[13] Although neither of these drugs are curative for IPF, nor have they definitively been shown to prolong survival, they are the first therapies that have been shown to impact the course of this disease. Furthermore, there are a multitude of additional drugs currently being investigated in late phase clinical trials that provide further hope that more effective treatment options are on the horizon.[27]

Non-pharmacologic therapy for IPF patients consists of supplemental oxygen administration for those who suffer from clinically significant resting or exertional hypoxemia and pulmonary rehabilitation to help preserve and even improve exercise tolerance.[1] Lung transplantation is the only treatment option that offers IPF patients with advanced disease the opportunity for prolonged survival, as it has been shown to reduce the risk of death at 5 years.[1,28] Referral for lung transplant evaluation should be considered in all patients with IPF. Unfortunately, many IPF patients are ineligible for lung transplant due to advanced age and/or co-morbid conditions at the time of presentation.[15]

## CONCLUSION

IPF is a chronic lung disease characterized by the progressive accumulation of scar tissue (fibrosis) in the lungs, leading to impaired gas exchange, difficulty breathing, and eventually death. IPF symptoms are non-specific and generally consist of insidious onset of dyspnea on exertion and chronic coughing. The diagnosis requires the identification of a UIP pattern of disease on HRCT scan and/or surgical lung biopsy and the exclusion of known causes of pulmonary fibrosis. Anti-fibrotic medications, namely pirfenidone and nintedanib, have been shown to slow disease progression in IPF and are now the mainstays of treatment along with nonpharmacologic therapies such as supplemental oxygen and pulmonary rehabilitation. Lung transplantation is the only intervention that has been shown to reduce mortality in IPF, but unfortunately many patients are ineligible due to advanced age and co-morbidities.

### References


1. Raghu G, Collard HR, Egan JJ, et al. ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824. doi: 10.1164/rccm.2009-040GL.
2. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history. Respirology. 2016 Apr;21(3):427-37. doi: 10.1111/resp.12683.
3. Marshall DC, Salciccioli JD, Shea BS et al. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database from 2001-2013. Eur Respir J. 2018 Jan 18;51(1):1701603. doi: 10.1183/13993003.01603-2017.
4. Hamman L, Rich AR. Fulminating Diffuse Interstitial Fibrosis of the Lungs. Trans Am Clin Climatol Assoc. 1935;51:154-63.
5. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998 Apr;157(4 Pt 1):1301-15. doi: 10.1164/ajrccm.157.4.9707039.
6. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):646-64. doi: 10.1164/ajrccm.161.2.ats3-00.
7. Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J. 2015 Sep;46(3):795-806. doi: 10.1183/09031936.00185114.
8. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. Clin Epidemiol. 2013 Nov 25;5:483-92. doi: 10.2147/CLEP.S54815.
9. Marshall DC, Salciccioli JD, Shea BS, et al. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database

from 2001-2013. Eur Respir J. 2018 Jan 18;51(1):1701603. doi: 10.1183/13993003.01603-2017.

10. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. Eur Respir J. 2015 Jun;45(6):1717-27. doi: 10.1183/09031936.00163814.
11. Pardo A, Selman M. Lung Fibroblasts, Aging, and Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc. 2016 Dec;13 Suppl 5:S417-S421. doi: 10.1513/AnnalsATS.201605-341AW.
12. Selman M, King TE, Pardo A; American Thoracic Society; European Respiratory Society; American College of Chest Physicians. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med. 2001 Jan 16;134(2):136-51. doi: 10.7326/0003-4819-134-2-200101160-00015.
13. Ahluwalia N, Shea BS, Tager AM. New therapeutic targets in idiopathic pulmonary fibrosis. Aiming to rein in runaway wound-healing responses. Am J Respir Crit Care Med. 2014 Oct 15;190(8):867-78. doi: 10.1164/rccm.201403-0509PP.
14. Raghu G, Remy-Jardin M, Myers JL, et al; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.
15. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med. 2001 Aug 16;345(7):517-25. doi: 10.1056/NEJMra003200.
16. Troy LK, Grainge C, Corte TJ, et al; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med. 2020 Feb;8(2):171-181. doi: 10.1016/S2213-2600(19)30342-X.
17. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. Lancet Respir Med. 2014 Jul;2(7):566-72. doi: 10.1016/S2213-2600(14)70101-8. Epub 2014 May 27. Erratum in: Lancet Respir Med. 2014 Jul;2(7):e12. PMID: 24875841.
18. Kaunisto J, Salomaa ER, Hodgson U, et al. Demographics and survival of patients with idiopathic pulmonary fibrosis in the FinnishIPF registry. ERJ Open Res. 2019 Jul 8;5(3):00170-2018. doi: 10.1183/23120541.00170-2018.
19. du Bois RM, Weycker D, Albera C, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011 Aug 15;184(4):459-66. doi: 10.1164/rccm.201011-1790OC.
20. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011 Feb 15;183(4):431-40. doi: 10.1164/rccm.201006-0894CI.
21. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75. doi: 10.1164/rccm.201604-0801CI.
22. Collard HR, Moore BB, Flaherty KR, et al; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007 Oct 1;176(7):636-43. doi: 10.1164/rccm.200703-463PP.
23. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354.
24. Collard HR, Ryu JH, Douglas WW, et al. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest. 2004 Jun;125(6):2169-74. doi: 10.1378/chest.125.6.2169.
25. Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2071-82. doi: 10.1056/NEJMoa1402584.
26. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2083-92. doi: 10.1056/NEJMoa1402582.
27. Trachalaki A, Irfan M, Wells AU. Pharmacological management of Idiopathic Pulmonary Fibrosis: current and emerging options. Expert Opin Pharmacother. 2021 Feb;22(2):191-204. doi: 10.1080/14656566.2020.1822326.
28. Thabut G, Mal H, Castier Y, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. J Thorac Cardiovasc Surg. 2003 Aug;126(2):469-75. doi: 10.1016/s0022-5223(03)00600-7.

## Authors

Julia K. Munchel, MD, Division of Pulmonary, Critical Care and Sleep Medicine; Rhode Island Hospital and Alpert Medical School of Brown University; Providence, RI.

Barry S. Shea, MD, Division of Pulmonary, Critical Care and Sleep Medicine; Rhode Island Hospital and Alpert Medical School of Brown University; Providence, RI.

## Correspondence

Julia K. Munchel, MD
Division of Pulmonary and Critical Care Medicine
Alpert Medical School of Brown University
Rhode Island Hospital
593 Eddy Street, POB 224
Providence, RI 02903
julia_munchel@brown.edu

# Diagnosis of Pulmonary Hypertension

NAVNEET SINGH, MD; CHRISTOPHER J. MULLIN, MD, MHS

**ABSTRACT**

Pulmonary hypertension (PH) is a chronic disease of elevated pulmonary artery pressure that can result from pulmonary vascular diseases or complicate left heart and lung disease. Pulmonary arterial hypertension (PAH) is a rare pulmonary artery vasculopathy that leads to progressive right heart failure and death. Timely and accurate diagnosis of PH is paramount, given the increased morbidity and mortality, but can be challenging given the nonspecific nature of the presenting symptoms and the many potential causative or contributing conditions. The diagnosis of PH remains clinical and the initial workup uses history, physical exam, and echocardiography to evaluate likelihood of disease, followed by characterization of left heart and lung disease and the appropriate evaluation for chronic thromboembolic disease. A right heart catheterization is requisite for the diagnosis and thus early referral to a PH expert center is strongly recommended, particularly for patients with high-risk features and in high-risk populations.

**KEYWORDS:** pulmonary hypertension, pulmonary arterial hypertension, right ventricle, right heart catheterization

## INTRODUCTION

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) greater than 20 mmHg[1], although prior guidelines and consensus statements used a definition of mPAP ≥25 mmHg to define the disease.[2,3] This recent change in definition was based on the observations that 20 mmHg is the upper limit of normal in healthy subjects and an mPAP between 21 and 24 mmHg is associated with poorer outcomes in certain disease states.[1] Pulmonary hypertension can often complicate left heart and lung disease, and when it does is associated with increased mortality. Pulmonary arterial hypertension (PAH) is a rare disease characterized by medial hypertrophy, intimal and adventitial fibrosis, in situ thrombosis, and plexiform lesions of the distal muscular pulmonary arteries,[4] which result in a rise in pulmonary vascular resistance (PVR) and pulmonary artery pressures, leading to progressive right heart failure and death. PAH is defined by presence of precapillary PH (mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg and PVR ≥3 WU) in the absence of significant left heart, lung, or chronic thromboembolic disease.

A diagnosis of pulmonary hypertension is often suspected in the setting of exertional dyspnea and suggestive findings on echocardiogram. The diagnostic questions posed in the initial evaluation of a patient in whom pulmonary hypertension is suspected are: does the patient have PH?, and if so, what is the cause and how severe is the PH? As such, an evaluation to correctly diagnose pulmonary hypertension requires 1) clinical suspicion based on history and examination, 2) echocardiography to evaluate for likelihood of PH, 3) characterization of the extent of any lung and left heart disease, 4) thorough evaluation for chronic thromboembolic disease and conditions associated with PAH, and 5) referral to a center with PH expertise for evaluation that typically includes right heart catheterization to define hemodynamics. Given the significant morbidity and mortality associated with both PH and PAH, seeking PH expertise early in the diagnostic evaluation is advised, particularly for patients with high-risk features.

## CLINICAL CLASSIFICATION

Pulmonary hypertension is classified into five groups, based on the World Symposium on Pulmonary Hypertension (WSPH) classification scheme, presented in **Table 1**. The purpose of this classification scheme is to group clinical conditions that share similar pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management.[1] WSPH Group 1 PAH is defined as precapillary PH in the absence of significant left heart, lung, or chronic thromboembolic disease. WSPH Group 2 PH is defined by presence of post-capillary PH (mPAP >20 mmHg and PAWP ≥15 mmHg), and WSPH Group 3 PH is defined by mPAP 21–24 mmHg with PVR ≥3 WU, or mPAP ≥25 mmHg.[5] WSPH Group 4 PH consists predominantly of chronic thromboembolic PH (CTEPH), which is defined by precapillary PH in the presence of chronic or organized flow-limiting thrombi/emboli in the elastic pulmonary arteries (PAs) after at least 3 months of effective anticoagulation. Finally, WSPH Group 5 PH includes a variety of diseases with unclear or multifactorial mechanisms. Although this is a heterogeneous and relatively understudied group

of diseases, it still represents a significant portion of disease seen in pulmonary hypertension centers. The clinical classification scheme provides a framework that allows for a comprehensive differential diagnosis in the evaluation of pulmonary hypertension. It should be noted that most of the WSPH Groups are based upon specific hemodynamic definitions, which emphasizes the importance of right heart catherization in the diagnosis of pulmonary hypertension.

Table 1. World Symposium on Pulmonary Hypertension (WSPH) Classification of Pulmonary Hypertension

| |
|---|
| **Group 1: Pulmonary arterial hypertension (PAH)** |
| 1.1 Idiopathic PAH<br>1.2 Heritable PAH<br>1.3 Drug- and Toxin-Induced PAH<br>1.4 PAH associated with:<br>1.4.1 Connective tissue disease<br>1.4.2 Human immunodeficiency virus infection<br>1.4.3 Portal hypertension<br>1.4.4 Congenital heart disease<br>1.4.5 Schistosomiasis<br>1.5 Long-term responders to calcium channel blockers<br>1.6 PAH with overt features of venous/capillary involvement (pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis)<br>1.7 Persistent pulmonary hypertension of the newborn |
| **Group 2: Pulmonary hypertension due to left heart disease** |
| 2.1 Heart failure with preserved left ventricular ejection fraction<br>2.2 Heart failure with reduced left ventricular ejection fraction<br>2.3 Valvular heart disease<br>2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH |
| **Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia** |
| 3.1 Obstructive lung disease<br>3.2 Restrictive lung disease<br>3.3 Other lung diseases with mixed restrictive and obstructive pattern<br>3.4 Hypoxia without lung disease<br>3.5 Developmental lung diseases |
| **Group 4: Pulmonary hypertension due to pulmonary arterial obstructions** |
| 4.1 Chronic thromboembolic pulmonary hypertension<br>4.2 Other pulmonary artery obstructions: sarcoma, other malignant or non-malignant tumors, arteritis without connective tissue disease, congenital pulmonary artery stenosis, parasites |
| **Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms** |
| 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders<br>5.2 Systemic and metabolic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, glycogen storage disease, Gaucher disease, neurofibromatosis.<br>5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis<br>5.4 Complex congenital heart disease |

Adapted from Simonneau, et al. 2019.[1]

However, the classification of an individual patient's PH combines hemodynamic data with a comprehensive clinical evaluation.

## EPIDEMIOLOGY

Pulmonary arterial hypertension (PAH) remains an uncommon disease; however, published estimates of epidemiology vary. This is likely due to geographic, racial, ethnic, and socioeconomic differences in prevalence, presentation, and outcomes, with variations in reporting and tracking among countries. Ranges for incidence are 1.5–3.2 persons per million per year and for prevalence are 12.4–268 persons per million, with a noted greater prevalence in data from nationalized systematic registries as compared to non-systematic registries.[6] Pulmonary hypertension (PH) as a whole also is relatively uncommon, with an incidence of 28.7 cases per 100,000 per year. However, the prevalence of the disease is reported to be increasing from 99.8 to 127.3 cases per 100,000 population from 1993 to 2012.[7] This is likely due to the increasing awareness of the disease, improvement in screening of high-risk populations, and greater availability of non-invasive diagnostic and screening tools. Importantly, WSPH Group 2 PH is the most common form of PH. One population-based cohort study found that Group 2 PH accounted for 34.2% of PH cases alone and another 29.3% of cases when combined with lung disease. PH due to left heart disease has contributed most to the increasing prevalence in the adult population, accounting for over 75% of all new cases.[7]

The incident population of PAH continues to be predominantly of female sex (62.1%) and younger at index date (mean age 65.1 years) as compared to PH (54.1% female sex and mean age 72.9 years).[7] This follows with the observation that new PH diagnoses are largely driven by those individuals with pre-existing left-sided heart and lung disease, whereas PAH is a primary pulmonary artery vasculopathy with a unique presentation and clinical course.

## HISTORY AND PHYSICAL EXAM

Although hemodynamic evaluation via right heart catheterization (RHC) is a crucial part of the evaluation process, the diagnosis of pulmonary hypertension remains a clinical one. Thus, a thorough history and physical exam is necessary prior to diagnostic interventions.

The most common presenting symptom in patients with pulmonary hypertension is dyspnea on exertion or a decrease in exercise capacity. Given the nonspecific nature of these symptoms, it is important to evaluate each patient for alternate etiologies of dyspnea, including obstructive airways disease and left ventricular or valvular dysfunction, among others. Symptoms including orthopnea and lower extremity edema are typically signs of advanced disease as they

indicate right ventricular dysfunction, which is a known late sequela of the disease.[8] When identified in a patient with lack of echocardiographic evidence of right-ventricular dysfunction, alternate diagnoses should be considered. Concerning symptoms such as dizziness or lightheadedness with exertion or syncope are known high-risk features in patients with right ventricular failure and should prompt an expedited workup.[8]

Of importance is the level of clinical suspicion that a patient may have WSPH Group 1 PAH or Group 4 PH versus Groups 2, 3, or 5 PH. The reason for this distinction is that Groups 2, 3, and 5 typically rely on treating the underlying disease and supportive therapy, whereas Groups 1 and 4 may require additional diagnostic interventions and the mainstay of treatment remains pulmonary vasodilators.

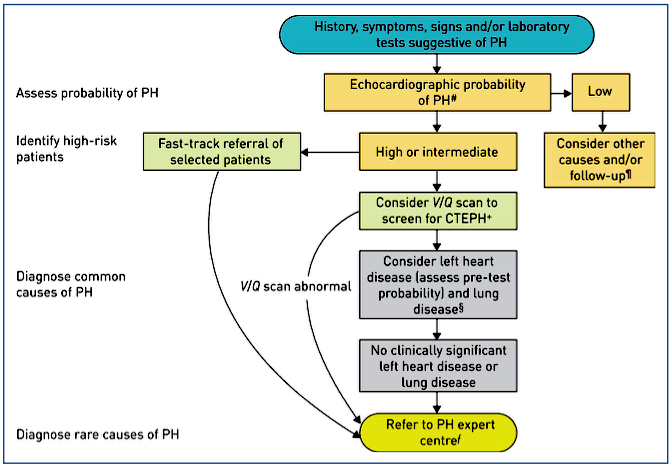
The historical factors that may raise suspicion for the presence of Group 1 PAH include a family history of PAH, history of exposure to particular drugs or toxins known to cause pulmonary arterial hypertension, including certain chemotherapeutic agents, anorexigens and methamphetamine,[8] a personal or family history of connective tissue disease (particularly scleroderma, lupus, and mixed connective tissue disease), known history of HIV infection, chronic liver disease with portal hypertension, and a history of congenital heart disease. A personal or family history of prior venous thromboembolism may raise suspicion for Group 4 PH, particularly CTEPH. However, lack of this history should not preclude additional diagnostic workup as the incidence of CTEPH following pulmonary embolism varies in the literature from 15% to 33% in Japanese cohorts[8,9] to 75% in a European and Canadian cohort.[10] Additional historical factors that may inform a diagnosis of Groups 2, 3, and 5 PH include general screening for left-sided or valvular heart diseases, obstructive airways diseases, sleep-disordered breathing, and interstitial lung diseases.

On physical exam, a loud pulmonic component of the second heart sound (P2), a tricuspid regurgitation murmur, and a palpable right ventricular heave may be identified. An increased jugular venous pulsation, hepatojugular reflex, and peripheral edema can all be seen with worsening right-ventricular function and failure. Care should be taken to also examine the patient for signs of related diagnoses. For example, an exam for undiagnosed connective tissue diseases may include evaluating for sclerodactyly, skin thickening, digital ulceration, telangiectasias, rashes, and joint edema.

## DIAGNOSTIC ALGORITHMS

The recommended diagnostic algorithm for pulmonary hypertension (**Figure 1**) is largely dependent on whether the workup is being performed outside a PH expert center, and if so, the probability of PH based on available data and thus the need for expedited referral. Echocardiographic signs that raise suspicion for PH are detailed below and in **Table 3**. These signs and high-risk symptoms (e.g., exertional dizziness, syncope) should prompt expedited referral to a PH expert center.

**Figure 1.** Diagnostic Algorithm for the Diagnosis of Pulmonary Hypertension Outside a Pulmonary Hypertension Expert Center




PH= pulmonary hypertension. CTEPH = chronic thromboembolic PH. Adapted from Frost, et al. 2019.[8]

### Transthoracic Echocardiography

Echocardiography is the most important non-invasive screening tool in the evaluation for PH. High-risk echocardiographic features should be used to expedite workup and referral for right heart catheterization (RHC), which remains mandatory to establish the diagnosis.

Based on echocardiographic data from healthy individuals at rest and expert opinion, the tricuspid regurgitation velocity (which is used to calculate the pulmonary artery systolic pressure or PASP) and the presence or absence of other signs of echocardiographic PH are used together to establish the echocardiographic probability of PH (**Tables 2 and 3**). Other signs of PH on echocardiography include right ventricular enlargement, decreased right ventricular systolic function, flattening of the interventricular septum, right atrial enlargement, lack of respiratory variation in the inferior vena cava, and the diameter of the pulmonary artery.[11-13]

**Table 2.** Echocardiographic probability of Pulmonary Hypertension in symptomatic patients with a suspicion of Pulmonary Hypertension

| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo "PH signs"* | Echocardiographic probability of PH |
|---|---|---|
| ≤ 2.8 or not measurable | No | Low |
| ≤ 2.8 or not measurable | Yes | Intermediate |
| 2.9 – 3.4 | No | |
| 2.9 – 3.4 | Yes | High |
| > 3.4 | Not required | |

PH = pulmonary hypertension. *See Table 3. Adapted from Galiè, et al. 2015.[2]

**Table 3.** Echocardiographic Signs Suggesting Pulmonary Hypertension

| The ventricles | Pulmonary artery | Inferior vena cava and right atrium |
|---|---|---|
| Right ventricle/left ventricle basal diameter ratio >1.0 | Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration) |
| Flattening of the interventricular septum (left ventricular eccentricity index > 1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/sec | Right atrial area (end-systole) >18 $cm^2$ |
| | PA diameter >25 mm | |

PA = pulmonary artery. Adapted from Galiè, et al. 2015.[2]

### Electrocardiography

Though a normal electrocardiograph (ECG) does not exclude the diagnosis of PH, changes may provide helpful clues. When present, ECG changes are associated with a worse prognosis and so may be used with other data to expedite a patient's workup.[14,15] Changes typically seen in the ECGs of patients with PH include p pulmonale, right ventricular (RV) strain pattern, RV hypertrophy, and right bundle branch block.

### Laboratory Testing

Routine hematology, biochemical, and thyroid testing are required for all patients being evaluated for pulmonary hypertension. Routine blood tests may reveal nonspecific signs such as hepatic congestion from right ventricular failure. An elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP is associated with worse outcomes.[16]

Serological assessment many be helpful in differentiating subtypes of the disease, thus all patients undergoing evaluation for PH require screening for connective tissue disease (CTD), HIV, and hepatitis. Because patients with CTD on the scleroderma spectrum are at particularly high risk for development of PAH, antinuclear antibodies (ANAs) are recommended in the initial workup for PH, although it should be noted that low titer positives (1:80) are frequent in patients who lack other convincing features of CTD.

### Pulmonary Function Testing

Clinical history and symptoms should guide the need for pulmonary function tests (PFTs). These tests should include total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO). While airways obstruction or restrictive physiology can be observed in Group 3 PH, patients with Group 1 PAH may demonstrate a mild restrictive component and a mild to moderate reduction in DLCO.[17] Marked reductions in DLCO may indicate pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).[18]

### Ventilation/Perfusion (V/Q) Scan

A V/Q scan to screen for chronic thromboembolic disease should be performed in all patients being evaluated for PH. CTEPH is likely underdiagnosed and remains elusive, in part due to the underutilization of V/Q scanning despite guideline recommendations.[19,20] A normal V/Q scan excludes CTEPH with a sensitivity of 90–100% and a specificity of 94-100%[21,22] and so is the preferred test for CTEPH screening.[19,23] An abnormal V/Q scan should prompt referral to a PH expert center as additional diagnostic interventions such as pulmonary angiography may need to be considered as part of the diagnostic evaluation.

### Chest Computed Tomography (CT)

Chest CT is not a diagnostic tool for PH; however, several features may be suggestive. These include an enlarged pulmonary artery (diameter ≥29mm), right ventricular dilation, right atrial dilation, and a main pulmonary artery/ascending aorta diameter ratio ≥1.[24] An examination of the lung parenchyma may also be helpful in identifying parenchymal lung diseases responsible for Group 3 PH.

## SCREENING IN HIGH-RISK POPULATIONS

### Scleroderma (Systemic Sclerosis) and Scleroderma Spectrum

The incidence of PAH in connective tissue diseases on the scleroderma spectrum is estimated between 5–12%, which is substantially more than the population at large.[25,26] Current guidelines recommend annual screening for PAH in patients with systemic sclerosis (SSc) with an uncorrected DLCO < 80% predicted.[2,3,27] Recommended screening tools include the DETECT algorithm, TTE or FVC/DLCO ratio > 1.6, and NT-proBNP greater than 2-fold the upper limit of normal.[8]

### Human Immunodeficiency Virus (HIV)

While the true incidence of PAH in persons infected with HIV is not clear, ongoing studies suggest that it may be higher than previously reported.[8] In order to enrich the population that would benefit from routine screening, additional concomitant risk factors that increase the risk of development of PAH in HIV-positive individuals should be used to guide selection of asymptomatic patients for screening. These include female sex, intravenous drug or cocaine use, hepatitis C virus infection, origin from a high-prevalence country, known negative regulatory factor (Nef) or transactivator of transcription (Tat) HIV proteins, and Black ethnicity in United States patients.[28-33]

## RIGHT HEART CATHETERIZATION

As the diagnosis and classification of pulmonary hypertension centers on hemodynamic definitions, correct performance and interpretation of right heart catheterization is essential for the diagnosis of PH. Comprehensive descriptions of RHC for the diagnosis of PH are reviewed elsewhere.[34] Proper set up for RHC requires appropriate calibration of all equipment, and leveling of transducers to the level of the left atrium – the midsagittal line in a supine patient.[35] Pressure measurements are performed during spontaneous respirations, with resting measurements made at end expiration. Correct measurement of PAWP during RHC is critical, as this is a measure prone to error by under- or over-wedging, and is necessary to distinguish between pre- and post-capillary PH. PAWP is typically measured at end expiration; however, measurements averaged over multiple respiratory cycles may be useful in patients with obesity or chronic obstructive pulmonary disease.

Similarly, measurement of cardiac output is critical in the diagnosis of PH, to calculate pulmonary vascular resistance and assess the severity of PH and any cardiac dysfunction. The thermodilution method of cardiac output measurement is the recommended technique[2] and requires a Swan Ganz catheter with a thermistor tip. Although there may be concerns about potential inaccuracy in the setting of low cardiac output, and/or significant tricuspid regurgitation, the thermodilution method has been shown to be accurate in these circumstances in pulmonary hypertension.[36] Measurement of central venous and pulmonary arterial saturations should be performed to evaluate for the presence of a left to right cardiac shunt. Vasoreactivity testing is performed by administration of a pulmonary vasodilator – typically inhaled nitric oxide (although intravenous epoprostenol, intravenous adenosine or inhaled iloprost can also be used) during RHC. A positive response is defined by a decrease in mPAP by ≥10 mmHg to mPAP ≤40 mmHg without a decrease in cardiac output.[1] This should be performed in all patients with suspected or confirmed idiopathic PAH, heritable PAH, or drug- and toxin-induced PAH, to identify a subset of patients who are likely to benefit from treatment with calcium channel blockers. Lastly, provocative challenges such as exercise or administration of a fluid bolus may be useful in certain clinical settings but should be performed by operators skilled in their performance and interpretation. Given the complexities of hemodynamic evaluation for the diagnosis and management of PH, RHC should be performed by an operator with skill and experience in pulmonary hypertension.

## CONCLUSION

The diagnosis of pulmonary hypertension can be challenging given the nonspecific nature of its presentation and multiple potential causes. Careful interpretation of history, physical exam, and echocardiogram is helpful to define the level of suspicion for the disease. Understanding the clinical classification and epidemiology of PH provides a framework for the differential diagnosis and diagnostic evaluation. Right heart catheterization remains mandatory to define hemodynamics and confirm the diagnosis of PH. Early referral to a PH center of expertise is necessary, particularly in patients with high-risk features and in high-risk populations.

### References


1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*. 2019;53.
2. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal*. 2016;37:67-119.
3. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F. Definitions and diagnosis of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62:D42-D50.
4. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *European Respiratory Journal*. 2019;53.
5. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S. Pulmonary hypertension in chronic lung disease and hypoxia. *European Respiratory Journal*. 2019;53.
6. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. *Pulmonary circulation*. 2021;11:2045894020977300.
7. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, Barber D, Johnson A, Doliszny KM, Archer SL. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. *Circulation: Cardiovascular Quality and Outcomes*. 2018;11:e003973.
8. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, Oudiz R, Satoh T, Torres F, Torbicki A. Diagnosis of pulmonary hypertension. *European Respiratory Journal*. 2019;53.
9. Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, Yamada N, Yao A, Ando M, Ogino H. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. *Circulation: Cardiovascular Quality and Outcomes*. 2017;10:e004029.
10. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation*. 2011;124:1973-1981.
11. Hellenkamp K, Unsöld B, Mushemi-Blake S, Shah AM, Friede T, Hasenfuß G, Seidler T. Echocardiographic estimation of mean pulmonary artery pressure: a comparison of different approaches to assign the likelihood of pulmonary hypertension. *Journal of the American Society of Echocardiography*. 2018;31:89-98.
12. Magnino C, Omede P, Avenatti E, Presutti D, Iannaccone A, Chiarlo M, Moretti C, Gaita F, Veglio F, Milan A. Inaccuracy of right atrial pressure estimates through inferior vena cava indices. *The American journal of cardiology*. 2017;120:1667-1673.

13. Focardi M, Cameli M, Carbone SF, Massoni A, De Vito R, Lisi M, Mondillo S. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *European Heart Journal-Cardiovascular Imaging*. 2015;16:47-52.
14. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, Rubenfire M. The prognostic role of the ECG in primary pulmonary hypertension. *Chest*. 2002;121:513-518.
15. Henkens IR, Gan CT-J, van Wolferen SA, Hew M, Boonstra A, Twisk JW, Kamp O, van der Wall EE, Schalij MJ, Noordegraaf AV. ECG monitoring of treatment response in pulmonary arterial hypertension patients. *Chest*. 2008;134:1250-1257.
16. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation*. 2000;102:865-870.
17. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. *Journal of the American College of Cardiology*. 2003;41:1028-1035.
18. Hadinnapola C, Bleda M, Haimel M, Screaton N, Swift A, Dorfmüller P, Preston SD, Southwood M, Hernandez-Sanchez J, Martin J. Phenotypic characterization of EIF2AK4 mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. *Circulation*. 2017;136:2022-2033.
19. McLaughlin VV, Langer A, Tan M, Clements PJ, Oudiz RJ, Tapson VF, Channick RN, Rubin LJ and Initiative PAH-QER. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. *Chest*. 2013;143:324-332.
20. Tapson VF, Platt DM, Xia F, Teal SA, de la Orden M, Divers CH, Satler CA, Joish VN, Channick RN. Monitoring for pulmonary hypertension following pulmonary embolism: the INFORM study. *The American journal of medicine*. 2016;129:978-985. e2.
21. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, Adil A-N. Ventilation–perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *Journal of nuclear medicine*. 2007;48:680-684.
22. He J, Fang W, Lv B, He J-G, Xiong C-M, Liu Z-H, He Z-X. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. *Nuclear medicine communications*. 2012;33:459-463.
23. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V. Chronic thromboembolic pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62:D92-D99.
24. Shen Y, Wan C, Tian P, Wu Y, Li X, Yang T, An J, Wang T, Chen L, Wen F. CT-base pulmonary artery measurementin the detection of pulmonary hypertension: a meta-analysis and systematic Review. *Medicine*. 2014;93.
25. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, Tiev K, Cappelli S, Diot E, Vacca A. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *The Journal of rheumatology*. 2010;37:2290-2298.
26. Mukerjee D, St George D, Coleiro B, Knight C, Denton C, Davar J, Black C, Coghlan J. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Annals of the rheumatic diseases*. 2003;62:1088-1093.
27. Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE, Hachulla E, Humbert M, Langleben D, Mathai SC. Recommendations for screening and detection of connective tissue disease–associated pulmonary arterial hypertension. *Arthritis & Rheumatism*. 2013;65:3194-3201.
28. Dhillon NK, Li F, Xue B, Tawfik O, Morgello S, Buch S, Ladner AOB. Effect of cocaine on human immunodeficiency virus–mediated pulmonary endothelial and smooth muscle dysfunction. *American journal of respiratory cell and molecular biology*. 2011;45:40-52.
29. Quezada M, Martin-Carbonero L, Soriano V, Vispo E, Valencia E, Moreno V, de Isla LP, Lennie V, Almería C, Zamorano JL. Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. *Aids*. 2012;26:1387-1392.
30. Dalvi P, O'Brien-Ladner A, Dhillon NK. Downregulation of bone morphogenetic protein receptor axis during HIV-1 and cocaine-mediated pulmonary smooth muscle hyperplasia: implications for HIV-related pulmonary arterial hypertension. *Arteriosclerosis, thrombosis, and vascular biology*. 2013;33:2585-2595.
31. Sangal RB, Taylor LE, Gillani F, Poppas A, Klinger JR, Ventetuolo CE. Risk of echocardiographic pulmonary hypertension in individuals with human immunodeficiency virus–hepatitis C virus coinfection. *Annals of the American Thoracic Society*. 2014;11:1553-1559.
32. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American society of echocardiography*. 2010;23:685-713.
33. Schwarze Zander C, Pabst S, Hammerstingl C, Ohlig J, Wasmuth J, Boesecke C, Stoffel Wagner B, Carstensen A, Nickenig G, Strassburg C. Pulmonary hypertension in HIV infection: a prospective echocardiographic study. *HIV medicine*. 2015;16:578-582.
34. Rosenkranz S, Preston IR. Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *European Respiratory Review*. 2015;24:642-652.
35. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *American journal of respiratory and critical care medicine*. 2014;190:252-257.
36. Hoeper MM, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, Fabel H. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *American journal of respiratory and critical care medicine*. 1999;160:535-541.

## Authors

Navneet Singh, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Christopher J. Mullin, MD, MHS, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

## Disclosures

None

## Correspondence

Christopher J. Mullin, MD, MHS
Division of Pulmonary, Critical Care and Sleep Medicine
Rhode Island Hospital
593 Eddy Street, POB Suite 224
Providence, RI 02903
401-444-2670
Fax 401-444-5914
christopher_mullin@brown.edu

# The Evolving Continuum of Diagnosis in the Modern Age of Non-Small Cell Lung Cancer

DANIEL DUSTIN, DO; DOUGLAS MARTIN, MD


## ABSTRACT

Lung cancer remains the most common cause of cancer-related deaths in the United States. Traditional treatment of non-small cell lung cancer has included surgical resection for suitable candidates with early stage (I/II) disease and various chemoradiotherapeutic regimens used for advanced disease, for which prognosis has been poor. Since the early 2000s, there has been a revolution in the diagnosis and treatment of non-small cell lung cancer driven by improved diagnostic techniques and therapies targeted to druggable oncogenic drivers or manipulation of the immunologic milieu in the tumor microenvironment. With this has come a need for frequently updated comprehensive data regarding response to treatment and acquired resistance to targeted therapies. In this article, we aim to provide a concise review of the state-of-the-art in lung cancer workup in 2021, with a focus on how molecular data now informs treatment decisions. With the burgeoning use of immunotherapeutic approaches, we will also discuss some of the complications seen, and briefly discuss their management.


**KEYWORDS:** Non-Small Cell Lung Cancer (NSCLC), Endobronchial Ultrasound (EBUS), Immunotherapy, Driver Mutations, Immune Related Adverse Events

## INTRODUCTION

Lung cancer represents 13% of all new cancer diagnoses and accounts for 25% of all cancer deaths.[1,2] Non-small cell lung cancer (including Adenocarcinoma, Squamous Cell, Large Cell) comprises approximately 85% of all lung cancers. While the introduction of low-dose CT (LDCT) screening holds promise in improving rates of early detection, lung cancer has traditionally presented at an advanced stage in more than 80% of patients. Prognosis for patients with Stage III or IV disease treated with chemoradiotherapeutic regimens has traditionally been dismal with five-year survival rates <25% in stage IIIA.

## DIAGNOSIS AND STAGING

Patients may present with a spectrum of disease from asymptomatic with small nodule(s) to severely ill with widely metastatic or bulky intrathoracic disease. For patients with small nodules (e.g., ≤ 8mm), validated guidelines are utilized to guide radiographic evaluation. The Fleischner Society Guidelines apply for incidentally found nodules while the Lung-RADS system is used for screen-detected nodules.[3,4] The latter differs due to the generally higher-risk characteristics of patients meeting screening criteria and the fact that the default in that population remains one year repeat low-dose screening scan.

The Tumor, Node, Metastasis (TNM) staging system is utilized in non-small cell lung cancer. Tissue acquisition is ideally performed from the area that provides the highest overall stage.[5] Surgical biopsy and resection are sometimes utilized in appropriate patients with high likelihood of early stage (Stages I/II) NSCLC. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) scan is commonly obtained to assess the mediastinum and to assess for the possibility of distant metastases, including to sites such as the adrenal glands or bone. Percutaneous biopsy is commonly performed for lung nodules (particularly peripheral ones), but bronchoscopic techniques guided by magnetic navigation, cone-beam computed tomography (CT), radial ultrasound, and robotic technology have gained an increasing role.[6] Endosonographic-based sampling techniques (linear endobronchial ultrasound (EBUS) from the tracheobronchial tree or endoscopic ultrasound (EUS) from the gastrointestinal tract ) are used in cases of suspected hilar or mediastinal nodal disease and facilitate their fine needle aspiration (FNA) guided by real time ultrasound imaging. Endosonographic techniques are also commonly used to exclude nodal disease prior to surgical resection or (usually in nonsurgical candidates) radiation therapy.[6] If imaging is suggestive of distant metastases, image-guided biopsy can establish both diagnosis and staging.

In patients without PET-detected extra thoracic disease, mediastinal lymph node sampling is commonly performed. A study by Um et al. demonstrated similar diagnostic yield with EBUS FNA showing a favorable side effect profile compared to mediastinoscopy.[7] For these reasons, EBUS is typically done first with mediastinoscopy reserved for cases of negative EBUS results with persistent clinical concern for nodal involvement. The lymph nodes targeted should be those that will give the highest potential stage.[8] Despite the excellent sensitivity of PET scan, endosonographic staging

studies have generally shown false negative rates for mediastinal disease of 5-10%. In one prospective trial of 35 non-small cell patients who underwent PET and EBUS, 10 had discordant results (histologic sampling down-staged six patients and upstaged four).[9] This study underscores the importance of histologic confirmation, as PET imaging also may demonstrate false positive findings in setting of active infections or noninfectious inflammatory conditions such as sarcoidosis.

With the growing use of molecularly targeted therapies, acquisition of sufficient cytologic or pathologic material to perform such studies has become critically important. EBUS has been shown to provide adequate tissue, especially when guided by rapid on-site cytologic evaluation (ROSE).[10] A broad array of needle sizes are now available, and studies have shown that EBUS-guided transbronchial needle aspiration (TBNA) can provide abundant material for a cell block which is subsequently sectioned for indicated studies.[10,11] Immunohistochemical studies remain important to the initial diagnosis and protein expression studies, but next generation sequencing (NGS) platforms promise to continue to revolutionize the diagnosis of driver mutation oncogenes.

## TRADITIONAL TREATMENT

Treatment has traditionally consisted of a combination of chemotherapy, radiation, and/or surgery depending on disease stage and patient factors (age, co-morbidities) (**Table 1**).[12]

**Table 1.** Treatment Options for Lung Cancer in 2004.

| Stage | Primary Treatment | Adjuvant Therapy | 5 Year Survival Rate |
|---|---|---|---|
| NSCLC Stage I | Surgical Resection | Chemotherapy | >60–70% |
| NSCLC Stage II | Surgical Resection | Chemotherapy with or without Radiotherapy | >40–50% |
| NSCLC Stage IIIA (Resectable) | Preoperative chemotherapy followed by surgical resection or surgical resection | Radiotherapy with chemotherapy or without chemotherapy | 15–30% |
| NSCLC Stage IIIA (Unresectable) or IIIB (Contralateral or supraclavicular lymph nodes) | Chemotherapy and Radiation either concurrent or sequentially | None | 10–20% |
| NSCLC Stage IIIB (pleural effusion) or Stage IV | Chemotherapy | None | 10–15% |
| SCLC Limited Disease | Chemotherapy with radiation therapy | None | 15–25% |
| SCLC Extensive Disease | Chemotherapy | None | <5% |

Adapted from Spira A and Ettinger DS. Multidisciplinary management of lung cancer.[12]

## MODERN ERA

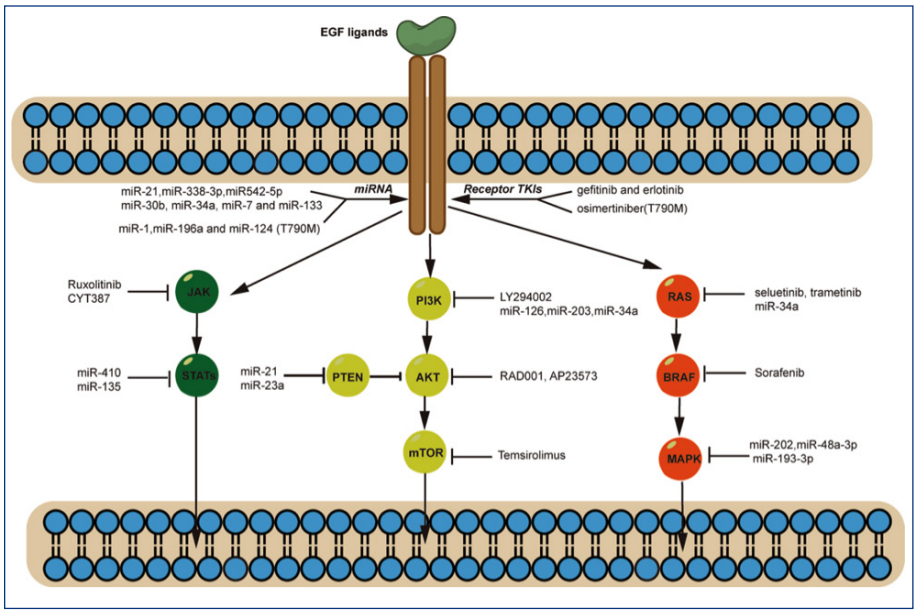
Since the early 2000s, the field has been revolutionized by the development and refinement of therapies in the areas of driver-mutation targeting, anti-angiogenesis, and immunotherapy. In particular, standard-of-care evaluation of newly diagnosed advanced NSCLC (particularly nonsquamous histologies) involves testing for at least the most common driver mutations with available therapies, as well as the PD-L1 protein expression as measured by the Tumor Proportion Score (TPS). The explosion in biomarker testing performed at one institution since 2004 can be seen in **Figure 1** in the article by VanderLaan PA, et al[13] at: https://pubmed.ncbi.nlm.nih.gov/29413057/.

## EPIDERMAL GROWTH FACTOR (EGFR)

The epidermal growth factor receptor is a tyrosine kinase receptor and member of the Human Epidermal Receptor (HER) family. Binding of this transmembrane protein leads to downstream signal transduction pathways that drive tumor growth. The first study to enroll NSCLC patients in treatment with an EGFR inhibitor began patient enrollment in 1998. The landmark I-PASS study later randomized over 1200 patients in East Asia with pulmonary adenocarcinoma to gefitinib or carboplatin with paclitaxel and showed significant progression-free survival in the gefitinib treated group who harbored an EGFR mutation.[14] While first well recognized in Asian populations (particularly never smoking young women), it is now recognized that 10-17% of patients with bronchogenic adenocarcinoma in the United States harbor an EGFR driver mutation.[15] Oral EGFR inhibition in treatment of advanced nonsurgical disease has evolved from second-line or maintenance therapy after chemotherapy through to first-line treatment.[16]

Treated EGFR mutant NSCLC typically develop resistance to earlier generation EGFR inhibitors at approximately 10 months. Most of these patients develop an EGFR T790M mutation for which third-generation inhibitors were developed.[15] Osimertinib is the prototypical third-generation therapy and has become the standard of care in EGFR mutant NSCLC due to improved systemic and central nervous system (CNS) control, as well as favorable side effect profile compared to earlier agents. The AURA3 study compared osimertinib to standard platinum therapy plus pemetrexed in patients previously treated with an earlier generation EGFR inhibitor and showed improved efficacy and side effect profile.[16] Osimertinib has also recently shown improved progression-free survival of 19 months vs 10 months versus first-generation therapies in the FLAURA trial.[17] Even more recently, the ADAURA study demonstrated that adjuvant osimertinib in surgically resected disease can have significant impact on disease-free survival (DFS).[18] However, controversy exists as to its role in the adjuvant setting at this time, given the uncertainty as to whether routine adjuvant

**Figure 2.** Current pathways from the EGFR protein and the respective molecular targets, either FDA-approved or in clinical trials.




From Yuan, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer.[19]

use would provide true benefit over initiation at disease recurrence in carefully monitored patients and the present lack of overall survival data.

Overall, EGFR driver mutation investigation and development of therapies to evade resistance have represented a landmark strategy and paradigm shift for targeted therapies going forward.[19] **Figure 2** presents a graphical representation of the EGF Receptor along with existing or potential targeted therapies against the receptor or its downstream effector pathways.

## ANAPLASTIC LYMPHOMA KINASE

The anaplastic lymphoma kinase (ALK) gene is located on chromosome 2 and encodes a tyrosine kinase that is normally found at low levels in the small intestine, nervous system, and testis in adults. Activating alterations render the gene constitutively active. ALK-EML4 represents a rearrangement thus far only identified in NSCLC. ALK driver mutations are found in 5% of NSCLC.[20] Trials testing the first ALK inhibitor (crizotinib) began only three years after the recognition of ALK-positive NSCLC.[21] Analogous to the evolution in EGFR inhibitors, ALK inhibition has improved with the newer agent alectinib showing a higher proportion of patients achieving overall response, improved CNS disease control, and better side-effect profile than crizotinib.[22] ALK can also form a fusion protein with other druggable oncogenes, including c-ros oncogene (ROS1) and mesenchymal-epithelial transition factor (MET). In terms of relevance to clinical practice, NSCLC with ROS1 mutations is responsive to ALK inhibitors.[23]

## OTHER MOLECULARLY TARGETED THERAPIES

Since the seminal research on mutant EGFR and ALK targeting, many additional molecular targets have been identified including mutations within BRAF, RET, and NTRK genes. These are found commonly in nonsmokers with newly diagnosed NSCLC and occur in a smaller proportion of patients compared to EGFR mutations. Driver mutations in MET occur in about 3–4% of NSCLC patients and, in contrast to EGFR and ALK, are more commonly seen in patients over 70.[24] KRAS is the most common driver mutation found in smoking-induced NSCLC, but targeted treatment had remained elusive until sotorasib, which was granted accelerated approval by the FDA in May 2021. This targets the G12C mutation, which is present in approximately 13% of all NSCLC.[25] In a recent Phase II trial from 2021, partial or complete remission was seen in 37.1% of the patients. The median progression-free survival was 6.8 months, and the median duration of response was 11.1 months.

## ANGIOGENESIS INHIBITION

In 2007, Sandler et al. published a landmark randomized control trial of the addition of the angiogenesis inhibitor bevacizumab to standard platinum-based therapy in the treatment of advanced (IIIB, IV) nonsquamous NSCLC. Median survival increased modestly from approximately ten to twelve months, but this was one of the first studies to show a survival advantage in advanced NSCLC with the addition of a novel/nonchemotherapy-based medication. Importantly, five patients in the bevacizumab treated group died of pulmonary hemorrhage, foreshadowing the era of novel treatment related adverse effects.[26] While angiogenesis inhibition has not shown robust benefit as the sole strategy in treatment of NSCLC, dual EGFR-VEGF pathway inhibition has shown significant promise, likely due to cross-talk and inhibition between these pathways.[27]

## IMMUNOTHERAPY

Immunotherapeutic approaches in cancer treatment are not new, as Interleukin-2 was an established yet radical treatment in attempts to cure renal cell carcinoma.[28] Increased recognition of the importance of the tumor microenvironment in the pathophysiology of malignant tumors led to efforts to utilize T-cell responses in antineoplastic therapy.

T-cells express the Programmed Cell Death-1 (PD-1) receptor while its ligand, PD-L1, is expressed on the surface of tumor cells or other cells in the tumor microenvironment. T-cells initially mount cytotoxic efforts towards neoplastic cells but the PD-L1/PD-1 interaction downregulates this response.[29]

Not all tumors express high levels of PD-L1. The tumor proportion score (TPS) is an immunohistochemical score of the percentage of viable cells expressing PD-L1 and has been used as a biomarker to select patients for clinical trials. Tumor heterogeneity may negatively impact small biopsy or cytologic specimens' abilities to provide a score representative of the tumor overall, and some studies have shown clinical benefit with immunotherapy regardless of PD-L1 expression.[30,31] Besides reflecting heterogeneity in tumor expression, this finding may also demonstrate the complexity of molecular pathways including T-cell/tumor interactions in the tumor microenvironment.

Initial studies demonstrating significant treatment effect utilizing immunotherapy in advanced malignancies not harboring a druggable oncogene (including NSCLC) were published in 2015. This led to the October 2015 FDA approval of pembrolizumab for advanced PD-L1 positive NSCLC that had progressed after other treatments.[30,31] Since that time, immunotherapy has revolutionized the approach to treatment of most solid-organ malignancies. In 2017, the placebo-controlled PACIFIC trial published results of consolidative durvalumab in unresectable stage III patients who did not have disease progression on concurrent chemoradiotherapy. There were demonstrated improvements in the primary end points of progression-free survival and overall survival.[32] These trials set the foundation for immunotherapy to completely change the treatment paradigm in stage IV and unresectable stage III disease.

Combination immunotherapeutic approaches utilizing inhibitors to the Cytotoxic T-lymphocyte Associated Antigen 4 (CTLA-4), such as ipilimumab with PD-L1 inhibitors, have been used extensively in treatment of metastatic melanoma and studied in NSCLC. Additional novel immunotherapeutic agents also hold substantial promise in NSCLC. Tiragolumab targets the immunomodulatory receptor TIGIT, which is a novel inhibitory immune checkpoint present on activated T-cells and NK cells. The CITYSCAPE trial is a phase II randomized trial that compared tiragolumab with atezolizumab versus atezolizumab alone in chemotherapy naive patients with high PD-L1 expression who did not have EGRF or ALK mutations. The treatment group showed improvement in overall response rate at 6 months (37% versus 21%) and a 42% reduction in the risk of disease as compared to the control arm.[33] This led to the approval of tiragolumab in conjunction with atezolizumab for NSCLC.

The burgeoning use of immunotherapy has led to increased recognition of immunotherapy-induced adverse events, which primarily take the form of autoimmune phenomenon. These complications have, in turn, their own important diagnostic and treatment considertions. Any organ system can be involved but dermatologic, gastrointestinal, hepatic, and endocrine systems are the most encountered. Use in patients with significant pre-existing autoimmune conditions or interstitial lung disease represents at least a relative contraindication.

Of the various immune-related adverse effects, respiratory complications are associated with the highest morbidity and mortality. Pneumonitis has an incidence rate of approximately 5%, and patients typically present with cough and dyspnea. Milder cases often improve with medication cessation, but those with higher-grade disease need glucocorticoid therapy. Refractory cases or severe disease are often co-treated with steroid sparing agents.[34] Empiric therapy is usually used without biopsy of affected tissue, though the emergence of the novel coronavirus complicated this decision in some patients due to overlap in patterns of chest imaging abnormalities. Patients receiving concomitant chemotherapy can also pose a more difficult diagnostic dilemma as they can remain at risk of a broad array of opportunistic infections and drug-induced complications. The CTLA4 inhibitors have been associated with the development of mediastinal and hilar lymphadenopathy, with EBUS FNA often demonstrating noncaseating granulomatous inflammation indistinguishable from sarcoidosis.[35]

## LIQUID BIOPSY

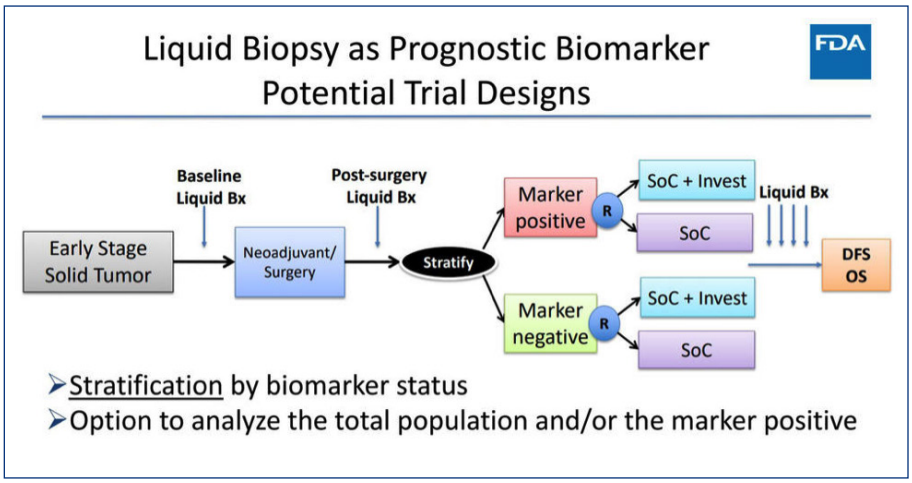
Given the known predilection for malignant involvement of the peripheral circulation, there has been an increasing desire to capture diagnostic and molecular data from peripheral blood. The first FDA approval of a "liquid biopsy" test occurred in 2016 with approval of a cell free DNA (cfDNA) test to identify candidates for erlotinib based on exon 19 deletions or exon 21 (L858R) mutations in EGFR. Such testing has become routine in testing for mutations in druggable oncogenes. Besides cfDNA, currently available specimens include circulating tumor DNA (ctDNA), Circulating Tumor Cells (CTC), microRNA, exosomes, and tumor-educated platelets.[36] These "liquid biopsies" hold tantalizing promise in lung cancer due to ease of acquisition coupled with the explosion in information obtainable from next generation sequencing platforms. This data will likely guide stages from asymptomatic screening to adjuvant treatment and through to early detection of relapse, monitoring of treatment response and resistance testing.[37]

The International Association for the Study of Lung Cancer (IASLC) recently released an updated consensus statement on the use of liquid biopsy techniques. Amongst other recommendations, the IASLC recommended use of NGS platforms rather than PCR-based technologies for determination of oncogene targets. The statement also highlights the paradigm shift away from tissue biopsy data as

the incontrovertible "gold standard" with realization that complementary genomic information can be obtained from plasma ctDNA analysis to inform druggable oncogene treatment. From a practical standpoint, for patients experiencing disease progression despite initial therapy, liquid biopsy techniques may represent the only feasible or safely accessible repository of tumor genomic data.[38]

Recognizing the value of liquid biopsies, the FDA recently published a guideline for clinical trials conducted as part of the drug approval process (**Figure 3**). The proposal regarding potential trial designs incorporates liquid biopsy information to stratify patients at multiple points throughout the trial.[39]

**Figure 3.** FDA Perspectives on the use of liquid biopsies in NSCLC trial designs.




SoC = Standard of Care, DFS = Disease Free Survival, OS = Overall Survival

## CONCLUSION

Over the past 15 years, there has been enormous progress in translating patient-specific cancer cell data into more effective treatment strategies in non-small-cell lung cancer, and this should only accelerate. Diagnostic strategies incorporating "liquid biopsies" will assuredly become more refined and important in the management of patients. Therapeutic approaches utilizing immunotherapy along with agents targeting druggable oncogenes and angiogenesis inhibitors as well as novel agents will continue. These novel therapies have unique side effect and adverse effect profiles in contrast to standard chemotherapeutics. An early referral to a pulmonologist can help facilitate the workup of pulmonary nodules since staging and adequate tissue sampling to assess these mutations are key to improving outcomes in NSCLC.

### References


1. Center for Disease Control and Prevention. U.S. Cancer Statistics Lung Cancer. https://www.cdc.gov/cancer/uscs/about/stat-bites/stat-bite-lung.htm. Accessed June 8, 2021.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. *CA: A Cancer Journal for Clinicians.* 2018; 68:7-30. doi:10.3322/caac.21442.
3. Lung-RADS Assessment Categories, Version 1.0. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADSTM).
4. MacMahon H., Naidich D.P., Goo J.M., et. al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology 2017; 284: pp. 228-243.
5. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. *Oncologist*. 2018;23(7):844-848. doi:10.1634/theoncologist.2017-0659.
6. Chandrika S, Yarmus L. Recent Developments in Advanced Diagnostic Bronchoscopy. European Respiratory Reviews. 2020; 29: 190184. DOI: 10.1183/16000617.0184-2019.
7. Um SW, Kim HK, Jung SH, Han J, Lee KJ, Park HY, Choi YS, Shim YM, Ahn MJ, Park K, Ahn YC, Choi JY, Lee KS, Suh GY, Chung MP, Kwon OJ, Kim J, Kim H. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. J Thorac Oncol 2015; 10: pp. 331-337.
8. Rivera M.P., Mehta A.C., Wahidi M.M. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: pp. e142S-e165S.
9. Steinfort DP, Siva S, Leong TL, et al. Systematic Endobronchial Ultrasound-guided Mediastinal Staging Versus Positron Emission Tomography for Comprehensive Mediastinal Staging in NSCLC Before Radical Radiotherapy of Non-small Cell Lung Cancer: A Pilot Study. *Medicine (Baltimore)*. 2016;95(8):e2488. doi:10.1097/MD.0000000000002488
10. Cicek T, Ozturk A, Yılmaz A, Aktas Z, Demirag F, Akyurek N. Adequacy of EBUS-TBNA specimen for mutation analysis of lung cancer. Clin Respir J. 2019 Feb;13(2):92-97. doi: 10.1111/crj.12985. PMID: 30582673.
11. Wahidi, Momen M. MD, MBA*; Davidson, Kevin MD†; Shofer, Scott MD, PhD*; Mahmood, Kamran MD, MPH*; Cheng, George MD, PhD*; Giovacchini, Coral MD*; Jones, Claudia MD‡; Jug, Rachel MB, BCh, BAO‡; Pavlisko, Elizabeth N. MD‡; Wang, Xiaofei PhD§; Gu, Lin MS§; Weimholt, Cody DO; Zhou, Zhongren MD; Chen, Alexander MD. Pilot Study of the Performance of 19-G Needle in Endobronchial Ultrasound-guided Transbronchial Aspiration for the Diagnosis and Testing of Molecular Markers in Lung Cancer. Journal of Bronchology & Interventional Pulmonology: July 2021 - Volume 28 - Issue 3 - p 209-214 doi: 10.1097/LBR.0000000000000736
12. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med. 2004 Jan 22;350(4):379-92. doi: 10.1056/NEJMra035536. Erratum in: N Engl J Med. 2009 Apr 30;360(18):1917. PMID: 14736930.
13. VanderLaan PA, Rangachari D, Majid A, Parikh MS, Gangadharan SP, Kent MS, McDonald DC, Huberman MS, Kobayashi SS, Costa DB. Tumor biomarker testing in non-small-cell lung cancer: A decade of change. Lung Cancer. 2018 Feb;116:90-95. doi: 10.1016/j.lungcan.2018.01.002. Epub 2018 Jan 4. PMID: 29413057; PMCID: PMC5806129.
14. Mok T.S., Wu Y.L., Thongprasert S., et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361: 947-957.
15. Sullivan I, Planchard D. Osimertinib in the treatment of patients with epidermal growth factor receptor T790M mutation-positive metastatic non-small cell lung cancer: clinical trial evidence and experience. *Ther Adv Respir Dis*. 2016;10(6):549-565.
16. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA; AURA3 Investigators. Osimertinib

or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640. doi: 10.1056/NEJMoa1612674. Epub 2016 Dec 6. PMID: 27959700; PMCID: PMC6762027.doi:10.1177/1753465816670498

17. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137. Epub 2017 Nov 18. PMID: 29151359.
18. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, Vu HV, Lu S, Lee KY, Akewanlop C, Yu CJ, de Marinis F, Bonanno L, Domine M, Shepherd FA, Zeng L, Hodge R, Atasoy A, Rukazenkov Y, Herbst RS; ADAURA Investigators. Osimertinib in Resected *EGFR*-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Epub 2020 Sep 19. PMID: 32955177.
19. Yuan, M., Huang, LL., Chen, JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Sig Transduct Target Ther* **4,** 61 (2019). https://doi.org/10.1038/s41392-019-0099-9
20. Sasaki T, Rodig SJ, Chirieac LR, Jänne PA. The biology and treatment of EML4-ALK non-small cell lung cancer. *Eur J Cancer*. 2010;46(10):1773-1780. doi:10.1016/j.ejca.2010.04.002
21. Solomon B.J., Mok T., Kim D.-W., Wu Y.-L., Nakagawa K., Mekhail T., Felip E., Cappuzzo F., Paolini J., Usari T., et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 2014;371:2167–2177. doi: 10.1056/NEJMoa1408440.
22. Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, Gadgeel SM, Cheema P, Pavlakis N, de Marinis F, Cho BC, Zhang L, Moro-Sibilot D, Liu T, Bordogna W, Balas B, Muller B, Shaw AT. (2019) Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX Study. J Thorac Oncol 14(7):1233– 1243.
23. Tang, Z., Zhang, J., Lu, X., et al. Coexistent genetic alterations involving *ALK*, *RET*, *ROS1* or *MET* in 15 cases of lung adenocarcinoma. *Mod Pathol* **31,** 307–312 (2018). https://doi.org/10.1038/modpathol.2017.109
24. Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted therapy in advanced non-small cell lung cancer: current advances and future trends. *J Hematol Oncol*. 2021;14(1):108. Published 2021 Jul 8. doi:10.1186/s13045-021-01121-2
25. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021; 384:2371-2381.
26. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50. doi: 10.1056/NEJMoa061884. Erratum in: N Engl J Med. 2007 Jan 18;356(3):318. PMID: 17167137.
27. Le X, Nilsson M, Goldman J, Reck M, Nakagawa K, Kato T, Ares LP, Frimodt-Moller B, Wolff K, Visseren-Grul C, Heymach JV, Garon EB. Dual EGFR-VEGF Pathway Inhibition: A Promising Strategy for Patients With EGFR-Mutant NSCLC. J Thorac Oncol. 2021 Feb;16(2):205-215. doi: 10.1016/j.jtho.2020.10.006. Epub 2020 Oct 20. PMID: 33096270.
28. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. JAMA. 1994 Mar 23-30;271(12):907-13. PMID: 8120958.
29. Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med. 2009 Dec 21;206(13):3015-29. doi: 10.1084/jem.20090847. Epub 2009 Dec 14. PMID: 20008522; PMCID: PMC2806460.
30. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823-1833. doi: 10.1056/NEJMoa1606774. Epub 2016 Oct 8. PMID: 27718847.
31. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856.
32. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, Cho BC, Planchard D, Paz-Ares L, Faivre-Finn C, Vansteenkiste JF, Spigel DR, Wadsworth C, Taboada M, Dennis PA, Özgüroğlu M, Antonia SJ. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. J Thorac Oncol. 2020 Feb;15(2):288-293. doi: 10.1016/j.jtho.2019.10.002. Epub 2019 Oct 14. PMID: 31622733; PMCID: PMC7244187.
33. Rodriguez-Abreu, D et al. CITYSCAPE: Primary Analysis of a Randomized, Double-Blind, Phase II Study of the Anti-TIGIT Antibody Tiragolumab plus Atezolizumab versus Placebo plus Atezolizumab as 1L Treatment in Patients with PD-L1-Selected NSCLC. Presented at: ASCO 2020 Virtual Scientific Program; 2020 May 29-31.
34. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rekhtman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2017 Mar;35(7):709-717. doi: 10.1200/JCO.2016.68.2005. Epub 2016 Sep 30. Erratum in: J Clin Oncol. 2017 Aug 1;35(22):2590. PMID: 27646942; PMCID: PMC5559901.
35. Tetzlaff MT, Nelson KC, Diab A, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a marker of therapy response in a subset of melanoma patients. J Immunother Cancer. 2018;6(1):14. Published 2018 Feb 12. doi:10.1186/s40425-018-0323-0
36. Freitas C, Sousa C, Machado F, et al. The Role of Liquid Biopsy in Early Diagnosis of Lung Cancer. Front Oncol. 2021;11:634316. Published 2021 Apr 16. doi:10.3389/fonc.2021.634316
37. Guibert N, Pradines A, Favre G, Mazieres J. Current and future applications of liquid biopsy in nonsmall cell lung cancer from early to advanced stages. Eur Respir Rev. 2020 Feb 12;29(155):190052. doi: 10.1183/16000617.0052-2019. PMID: 32051167.
38. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, Bivona T, Diehn M, Dive C, Dziadziuszko R, Leighl N, Malapelle U, Mok T, Peled N, Raez LE, Sequist L, Sholl L, Swanton C, Abbosh C, Tan D, Wakelee H, Wistuba I, Bunn R, Freeman-Daily J, Wynes M, Belani C, Mitsudomi T, Gandara D. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer: A Consensus Statement from The International Association for the Study of Lung Cancer (IASLC). J Thorac Oncol. 2021 Jul 8:S1556-0864(21)02284-X. doi: 10.1016/j.jtho.2021.06.017. Epub ahead of print. PMID: 34246791.
39. Nyberg, Kara, et al. "FDA Perspectives on the Use of LIQUID Biopsy in NSCLC." IASLC, 30 July 2021, www.iaslc.org/iaslc-news/ilcn/fda-perspectives-use-liquid-biopsy-nsclc.

## Authors

Daniel Dustin, DO, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Douglas Martin, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

## Correspondence

Douglas Martin, MD

Division of Pulmonary Critical Care and Sleep Medicine

593 Eddy Street

Providence, Rhode Island 02903

# A Case of Recurrent Malignant Melanoma of the Left Foot with In-Transit Metastases

DANIEL J. OLIVIERI, BS; DAITHI S. HEFFERNAN, MD, FACS, AFRCSI; R. JAMES KONESS, MD, FACS


## ABSTRACT

We report a 73-year-old male with recurrent amelanotic malignant melanoma of the left foot with in-transit metastases to the left thigh. In-transit metastatic melanoma can often represent a diagnostic and therapeutic challenge for physicians. This patient was treated with talimogene laherparepvec injections (T-VEC; Imlygic) in the left inguinal and the left plantar region every two weeks for one year as oncolytic viral therapy for advanced non-operable malignant melanoma. He then received consistent follow-up including blood work and PET scans every four months, and he also required further lymph node surgical dissection. To date, our patient has survived 3 years and 11 months, which is 27 months longer than the estimated median survival of 1 year 8 months for patients diagnosed with in-transit metastatic melanoma.


**KEYWORDS:** melanoma, in-transit metastasis, oncology, surgery

## INTRODUCTION

Melanoma is the deadliest form of skin cancer worldwide, with an overall incidence of approximately 21.8 per 100,000 Americans and increasing.[1] Metastatic melanoma is a relatively rare presentation at initial diagnosis, and it is associated with less than a 15% 5-year survival rate.[2] In-transit metastases are defined as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not located beyond the regional nodal basin.[3] In-transit melanoma – with an incidence of 4% for all melanoma patients – can present in a variety of pigmentations and textures and even masquerade as a rash.[3] As a result, the insidious presentation of in-transit metastasis represents a challenging diagnosis for even the most astute clinicians.[3] We present a case of a 73-year-old man diagnosed with in-transit metastasis for recurrent BRAF negative malignant melanoma of the left foot staged pT4bN2aMx (AJCC 7th edition TNM staging: pIIIC).

**Methodology:** A case report.

## RESULTS

A 73-year-old man with type II diabetes controlled on metformin first presented to the Providence VA Medical Center Podiatry Clinic in March 2016 for routine diabetic foot care. The initial examination was notable for a 1 cm full-thickness ulcer with a granular base and swelling on his left foot's mid plantar region, most concerning for traumatic injury to the left foot with potential for foreign body insertion. The patient denied any fever, chills, nausea, vomiting, or night sweats. An MRI of the left foot ruled out a retained foreign body. Podiatry recommended proper diabetic foot care, including daily foot inspections and regular outpatient follow-up at three-month intervals.

Nine months later, the patient noticed increased discomfort across the left plantar region while walking barefoot. The podiatry service then performed an incisional biopsy of the plantar lesion which demonstrated superficial and deep mixed inflammatory infiltrate including plasma cells, lymphocytes, and eosinophils with CD3+ T-cells, CD20+ B-cells, and CD163+ histiocytes, suggestive of melanoma of the left plantar foot. Of note, Sox10 was negative for melanoma. A multi-disciplinary team approach discussed the options with the patient. These included offering the patient aggressive therapeutic modalities including wide local excision with possible skin graft and sentinel lymph node biopsy, as well as a potential need for chemotherapy. Given the graveness of malignant melanoma, the option of no further excision and focusing on palliative therapeutic modalities were also discussed. A wide local surgical excision to achieve a 2-centimeter margin with skin graft was undertaken with an associated sentinel lymph node biopsy. The sentinel lymph node biopsy was negative for metastatic disease. His post-operative course was complicated by wound infection and delayed wound healing which necessitated further skin grafting in consultation with plastic surgery.

Clinical follow-up was performed every three to six months with Dermatology, Oncology, and General Surgery in a multi-disciplinary fashion. This assessed for local recurrence as well as emergence of new lesions. Follow-up imaging included sequential PET scans which were obtained every four months. A follow-up PET scan seven months later revealed satellite disease recurrence on the plantar aspect of the left foot and metastases to the groin with associated left inguinal lymphadenopathy. Satellite disease is defined as

intra-lymphatic metastases less than two centimeters from the primary lesion.[4] A punch biopsy was positive for melanoma and left inguinal lymph node cytology via fine needle aspiration was also consistent with malignant melanoma. The patient then began talimogene laherparepvec injections (T-VEC; Imlygic) directly in the left inguinal region and the left plantar region every two weeks for a year as oncolytic viral therapy for advanced non-operable malignant melanoma. Follow-up imaging and biopsies approximately eight months later demonstrated no residual malignant melanoma on the left foot but were notable for a residual left medial inguinal lymph node positive for malignant melanoma. Surgical left inguinal lymph node dissection was completed. The T-VEC adjuvant therapy was completed four months after the lymph node dissection. A follow-up PET scan 14 months later identified a positive soft tissue deposit located anteromedial to the left knee, which was surgically removed. Corresponding surgical pathology was consistent with BRAF negative metastatic malignant melanoma (in-transit metastases), and the patient was started on cycles of monthly systemic immunotherapy of nivolumab (opdivo) 480 mg for twelve months.

Follow-up imaging was negative for melanoma until a PET CT and U/S of left thigh performed in December 2020 identified a 4 mm soft tissue deposit seen on nuclear imaging only, and an FNA was consistent with another in-transit deposit of disease. Given that this patient has survived well past the median survival of 20 months (now being 47 months), he underwent further surgical resection of the newly identified in-transit metastases.

**Table 1.** Summary of 2019 American Academy of Dermatology Malignant Melanoma Surveillance Guidelines[5,8-10,13]

| Stage at initial diagnosis[a] | Time Frame | Recommended surveillance |
|---|---|---|
| Stage 0 (melanoma in situ) | Years 0–2 | Physical exam and full skin exam at least every 6–12 months |
| | Years 2+ | Annual physical examination and full skin exam |
| Stage IA–IIA | Years 0–5 | Physical exam and full skin exam at least every 6–12 months |
| | Years 5+ | Annual physical examination and full skin exam |
| Stage IIB or greater[b,c] | Year 0–2 | Physical examination and full skin exam at least every 3–6 months<br>Surveillance imaging recommended based on recurrence risk[5] |
| | Year 3–5 | Physical examination and full skin exam at least every 6 months<br>Surveillance imaging recommended based on recurrence risk[5] |
| | Year 5+ | Annual physical examination and full skin exam |

[a] Staging guidelines correspond with American Joint Committee on Cancer (AJCC) 7th Edition

[b] National Cancer Comprehensive Network (NCCN) guidelines include radiological surveillance for stage IIB or greater at the 3 and 12-month interval for up to 3–5 years.[5]

[c] Patients with in-transit metastases are classified as Stage IIIB or IIIC, corresponding to lymph node involvement.[6]

## DISCUSSION

In-transit metastases represent one of the most significant diagnostic and therapeutic challenges in the long-term management of melanoma. The physical examination findings of patients with in-transit melanoma are often lacking, and therefore strict follow-up imaging (i.e., PET or CT scan) is critical to minimize the risk of missing an in-transit metastasis. Additionally, surveillance is recommended at intervals ranging from three–twelve months for up to five years (**Table 1**).[5] Imaging intervals depend on pathologic findings, adjuvant therapy, and clinical course. The identification of in-transit metastases might warrant a referral to a surgical oncologist for disease removal – a typically effective strategy if the recurrence is localized to a small number of sites (i.e., 1–3). However, given that in-transit metastases are rarely localized to a few locations, medical-surgical collaboration is often required.[6] Despite robust disease management and surveillance, in-transit metastases carry a poor prognosis with a 5-year survival rate of approximately 25%.[7] Systemic immunotherapy or chemotherapy is often ineffective, and surgical removal may also be unsuccessful depending on disease presentation and location.[6] These failures in the response of in-transit metastases have necessitated the development of novel regional pharmacologic therapies.[6]

In-transit metastases are a critical and often morbid component of malignant melanoma care. Initial work-up and management of the primary melanoma are vital. Suspicious skin lesions require a thorough work-up and/or referral to a dermatologist if needed. Current American Academy of Dermatology (AAD) guidelines recommend a narrow excisional/complete biopsy of a skin lesion with 1- to 3-mm margins, typically completed via elliptical excision (i.e., "fusiform"), punch excision, or deep shave (i.e., "saucerization") removal, for definitive diagnosis of cutaneous melanoma.[8] The deep shave removal is currently the most frequent diagnostic method utilized in the U.S. due to accessibility and cost.[8] Clinicians may consider sentinel lymph node biopsy if there is a high index of suspicion for metastatic spread.[8,9] While surveillance guidelines for malignant melanoma vary by society, surveillance frequency generally correlates to the tumor's staging and/or pathologic biopsy based on Breslow thickness.[10] Staging of melanoma is critical to directing how lesions and patients are to be followed. The AJCC Cancer Staging Manual[11] delineates the nature and degree of clinical or radiographic surveillance based

on the initial depth of melanotic lesions. These range from clinical and dermatology examinations for patients with Stage I/IIA lesions up to requirements for serial ultrasound imaging of the affected nodal field as well as PET/CT surveillance.[11,12] Initial clinical suspicion for possible risk of potential in-transit metastases included Stage III or greater, or evidence of ulceration at the time of the initial biopsy. A summary of current AAD surveillance guidelines for malignant melanoma are presented in **Table 1.**[8-10,13] After pathologic diagnosis of malignant melanoma, treatment generally involves surgical resection +/– adjuvant therapy. Pathology directly informs the likelihood of melanoma recurrence and systemic spread.[9,10]

A multi-disciplinary approach to disease surveillance and regular follow-up is crucial in the long-term care of malignant melanoma. Given the critical component of the physical exam in patient surveillance, it is often best advised that one designated member from within the broader multi-disciplinary team be primarily responsible for overseeing long-term disease surveillance. Given the collaborative nature of these teams, all providers are equally suited to guide the patient through the treatment course; it is essential that patients consistently utilize a singular provider to monitor surveillance. Unlike in primary melanoma, secondary melanoma is more often discovered by a healthcare professional rather than patients.[9] One important consideration for provider selection is accessibility, wherein the patient needs to consistently schedule appointments with appropriate frequency (**Table 1**). Additionally, the surveilling provider should also communicate screening results with the rest of the treatment team; extensive collaboration among dermatologists, surgical oncologists, medical oncologists, and primary care physicians can improve the long-term outcomes of malignant melanoma.

The reported median survival time following the diagnosis of in-transit metastases is approximately 20 months.[14] Read et al. reported a median survival time of 19.9 months, whereas Mervic noted a significant discrepancy in sex, with men often presenting with a higher stage of melanoma and significantly shorter survival time from the diagnosis.[14,15] Given the often innocuous clinical findings of in-transit melanoma, much of this poor survival is often attributed to the difficulty in diagnosing the in-transit component. Following identification of in-transit metastases, the 5-year survival rate is reported to be 25%.[14] The current standard treatment for in-transit metastases includes wide local excision with up to 2 cm margins as well as potentially therapeutic nodal basin excisions. Systemic chemotherapy ranges from dacarbazine to PD-1 based immunotherapy. Specific considerations include the initial presentation, radiographic location, and patient choice.[6,10,14] Other treatment plans for in-transit metastases might include isolated limb infusion and isolated limb perfusion therapy.[16] Isolated limb perfusion therapy utilizes the placement of venotomy and arteriotomy catheter into major blood vessels localized near the tumor to regionally transmit chemotherapy and minimizing the systemic toxicity of chemotherapy.[16] Isolated limb infusion therapy, on the other hand, utilizes a percutaneous catheter thereby reducing time and cost of treatment duration.[16] Last, one recent innovation in immunotherapy is talimogene laherparepvec (T-VEC, Imlygic) – a genetically modified strain of HSV-1 – as injectable oncolytic viral therapy for non-operable malignant melanoma.[17,18] T-VEC therapy utilizes a combination of direct tumor cell lysis and upregulation of regional host immune response to eliminate regional metastases and reduce the need for potentially toxic systemic chemotherapy.[19] As a result, the utilization of novel oncolytic viral therapies such as T-VEC represent a potentially important breakthrough in cancer pharmacology.[19] Currently, T-VEC is approved by the U.S. Food and Drug Administration to treat non-operable Stage IIB–IV M1c melanoma located in a region where direct injection is possible.[20] Despite T-VEC's novel development, high financial cost (estimated to be $65,000) and low provider awareness might currently preclude more ubiquitous utilization.[21] Oncolytic viral therapy is currently being investigated as treatment in other cancers, including bladder cancer (adenovirus) and hepatocellular carcinoma (vaccinia virus).[22]

## CONCLUSION

In-transit metastases represent a diagnostic and therapeutic challenge for oncologic care, particularly in melanoma. Concomitant follow-up imaging every four to twelve months and T-VEC adjuvant therapy may help reduce rates of metastatic recurrence. Although the median survival time following the diagnosis of in-transit metastases is less than two years[23], T-VEC and immunotherapy most likely prolonged the life in our patient with malignant melanoma. Extensive collaboration among primary care physicians, dermatologists, medical oncologists, and surgical oncologists can help prolong the survival of patients with in-transit metastases from recurrent malignant melanoma.

### References


1. Centers for Disease Control and Prevention. "Melanoma Incidence and Mortality, United States—2012–2016." (2019).
2. Tas, Faruk. "Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors." Journal of oncology 2012 (2012).
3. Perone, Jennifer A., et al. "Contemporary approaches to in-transit melanoma." Journal of oncology practice 14.5 (2018): 292-300.
4. Bann, Darrin V., et al. "Satellite and in-transit metastatic disease in melanoma skin cancer: a retrospective review of disease presentation, treatment, and outcomes." Dermatologic Surgery 45.3 (2019): 371-380.
5. Freeman, Morganna, and Shachar Laks. "Surveillance imaging for metastasis in high-risk melanoma: importance in individualized patient care and survivorship." *Melanoma management* vol. 6,1 MMT12. 18 Apr. 2019, doi:10.2217/mmt-2019-0003

6. Turley RS, Raymond AK, Tyler DS. Regional treatment strategies for in-transit melanoma metastasis. Surg Oncol Clin N Am. 2011 Jan;20(1):79-103. doi: 10.1016/j.soc.2010.09.008.
7. Trotter, Shannon C., et al. "A global review of melanoma follow-up guidelines." The Journal of clinical and aesthetic dermatology 6.9 (2013): 18.
8. Swetter, Susan M., et al. "Guidelines of care for the management of primary cutaneous melanoma." *Journal of the American Academy of Dermatology* 80.1 (2019): 208-250.
9. Freeman, Morganna, and Shachar Laks. "Surveillance imaging for metastasis in high-risk melanoma: importance in individualized patient care and survivorship." *Melanoma management* vol. 6,1 MMT12. 18 Apr. 2019, doi:10.2217/mmt-2019-0003
10. Turley RS, Raymond AK, Tyler DS. Regional treatment strategies for in-transit melanoma metastasis. Surg Oncol Clin N Am. 2011 Jan;20(1):79-103. doi: 10.1016/j.soc.2010.09.008.
11. Byrd, David R., et al. AJCC cancer staging manual. Ed. Stephen B. Edge. Vol. 649. New York: Springer. (2010).
12. Mar, Victoria J., et al. "Diagnosis and management of cutaneous melanoma." Australian journal of general practice 49.11 (2020): 733.
13. Bichakjian CK, Halpern AC, Johnson TM, et al. "Guidelines of care for the management of primary cutaneous melanoma." American Academy of Dermatology. J Am Acad Dermatol. 2011;65:1032-1047.
14. Read, R.L., Haydu, L., Saw, R.P.M. *et al.* In-transit Melanoma Metastases: Incidence, Prognosis, and the Role of Lymphadenectomy. *Ann Surg Oncol* **22,** 475–481 (2015). https://doi.org/10.1245/s10434-014-4100-0.
15. Mervic L. Time course and pattern of metastasis of cutaneous melanoma differ between men and women. PLoS One. 2012;7(3):e32955. doi: 10.1371/journal.pone.0032955. Epub 2012 Mar 6.
16. Testori A, Verhoef C, Kroon HM, et al. Treatment of melanoma metastases in a limb by isolated limb perfusion and isolated limb infusion. J Surg Oncol. 2011 Sep;104(4):397-404.
17. Andtbacka, R. H., et al. "Talimogene laherparepvec improves durable response rate in patients with advanced melanoma." J clin Oncol 33.25 (2015): 2780-2788.
18. Rehman, Hasan, et al. "Into the clinic: Talimogene laherparepvec (T-VEC), a first-in-class intratumoral oncolytic viral therapy." Journal for immunotherapy of cancer 4.1 (2016): 1-8.
19. Kohlhapp, Frederick J., and Howard L. Kaufman. "Molecular pathways: mechanism of action for talimogene laherparepvec, a new oncolytic virus immunotherapy." Clinical Cancer Research 22.5 (2016): 1048-1054.
20. "IMLYGIC (talimogene laherparepvec)". U.S. Food and Drug Administration. Accessed 24 Jan 2021. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/imlygic-talimogene-laherparepvec.
21. Orloff, Marlana. "Spotlight on talimogene laherparepvec for the treatment of melanoma lesions in the skin and lymph nodes." Oncolytic virotherapy vol. 5 91-98. 4 Oct. 2016, doi:10.2147/OV.S99532.
22. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Sci. 2016 Oct;107(10):1373-1379. doi: 10.1111/cas.13027. Epub 2016 Sep 9.
23. Read, Rebecca L., et al. "In-transit melanoma metastases: incidence, prognosis, and the role of lymphadenectomy." Annals of surgical oncology 22.2 (2015): 475-481.


## Authors


Daniel J. Olivieri, BS, is a medical student at the Warren Alpert Medical School of Brown University, Providence, RI.

Daithi S. Heffernan, MD, FACS, AFRCSI, is a trauma and critical care surgeon and an Associate Professor of Surgery at the Warren Alpert Medical School of Brown University, Providence, RI.

R. James Koness, MD, FACS, is a surgical oncologist and a Clinical Assistant Professor of Surgery at the Warren Alpert Medical School of Brown University, Providence, RI. He also is the Director of the Breast Health Program at Roger Williams Medical Center, Providence, RI.


## Disclaimer

The views expressed here are those of the authors and do not necessarily reflect the position or policy of the US Department of Veterans Affairs or the US government.

## Financial Disclosure


No author has a financial or proprietary interest in any material or method mentioned. No financial support was received in any public or private manner for the completion of this study.


## Correspondence


Daithi S. Heffernan, MD
Department of Surgery
VA Medical Center Providence
830 Chalkstone Ave
Providence, RI 02908
401-273-7100
daithi_heffernan@brown.edu

# Diagnosing Lemierre's Syndrome as the Cause of Multifocal Pneumonia During the COVID-19 Pandemic

CULLEN SOARES, MD; KRISTY BLACKWOOD, BA; MARC VECCHIO, MD; ELIZABETH R. FRANCIS, MD, MPH; SHENJUN ZHU, MD; JENNIE JOHNSON, MD

## ABSTRACT

A 21-year-old male with no past medical history presented with a sore throat, cough, and shortness of breath after attending a party days earlier. He was initially treated for community-acquired pneumonia, but subsequently developed a new oxygen requirement. CT imaging of the chest showed multifocal airspace disease, concerning for COVID-19. Testing for SARS-CoV-2 was negative by RT-PCR and antibody testing. Blood cultures subsequently grew *Streptococcus anginosus*. A CT scan of his neck demonstrated a right peritonsillar abscess and right internal-jugular thrombus, consistent with Lemierre's syndrome. He underwent incision and drainage of the peritonsillar abscess and completed 4 weeks of IV antibiotics, which improved his symptoms. It is important to recognize that the differential diagnosis of multifocal pneumonia is broad and includes Lemierre's syndrome. The COVID-19 pandemic presents challenges with regards to anchoring bias for multifocal pneumonia.

**KEYWORDS:** Lemierre's syndrome; multifocal pneumonia; COVID-19; peritonsillar abscess; anchoring bias

## BACKGROUND

The COVID-19 pandemic has had a significant impact on the delivery of health care with specialized precautions and limited face-to-face interactions. Lack of personal protective equipment, a paucity of testing, shelter in place and stay-at-home orders, as well as patient avoidance of medical settings during the initial phases of the pandemic affected both urgent and non-emergent care.[1,2,3]

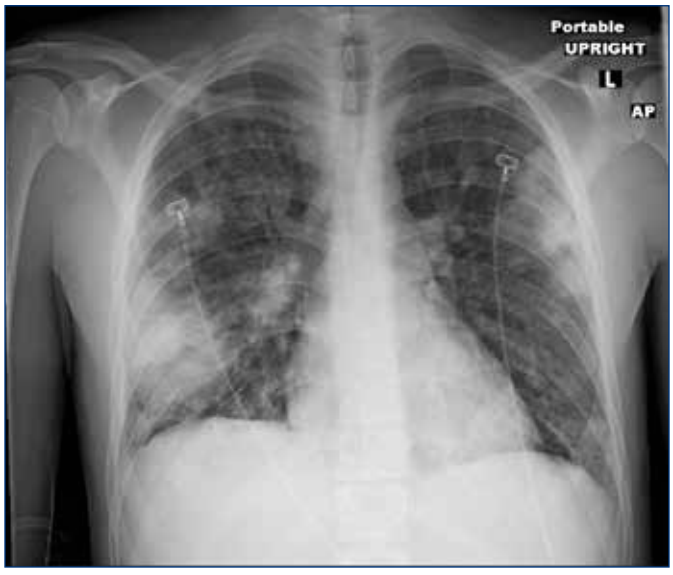
Given the widespread community transmission of SARS-CoV-2, it was important to cohort patients with COVID-19 together and to separate them from patients without COVID-19 symptoms. As such, determining whether or not a patient had COVID-19 became very important to reduce transmission.[1] This strong focus on determining a patient's COVID-19 status up front presented challenges with anchoring biases as illustrated in the following case.

## CASE REPORT

A 21-year-old male with no significant past medical history presented to an outside hospital's emergency department with sore throat, fever, chills, muscle aches, and non-bloody emesis. The patient attended a July 4th party with about 20 individuals and his symptoms began the following day and worsened as the week progressed. Five days later he developed a cough with non-radiating bilateral chest pain, exacerbated by coughing. He presented to the emergency department with an unremarkable physical exam, and was found to have multifocal airspace disease on chest X-ray. Labs were notable for sodium of 125, potassium of 3.5, and white blood cell count (WBC) of 12.1k with 6% bands. SARS-CoV-2 RT-PCR was collected. The patient was discharged from the ED with doxycycline for empiric treatment of bacterial pneumonia while awaiting the SARS-CoV-2 RT-PCR result, which was subsequently negative.

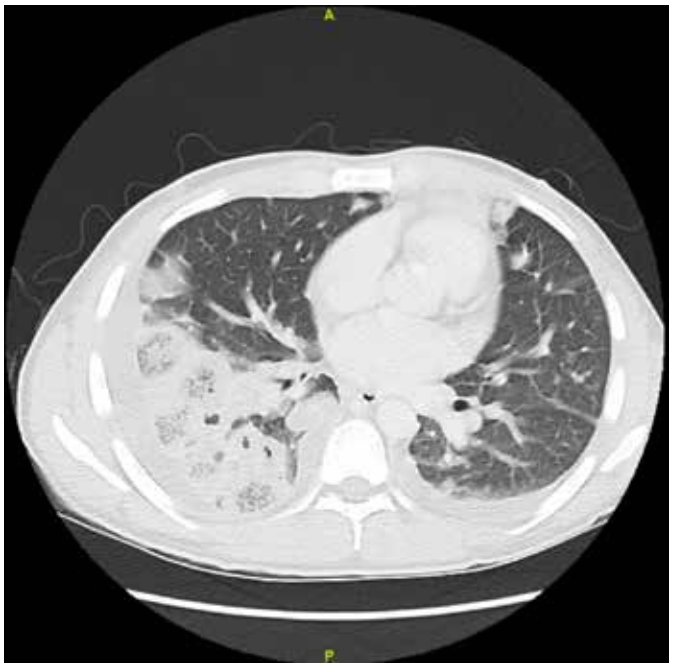
The patient presented again 3 days later with worsening cough, chest pain, and shortness of breath. Exam was notable for new pharyngeal exudates and posterior oropharyngeal erythema, diffuse rales, and he appeared to be in acute distress. Chest X-ray was repeated (**Fig. 1**) and showed worsening multifocal airspace disease. Repeat SARS-CoV-2 RT-PCR, respiratory pathogen panel (RPP), and streptococcal throat

**Figure 1.** Chest X-ray showing bilateral multifocal airspace disease.



culture and group A PCR were negative. Blood cultures were sent. The patient was found to be hypoxic requiring 2 L of supplemental oxygen by nasal cannula to maintain normal oxygen saturation. Despite negative SARS CoV-2 tests, the new oxygen requirement and abnormal laboratory and X-ray findings were concerning for impending decompensation for what was presumed to be COVID-19, and the patient was transferred to our facility in the event of worsening hypoxic respiratory failure requiring intubation.

**Figure 2.** CTA Chest PE protocol (axial view) showing dense consolidation on right side.



At the accepting hospital, CT angiogram (CTA) was performed to rule out pulmonary embolism, as the patient had an elevated d-dimer level and persistent oxygen requirement. The CTA was negative for acute pulmonary embolus but demonstrated multifocal airspace disease (**Fig. 2**). SARS-CoV-2 IgG antibody was sent (IgM testing was not available) due to concern for possible COVID-19 and the potential for false-negative RT-PCR tests. He was started empirically on piperacillin-tazobactam as antibiotic coverage for severe bacterial pneumonia. SARS-CoV-2 antibodies were negative, but blood cultures drawn prior to transfer grew gram-positive cocci, subsequently identified as *Streptococcus anginosus*, a non-group A streptococcal organism. At this point, given positive blood cultures and multiple negative tests for SARS-CoV-2, the diagnosis of COVID-19 was ruled out by day 9 of symptoms, and COVID-19 isolation precautions were removed. Antibiotic regimen was tailored to ceftriaxone and vancomycin. Due to his initial presenting complaint of sore throat, a CT scan of the neck was performed revealing a non-occlusive thrombus in the right internal jugular vein (**Fig. 3**) with a right peritonsillar abscess. Repeat CT scan of the neck (**Fig. 4**) several days later demonstrated interval increase in size of the peritonsillar abscess. Otolaryngology (ENT) was consulted and performed a bedside incision and drainage. Hematology was consulted

**Figure 3.** Contrast CT Neck (coronal view) showing with right internal jugular vein thrombus.

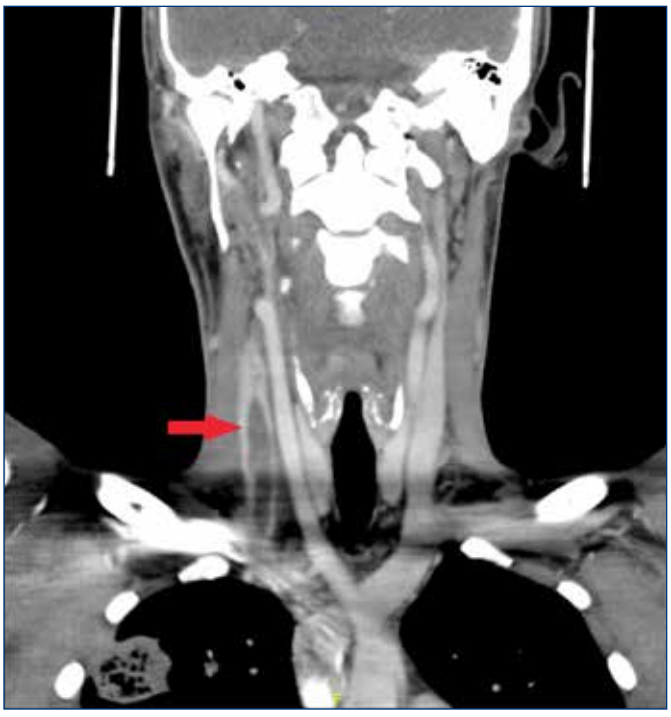
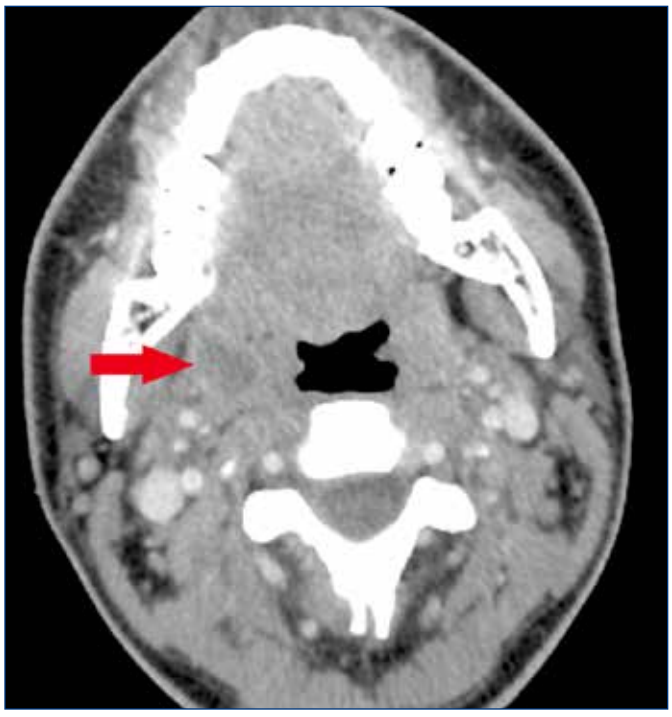


**Figure 4.** Contrast CT Neck (axial view) showing right peritonsillar abscess.



and recommended against anticoagulation. MRI of the brain revealed no associated emboli. The patient's oxygen requirement ultimately resolved, and the patient was discharged on ceftriaxone for a total of 4 weeks. The patient was noted to have clinical improvement and resolution of his symptoms 2 weeks after hospital discharge at an Infectious Disease follow-up appointment.

## DISCUSSION

Lemierre's syndrome, first described in 1936 by the French physician André-Alfred Lemierre, typically occurs in healthy teenagers and young adults, and is characterized by anaerobic septic emboli originating from a primary oropharyngeal infectious site, such as a tonsillar or peritonsillar abscess.[4] The abscess causes thrombophlebitis of the internal jugular vein, owing to its close proximity to the oropharynx. Symptoms typically begin with a sore throat followed by high fevers, rigors, and jaw and neck muscle pain. Rigors can peak around days 8 to 12. Pulmonary abscesses can cause blood-stained or rusty sputum and chest pain.[4] Organisms such as *Fusobacterium necrophorum, Fusobacterium nucleatum, Fusobacterium* species, *Streptococci* species, *Staphylococcus aureus, MRSA, Klebsiella pneumoniae, Pseudomonas aeruginosa* are typically implicated.[5]

With the widespread use of antibiotics, Lemierre's syndrome is rare and is sometimes referred to as "the forgotten disease."[2,5] This classic presentation of Lemierre's syndrome was not high on the initial differential diagnosis for the patient's worsening multifocal pneumonia due to his presentation with non-specific COVID-like symptoms following attendance at a large gathering. At the time of diagnosis in July 2020, the prevalence of COVID-19 in Rhode Island was estimated at 4% with 11.6% of confirmed cases being hospitalized.[6] Because of the ongoing COVID-19 pandemic and concern for a highly transmissible infectious disease, the initial diagnosis of multifocal pneumonia was thought to be due to COVID-19, as this had been the most common form of multifocal pneumonia present in the community. As a result, Lemierre's syndrome was not on the differential when this patient was initially evaluated and triaged, due to anchoring bias towards COVID-19, despite physical exam findings suggestive of Lemierre's.

Similar cases have been reported in adolescents and young adults ultimately diagnosed with Lemierre's syndrome following presumed COVID-19 infection.[7,8] Key to making the diagnosis of Lemierre's syndrome in this case was re-consideration of the patient's presenting symptoms, especially his sore throat. His infectious work-up at that point (two negative SARS-CoV-2 RT-PCR, negative SARS-CoV-2 antibody, negative RPP, negative throat culture and blood cultures positive for *Streptococcus anginosus*) led to CT of the neck which demonstrated a tonsillar abscess and septic internal jugular thrombus.

Lemierre's syndrome is typically diagnosed clinically: an adolescent or young adult experiences sore throat followed by fevers, chest pain, and shortness of breath. Blood cultures or drainage of a pharyngeal abscess can confirm the causative organism and guide antibiotic treatment. Length of antibiotic therapy is on the order of weeks, and selection guided by the causative organism, though usually a penicillin.[5] Anticoagulation for associated septic thrombi is controversial, and there is little research on this particular aspect of the syndrome.[5,9]

With the COVID-19 pandemic there has been a strong focus on avoiding physical contact between patients and physicians on multiple levels to protect physicians from potentially sick patients and vice versa.[11] Physical exam components that could be aerosol-generating are minimized to decrease the risk of generating infectious droplets.[12] Incomplete physical exams can potentially lead to delayed diagnoses. However, in this patient's case, the history and examination pointed towards an ongoing pharyngeal infection and subsequent respiratory distress. The respiratory distress component was focused on more than the accompanying sore throat, leading to the anchoring bias towards COVID-19. In retrospect, this combination of findings is typical for a presentation of Lemierre's syndrome.

This case demonstrates the risks of anchoring bias (focusing on a particular facet of a case) and premature closure (closing of the diagnostic process before all relevant information is obtained)[10] as COVID-19 was initially highest on the differential given its high community prevalence at the time of presentation. Lemierre's syndrome was not considered despite initial complaints of sore throat, and congruent examination findings. The consequences of these cognitive errors are well documented, and include increased medical errors, lower standard-of-care ratings, and increased complications.[13,14]

## CONCLUSIONS

The diagnosis of multifocal pneumonia and presumed COVID-19 distracted from further evaluation of the patient's chief complaint of sore throat. Consequently, the non-occlusive thrombus and peritonsillar abscess were not identified for several days after initial presentation. These factors resulted in the delay in treatment of a classic presentation of Lemierre's syndrome in a young adult. The breadth of symptoms associated with SARS-CoV-2 overlap significantly with other illnesses, reinforcing the importance of a broad differential diagnosis in such cases.

## References


1. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic. *CDC*. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. February 10, 2021. Accessed June 8, 2021.
2. Binnicker MJ. Challenges and controversies to testing for covid-19. *J Clin Microbiol.* 2020;58(11).
3. Provenzano DA, Sitzman BT, Florentino SA, Buterbaugh GA. Clinical and economic strategies in outpatient medical care during the COVID-19 pandemic. *Reg Anesth Pain Med.* 2020;45(8):579-585.
4. Lemierre A. On certain septicæmias due to anaerobic organisms. *The Lancet*. 1936;227(5874):701-703.
5. Johannesen K, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. *Infect Drug Resist.* 2016;9:221-227.
6. McQuade B, Fulton J, Trikalinos T, et al. COVID-19 Hospitalizations: Trends, Demographics, and Risk Factors for Critical Illness. Rhode Island Department of Health. https://health.ri.gov/publications/issuebriefs/COVID19-Hospitalizations Published September 2020. Accessed May 17, 2021.
7. Karn MN, Johnson NP, Yaeger SK, Fugok KL. A teenager with fever, chest pain, and respiratory distress during the coronavirus disease 2019 pandemic: a lesson on anchoring bias. *J Am Coll Emerg Physicians Open.* Published online September 26, 2020.
8. Repper DC, Arrieta AC, Cook JE, Renella P. A case of lemierre syndrome in the era of covid-19: all that glitters is not gold. *Pediatric Infectious Disease Journal.* 2020;39(12):e445-e447.
9. Gore MR. Lemierre syndrome: a meta-analysis. *Int Arch Otorhinolaryngol.* 2020;24(3):e379-e385.
10. Restrepo D, Armstrong KA, Metlay JP. Annals clinical decision making: avoiding cognitive errors in clinical decision making. *Ann Intern Med.* 2020;172(11):747-751.
11. Hu A. Connection in the time of COVID-19. *Univ Toronto Med J.* 2021;98(2):22.
12. Griffin KM, Karas MG, Ivascu NS, Lief L. Hospital preparedness for covid-19: a practical guide from a critical care perspective. *Am J Respir Crit Care Med.* 2020;201(11):1337-1344.
13. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. *BMC Med Inform Decis Mak.* 2016;16(1):138.
14. Antonacci AC, Dechario SP, Antonacci C, et al. Cognitive bias impact on management of postoperative complications, medical error, and standard of care. *J Surg Res.* 2021;258:47-53.


## Authors


Cullen Soares, MD, Resident Physician, Internal Medicine, Brown University/Rhode Island Hospital.

Kristy Blackwood, BA, Medical Student, Brown University.

Marc Vecchio, MD, Resident Physician, Internal Medicine, Brown University/Rhode Island Hospital.

Elizabeth R. Francis, MD, MPH, Resident Physician, Internal Medicine, Brown University/Rhode Island Hospital.

Shenjun Zhu, MD, Hospitalist Medicine Attending Physician, The Miriam Hospital, Brown University.

Jennie Johnson, MD, Infectious Diseases Attending Physician, The Miriam Hospital, Brown University.


## Disclosures

No project Support/Funding

## Disclaimer

This work does not represent the views of Brown University, Rhode Island Hospital, The Miriam Hospital, or Lifespan.

## Correspondence

Cullen Soares, MD
cullen_soares@brown.edu

# SARS-CoV-2 Variants in Rhode Island

RAMI KANTOR, MD; VLADIMIR NOVITSKY, MD, PhD; KRISTIN CARPENTER-AZEVEDO, MSc; MARK HOWISON, MSc; AKARSH MANNE, MSc; JOSEPHINE K. DARPOLOR, PhD; APRIL BOBENCHIK, PhD; ANUBHAV TRIPATHI, PhD; RICHARD C. HUARD, PhD; EWA KING, PhD

**ABSTRACT**

COVID-19 is a worldwide public health emergency caused by SARS-CoV-2. Genomic surveillance of SARS-CoV-2 emerging variants is important for pandemic monitoring and informing public health responses. Through an interstate academic-public health partnership, we established Rhode Island's capacity to sequence SARS-CoV-2 genomes and created a systematic surveillance program to monitor the prevalence of SARS-CoV-2 variants in the state. We describe circulating SARS-CoV-2 lineages in Rhode Island; provide a timeline for the emerging and expanding contribution of variants of concern (VOC) and variants of interest (VOI), from their first introduction to their eventual predominance over other lineages; and outline the frequent identification of known adaptively beneficial spike protein mutations that appear to have independently arisen in non-VOC/non-VOI lineages. Overall, the described Rhode Island-centric genomic surveillance initiative provides a valuable perspective on SARS-CoV-2 in the state and contributes data of interest for future epidemiological studies and state-to-state comparisons.

**KEYWORDS:** COVID-19, SARS-CoV-2, variants, public health, genomic sequencing, viral mutations

## BACKGROUND

The 2019 coronavirus disease (COVID-19) pandemic has resulted in 180,569,875 infections and 3,912,211 deaths worldwide as of June 26, 2021.[1] Since publication of the first genomic sequence for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2),[2] we have witnessed the development of viral mutations throughout the SARS-CoV-2 genome, with gradual predominance of those with major selective advantages.[3,4] These viruses with mutations, termed variants, though feared in the context of this and other pandemics, are expected as a natural part of virus life cycles.[5] Viruses, including SARS-CoV-2, mutate routinely as they evolve due to error-prone replication processes, during which mutations accumulate.[6] What matters most is whether these mutations have epidemiologic and clinical implications.

Driven by epidemiological necessity, genomic surveillance efforts increased towards the end of 2020 and it became increasingly clear that multiple SARS-CoV-2 variants with enhanced fitness were emerging independently in different parts of the world, including the United Kingdom,[7] South Africa,[8] Brazil,[9] California,[10] New York,[11] and most recently India.[12] Within a short time, the United States Centers for Disease Control and Prevention (CDC) defined, in an evolving process, viral variants of interest (VOI), with mutations of likely clinical and public health significance based on available data; variants of concern (VOC), with mutations of known significance; and variants of high consequence, with mutations of high significance, against which prior prevention and medical efforts fail.[13] Though existing nomenclature of SARS-CoV-2 variants remains a challenge,[14] the World Health Organization (WHO) recently proposed a simplification,[15] and, as of this writing, CDC-defined VOI include lineages B.1.427 and B.1.429 (both WHO Epsilon), first identified in California; B.1.525 (Eta) and B.1.526 (Iota), first identified in New York; B.1.617.1 (Kappa) and B.1.617.3 in India; and P.2 (Zeta) in Brazil; and VOC include lineages B.1.1.7 (Alpha), first identified in the United Kingdom; B.1.351 (Beta) in South Africa; B.1.617.2 (Delta) in India; and P.1 (Gamma) in Brazil. There are no currently defined variants of high consequence.[13]

VOC and VOI are elevated to these designations from conventional viral variants due to their mutations with clinical and public health impact. Though these mutations occur throughout the ~30,000 nucleotide span of the SARS-CoV-2 genome, the most strategically located ones are in or close to the receptor binding domain (RBD) of the viral spike protein. This specific location mediates the viral binding to the angiotensin-converting enzyme 2 (ACE2) human cellular receptor, and the resulting membrane fusion and viral replication cycle, making it also a prime target of innate and adaptive antiviral responses.[16]

As of June 25, 2021, Rhode Island (RI) has had a total of 152,514 positive COVID-19 cases, and 2,728 associated deaths.[17] In April 2020, the Kantor laboratory at the Providence-Boston Center for AIDS Research set up the capacity for SARS-CoV-2 whole genome sequencing to examine variant and mutation evolution in RI.[18] This initial, academic interest has been since formalized and significantly enhanced by the RI State Health Laboratory (RISHL), and regional and

national collaborators, aided by the large genomic surveillance investment and analytic tools development in the United States and globally.[19-22] In this manuscript we present the evolving status of the large-scale surveillance of SARS-CoV-2 variants in RI, raise awareness to their existence, and discuss their potential implications for public health responses, as we continue to fight this global pandemic.

## METHODS

### Collection of SARS-CoV-2 samples

The RISHL established a system for the collection of residual specimens from clinical laboratories involved in SARS-CoV-2 diagnostic testing for RI residents. The system was designed to provide specimens from infected individuals who were hospitalized, reside or work at long-term care facilities, correctional facilities staff and inmates, K–12 school students and staff, colleges and universities, and the general population seeking SARS-CoV-2 testing. Samples were submitted to the RISHL, de-identified and sequenced by collaborating laboratories, including the CDC, Broad Institute and Kantor Laboratory. The RISHL also established an independent SARS-CoV-2 sequencing capacity. In a parallel effort, CDC contracted several commercial laboratories to sequence SARS-CoV-2 from diagnostic specimens. Sequences generated in these laboratories are submitted to public databases, including the Global Initiative on Sharing All Influenza Data (GISAID).[20] The work presented here includes sequences originating from RI residents that were aggregated from GISAID.

### SARS-CoV-2 sequencing and sequence analysis

Sequencing methods varied by individual protocols of laboratories wherein samples were processed. For illustration, in the Kantor laboratory and RISHL, for specimens with low (<30) cycle thresholds (Ct), RNA was extracted, reverse transcribed and amplified, and the entire SARS-CoV-2 genome was sequenced by next generation sequencing (NGS) using the Illumina MiSeq platform. Genomic analyses of statewide SARS-CoV-2 sequences were conducted at the Kantor laboratory, with available tools and custom python scripts.[21-23] Scripts used for analyses pipelines are available under an open-source license from https://github.com/kantorlab/covid-pipeline.

### Analysis of SARS-CoV-2 mutations

To investigate development of viral mutations outside known VOC/VOI, we first examined occurrence of SARS-CoV-2 spike protein mutations that have been associated with a VOC or VOI by CDC definitions,[13] but that occurred at least once in variants *not* classified as VOC or VOI. We examined the five most frequent mutations and aggregated the remaining as 'other'. We also specifically examined occurrence of VOC/VOI mutations between amino acid positions 417–501 in the spike RBD, which have been more commonly associated with poor clinical outcomes like increased transmission and disease severity, and immune escape.

### Phylogenetic analysis

To provide a snapshot of the phylogenetic spectrum of available RI SARS-CoV-2 sequences from the start of the COVID-19 pandemic, we created a maximum likelihood tree with RAxML,[24] that includes the earliest (i) RI non-VOC/non-VOI sequence per month since the start of the epidemic; (ii) VOC sequence per month since its detection in RI; (iii) VOI sequence per month since its detection in RI; the earliest and latest available non-VOC/non-VOI sequences from each New England state (Maine, New Hampshire, Vermont, Massachusetts, Connecticut) and New York; one reference sequence for each of the VOI/VOC; and the original SARS-CoV-2 sequence from Wuhan (used as a root). The number of sequences included was limited to allow a reasonable tree resolution.

## RESULTS

The first COVID-19 case was detected at the RISHL on 2/29/20 and sequenced by the CDC. A selection of succeeding isolates provided by the RISHL to the Kantor laboratory and the CDC were further sequenced through December of 2020 (n=99). December of 2020 was punctuated by a heightened concern over the B.1.1.7 variant that was emerging in the USA and it was recognized that a (albeit nonspecific) marker for B.1.1.7 was that it displayed a "S-gene target failure" (SGTF) profile by some real-time PCR assays.[25] During that time, the RISHL began to see an alarming increase in the number of positive specimens that were SGTF and rapidly scaled up sequencing efforts in order to ascertain whether B.1.1.7 was circulating in RI. It was not B.1.1.7 yet, as most of the November–December 2020 SGTF lineage was actually the B.1.375 variant.[25] It was not until 1/19/21 that the first B.1.17 variant was detected in RI. The expansion of sequencing efforts succeeded thanks to regional collaborations with the Massachusetts Department of Health and the Sabeti Laboratory at the Broad Institute, Cambridge, MA. Indeed, from December 2020 through June 2021 the number of SARS-CoV-2 isolates successfully sequenced from RI residents by the collaborative has substantially increased by almost 40-fold and, as of 6/24/21, 3,963 SARS-CoV-2 RI sequences were available (**Figure 1, see Appendix**).

Given RI's proximity to major US population centers, the observed wide diversity of SARS-CoV-2 lineages was not surprising. Indeed, of the total 3,963 RI sequences available as of this writing, 1,489 (38%) are VOC, 1,177 (30%) are VOI, and 1,297 (33%) are considered non-VOC/non-VOI (**Table 1**).

Phylogenetic analyses of the RI SARS-COV-2 spectrum throughout the COVID-19 pandemic demonstrated expected clustering by VOC/VOI, dispersion of RI sequences among

**Table 1.** SARS-CoV-2 Variants of Concern / Interest in RI as of June 24, 2021.

| Variant of Concern | Region Variant Originally Identified | Number of Total Cases | Range of Sampling Dates |
|---|---|---|---|
| B.1.1.7 (Alpha) | UK | 1248 | Jan 19 to Jun 05, 2021 |
| B.1.351 (Beta) | South Africa | 8 | Mar 16 to May 25, 2021 |
| B.1.617.2 (Delta) | India | 9 | Apr 20 to May 25, 2021 |
| P.1 (Gamma) | Brazil | 224 | Mar 03 to Jun 03, 2021 |
| **Variant of Interest** | **Region Variant Originally Identified** | **Number of Total Cases** | **Range of Sampling Dates** |
| B.1.427 (Epsilon) | California, USA | 41 | Jan 27 to Apr 15, 2021 |
| B.1.429 (Epsilon) | California, USA | 94 | Jan 06 to Apr 29, 2021 |
| B.1.525 (Eta) | New York, USA | 51 | Feb 03 to Apr 27, 2021 |
| B.1.526 (Iota) | New York, USA | 991 | Jan 07 to Jun 03, 2021 |
| B.1.617.1 (Kappa) | India | 0 | — |
| B.1.617.3 | India | 0 | — |
| P.2 (Zeta) | Brazil | 0 | -— |

regional sequences, and evolution of mutations over time. This latter point is indicated by early sequences in the pandemic being closer to the root of the phylogenetic tree, and more recent sequences being more distal descendants of the original Wuhan strain (**Figure 2, see Appendix**).

Multiple and diverse non-VOC/non-VOI lineages have been circulating in RI throughout the pandemic, with changing proportions over time (**Figures 3A, 3B, see Appendix**). Only few lineages such as B.1.375 and B.1.2 made up substantial numbers of non-VOC/non-VOI sequences at any one time, with considerable subsequent declines of B.1.375 and B.1.2. Before January 2021, none of the then available sequences (n=197) would be considered VOC/VOI.

Between January 2021 and May 2021, a steadily increasing proportion of sequenced RI samples were VOC/VOI; from 12/205 (6%) in January to 684/771 (89%) in May 2021 (**Figure 3A**). Indeed, on a weekly basis, from January 2021, VOC/VOI proportions have steadily increased, effectively supplanting non-VOC/non-VOI lineages (**Figure 3C, see Appendix**). For example, of the 109 RI samples sequenced in the week of 5/23/21-5/29/21, 72 (66%) are VOC and 23 (21%) are VOI. **Table 1** lists cases identified as VOCs and VOIs at the time of this writing. Current data are maintained by the RI Department of Health and are available at https://ri-department-of-health-covid-19-variant-data-rihealth.hub.arcgis.com/. Overall, all four VOCs (B.1.1.7, B.1.351, B.1.617.2 and P.1) and four (B.1.427, B.1.429, B.1.525 and B.1.526) of the seven defined VOIs were detected in RI (**Table 1; Figure 3C**). The first VOC detected in RI was B.1.429 in January 2021. The most frequently occurring VOC is B.1.1.7, first sequenced 1/19/21, then growing rapidly to 31% of sequences by June 5, 2021. Other common lineages include VOC P.1 and VOI B.1.526. As of this writing, B.1.1.7, P.1, and B.1.526 have each remained at an overall consistent proportion of all identified cases from the weeks of April 4 to May 29, 2021: 48% to 48%, 4% to 15%, and 30% to 21%, respectively (**Figure 3C**).

Multiple spike protein mutations associated with certain VOC and/or VOI also occurred in RI sequences from non-VOC/non-VOI lineages. Out of 53 spike mutations/deletions associated with any VOC/VOI per CDC,[13] 41 occurred in at least one RI sequence that was not the VOC/VOI with which that mutation is most commonly associated (**Figure 4, see Appendix**). The five most prevalent mutations included L5F (associated with B.1.526; n=828), T95I (B.1.526, B.1.617.1; n=788), D253G (B.1.526; n=774), S477N (B.1.526; n=742), and V1176F (P.2; n=243).

Of nine mutations at seven positions within the SARS-CoV-2 RBD (positions 417-501) associated with VOC/VOI, seven (including S477N, as above) occurred outside of their VOC/VOI associated lineages, including K417T (associated with P.1; n=61), L452R (B.1.427, B.1.429, B.1.526.1, B.1.617, B.1.617.1, B.1.617.2, B.1.617.3; n=46), T478K (B.1.617.2; n=27), E484K (B.1.1.7, B.1.351, B.1.525, B.1.526, P.1, P.2; n=191), S494P (B.1.1.7; n=81), and N501Y (B.1.1.7, B.1.351, P.1; n=113) (**Figure 5, see Appendix**). The proportion of mutations in spike protein sequences overall and within the RBD shifted over time from an initial predominance of other spike mutations like the H69-V70 deletion, to an increasing input of L5F, T95I, D253G, S477N, and V1176F detected mutations (**Figures 4, 5**).

## DISCUSSION

We present current data on SARS-CoV-2 genomic surveillance in RI, demonstrating an exponential increase in statewide sequencing capacity, heterogenous lineage dynamics, overtake of the sequence landscape by VOC and VOI during March/April of 2021, and continued evolution of mutations of significance in non-VOC/non-VOI lineages. Accumulating and routinely updated data on SARS-CoV-2 VOC/VOI in RI can be seen in a website maintained by the authors and the RI Department of Health.[23] Though these observations may not be unique to RI, a statewide comprehensive approach is, and it continues to enable monitoring, linking to epidemiology and investments in genomic surveillance within the state. Such efforts will ensure increased awareness, optimal understanding, and efficient public health responses to this evolving pandemic as we continue to implement vaccination and prepare for pre-COVID-19 era normalcy.

Of 3,963 SARS-CoV-2 RI sequences by the end of June 2021, most common lineages increasingly belong to VOC B.1.1.7 and to a lesser extent VOC P.1 and VOI B.1.526, as in the other northeastern USA states.[26] Most other VOC/VOI

(except P.2, B.1.617.1 and B.1.617.3) have also been detected in RI, some in small numbers. Global challenges associated with these VOC/VOI continue to be encountered, including increased transmissibility,[27] more severe disease outcomes,[28] re-infection,[29] and vaccine and treatment evasions.[30,31] At this point in time, the impact of knowing variant designation on an individual clinical level is limited, primarily due to delay in obtaining sequences. However, on a population level this information continues to be important, and it can inform treatment, prevention, and public health.[32] Interpretation of specific variant-outcome associations data should be done with caution, considering their continuous evolution.

VOC and VOI can be transmitted through travel, migration, and immigration. However, as we show, mutations of significance that are in these VOC/VOI, including those at strategic viral locations that may have negative functional impact (e.g. increased transmissibility via improved affinity of the viral RBD to the human ACE2 receptor, or immune evasion by decreased human antibody binding to the viral RBD) can also develop *de novo*, most likely by selective pressure from the immune system, treatments and vaccines.[4] This continues to be concerning, and as currently seen in India, the emergence of new variants can be fueled by high population density and insufficient vaccinations, allowing abundant viral replication and mutation evolution and fixation.[33]

A partnership of multiple academic labs, including the Kantor and Sabeti Laboratories, and the RI Department of Health State Health Laboratories is at the basis of this successful establishment of SARS-CoV-2 genomic surveillance in RI. This existing RI collaboration was in place prior to the COVID-19 pandemic, and mostly focused on HIV genomics and investigation of methods to minimize HIV transmission.[34-37] Leveraging these collaborations, we have established SARS-CoV-2 data generation, quality control, bioinformatics pipelines, interpretation and reporting systems that inform public health and allow integration with epidemiological and geographic data for the benefit of RI residents. Such intra-state and regional processes augment nationwide and global efforts to monitor and respond to the COVID-19 pandemic as it develops.

SARS-CoV-2 genomic surveillance is challenging, and limitations exist. Accurate and representative population sampling is difficult, particularly considering that successful sequencing is only feasible for certain samples, i.e., those with relatively low Ct's, representing high viral levels. Reporting of sequencing data to public health is not yet standardized and requires substantial efforts to combine with relevant demographic data. Additionally, rapid development of pandemic-related events and SARS-CoV-2 genome sequencing efforts have made it challenging to agree on nomenclature, lineage delineation, genomic quality control measures, and relevant mutation lists, to name a few.

In conclusion, SARS-CoV-2 VOC and VOI have become dominant in RI, as well as in the surrounding New England states and the rest of the country, which deserves awareness from the general RI population and health providers. The continued decrease in new cases in RI despite the proportional predominance of VOC/VOI is encouraging and can most likely be attributed to optimized public health measures and high (~75% of those >18 years) vaccination rate in the state. SARS-CoV-2 is still circulating, particularly globally, and we must continue to be aware, understand and monitor evolving SARS-CoV-2 variants, especially those that become of concern or interest. Conventional mitigation measures that have been used throughout this pandemic, including masking, social distancing, avoiding large gatherings, decreasing travel, and increasing testing, quarantining and contact tracing, remain available in the event of variant-induced surge of cases. Importantly, ensuring global availability of vaccinations, and continuing focus on high vaccination rates in the US, will protect us all and allow us to get back to our pre-pandemic lives.

## Appendix

### References


1. Johns Hopkins COVID-19 Dashboard. Accessed 6/26/21, https://coronavirus.jhu.edu/
2. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. Mar 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7
3. Korber B, Fischer WM, Gnanakaran S, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell*. Aug 20 2020;182(4):812-827 e19. doi:10.1016/j.cell.2020.06.043
4. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol*. Jul 2021;19(7):409-424. doi:10.1038/s41579-021-00573-0
5. Grubaugh ND, Petrone ME, Holmes EC. We shouldn't worry when a virus mutates during disease outbreaks. *Nat Microbiol*. Apr 2020;5(4):529-530. doi:10.1038/s41564-020-0690-4
6. Callaway E. The coronavirus is mutating - does it matter? *Nature*. Sep 2020;585(7824):174-177. doi:10.1038/d41586-020-02544-6
7. Wise J. Covid-19: New coronavirus variant is identified in UK. *BMJ*. Dec 16 2020;371:m4857. doi:10.1136/bmj.m4857
8. Tegally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature*. Apr 2021;592(7854):438-443. doi:10.1038/s41586-021-03402-9
9. Faria NR, Mellan TA, Whittaker C, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science*. May 21 2021;372(6544):815-821. doi:10.1126/science.abh2644
10. Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E. Emergence of a Novel SARS-CoV-2 Variant in Southern California. *JAMA*. Apr 6 2021;325(13):1324-1326. doi:10.1001/jama.2021.1612
11. Annavajhala MK, Mohri H, Zucker JE, et al. A Novel SARS-CoV-2 Variant of Concern, B.1.526, Identified in New York. *medRxiv*. Feb 25 2021;doi:10.1101/2021.02.23.21252259
12. Yadav PD, Sapkal GN, Abraham P, et al. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. *Clin Infect Dis*. May 7 2021;doi:10.1093/cid/ciab411

13. CDC. SARS-CoV-2 Variant Classifications and Definitions. Accessed 5/12/21, https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html
14. Callaway E. 'A bloody mess': Confusion reigns over naming of new COVID variants. *Nature*. Jan 2021;589(7842):339. doi:10.1038/d41586-021-00097-w
15. WHO. Tracking SARS-CoV-2 variants. Accessed 6/28/21, https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
16. V'Kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol*. Mar 2021;19(3):155-170. doi:10.1038/s41579-020-00468-6
17. RIDOH COVID-19. Accessed 6/28/21, https://ri-department-of-health-covid-19-data-rihealth.hub.arcgis.com/
18. Brown University COVID-19 seed awards. Accessed 6/28/21, https://www.brown.edu/research/conducting-research-brown/finding-funding/internal-funding-opportunities/brown-covid-19-research-seed-fund-awardees
19. White House COVID-19 genomic surveillance funding. Accessed 6/28/21, https://www.whitehouse.gov/briefing-room/statements-releases/2021/04/16/fact-sheet-biden-administration-announces-1-7-billion-investment-to-fight-covid-19-variants/
20. GISAID. Accessed 6/28/21, https://www.gisaid.org/
21. Pangolin. Accessed 6/28/21, https://cov-lineages.org/
22. Nextstrain. Accessed 6/28/21, https://nextstrain.org/
23. RIDOH COVID-19 variants. Accessed 6/28/21, https://ri-department-of-health-covid-19-variant-data-rihealth.hub.arcgis.com/
24. Stamatakis A. RAxML version 8: a tool for phylogenetic analysis and post-analysis of large phylogenies. *Bioinformatics*. Feb 7 2014;doi:btu033[pii]10.1093/bioinformatics/btu033
25. Vogels CBF, Breban MI, Ott IM, et al. Multiplex qPCR discriminates variants of concern to enhance global surveillance of SARS-CoV-2. *PLoS Biol*. May 2021;19(5):e3001236. doi:10.1371/journal.pbio.3001236
26. CDC COVID-19 data tracker. Accessed 6/28/21, https://covid.cdc.gov/covid-data-tracker/#variant-proportions
27. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. Apr 9 2021;372(6538)doi:10.1126/science.abg3055
28. Davies NG, Jarvis CI, Group CC-W, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature*. May 2021;593(7858):270-274. doi:10.1038/s41586-021-03426-1
29. Nonaka CKV, Franco MM, Graf T, et al. Genomic Evidence of SARS-CoV-2 Reinfection Involving E484K Spike Mutation, Brazil. *Emerg Infect Dis*. May 2021;27(5):1522-1524. doi:10.3201/eid2705.210191
30. Garcia-Beltran WF, Lam EC, St Denis K, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell*. Apr 29 2021;184(9):2523. doi:10.1016/j.cell.2021.04.006
31. Zhou D, Dejnirattisai W, Supasa P, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. *Cell*. Apr 29 2021;184(9):2348-2361 e6. doi:10.1016/j.cell.2021.02.037
32. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nature medicine*. Apr 2021;27(4):717-726. doi:10.1038/s41591-021-01294-w
33. Mallapaty S. India's massive COVID surge puzzles scientists. *Nature*. Apr 2021;592(7856):667-668. doi:10.1038/d41586-021-01059-y
34. Alexander NE, Chan PA, Rogo TO, et al. Interrupting transmission of HIV and other sexually transmitted infections in Rhode Island. *Med Health R I*. Aug 2012;95(8):241-4.
35. Chan PA, Kazi S, Rana A, et al. Short communication: new HIV infections at Southern New England academic institutions: implications for prevention. *AIDS Res Hum Retroviruses*. Jan 2013;29(1):25-9. doi:10.1089/AID.2012.0130
36. Novitsky V, Steingrimsson JA, Howison M, et al. Empirical comparison of analytical approaches for identifying molecular HIV-1 clusters. *Sci Rep*. Oct 29 2020;10(1):18547. doi:10.1038/s41598-020-75560-1
37. Novitsky V, Steingrimsson J, Howison M, et al. Longitudinal typing of molecular HIV clusters in a statewide epidemic. *AIDS*. May 24 2021;doi:10.1097/QAD.0000000000002953

## Acknowledgments

We gratefully acknowledge the laboratories performing testing of diagnostic specimens and the laboratories responsible for SARS-CoV-2 sequencing of RI samples. In particular, the support provided by Bronwyn McInnis, Daniel Park and Katie Sidle of the Broad Institute, and Glen Gallagher of MA DPH Laboratory; Dr. Charlene Johnson at Dominion Laboratories, Dr. Walther Pfeifer at East Side Clinical Laboratories, and the University of RI Genomics and Sequencing Center, supported in part by the National Science Foundation EPSCoR Cooperative Agreement #OIA-1655221. This work was also supported in part by the Brown University COVID-19 Research Seed Fund Award.

## Disclaimer

The views expressed herein are those of the authors.

## Authors

Rami Kantor, MD, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

Vladimir Novitsky, MD, PhD, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

Kristin Carpenter-Azevedo, MSc, Rhode Island Department of Health, State Health Laboratories, Providence, RI.

Mark Howison, MSc, Research Improving People's Life, Providence, RI.

Akarsh Manne, MSc, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

Josephine K. Darpolor, PhD, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

April Bobenchik, PhD, Rhode Island Hospital, Providence, RI.

Anubhav Tripathi, PhD, Brown University School of Engineering, Providence, RI.

Richard C. Huard, PhD, Rhode Island Department of Health, State Health Laboratories, Providence, RI.

Ewa King, PhD, Rhode Island Department of Health, State Health Laboratories, Providence, RI.

## Correspondence

Rami Kantor, MD
The Miriam Hospital
164 Summit Avenue, RISE Building, Room 154
Providence, RI 02906
401-793-4997
Fax 401-793-4709
rkantor@brown.edu

# College-level Baccalaureate-MD Student Perceptions of Research and Research-Oriented Careers

JOHN C. LIN; JULIANNE Y. IP, MD; MELISSA A. CLARK, PhD; PAUL B. GREENBERG, MD, MPH


## ABSTRACT

**PURPOSE:** Concern about the decline in physician scientists has generated interest in promoting research participation among medical students. This study aimed to examine perceptions of research and research-oriented careers among college-level baccalaureate-MD (BA/MD) students at one institution in the United States.

**METHODS:** A cross-sectional survey was distributed to a sample of 241 BA/MD students. Descriptive statistics were used to examine research perceptions of participants.

**RESULTS:** The response rate was 52% (126/241). Most respondents conducted scientific research in high school and were interested in research-oriented careers. Most students participated in a research program (research course, faculty mentorship, or research grant), disseminated their research, and believed that research programs would be helpful for their research participation. The most common perceived barriers were a lack of time, interest, and prior research experience.

**CONCLUSIONS:** College-level BA/MD students had positive perception of research-oriented careers and found student research programs helpful. However, addressing key barriers such as lack of time, interest and experience will help expand BA/MD student engagement in research.


**KEYWORDS:** survey, research perceptions, BA/MD students

## INTRODUCTION

The United States physician scientist workforce has declined and aged in recent years.[1] Policymakers and scientists have been increasingly raising concerns about the decline in physician-scientists.[1-4] Studies have largely focused on medical students and residents as target populations for exposure to research supporting programs as ways to grow the pipeline of future academic physicians.[5] However, a large proportion of medical students do not participate or have little interest in participating in research.[6,7]

It has been proposed that future physicians should be exposed to research earlier, making college students enrolled in US institutions with baccalaureate-MD (BA/MD) programs a prime target population for research supporting programs.[8,9] Furthermore, as college undergraduates, BA/MD students may not face the same time constraints as their medical school counterparts.[10] However, there is a dearth of studies on the research perceptions and the scientific experience of college students in BA/MD programs.

Herein, we surveyed college students in one BA/MD program to better understand their perceptions of research and research-oriented careers, including perceived barriers and solutions to increasing their participation in research.

## METHODS

The Brown University Institutional Review Board determined this study did not meet the definition of human participants research and did not require formal review.

We administered an anonymous cross-sectional online survey to the 241 college students enrolled in the Brown University Program in Liberal Medical Education (PLME) during the 2020-2021 academic year to evaluate their research interest and practices.[11] Survey questions were adapted from previous studies assessing research perceptions among medical students,[6,7,12] and the survey instrument was designed using Qualtrics (Provo, UT).[13] A survey methodologist (MAC), university dean (JYI), and a group of three college students critically reviewed the survey instrument, which was then revised based on their feedback. The survey was emailed to the PLME listserv provided by the program dean (JYI) and distributed in the PLME Facebook groups.

The survey included questions in eight areas: research exposure, research program support, potential research program helpfulness, research engagement, research barriers, research output, interest in a research-oriented career, and demographics. Research programs were defined as a specialized research course (providing course credit for independent research), faculty mentorship program (matching students with research faculty), or a student research grant (financial support for research). The survey instrument can be found here: https://doi.org/10.26300/dhss-8670

Statistical analyses were conducted using Stata (StataCorp, College Station, Texas).[14] Descriptive statistics were used to characterize the research perceptions of PLME students. Research participation of PLME students were compared by class level using descriptive statistics and $\chi^2$ tests. Significance levels were set at $p < 0.05$.

## RESULTS

The overall response rate was 52% (126/241). Respondent characteristics are shown in **Table 1**. Most respondents were male (55%; 69/126), graduates of public high schools (65%; 82/126), and graduates of high schools located in the US (85%; 107/126).

**Table 1.** Demographic characteristics of respondents.

| Demographics | Respondents (n = 126) |
|---|---|
| **Gender, n (%)** | |
| Male | 69 (55) |
| Female | 39 (31) |
| Non-binary | 1 (1) |
| Refused to answer | 17 (13) |
| **Race, n (%)** | |
| Non-URM | 82 (65) |
| URM | 24 (19) |
| Refused to answer | 20 (16) |
| **Class year, mean (SD)** | 1.37 (1.26) |
| First year, n (%) | 44 (35) |
| Second year | 12 (10) |
| Third year | 25 (20) |
| Fourth year or more | 30 (24) |
| Refused to answer | 15 (12) |
| **High school status, n (%)** | |
| Public | 82 (65) |
| Private | 29 (23) |
| Refused to answer | 15 (12) |
| **High school location, n (%)** | |
| United States | 107 (85) |
| International | 4 (3) |
| Refused to answer | 15 (12) |

SD: standard deviation; URM: underrepresented minority.

Respondent perceptions of research are shown in **Table 2**. Most respondents conducted scientific research in high school (56%; 70/126) or in college (52%; 65/126). First-year student respondents were less likely to participate in undergraduate research than those in higher class levels (14% [6/44] vs 72% [48/67]; $p < 0.001$) but both groups had similar rates of participation in high school research (57% [25/44] vs 55% [37/67]; $p = 0.869$).

The majority of respondents were interested in a research-oriented career (64%; 84/126). Most respondents perceived a faculty mentorship program (72%; 95/126), research grant program (67%; 89/126), or research course (64%; 84/126) as helpful for participating in research. The most common barriers to research participation were lack of time (55%; 72/126), interest (42%; 53/126), or prior research experience (36%; 45/126). When queried for other research barriers not listed in the survey, seven students

**Table 2: Student perceptions of research.**

| Topic (n = 126) | Respondents, n (%) |
|---|---|
| **Scientific research experiences in high school** | |
| No | 56 (44) |
| Yes | 70 (56) |
| **Research experiences as an undergraduate student** | |
| No | 61 (48) |
| Yes | 65 (52) |
| **Personal barriers at Brown to participating in research[a]** | |
| Lack of interest | 53 (42) |
| Lack of time | 72 (57) |
| Lack of opportunities | 34 (27) |
| Lack of prior research experience | 45 (36) |
| Lack of scientific background | 44 (35) |
| Lack of funding | 26 (21) |
| Lack of faculty support | 16 (13) |
| Other ("Remote", "COVID-19") | 10 (8) |
| **Programs that could facilitate participation in research[a]** | |
| A specialized course for research (i.e., CURE or independent study) | 84 (67) |
| A faculty mentorship program (i.e., Medicine in Action) | 95 (75) |
| A research funding program (i.e., UTRA, SRA) | 89 (71) |
| Other ("External research funding and opportunities") | 2 (2) |
| **Plans to participate in research during your medical career** | |
| No | 4 (3) |
| Yes | 84 (67) |
| Don't know | 0 (0) |
| Refused to answer | 38 (30) |

CURE: Course-Based Undergraduate Research Experience; SRA: Summer Research Assistantship; UTRA: Undergraduate Teaching and Research Award.
[a]Students were asked to "Mark all that apply" for this question.

**Table 3.** Experiences and perceptions of students participating in undergraduate research.

| Topic (n = 65) | Respondents, n (%) |
|---|---|
| **Research experience[a]** | |
| Supervised by a faculty mentor | 46 (71) |
| Based in a laboratory setting | 28 (43) |
| Based in a clinical care setting | 17 (26) |
| Based in other settings | 8 (12) |
| None of the above | 0 (0) |
| **Scholarly output[a]** | |
| Abstract | 13 (20) |
| Poster presentation | 17 (26) |
| Oral presentation | 19 (29) |
| Published paper | 15 (23) |
| Other ("Video presentation") | 3 (5) |
| **Desired goal of research[a]** | |
| Knowledge | 33 (51) |
| Abstract/Presentation | 14 (22) |
| Publication | 22 (34) |
| Qualifications for Residency | 22 (34) |
| Long-term Career Goals | 26 (40) |
| Other | 0 (0) |
| **Programs that facilitated participation in research[a]** | |
| A specialized course for research (i.e., CURE or independent study) | 17 (26) |
| A faculty mentorship program (i.e., Medicine in Action) | 7 (11) |
| A research funding program (i.e., UTRA, SRA) | 26 (40) |
| Other ("More funding", "guidance") | 4 (6) |

CURE: Course-Based Undergraduate Research Experience; SRA: Summer Research Assistantship; UTRA: Undergraduate Teaching and Research Award.
[a]Students were asked to "Mark all that apply" for this question.

(5%) responded that "COVID-19" or "remote studying" were significant barriers.

Research perceptions among the 65/126 (52%) respondents with undergraduate research experience are shown in **Table 3**. The most cited motivation for research participation was an interest in obtaining knowledge (51%; 33/65). Most respondents reported receiving faculty mentorship (71%; 46/65) and participation in a research program (51%; 33/65). The majority of respondents disseminated their research (62%; 40/65), most commonly though presentations or papers.

## DISCUSSION

This survey suggests that most BA/MD students had positive perceptions of research and research-oriented careers. The majority of respondents believed that a faculty mentorship program, research course, or research grant would assist them in participating in research. The most common barriers to research were lack of time, interest, and research experience. Most respondents disseminated their research through presentations or papers.

The importance of faculty mentorship is supported by the literature on medical student research.[15-18] As a result of participating in faculty mentorship programs, medical students had more interest in research-oriented careers, increased research productivity, and stronger research skills.[15-17] Faculty mentorship can also address barriers to research participation such as lack of research experience and subject matter knowledge.[17] Studies suggest finding research mentors is a significant challenge for medical students.[6,7] To help address this barrier, Brown University PLME students have access to resources such as an annual PLME-compiled research project list and the Medicine in Action program, which helps to match students with academic physicians.[19,20]

Medical students who complete specialized research courses become more interested in conducting research and acquiring scientific knowledge.[21-23] Research courses also provide protected time and exposure to research methodology, addressing student barriers such as lack of time and experience.[22] Independent study courses, preclinical electives, and Course-Based Undergraduate Research Experience (CURE) classes are options available to Brown University PLME students.[24-26]

Student research grants provide exposure to research and generate interest in research.[27] Approximately 45 percent of Brown University college students receive need-based financial aid[28] and are eligible to participate in work-study programs to pay for educational expenses.[29] Research grants offer an alternative to employment and may support living and educational expenses. Studies suggest that inadequate funding is an important barrier for medical students.[6,7] However, few respondents in our survey reported this as a barrier. The availability of targeted research grants for PLME students such as the Summer Research Assistantships, Undergraduate Teaching and Research Awards, and Summer/Semester Projects for Research, Internships, and Teaching may be a factor.[19,30,31]

Most respondents who conducted scientific research presented or published their findings. An important reason may be the longitudinal nature of undergraduate research experiences, which have significantly higher publication rates than shorter research experiences,[32] due to extended support from research grants and faculty mentorship programs.[33]

Another barrier to research participation was the coronavirus disease 2019 (COVID-19) pandemic. At Brown University, first-year and other remote students were not allowed on campus during the fall semester and had no access to laboratory-based research.[34] Not surprisingly, we found first-year student respondents had significantly less undergraduate but similar high school research experience compared to upper-year students. The pandemic has underscored the need to develop viable remote alternatives for BA/MD students to engage in research.[35] However, another possible reason for the lower research participation among first-year students is that PLME faculty advisors often encourage first-year students to explore new fields in their first semester prior to committing to research experiences.

This study has several limitations. First, our survey relied on self-reported research participation, which may be subject to response bias given the potential for inaccurate reporting.[36] Second, this survey was distributed near the conclusion of the 2020–2021 academic year – two weeks prior to final exams – which may have affected response rates. Third, the PLME provides many research programs and substantial academic flexibility that other BA/MD programs may not offer, which may limit the generalizability of this study.[10] Fourth, there may have been response bias in the survey, although our response rate was higher than comparable medical student surveys (37–47%).[6,37]

In sum, this survey suggests that faculty mentorship, research courses, and research funding programs are important to encourage BA/MD students to acquire research experience. Larger studies with BA/MD programs from multiple institutions are needed to comprehensively assess student research perceptions and inform programs that will help create a pipeline of future clinician-scientists.

### References


1. National Institutes of Health. Physician-Scientist Workforce (PSW) Report 2014: Executive Summary. Washington, D.C. 2014.
2. Daye D, Patel CB, Ahn J, Nguyen FT. Challenges and opportunities for reinvigorating the physician-scientist pipeline. J Clin Invest. 2015;125(3):883-7.
3. Milewicz DM, Lorenz RG, Dermody TS, Brass LF, National Association of MD-PhD Programs Executive Committee. Rescuing the physician-scientist workforce: the time for action is now. J Clin Invest. 2015 Oct;125(10):3742-7.
4. Schafer AI. The vanishing physician-scientist? Transl Res. 2010 Jan;155(1):1-2.

5. Kosik RO, Tran DT, Fan AP-C, Mandell GA, Tarng DC, Hsu HS, et al. Physician Scientist Training in the United States: A Survey of the Current Literature. Eval Health Prof. 2016 Mar;39(1):3-20.
6. Siemens DR, Punnen S, Wong J, Kanji N. A survey on the attitudes towards research in medical school. BMC Med Educ. 2010 Jan;10:4.
7. Funston G, Piper RJ, Connell C, Foden P, Young AMH, O'Neill P. Medical student perceptions of research and research-orientated careers: An international questionnaire study. Med Teach. 2016 Oct;38(10):1041-8.
8. Gordon R. The vanishing physician scientist: a critical review and analysis. Account Res. 2012;19(2):89-113.
9. Tran EM, Ip J, Greenberg PB. Engaging College-Level Baccalaureate-MD Students in Clinical Research. R I Med J. 2018 Sep;101(7):35-8.
10. Eaglen RH, Arnold L, Girotti JA, Cosgrove EM, Green MM, Kollisch DO, et al. The scope and variety of combined baccalaureate-MD programs in the United States. Acad Med. 2012 Nov;87(11):1600-8.
11. Brown University. Program in Liberal Medical Education Providence, RI: Warren Alpert Medical School of Brown University; 2021. Available at: https://www.brown.edu/academics/medical/plme/. Accessed May 1, 2021.
12. Association of American Medical Colleges. Matriculating Student Questionnaire (MSQ) Washington, D.C.: Association of American Medical Colleges; 2020 Jun. Available at: https://www.aamc.org/data-reports/students-residents/report/matriculating-student-questionnaire-msq. Accessed May 1, 2021.
13. Qualtrics. Version April 2021 Provo, UT: Qualtrics; 2021. Accessed April 1, 2021.
14. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp, LLC; 2019.
15. Farkas AH, Allenbaugh J, Bonifacino E, Turner R, Corbelli JA. Mentorship of US Medical Students: a Systematic Review. J Gen Intern Med. 2019;34(11):2602-9.
16. Zuzuárregui JRP, Hohler AD. Comprehensive Opportunities for Research and Teaching Experience (CORTEX): A mentorship program. Neurology. 2015;84(23):2372-6.
17. Frei E, Stamm M, Buddeberg-Fischer B. Mentoring programs for medical students--a review of the PubMed literature 2000-2008. BMC Med Educ. 2010 Apr;10:32.
18. Buddeberg-Fischer B, Herta K-D. Formal mentoring programmes for medical students and doctors--a review of the Medline literature. Med Teach. 2006;28(3):248-57.
19. Program in Liberal Medical Education. PLME Summer Research Assistantship in Social/Behavioral Sciences, Clinical Medicine, or Biomedical Sciences Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/academics/medical/plme/current-students/enrichment-activities/research-opportunities/plme-summer-research-assistantship-soc. Accessed May 9, 2021.
20. Program in Liberal Medical Education. Medicine in Action Program Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/academics/medical/plme/current-students/enrichment-activities/medicine-action-program. Accessed May 9, 2021.
21. Ommering BWC, Blankenstein FMv, Diepen Mv, Dekker FW. Academic Success Experiences: Promoting Research Motivation and Self-Efficacy Beliefs among Medical Students. Teach Learn Med. 2021:1-11.
22. Nazha B, Salloum RH, Fahed AC, Nabulsi M. Students' perceptions of peer-organized extra-curricular research course during medical school: a qualitative study. PLoS One. 2015;10(3):e0119375.
23. Möller R, Shoshan M, Heikkilä K. What is the reward? Medical students' learning and personal development during a research project course. Med Educ Online. 2015;20:28441.
24. Program in Liberal Medical Education. Preclinical Electives Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/academics/medical/plme/current-students/enrichment-activities/preclinical-electives. Accessed May 9, 2021.
25. The Science Center. Research-Based "CURE" Courses at Brown Providence, RI: Brown University; 2021. Accessed May 3, 2021.
26. Dean of the College. Independent Study Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/academics/college/degree/course-options/independent-study. Accessed May 9, 2021.
27. Zier K, Friedman E, Smith L. Supportive programs increase medical students' research interest and productivity. J Investig Med. 2006 May;54(4):201-7.
28. Tabak J. Brown's newest undergraduates, by the numbers Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/news/2021-01-20/numbers. Accessed May 8, 2021.
29. Office of Financial Aid. Federal Work-Study and Campus Employment Providence, RI: Brown University; 2021. Accessed May 8, 2021.
30. CareerLAB. BrownConnect Collaborative SPRINT Awards Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/campus-life/support/careerlab/brownconnect-collaborative-sprint-awards. Accessed May 9, 2021.
31. The College. Undergraduate Teaching and Research Awards Providence, RI: Brown University; 2021. Available at: https://www.brown.edu/academics/college/fellowships/utra/. Accessed May 9, 2021.
32. Dyrbye LN, Davidson LW, Cook DA. Publications and presentations resulting from required research by students at Mayo Medical School, 1976-2003. Acad Med. 2008;83(6):604-10.
33. Amgad M, Tsui MMK, Liptrott SJ, Shash E. Medical Student Research: An Integrated Mixed-Methods Systematic Review and Meta-Analysis. PLoS One. 2015;10(6):e0127470.
34. Goldstein L. Nearly 800 students to attend Brown remotely for fall semester Providence, RI: Brown Daily Herald; 2020. Available at: https://www.browndailyherald.com/2020/08/10/nearly-800-students-attend-brown-remotely-fall-semester/. Accessed May 8, 2021.
35. Sohrabi C, Mathew G, Franchi T, Kerwan A, Griffin M, Mundo JSCD, et al. Impact of the coronavirus (COVID-19) pandemic on scientific research and implications for clinical academic training - A review. Int J Surg. 2021;86:57-63.
36. Feller E. Deceit, lies and plagiarism in residency applications. R I Med J. 2019;102(2):8-9.
37. Muhandiramge J, Vu T, Wallace MJ, Segelov E. The experiences, attitudes and understanding of research amongst medical students at an Australian medical school. BMC Med Educ. 2021;21(1):267.


## Acknowledgments

We thank Dr. Judy Jang, MD, Assistant Dean and Assistant Professor of Medicine at Brown University, for critically reviewing the paper.

## Authors

John C. Lin, Student in Program in Liberal Medical Education, Brown University, Providence, RI.

Julianne Y. Ip, MD, Associate Dean of Medicine (Program in Liberal Medical Education and Visiting International Medical Students); Professor of Medical Science, and Professor of Family Medicine, Alpert Medical School of Brown University, Providence, RI.

Melissa A. Clark, PhD, Associate Dean for Academic Affairs; Professor of Health Services, Policy and Practice; Professor of Obstetrics and Gynecology, Brown University, Providence, RI.

Paul B. Greenberg, MD, MPH, Professor of Surgery (Ophthalmology), Alpert Medical School of Brown University, Providence, RI; (Acting) Chief Academic Affiliations Officer, Office of Academic Affiliations, US Department of Veterans Affairs, Washington, DC.

## Disclaimer

The views expressed here are those of the authors and do not necessarily reflect the position or policy of the US Department of Veterans Affairs or the US government.

## Correspondence

Paul B. Greenberg, MD, MPH
Division of Ophthalmology, Brown University
Coro Center West, 1 Hoppin St, Suite 200
Providence, Rhode Island USA 02903
401-444-4669
paul_greenberg@brown.edu

# Antibiotics and the Human Microbiome: A Survey of Prescribing Clinicians' Knowledge and Opinions Regarding the Link between Antibiotic-Induced Dysbiosis and Immune-Mediated Disease

MATTHEW H. WILSON, MD, ScM; MICHAEL J. MELLO, MD, MPH; PHILIP A. GRUPPUSO, MD

**ABSTRACT**

Altered composition or function of the human microbiome, termed dysbiosis, has been associated with a variety of immune-mediated diseases. Antibiotic use is a well-studied cause of dysbiosis. We conducted an electronic survey of 351 antibiotic-prescribing clinicians in Rhode Island to evaluate antibiotic prescription patterns, knowledge and opinions regarding the importance of the human microbiome and its relation to antibiotics and the immune system. We found that clinicians view the health of the human microbiome as important when prescribing antibiotics; however, they do not feel well-informed or confident in their knowledge about the microbiome or its relevance to patient health. A higher level of self-reported knowledge about the microbiome was associated with increased importance placed on the microbiome and its relevance to medical practice. Our results indicate that clinicians may benefit from continuing medical education on the link between antibiotic-induced dysbiosis and immune-mediated disease.

**KEYWORDS:** microbiome, antibiotics, dysbiosis, autoimmune, atopy, inflammation

## INTRODUCTION

The human body hosts over 100 trillion interdependent commensal, symbiotic, and pathogenic microorganisms collectively termed the human microbiome.[1] These microorganisms regulate critical processes including energy metabolism[2] and immune system homeostasis.[1] Change in the microbiome composition and function, termed dysbiosis,[3] has been associated with many immune-mediated diseases, including disorders that are atopic,[4] inflammatory,[5] and autoimmune.[6,7] Several studies have demonstrated that antibiotics cause dysbiosis in mice and humans. Even short-term antibiotic treatment can decrease microbial biodiversity, alter microbiome metabolic functions, and alter susceptibility of the host gut to colonization by pathogenic microorganisms,[8] which can persist for months after treatment.[9]

The incidence and prevalence of many immune-mediated diseases, such as multiple sclerosis,[10] type I diabetes,[11] and inflammatory bowel disease,[12] have markedly increased over the past several decades.[13] Environmental factors, including antibiotic-induced dysbiosis, may contribute to disease pathogenesis. Indeed, human cohort studies have demonstrated an association between perinatal antibiotic use and risk in the offspring of atopic dermatitis[14] and allergic asthma.[15] Moreover, perinatal and neonatal use of certain antimicrobials is associated with increased risk of type I diabetes in the offspring.[16]

Antibiotics comprise roughly 25% of medications prescribed for children,[17] and an estimated 1 in 4 antibiotic prescriptions is inappropriate.[18] Given the high frequency of inappropriate antibiotic use, the increasing incidence of immune-mediated diseases in developed countries, and growing evidence that links antibiotic-induced dysbiosis with immune-mediated disease, it is important to study this relationship from the perspective of the clinician in practice. Herein, we present the results of an electronic survey of Rhode Island prescribers aimed at evaluating clinicians' antibiotic prescription patterns, their knowledge and opinions of the importance of the human microbiome, and its relation to antibiotics and the immune system.

## MATERIALS & METHODS

### Survey Development

Survey questions utilized a 5-point Likert scale (1 = Strongly agree, 2 = Agree, 3 = Neither agree nor disagree, 4 = Disagree, 5 = Strongly disagree), ranking options, and multiple choice. Questions were designed to evaluate clinician knowledge and opinions regarding antibiotic prescribing patterns and antibiotic-mediated effects on the human microbiome. Additional demographic questions included years in medical practice, medical specialty, practice location, and prescription patterns.

The survey was pilot-tested with seven Rhode Island physician volunteers who provided feedback on the survey's grammar, clarity, content, and functionality. The Brown University Institutional Review Board (IRB) approved the study. The survey email list was obtained through the Rhode Island Department of Health's publicly available licensee list of all physicians (including MD, DO, and limited practice), nurses (including APRN, LPN, and, RN) and physician assistants. Only those clinicians able to prescribe antibiotics, (MD, DO, PA, APRN) were included.

The survey was emailed via Qualtrics Experience Management (XM) Survey software to 3,108 unique email addresses in the Fall of 2019. Reminder emails were sent one and two months after the original distribution of the research survey.

### Data Analysis

For Likert-type scale questions, responses were numerically coded as above. Mean answer values were compared to calculate statistically significant difference between groups. To quantify self-reported antibiotic knowledge, the average of the numerical values of each participant's responses to the Likert-type questions, "I would feel confident in my knowledge when discussing the human microbiome with patients," and "I consider myself well-informed regarding the significance of the human microbiome with respect to medical practice," were calculated. Individuals were classified as "self-reported knowledgeable" if the average value was greater than 3 and "self-reported unknowledgeable" if the average value was less than or equal to 3.

Prescription frequency was categorized as "Frequently" (daily or weekly), or "Infrequently" (monthly, less than monthly, or never). Regarding practice location, urgent care practitioners were combined with Emergency Department clinicians.

Statistical analyses and figure generation were performed using OriginPro 2018b software. A two-tailed Exact test was used for all statistical comparisons of two groups. Comparisons of more than two groups were performed using one-way ANOVA with Tukey Post-Hoc test.

## RESULTS

### Characteristics of Respondents

The Survey response rate was 11.3% and a demographic breakdown of the 351 clinician survey respondents is reported in **Table 1 (See Supplement)**. Most respondents were physicians (92%), the majority of whom practiced either internal medicine, family practice, or pediatrics (combined 42.4% of physician respondents) in the outpatient setting (55.7% of all respondents). The majority of respondents have practiced for >20 years and prescribe antibiotics frequently (daily or weekly).

### Univariate Analyses

Survey participants viewed clinical reference tools (e.g., UpToDate) as the most important resource when selecting antibiotics (mean rank = 2.26) (**See Supplement, Figure 1**). Infectious disease physician consultation was least important (mean rank = 4.14).

The majority of respondents viewed "prevention of antibiotic resistance" as the most important factor when prescribing antibiotics (mean rank = 1.52; **See Supplement, Figure 2**). However, almost as many respondents ranked "protecting the microbiome" as #1 or #2 (N=132) compared with "avoiding adverse effects" (N=147). Moreover, "protecting the microbiome" (mean rank = 3.04) was viewed more importantly than "reducing costs of care" and "improving patient compliance" (mean ranks = 3.65 and 4.13, respectively).

Most prescribers (89.3%) agreed or strongly agreed that it is important for clinicians to learn about the human microbiome, and 82.1% agreed or strongly agreed that careful selection of antibiotics is important to protect the human microbiome (**See Supplement, Figures 3,4**). However, only 38.7% consider themselves well-informed regarding the clinical relevance of the microbiome, and only 35.8% reported sufficient confidence in their knowledge of the microbiome to discuss its clinical relevance with patients.

Respondents showed the greatest degree of uncertainty when questioned about the connection of the microbiome and the immune system. Approximately 40% of respondents neither agreed nor disagreed with the statement "antibiotic-induced dysbiosis is a feasible predisposing factor for the development of immune-mediated disease," although very few (3.6%) disagreed or strongly disagreed. Most respondents (80.1%) agreed or strongly agreed that they would change their prescribing behaviors given evidence linking antibiotic-induced dysbiosis and development of immune-mediated diseases.

### Bivariate Analyses

Emergency Department (ED) providers placed significantly higher mean importance on antibiograms than prescribers from inpatient practice, whereas outpatient prescribers placed highest mean importance on clinical reference tools (**See Supplement, Table 2**). All prescribers placed the least mean importance on infectious disease physician consultation. However, inpatient clinicians placed significantly more importance on infectious disease physician consultation than ED and outpatient prescribers. Outpatient clinicians valued prior clinical experience significantly higher than did inpatient or ED clinicians. Responses to items from Figure 2 did not vary by practice location (data not shown).

Regarding questionnaire items assessing perceived importance of the human microbiome, we found ED clinicians agreed significantly more with the statement: "There is insufficient primary research as a field of study for clinicians to consider how the human microbiome affects patient health," than inpatient or outpatient clinicians (**See Supplement, Table 3**). All other questionnaire items lacked statistically significant differences based on practice location.

Finally, regarding clinicians' opinions on potential effects of antibiotics on the human microbiome, we found clinicians practicing in the ED were significantly more resistant to changing their prescription patterns if presented evidence that antibiotic-induced dysbiosis predisposes patients to the development of immune-mediated disease compared with inpatient or outpatient prescribers (**See Supplement, Table 4**). All other responses by clinicians from each practice location reflected univariate trends.

We found that self-reported knowledge did not influence clinician mean ranking scores for the relative importance of clinical reference tools (data not shown). However, self-reported knowledgeable clinicians agreed significantly more with all statements attesting to the importance of the microbiome and with statements linking the microbiome and immune-mediated disease. (**See Supplement, Tables 5,6**).

To determine whether clinicians' responses to questionnaire items differed by antibiotic prescription frequency, we compared frequently-prescribing (daily or weekly), and infrequently-prescribing (monthly or less frequently) clinicians. We found frequently-prescribing clinicians agreed significantly more with the statement: "It is safer to prescribe narrow-spectrum antibiotics than broad-spectrum antibiotics because more selective killing of pathogenic organisms maintains the diversity of the human microbiome," (data not shown). No other statistically significant differences were found for any other questionnaire item.

## DISCUSSION

Perturbation of the normal flora of the microbiome, termed dysbiosis, is associated with a variety of immune-mediated diseases.[4,5,6,7] Based on the established relationship between antibiotic use and dysbiosis,[8] and that recent years have seen increased worldwide incidence and prevalence of immune-mediated diseases[13] and significant inappropriate use of antibiotics,[17,18] antibiotic-induced dysbiosis represents a potential environmental contributor to the development of these diseases. As a preliminary approach to providing a context, we assessed caregiver attitudes and knowledge relevant to this relationship.

Although the microbiome demonstrates marked differences in composition depending on environmental factors like age, geography, ethnicity, and diet,[19,20] consistent changes in microbiome composition have been observed in response to certain antibiotics. For instance, vancomycin and amoxicillin reduce populations of *Enterobacteriaceae* and *Bifidobacterium*, respectively.[2] Similarly, specific changes in the microbiome have been linked with specific disease states.[15,21-23] For instance, atopic dermatitis and asthma have been associated with a decreased total diversity of the human microbiome, whereas inflammatory bowel disease has been linked with decreased proportions of *Clostridia* and *Bacteroides* and increased proportions of *Enterobacteriaceae.*[24,25]

Separated only by intestinal epithelial cells and a thin layer of overlying mucus,[20] the host immune system and intestinal commensal microorganisms interact via well-established molecular mechanisms including toll-like receptor and cluster-of-differentiation signaling.[14,26] For instance, *B. fragilis* use a capsular polysaccharide to induce anti-inflammatory IL-10 expression from dendritic cells via TLR-2 signaling, and *Clostridium* strains can induce TGF-β expression from intestinal epithelial cells.[2] Both mechanisms enhance the function of regulatory T cells (Treg), which are critical for development of immunogenic tolerance. Additionally, microbial fermentation products such as propionate and butyrate may epigenetically enhance Treg function by upregulating the Foxp3 transcription factor.[2]

Germ-free animals have been found to have defects in the development of gastric-associated lymphoid tissue, Peyer's patches, and mesenteric lymph nodes.[17] Perhaps even more importantly, recent studies have shown a dependence of thymic lymphocyte development on the presence of gut microbes in early life.[27] Given these observations, it follows that dysbiosis in early life may disrupt the development of immunogenic tolerance.

Although the human microbiome has been a prominent topic of research in recent years, few studies have been aimed at evaluating the consequences of antibiotic-induced dysbiosis. Nonetheless, the aforementioned evidence supports a connection between antibiotic-induced dysbiosis and subsequent immune-mediated disease. It follows that a clinician's antibiotic prescribing patterns might influence patients' microbiomes towards a dysbiotic state. To our knowledge, our study is the first survey of medical providers evaluating prescriber awareness and opinions regarding the link between antibiotics, microbiome dysbiosis, and immune-mediated disease.

When asked to rank five commonly utilized clinical resources when prescribing antibiotics most clinicians placed first- or second-most importance on the use of antibiograms, prior clinical experience, and clinical reference tools, whereas antimicrobial stewardship programs and infectious disease physician consultations were considered less important. Given the emerging nature of information on antibiotic use, dysbiosis and immune-mediated disease, antimicrobial stewardship programs assume a unique role.

The observation that clinicians overwhelmingly agreed that prescription of specific antibiotics is important in preventing antibiotic resistance was expected. In contrast, we were surprised to learn that prescribers viewed protection of the human microbiome to be almost as important as avoiding adverse effects when selecting antibiotics. Moreover, almost 90% of clinicians agreed or strongly agreed that it is important for clinicians to acquire knowledge regarding the human microbiome and that alterations to the human microbiome have important implications for human health. Fewer than 40% of respondents considered themselves knowledgeable in this area.

Finally, we found a high degree of uncertainty with statements about the link between dysbiosis and autoimmune diseases, with many respondents neither agreeing nor disagreeing. Overall, our data suggest prescribers recognize the importance of the microbiome when prescribing antibiotics but do not feel confident in their relevant knowledge.

Opinions regarding the human microbiome appear to

differ across practice settings. This may, at least in part, be due to differences in time and resource constraints or patient populations treated. ED providers valued consultation of other providers less than inpatient providers. However, ED providers more highly valued quicker clinical references (e.g., UpToDate) than did inpatient providers. Additionally, ED providers agreed more than inpatient and outpatient providers that the human microbiome is insufficiently well understood to consider during medical practice. ED providers were also more resistant to modifying their prescribing practices given evidence linking antibiotic-induced dysbiosis and immune-mediated disease. Inpatient providers more equally utilized all mentioned clinical resources, perhaps highlighting the need for additional expertise when caring for patients with multiple complex medical issues in the inpatient setting.

As our study findings are limited to Rhode Island and our response rate was low, our results may have limited generalizability. Additionally, our use of "self-reported knowledge (of the human microbiome)" is a limitation of the study because we were unable to assess actual knowledge of the human microbiome. Nonetheless, as expected, we found respondents with a higher self-reported knowledge thought the microbiome was more important and considered it more highly when prescribing antibiotics. However, self-reported knowledge was not associated with a difference in the resources utilized or factors considered when prescribing antibiotics. Future studies assessing concrete knowledge of the pathophysiologic effects of antibiotics on the human microbiome would reveal whether the above is indicative of a Dunning-Kruger effect.

More frequent antibiotic prescribers have a larger impact on patients' microbiomes. However, we found almost no significant differences in any survey responses based on prescription frequency. The lack of an overall trend suggests frequently-prescribing clinicians do so for reasons unrelated to knowledge or opinions regarding the microbiome (e.g., patient pathology, patient volume, or low confidence in clinical knowledge).

Given our findings, investigation into clinicians' actual knowledge regarding the human microbiome seems warranted. The low confidence in reported knowledge of the human microbiome indicates clinicians might benefit from continuing medical education regarding antibiotic-induced dysbiosis and immune-mediated disease, particularly given the growing research in this field and growing clinical importance for individuals and populations. Additionally, further primary research investigating the link between dysbiosis and development of specific immune-mediated diseases could highlight appropriate narrow-spectrum pathogen-specific antimicrobials to promote microbiome health.

## References


1. Toor D, Wsson MK, Kumar P, et al. Dysbiosis Disrupts Gut Immune Homeostasis and Promotes Gastric Diseases. *Int J Mol Sci.* 2019;20(10).
2. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. *Cellular Microbiology.* 2014;16(7):1024-1033.
3. Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. *Frontiers in microbiology.* 2015;6:1543.
4. Lee SY, Lee E, Park YM, Hong SJ. Microbiome in the Gut-Skin Axis in Atopic Dermatitis. *Allergy Asthma Immunol Res.* 2018;10(4):354-362.
5. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A.* 2007;104(34):13780-13785.
6. Abdellatif AM, Sarvetnick NE. Current understanding of the role of gut dysbiosis in type 1 diabetes. *Journal of Diabetes.* 2019;11(8):632-644.
7. Girbovan A, Sur G, Samasca G, Lupan I. Dysbiosis a risk factor for celiac disease. *Med Microbiol Immunol.* 2017;206(2):83-91.
8. Lange K, Buerger M, Stallmach A, Bruns T. Effects of Antibiotics on Gut Microbiota. *Digestive diseases (Basel, Switzerland).* 2016;34(3):260-268.
9. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS biology.* 2008;6(11):e280.
10. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010;9(5):520-532.
11. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabet Med.* 2006;23(8):857-866.
12. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142(1):46-54.e42; quiz e30.
13. Lerner A, Patricia W, Matthias T. The World Incidence and Prevalence of Autoimmune Diseases is Increasing. *International Journal of Celiac Disease.* 2015;3:151-155.
14. Lee SY, Yu J, Ahn KM, et al. Additive effect between IL-13 polymorphism and cesarean section delivery/prenatal antibiotics use on atopic dermatitis: a birth cohort study (COCOA). *PloS one.* 2014;9(5):e96603.
15. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology.* 2015;45(1):137-145.
16. Kilkkinen A, Virtanen SM, Klaukka T, et al. Use of antimicrobials and risk of type 1 diabetes in a population-based mother–child cohort. *Diabetologia.* 2006;49(1):66-70.
17. Vangay P, Ward T, Jeffrey, Knights D. Antibiotics, Pediatric Dysbiosis, and Disease. *Cell Host & Microbe.* 2015;17(5):553-564.
18. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *JAMA.* 2016;315(17):1864.
19. Gupta VK, Paul S, Dutta C. Geography, Ethnicity or Subsistence-Specific Variations in Human Microbiome Composition and Diversity. *Frontiers in microbiology.* 2017;8:1162-1162.
20. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nature Reviews Immunology.* 2017;17(4):219-232.
21. Goulet O. Potential role of the intestinal microbiota in programming health and disease. *Nutrition reviews.* 2015;73 Suppl 1:32-40.

22. Ipci K, Altintoprak N, Muluk NB, Senturk M, Cingi C. The possible mechanisms of the human microbiome in allergic diseases. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2017;274(2):617-626.
23. Miyoshi J, Bobe AM, Miyoshi S, et al. Peripartum Antibiotics Promote Gut Dysbiosis, Loss of Immune Tolerance, and Inflammatory Bowel Disease in Genetically Prone Offspring. *Cell reports.* 2017;20(2):491-504.
24. Li M, Wang M, Donovan SM. Early development of the gut microbiome and immune-mediated childhood disorders. *Seminars in reproductive medicine.* 2014;32(1):74-86.
25. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical & Experimental Allergy.* 2014;44(6):842-850.
26. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell.* 2004;118(2):229-241.
27. Ennamorati M, Vasudevan C, Clerkin K, et al. Intestinal microbes influence development of thymic lymphocytes in early life. *Proc Natl Acad Sci U S A.* 2020;117(5):2570-2578.

## Authors

Matthew Wilson, MD, ScM, Warren Alpert Medical School of Brown University, MD'20; Resident Physician in Diagnostic Radiology, Johns Hopkins University, Baltimore, MD.

Michael J. Mello, MD, MPH, Professor of Emergency Medicine, Professor of Medical Science, Section of Medical Education; Director, Master of Science in Population Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Philip A. Gruppuso, MD, Professor of Pediatrics, Professor of Molecular Biology, Cell Biology and Biochemistry (Research), Professor of Medical Science, Warren Alpert Medical School Brown University, Providence, RI.

## Correspondence

Philip A. Gruppuso, MD
Department of Pediatrics
Division of Pediatric Endocrinology
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
401-444-5504
philip_gruppuso@brown.edu

# Monitoring Vaccine Adverse Event Reporting System (VAERS) Reports Related to COVID-19 Vaccination Efforts in Rhode Island

EVGENIA KARAYEVA, MPH; HYUN WOO KIM, BS; UTPALA BANDY, MD, MPH;
AILIS CLYNE, MD, MPH; THEODORE P. MARAK, MPH

## INTRODUCTION

Co-developed and maintained by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), the Vaccine Adverse Event Reporting System (VAERS) serves as a national passive surveillance system for continuous monitoring of vaccine safety once it has been distributed in the marketplace.[1,2] Any individual may report an adverse event following immunization (AEFI) to VAERS, without temporal limits or specifications of what type of events constitute an adverse reaction. Reports can be submitted online or email/faxed to the CDC. VAERS accepts and monitors spontaneous reports of adverse reactions or side effects that individuals may experience post immunization, some of which have not been observed during clinical trials and may indicate a possible safety concern with the vaccine.[3]

Prior to the 2019 coronavirus (COVID-19) pandemic, the immunization program at the Rhode Island Department of Health (RIDOH) had limited interaction with the VAERS operations at CDC; RIDOH did not receive state-level VAERS data regularly and had no protocol or necessity for receiving, storing, and reviewing RI VAERS reports. Following the release of the COVID-19 vaccines in the United States, the CDC has actively shared Rhode Island resident VAERS reports with RIDOH. A vaccine surveillance team was established within the COVID-19 Epidemiological Operations (Epi-Ops) Unit to maintain and review VAERS reports following COVID-19 immunization. The purpose of the state program is to organize and summarize both the operations of RIDOH COVID-19 vaccine surveillance team and the information included in VAERS reported in Rhode Island.

## METHODS

Anyone can submit a report of a suspected vaccine adverse event to VAERS, including a patient, family member, or health care provider. When a person calls RIDOH with information on an event or requests assistance regarding the VAERS reporting process, the COVID-19 vaccine surveillance team assists the caller in completing and submitting a VAERS report. After receipt and review by the federal VAERS program, VAERS report data is shared with the appropriate state Department of Health. The CDC sends Rhode Island VAERS reports in an excel format to the RIDOH. The vaccine surveillance team at RIDOH maintains an internal cumulative spreadsheet of all the VAERS reports pertaining to RI residents. The clinical staff on the team review the VAERS report details and classify the reported event.[4] Classification of VAERS reports into specific categories helps the team summarize adverse events following AEFIs to identify cases of significant interest and respond to media and data requests in a timely manner.

Reported adverse events are classified by VAERS as:[5]

**1. Serious adverse events (as defined by federal law), regardless of causality, including:**

- death
- a life-threatening event
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect
- an important medical event that, based on appropriate medical judgement, may jeopardize the individual and may require medical or surgical intervention

**2. Non-serious adverse events:**

- non-life-threatening events that resolves with or without the assistance of medications
- fever, arm soreness, and mild irritability.

**3. Vaccine administration errors whether or not associated with an adverse event:**[6]

- any preventable events that may cause or lead to patient harm or inappropriate vaccine use
- some vaccine administration errors that have been reported include immunization of unauthorized age groups, incorrect administration of a higher or lower dose, and inappropriate storage and handling of the vaccine

**4. Cases of COVID-19 infection only**

**5. Reports that indicate no adverse event occurred**

Reports that indicate diagnosis of COVID-19 infection only and reports that did not indicate any adverse event occurred are removed from the final VAERS count. Sub-categories by intervention received and events of interest allow for further classification of VAERS reports. Interventions include self-treatment (where the patient receives no clinical support and only undergoes self-care at home with or without use of over-the-counter medications), medical (minimum of a medical evaluation by a healthcare professional at the vaccine site or at another clinical location. These may also include other interventions such as lab work, IV fluids, medication, steroid treatment etc.), and surgical interventions, which may be minor (e.g., incision and drainage) or major. Events of interest include reports of anaphylaxis, Guillain-Barré syndrome, immediate allergic reactions, thromboembolic events, myocarditis/pericarditis, and select others.[7] Events of interest are included when the event or condition noted on the VAERS report can be confirmed by a medical provider.

Due to the nature of a passive surveillance system, not all VAERS reports received will have complete information and may be missing individual patient identifiers, vaccine and dose information, or have incomplete descriptions of the reaction. The epidemiologist and nurses on the team utilize additional data sources and outreach to the patient or adverse event reporter to obtain more detailed information when appropriate. For example, the team can leverage resources like the state's immunization registry to confirm vaccine date and dose information if the patient identifiers are shared in the VAERS report. Other reports may require additional follow-up with the reporting physician or hospital for medical records to gain a clearer understanding of the significance of the event. These types of outreach efforts are focused on reported cases of deaths and other events of interest. The cumulative list is analyzed to produce a weekly VAERS report describing the outcomes and trends seen in the VAERS data. The COVID-19 vaccine surveillance team meets weekly to review new reports and trends in the volume and types of reports received.

## RESULTS

The vaccine surveillance team received the first reports of an adverse event related to the COVID-19 vaccine on January 8th, 2021. Overall, between January 8, 2021 and July 16, 2021, 1,510 vaccine adverse events were reported in Rhode Island. Excluding 18 reports that were classified as not true AEFIs and 13 reports that described COVID-19 infection only, there were 1,479 (97.95%) adverse events reported.

For outcomes of adverse events following immunization, most reports received have been for non-serious adverse events (79.4%). **[Table 1]** Serious events made up 11.13% of all Rhode Island VAERS reports. 39.15% of the VAERS reported having recovered from the adverse event at the time the report was completed. 89 VAERS reports (6.02%) indicated hospitalization after experiencing an adverse event following immunization. 16 reports (1.08%) resulted in death and while 6 AEFIs occurred during pregnancy, none resulted in a congenital anomaly or birth defect. 25 AEFIs (1.69%) reported persistent or significant incapacity. Some of these outcomes included incapacity or loss of feeling in limbs, persistent memory loss, facial paralysis, and loss of hearing. 15.75% AEFIs reported visits to either the emergency room or an urgent care clinic. 112 AEFIs (7.57%) indicated vaccine administration error. 89 VAERS reports (6.02%) resulted in hospitalizations following AEFIs, and among these, 4 resulted in death. There was a total of 16 deaths reported in VAERS. All deaths and hospitalizations following AEFI are reported to VAERS, regardless of cause. As a result, not all reported deaths and hospitalizations are attributable to COVID-19 vaccination.[8] **[Table 2]**

**Table 1.** Classification of reported VAERS in Rhode Island [1/8/2021–7/16/2021]

| Classification of VAERS | Count (n=1510) | Percent |
|---|---|---|
| Non-serious | 1199 | 79.40% |
| Serious | 168 | 11.13% |
| Vaccine Administration Error | 112 | 7.42% |
| Not a VAERS | 18 | 1.19% |
| COVID-19 Infection Only | 13 | 0.86% |

**Table 2.** Outcomes from VAERS reports in Rhode Island [1/8/2021–7/16/2021]

| Outcomes | Count | Percent |
|---|---|---|
| **Non-serious** | | |
| Recovered at the time of adverse event | 579 | 39.15% |
| Treated at Vaccine Site | 174 | 11.76% |
| Office/clinical visit | 321 | 21.70% |
| **Serious** | | |
| Hospitalization | 89 | 6.02% |
| Persistent or significant incapacity | 25 | 1.69% |
| Congenital anomaly or birth defect | 0 | 0% |
| Death | 16 | 1.08% |
| **Other** | | |
| Emergency room/urgent care visit | 233 | 15.75% |
| Vaccine Administration Error | 112 | 7.57% |

Note: All vaccine adverse event outcomes listed in table are reported in VAERS. The total reported adverse events following vaccination may not equal the total number of VAERS reports received as one individual can have multiple outcomes.

## DISCUSSION

As of 7/16/2021, over one million (1,301,183) doses of COVID-19 vaccine were administered to 701,708 RI residents.[9] The VAERS program received 1,479 reports of vaccine adverse events following COVID-19 vaccination among RI residents. The establishment of the COVID-19 vaccine surveillance team has equipped RIDOH with the ability to receive, review, classify and track RI VAERS data and monitor trends in reported events. Importantly, the team serves as a resource for individuals and health care providers who need information or assistance with submitting a VAERS report. Ensuring that all possible vaccine adverse events are reported improves the ability of the federal VAERS program to serve as an important component of maintaining vaccine safety.

States are limited in their ability to determine causality between vaccination and reported events due to the relatively low volume of reports per vaccinated persons. In addition, there is still a challenge to confirm validity of some self-reported reactions as VAERS does not require submission of clinical evidence of the reaction. It is difficult for the state to draw conclusions about vaccinations in Rhode Island or to make recommendations. However, because the VAERS program is national and pooling data from all states, it aims to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." At the national level, if a safety signal is found in VAERS, further analyses and studies are performed to better assess health risks and possible connections between adverse events and a vaccine.

Ensuring COVID-19 vaccine safety and building vaccine confidence are critical to ending the pandemic. RIDOH is committed to supporting Rhode Islanders in reporting to VAERS and to contribute to the national significance of this safety-monitoring program.

### References


1. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, Wassilak SG. (1994). The Vaccine Adverse Event Reporting System (VAERS). *Vaccine*, *12*(6), 542–550. https://doi.org/10.1016/0264-410x(94)90315-8
2. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. (2015). Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*, *33*(36), 4398–4405. https://doi.org/10.1016/j.vaccine.2015.07.035
3. Miller ER, Cano M, Hibbs B, Suragh T. (2021, February 23). *Chapter 21: Surveillance for Adverse Events Following Immunization Using the Vaccine Adverse Event Reporting System (VAERS)*. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html.
4. U. S. Code of Federal Regulations, 21 CFR 600.80 *Postmarketing reporting of adverse experiences*. 2014 Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=9c976e3d7aaffe791fc5b2ccc7ec7420&mc=true&node=se21.7.600_180&rgn=div8.Accessed July 28, 2021.
5. Centers for Disease Control and Prevention (CDC). (2021, March 8). 10 Things Healthcare Providers Need to Know about the Vaccine Adverse Event Reporting System (VAERS). https://www.cdc.gov/coronavirus/2019-ncov/downloads/vaccines/10-things-healthcare-providers-need-to-know-about-VAERS.pdf.
6. Centers for Disease Control and Prevention (CDC). (2021, May 28). COVID-19 Vaccine Administration Errors and Deviations. https://www.cdc.gov/vaccines/covid-19/downloads/covid19-vaccine-errors-deviations.pdf.
7. AERS Team Immunization Safety Office, Division of Healthcare Quality Promotion National Center for Emerging and Zoonotic Infectious Diseases Centers for Disease Control and Prevention. (n.d.). *Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19* (as of 4 December 2020). https://www.cdc.gov/vaccinesafety/pdf/VAERS-COVID19-SOP-4-Dec-2020-508.pdf.
8. Miller ER, Moro PL, Cano M, Shimabukuro TT. (2015). Deaths following vaccination: What does the evidence show? *Vaccine*, *33*(29), 3288–3292. https://doi.org/10.1016/j.vaccine.2015.05.023
9. *Rhode Island Covid-19 Vaccine Data*. Rhode Island COVID-19 Vaccine Data. (2021, July 16). https://ri-department-of-health-covid-19-vaccine-data-rihealth.hub.arcgis.com/. Accessed July 16, 2021.


### Acknowledgments

The authors would like to thank the following RIDOH staff: Suzanne Bornschein, Jennifer Clarke, Sheila Tumilty, Beth Butler, and Lisa Gargano for their contributions to the vaccine surveillance program within the COVID-19 Epi-Ops Unit of RIDOH.

### Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Rhode Island Department of Health.

### Authors

Evgenia Karayeva, MPH, Lead Public Health Epidemiologist COVID-19 Unit, Rhode Island Department of Health.

Hyun Woo Kim, BS, Public Health Epidemiologist COVID-19 Unit, Rhode Island Department of Health.

Utpala Bandy, MD, MPH, State Epidemiologist, Rhode Island Department of Health.

Ailis Clyne, MD, MPH, Medical Director COVID-19 Unit, Rhode Island Department of Health.

Theodore P. Marak, MPH, Team Lead COVID-19 Unit, Rhode Island Department of Health.

# Rhode Island Monthly Vital Statistics Report
# Provisional Occurrence Data from the Division of Vital Records

| VITAL EVENTS | REPORTING PERIOD | | |
|---|---|---|---|
| | MARCH 2021 | 12 MONTHS ENDING WITH MARCH 2021 | |
| | Number | Number | Rates |
| Live Births | 953 | 10,805 | 10.2* |
| Deaths | 965 | 12,582 | 11.9* |
| Infant Deaths | 6 | 56 | 5.2# |
| Neonatal Deaths | 4 | 38 | 3.5# |
| Marriages | 220 | 4,619 | 4.4* |
| Divorces | 302 | 2,106 | 2.0* |

* Rates per 1,000 estimated population

# Rates per 1,000 live births

| Underlying Cause of Death Category | REPORTING PERIOD | | | |
|---|---|---|---|---|
| | SEPTEMBER 2020 | 12 MONTHS ENDING WITH SEPTEMBER 2020 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 174 | 2,382 | 224.9 | 3,259.5 |
| Malignant Neoplasms | 187 | 2,198 | 207.5 | 4,509.5 |
| Cerebrovascular Disease | 30 | 433 | 40.9 | 630.0 |
| Injuries (Accident/Suicide/Homicide) | 89 | 953 | 90.0 | 13,881.5 |
| COPD | 40 | 479 | 45.2 | 475.0 |

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,059,361 for 2019 (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

Favorite
Healthcare Staffing

# Rhode Island's Medical Staffing Experts

Favorite Healthcare Staffing provides a comprehensive range of staffing services at preferred pricing to RIMS members. Call today to see why we are the favorite choice of healthcare professionals and physician practices across the US!

401.354.7115

MedicalStaffing@FavoriteStaffing.com

Favorite Healthcare Staffing is a Valued Sponsor of the Rhode Island Medical Society

AA / EOE / M / F / V / D

# SARS-CoV-2 Variants and their Clinical Implications

ELEFTHERIOS MYLONAKIS, MD, PhD

The COVID-19 pandemic continues to impact every aspect of our daily lives and stress our health resources and the SARS-CoV-2 variants have contributed to this unpredictable dynamic. This aspect of the pandemic was underappreciated during its early stages, but with millions of infections around the world and each infected individual having billions of copies of the virus, it was only a matter of time for clinically important variants to emerge.

At the beginning of the pandemic, variants of SARS-CoV-2 containing the D614G aspartic acid-to-glycine substitution at amino acid position 614 of the spike (S) protein rapidly became dominant, mostly due to increased receptor-binding avidity to the angiotensin-converting enzyme 2 (ACE2) receptor. Then, the B.1.1.7 (Alpha) and P.1 (Gamma) moved from the UK and Brazil, respectively, and necessitated national and global monitoring and naming systems, such as the one coordinated by the World Health Organization (WHO).[2]

Importantly, these variants of concern (VOCs) are associated with changes in transmissibility and make a difference in the dynamic of the pandemic and move epidemiologic and modeling targets, including of the so-called "herd immunity." Moreover, preliminary data suggest that even some of the monoclonal antibodies may be less effective for treating cases of COVID-19 caused by certain variants.[3] It is remarkable how small changes in the virus can have such profound clinical ramifications. For example, the B.1.1.7 (Alpha) variant carries a mutation in the S protein (N501Y) that, along with numerous other B.1.1.7 lineage-defining mutations, alter the conformation of the receptor-binding domain. This relatively small change was enough to make this the predominant variant around the globe.

In this issue, Kantor et al. present the important landscape of the SARS-CoV-2 variants in RI. They report that these variants represent the major lineages noted among the 3,963 SARS-CoV-2 RI sequences detailed in their paper.[1] As they show, a number of variants of interest (VOI) and all four VOCs (the term that describes VOIs with demonstrated ability to alter the epidemiologic and/or clinical aspects of COVID-19) have been detected in our state and they are: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta).[1]

Also, the report by Kantor et al. hints at the next "elephant in the room." The report notes 9 cases associated with B.1.617.2 (Delta) between 4/2021 and 5/25/2021. We have been following the unthinkable loss of life and human suffering in India and around the world that B.1.617.2 (Delta) has been causing. This variant had an exponential increase over the past several weeks and currently is associated with the vast majority of cases in the US. Preliminary reports detail that this variant causes clinical disease up to 2 days earlier, can result in viral loads in the respiratory tract that are 1,000-fold higher, and cause more reinfections or even evade, in some degree, vaccine-induced immune responses. Even the clinical symptomatology, with more patients presenting with pharyngitis and upper respiratory symptoms, seems to be different. Indeed, in the few weeks that have passed between the submission of the Kantor et al. paper and the writing of this editorial, the Delta variants in RI have increased, and at the time of this writing amount to 42 and have become the majority of sequenced SARS-CoV-2 isolates in RI (https://ri-department-of-health-covid-19-variant-data-rihealth.hub.arcgis.com/).

Looking at this rapidly evolving dynamic, one question comes to mind: When will the virus reach peak fitness? Coronaviruses, as other RNA viruses, acquire mutations quickly during viral replication in the host cytoplasm. With vaccinations in some countries not expected to start in earnest for over a year from now, with immune-suppressed individuals who have marginal response to the vaccine and long periods of viral shedding, and with the potential for declining immunity that could necessitate boosters and next- generation vaccines, it is reasonable to assume that changes in the virus will continue to challenge us.

However, the emergence of variants should not compromise our determination, but reinvigorate our unwavering adherence to disease-control measures, masking, and vaccination.[4] Science will continue to provide us with tools to fight the virus. The RI-centric genomic surveillance program described by Kantor et al. monitors the prevalence of SARS-CoV-2 variants in our state and provides invaluable information in order to prepare our health systems, advise our patients, and optimize the deployment of resources. The health partnership between the Kantor Laboratory at the Providence-Boston Center for AIDS Research and The Miriam Hospital, the RI State Health Laboratory (RISHL), and their collaborators[1] provides essential and clinically relevant information for the more equitable distribution of vaccines and other resources, as well as for updating best practices in real time. As the pandemic will continue to seek and exploit our weaknesses, it is the realization that we need to come together that will guide us out of the pandemic quicker and with the least possible human loss and despair.

## References


1. Kantor R, Novitsky V, Carpenter-Azevedo K, Howison M, Manne A, Darpolor JK, Bobenchik A, Tripathi A, Huard RC, King E. SARS-CoV-2 Variants in Rhode Island. R I Med J (2013). 2021 Sep 1;104(7):16-20.PMID: 34279520
2. Tracking SARS-CoV-2 variants. Available at https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/(accessed7/27/21)
3. Hoffmann M, Arora P, Groß R, Seidel A, Hörnich BF, Hahn AS, Krüger N, Graichen L, Hofmann-Winkler H, Kempf A, Winkler MS, Schulz S, Jäck HM, Jahrsdörfer B, Schrezenmeier H, Müller M, Kleger A, Münch J, Pöhlmann S. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell. 2021 Apr 29;184(9):2384-2393.e12. doi: 10.1016/j.cell.2021.03.036. Epub 2021 Mar 20.PMID: 33794143
4. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. N Engl J Med. 2021 May 13;384(19):1866-1868. doi: 10.1056/NEJMc2100362. Epub 2021 Mar 24. PMID: 33761203


## Author


Eleftherios Mylonakis, MD, PhD, Charles C.J. Carpenter Professor of Infectious Disease; Chief, Infectious Diseases Division, The Miriam and Rhode Island Hospitals; Professor of Medicine and Professor of Molecular Microbiology, Warren Alpert Medical School of Brown University, Providence, RI.


## Correspondence


Eleftherios Mylonakis, MD, PhD
Rhode Island Hospital
593 Eddy Street, POB, 3rd Floor
401-444-7856
Fax 401-444-8179
emylonakis@lifespan.org

# Emerging Advances and Existing Barriers for Medication Abortion

TAYLOR FREEBURG, MD'22; MEGHNA NANDI, MD'21; ANDREA ARENA, MD

The COVID-19 pandemic has magnified existing barriers to abortion access including cost, limited appointments, and transportation.[1] Notably, these barriers likely had a disproportionate impact on people of low-income backgrounds and communities of color, who were more likely to face economic hardship during the pandemic. In response to these barriers and the increasing use of telemedicine, abortion providers have developed new methods for medication abortion care delivery to limit in-person contact and increase accessibility. As these new options for abortion care delivery emerged, some states have responded with increasingly restrictive legislation to limit abortion access. In this commentary, we discuss emerging options for medication abortion delivery and remaining barriers to access.

## Reducing barriers through medication abortion

Medication abortion, achieved by administering Mifepristone and then Misoprostol, is a safe, effective abortion option that circumvents barriers to procedural abortion including in-person contact and limited providers with the required skillset. Currently, medication abortion is approved by the U.S. Drug and Food Administration (FDA) up to 70 days gestational age. Since the FDA-approved medication abortion in 2000, its use has grown, with nearly half of abortions at nine weeks gestation or less being medication abortions nationally in 2018.[2] The expected effects of medication abortion are heavy bleeding and cramping as the uterine contents are expelled over several days. If a medication abortion does not remove all fetal tissue, a secondary aspiration procedure may be necessary (6.2% of patients in a nationwide study).[3] Medication abortion is a generally safe, effective alternative to procedural abortion, especially for earlier gestations.

## Restrictions on medical abortion

Despite the ease of use and pressing need, medication abortion has historically been limited by federal regulations. Mifepristone is tightly regulated under the Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA, even though the safety of Mifepristone is well established.[4] Mifepristone is easy to use and has well-established dosing protocols, unlike many medications that are not under REMS and require close monitoring or titrating, such as Warfarin and Valproic Acid. Although REMS is intended to minimize harms, the policy creates barriers to Mifepristone access since the drug cannot be dispensed at pharmacies. To prescribe Mifepristone, physicians must register with a distributor, stock the drug in their office, and provide a medication guide and agreement to the patient. Though the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP) have long called for removal of the Mifepristone REMS classification; the pandemic brought renewed attention to the issue, in part because in-person visits put patients and providers at risk for COVID-19.[5,6] In April 2021, the FDA temporarily suspended the REMS requirement that Mifepristone must be dispensed in a clinic, medical office, or hospital. This new policy follows a legal battle which began in May 2020, when the American Civil Liberties Union (ACLU) filed a lawsuit against the FDA on behalf of the ACOG which challenged the validity of REMS. Notably, the District Court of Maryland had previously blocked the REMS measure in July 2020 and Mifepristone remained free from REMS jurisdiction until January 2021, when the U.S. Supreme Court reinstated the regulations.[7,8] The temporary relaxation of the Mifepristone REMS is linked to the development of teleabortion clinics and increased options for patients to fill Mifepristone prescriptions that have transformed medication abortion delivery.

## Telemedicine and abortion

The temporary suspension of the REMS has enabled opportunities to deliver medication abortion care that capitalizes on the accelerated use of telehealth. The Reproductive Health Access Project has developed a "no-touch" medication abortion protocol that outlines an approach where a patient is evaluated by video or phone and gestational age is determined by last menstrual period rather than in-person ultrasound.[9] In the first three months of the pandemic, one study surveying independent abortion providers found that 71% of providers moved to telehealth for follow-up and 41% for consultation.[10] Digital abortion clinics such as Hey Jane and TelAbortion that offer telehealth visits and then ship abortion pills to patients also emerged in the past year.[11,12]

Even prior to the pandemic, there was abundant global evidence supporting telemedicine for medication abortion. The findings from these studies suggest that rates of completion and complications of first-trimester medication abortions through telemedicine are similar to those following medication abortions started in the clinic.[13] One observational study from the United Kingdom followed outcomes of 663 patients who completed medication abortion at home through a telemedicine program without routine ultrasound. These patients had high rates of abortion completion and low rates of complications, similar to studies of patients who had ultrasounds and took Mifepristone in a clinical setting. Although pre-abortion ultrasound was not used routinely, in one-fifth of the patients, imaging was deemed necessary for cases in which gestational age was uncertain or to confirm location of pregnancy.[14] These findings are in line with the National Abortion Federation guidelines, which state that ultrasound is not required for first-trimester abortion care, but may be used inform clinical decision-making when gestational age cannot be determined by other means.[15]

## Ongoing challenges facing medical abortion

The challenges of this past year have increased barriers to abortion access and thereby cast heightened scrutiny to current federal and state restrictions for medication abortion. The temporary suspension of REMS along with the increased use of telehealth nationally has created opportunities for increased flexibility and privacy for patients seeking medication abortion. These changes address barriers such as limited appointments and transportation; however, ongoing challenges to abortion access remain. People of low-income backgrounds may not have access to a computer to participate in telehealth or stable housing to endure the several days of heavy bleeding associated with medication abortion. Furthermore, the cost of a medication abortion can be prohibitive especially considering that RI's Medicaid program does not cover abortion except in cases of rape, incest, or life endangerment. In RI nearly 1 in 3 residents have public insurance and therefore cannot use their health insurance for an abortion. Currently there is proposed legislation at the state level, the Equality in Abortion Coverage Act, which would expand abortion coverage to government employees and users of Medicaid. It is currently being held in both chambers, and it is imperative for the medical community to throw their support behind these changes.[16]

The relaxation of REMS and expansion of telehealth have increased access to medication abortions; however, increasingly restrictive legislation makes decreasing barriers to abortion particularly urgent. Recently Texas passed a new law, one of several across the US banning abortions at six weeks gestation, only two weeks after the first missed period, before most individuals know they are pregnant. Texas' new law includes an unusual twist in that it allows any individual to sue people who "aid or abet" an abortion patient. A coalition of abortion providers filed a federal lawsuit to challenge this new law before it takes effect on September 1st.[17] In this increasingly restrictive and punitive climate, medication abortion, especially through a primary care office or telemedicine, provides a point of access. ❖

## References


1. Bayefsky MJ, Bartz D, Watson KL. Abortion during the Covid-19 Pandemic - Ensuring Access to an Essential Health Service. N Engl J Med. 2020;382(19):e47. doi:10.1056/NEJMp2008006
2. Kortsmit K, Jatlaoui TC, Mandel MG, et al. Abortion Surveillance – United States, 2018. MMWR Surveill Summ. 2020; 69(7):1-29. doi:10.15585/mmwr.ss6907a1
3. Meaidi A, Friedrich S, Gerds TA, Lidegaard O. Risk factors for surgical intervention of early medical abortion. Am J Obstet Gynecol. 2019;220(5):478.e1-478.e15. doi:10.1016/j.ajog.2019.02.014
4. Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M, Grossman D, Pendergast MK, Westhoff CL, Winikoff B. Sixteen Years of Overregulation: Time to Unburden Mifeprex. N Engl J Med. 2017 Feb 23;376(8):790-794. doi: 10.1056/NEJMsb1612526. PMID: 28225670.
5. Improving Access to Mifepristone for Reproductive Health Indications. ACOG. 2018 June. https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications
6. Munger M. Letter to FDA on REMS Requirements for Mifepristone. AAFP. 2019 June 20. https://www-aafp.org.AAFP/documents/advocacy/prevention/women/LT-FDA-Mifepristone REMS-062019.pdf
7. American College of Obstetricians and Gynecologists v. U.S. Food and Drug Administration. Civil action no. TDC-20-1320 (D. MD. 2020).
8. American College of Obstetricians and Gynecologists v. U.S. Food and Drug Administration. No. 20A34. 592 U.S. (2021).
9. No Touch Medication Abortion Protocol. Reproductive Health Access Project. 2020 March 26. Accessed 2021 March 16. https://www.reproductiveaccess.org/resource/no-touch-mab-protocol/
10. Upadhyay UD, Schroeder R, Roberts SCM. Adoption of no-test and telehealth medication abortion care among independent abortion providers in response to COVID-19. Contracept X. 2020;2:100049. doi:10.1016/j.conx.2020.100049
11. Hey Jane. Accessed 2021 January 10. https://www.heyjane.co/.
12. TelAbortion. Accessed 2021 January 10. https://www.telabortion.org.
13. Endler M, Lavelanet A, Cleeve A, Ganatra B, Gomperts R, Gemzell-Danielsson K. Telemedicine for medical abortion: a systematic review. BJOG. 2019;126(9):1094-1102. doi:10.1111/1471-0528.15684
14. Reynolds-Wright JJ, Johnstone A, McCabe K, Evans E, Cameron S. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic [published online ahead of print, 2021 Feb 4]. BMJ Sex Reprod Health. 2021;bmjsrh-2020-200976. doi: 10.1136/bmjsrh-2020-200976
15. Clinical Policy Guidelines for Abortion Care. National Abortion Federation. 2020. https://prochoice.org/providers/quality-standards/
16. Valverde B, Cano S, Goldin G, Mack T, Sosnowski, Euer D, Acosta J, Kallman M, Coyne C, Pearson R. Equality in Abortion Coverage Act. State of RI General Assembly. 2021; LC000764. http://webserver.rilin.state.ri.us/BillText/BillText21/SenateText21/S0267.pdf
17. Dias E. Lawsuit Takes Aim at Citizen-Enforced Texas Abortion Law. The New York Times. 2021 July 13. Accessed 2021 July 16. https://www.nytimes.com/2021/07/13/us/texas-abortion-lawsuit.html


## Acknowledgments

We thank Dr. Daria Szkwarko, Dr. Rebecca Allen, and Dr. Edward Feller for their insightful discussions of this topic.

## Authors

Taylor Freeburg, MD'22, Warren Alpert Medical School of Brown University, Providence, RI.

Meghna Nandi, MD-ScM'21, Primary Care-Population Medicine Program, Warren Alpert Medical School of Brown University, Providence, RI.

Andrea Arena, MD, Clinical Assistant Professor of Family Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

## Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Warren Alpert Medical School of Brown University.

## Funding

None

## Correspondence

Taylor Freeburg, MD'22
Brown University
Box G-9999
Providence, RI 02912
taylor_freeburg@brown.edu

# Recollections & Reflections of 9/11/01

**Shown above:** 2020 Tribute.
[NATIONAL SEPTEMBER 11 MEMORIAL & MUSEUM; WWW.911MEMORIAL.ORG]

**Cover photo:** *Tribute in Light* is a commemorative public art installation first presented six months after 9/11 and then every year thereafter, from dusk to dawn, on the night of September 11. [CREATIVE COMMONS, WIKIMEDIA]

The Community Plaza in front of the National September 11 Memorial & Museum (more frequently known simply, as the 9/11 Memorial) at Ground Zero.
[NATIONAL SEPTEMBER 11 MEMORIAL & MUSEUM; WWW.911MEMORIAL.ORG]

Memorial photograph wall of people killed on display at the World Trade Center Memorial and Museum in New York City, built on the site of the terrorist attack that brought down the World Trade Center's Twin Towers on 9/11/2001.
[LIBRARY OF CONGRESS, HIGHSMITH, CAROL M., PHOTOGRAPHER]

# September 11, 2001 – A Recollection of a Tragic Day in my Hometown

KENNETH S. KORR, MD, FACC

New York City fire fighters amid debris at the World Trade Center. [LIBRARY OF CONGRESS]

New York City fire fighter and another man covering his eyes on street in front of burning buildings following the Sept. 11th terrorist attack on the World Trade Center. [LIBRARY OF CONGRESS]

Two men assisting and walking with an injured woman down a street littered with paper and ashes, following the attack. [LIBRARY OF CONGRESS, PHOTOGRAPHER DON HALASY]

It was a typical hectic Monday in the Cardiac Catheterization Laboratory at The Miriam Hospital – a packed schedule with the usual number of electives plus half a dozen urgent add-on cases from the weekend. We were well along into the first case, a double-vessel stent in an elderly woman admitted with unstable angina, when a nurse came in saying there was a fire or something going on at The World Trade Center in Manhattan. Finishing that case, I joined several staff members in the break room, huddled around the TV, watching scenes of smoke billowing from the upper floor of one of the Twin Towers against the crystal-clear blue of the New York City skyline. It was still early, around 9:30 a.m., and it wasn't fully clear yet what was happening. And we had a busy schedule to get through, so it was on to the next case.

All day, between cases, I returned to the TV in the break room to watch as the events unfolded. Now both towers were ablaze and the Pentagon had been hit. Something was going on in a field in Pennsylvania. It seemed that we were under some sort of attack, but by whom and what other targets were out there? There was the usual array of TV commentators speculating on events but nothing from the President or any other government officials.

I grew up in NYC and my wife and I had many extended family members scattered throughout the boroughs. And I can recall watching as the Twin Towers were erected over several years, driving with my Dad, back and forth from work in lower Manhattan. I went through a mental checklist of who might be where, my brother-in-law, my cousins, close friends. It was surreal, as the day moved along from case to case and we worked our way through the schedule.

Between cases it was back to that TV in the break room to catch up on unfolding events. Extended family were checking in now and we (in Rhode Island) were the designated rendezvous point in case NYC had to be evacuated. By the end of the afternoon the situation was becoming tragically clearer. We had been attacked by terrorists who had hijacked planes and flown them into the Twin Towers and the Pentagon. A third plane possibly designated for the White House had gone down in a field in Pennsylvania, thwarted by a heroic and self-sacrificing group of passengers who attacked the hijackers.

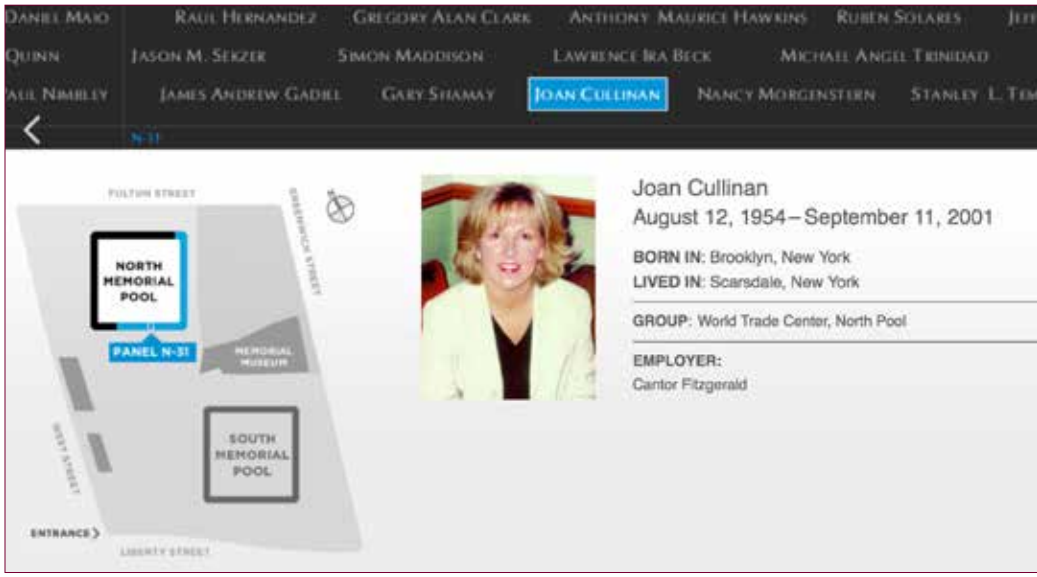
Looking back, it all seems emotionally overwhelming, but at the time we just carried on from one patient to the next until all the cases were finished. Now, 20 years later, as we emerge from a year-long pandemic, I can still readily recall the events of that day and our subsequent resilience as a nation in time of crisis. ❖

**Author**

Kenneth S. Korr, MD, FACC, is Associate Professor of Medicine Emeritus at the Alpert Medical School of Brown University and Associate Editor of the *Rhode Island Medical Journal.*

# 9/11: Remembering the Fallen 20 Years Later

MARY KORR
RIMJ MANAGING EDITOR




The 9/11 Memorial & Museum has a searchable database to find the location of the names on the Memorial wall of those who perished. [NAMES.911.MEMORIAL.ORG]

I remember the shock that swept across the country and the world on that Monday morning. In my house in Barrington, at about 9:30 a.m., the phone rang. "Did you see what happened? Planes crashed into The World Trade Center!" my friend Miriam exclaimed, knowing my husband and I were from the City.

I turned on the news and gasped…the Twin Towers, smoke blackening the blue September sky. I hoped my brother was not in the City. Later, I found out he was on his way to Kennedy Airport. The driver had the radio on and it was all over the news. No one knew what was happening. My brother called the airline – all flights were cancelled.

Mailboxes and the walls of buildings in the area were filled with messages from the families and friends of the missing post-9/11, searching for any information on their loved ones. [LIBRARY OF CONGRESS]

The phone rang again. "*Maria, que pasa, que pasa, que pasa*? *Que horrible! Quantas kilometres de Nueva York a Rhode Island*?" It was Francisco de Linares, a psychiatrist in Malaga, Spain. His daughter was doing a year abroad, living with us and attending Barrington High School with our son. "*Ana esta bien, somos mas de tres cientos kilometres de Nueva York. Estamos bien in Rhode Island*," I said, watching the devastation unfold on the TV. At 9:59 a.m. the South Tower collapsed.

The phone rang again. It was my son calling from Barrington High School. "What happened? Is anyone we know in there? Is the family OK?" I told him I was checking. "Tell Ana to call her dad. He's frantic. He said he's coming here to bring her home. I told him not to get on a plane. It may not be over."

The phone rang again. My sister told me our cousin's wife Joan worked in the North Tower, on one of the top floors. I stared at the TV as the North Tower collapsed at 10:28 a.m. She was among the 658 employees of Cantor Fitzgerald who were victims of the al Qaeda terrorist attacks that day. Joan and her husband, my cousin Tom, a psychologist practicing in New York, had filed papers a few days before to adopt a child from China. At her funeral, which my brother attended, Tom said Joan had also decided to change careers and had sent out applications to graduate schools to pursue a career in clinical social work. "Maybe, one of these days, we'll get an acceptance letter," he told the mourners.

My husband and I felt compelled to visit the site – to see what was still unbelievable, surreal. We drove down a few weeks later, and walked past the cordoned-off areas, workers and dogs still sifting through the millions of tons of debris, smoke still rising, embers hissing. I stopped in front of a nearby church. Names of the missing were posted on the announcement board, with photos, contact numbers…forever missing. Soon, we were covered in ash and coughing. A war zone.

This year, Joan's name, along with the 2,595 people inside and near the towers who were killed, and the 157 people who were aboard the flights who perished that day in the terrorist attacks, will be read at the 20th anniversary commemorations to be held at the 9/11 Memorial and Museum, located at Ground Zero. The custom began with the first anniversary of the attacks, in 2002, but was cancelled last year due to the pandemic. Six moments of silence will mark the times when each of the Towers was struck, when each fell, and the times corresponding to the attack at the Pentagon, and the crash of the United Airlines hijacked plane in Pennsylvania.

And for all those lost and the responders who, to this day, suffer from the effects of the toxins, the sky will light up once again, as the twin beams of the *Tribute in Light* illuminate the City skyline above Ground Zero – as bright and blue as that late summer day 20 years ago. ❖

# Working for You: RIMS advocacy activities

### August 2, Monday

Alpert Medical School Class of 2025 orientation: **Catherine A. Cummings, MD**, President

### August 3, Tuesday

RIMS Physician Health Committee (PHC): **Herbert Rakatansky, MD**, Chair (via teleconference)

### August 11, Wednesday

RI Department of Health (RIDOH) Board of Medical Licensure and Discipline

Governor's Overdose Intervention and Prevention Task Force: **Sarah Fessler, MD**, RIMS Past President

RODEO (Retired Old Doctors Eating Out) luncheon at the Squantum Association: **Arun Singh, MD**, presiding, assisted by **Dr. Candace L. Dyer** and **Dr. Fredric V. Christian**

### August 12, Thursday

Meeting with the Health Insurance Commissioner and OHIC staff regarding next generation Affordability Standard concept presentation: **Catherine A. Cummings, MD**, President

### August 16, Monday

Meeting with Blue Cross & Blue Shield of Rhode Island (BCBSRI): **Catherine A. Cummings, MD**, President; **Elizabeth Lange, MD**, President-elect

### August 17, Tuesday

Office of the Health Insurance Commissioner (OHIC) Health Insurance Advisory Council (HIAC): **Catherine A. Cummings, MD**, President

### August 19, Thursday

Substance Use Prevention Education and Recovery (SUPER) PAC birthday party and awards

### August 24, Tuesday

Meeting regarding fundraising for the Speaker of the House of Representatives

Presentation to the Lifespan CMOs regarding the RIMS Physician Health Program: **Dr. Herbert Rakatansky**, **Dr. R. William Corwin**, and **Kathleen Boyd, MSW, LICSW**

### August 26, Thursday

Governor's Overdose Task Force Racial Equity Work Group

### August 31, Tuesday

RIDOH Harm Reduction Center Advisory Committee: **Elizabeth Samuels, MD**; **Rahul Vanjani, MD**

**RIMS NOTES: *News You Can Use***

Our biweekly e-newsletter is published on alternate Fridays exclusively for RIMS members. Contact Dulce Cosme if you've missed an issue, dcosme@rimed.org.

# CONVIVIUM

## THURSDAY, SEPTEMBER 23, 2021

RIMS ANNUAL MEMBERSHIP CONVIVIUM and AWARDS DINNER

Reception at 6:00 pm, Dinner at 7:00 pm

The Squantum Association, East Providence

**POSTPONED**
**UNTIL FURTHER NOTICE**

Please join us for good food, good music, and good company
as we honor outgoing Presidents
Christine Brousseau, MD, (2019–2020), and Catherine Cummings, MD, (2020–2021),
inaugurate our new leadership team, and
celebrate 210 years of organized medicine in Rhode Island.

**Watch for your invitation soon.**

# RIMS CORPORATE AFFILIATES

The Rhode Island Medical Society continues to drive forward into the future with the implementation of various new programs. As such, RIMS is expanded its Affinity Program to allow for more of our colleagues in healthcare and related business to work with our membership. RIMS thanks these participants for their support of our membership.

Contact Marc Bialek for more information: 401-331-3207 or mbialek@rimed.org

## Neighborhood Health Plan OF RHODE ISLAND™

www.nhpri.org

Neighborhood Health Plan of Rhode Island is a non-profit HMO founded in 1993 in partnership with Rhode Island's Community Health Centers. Serving over 185,000 members, Neighborhood has doubled in membership, revenue and staff since November 2013. In January 2014, Neighborhood extended its service, benefits and value through the HealthSource RI health insurance exchange, serving 49% the RI exchange market. Neighborhood has been rated by National Committee for Quality Assurance (NCQA) as one of the Top 10 Medicaid health plans in America, every year since ratings began twelve years ago.

## RHODE ISLAND PHYSICIANS CORPORATION PRIMARY CARE

www.ripcpc.com

RIPCPC is an independent practice association (IPA) of primary care physicians located throughout the state of Rhode Island. The IPA, originally formed in 1994, represent 150 physicians from Family Practice, Internal Medicine and Pediatrics. RIPCPC also has an affiliation with over 200 specialty-care member physicians. Our PCP's act as primary care providers for over 340,000 patients throughout the state of Rhode Island. The IPA was formed to provide a venue for the smaller independent practices to work together with the ultimate goal of improving quality of care for our patients.

## RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program

ANCHOR MEDICAL ASSOCIATES

Block Island Medical Center

BROWN SURGICAL ASSOCIATES
BROWN PHYSICIANS, INC.

COASTAL MEDICAL
LEADERS IN HEALTHCARE

CCAP
COMPREHENSIVE COMMUNITY ACTION PROGRAM
YOUR COMMUNITY'S HELPING HAND

east bay community action program
THE BRIDGE to SELF-RELIANCE

Diabetes & Endocrinology Associates, Inc.

Orthopaedic Associates, Inc.

Ortho Rhode Island

PCHC
PROVIDENCE COMMUNITY HEALTH CENTERS

RI ENT

Rhode Island Eye INSTITUTE

SKIN PROS

The Providence CENTER

Thundermist HEALTH CENTER

Tri-County Community Action Agency
*Helping people. Changing lives.*

UNIVOTO
University Otolaryngology

WellOne
Primary Medical and Dental Care

Wood River Health Services
*The Heart of South County since 1976*

For more information about group rates, please contact Marc Bialek, RIMS Director of Member Services

## FDA extends expiration date on Pfizer-BioNTech vaccine kept in ultra-low storage

The United States Food and Drug Administration (FDA) has approved an amendment to the EUA for Pfizer-BioNTech extending the expiration dates of COVID-19 vaccine from 6 to 9 months.

Cartons and vials of Pfizer-BioNTech COVID-19 Vaccine with an expiry date of August 2021 through February 2022 printed on the label may remain in use for 3 months beyond the printed date as long as authorized storage conditions between –90°C to –60°C (–130°F to –76°F) have been maintained. Please note: the ultra-cold temperature range has been broadened to include –90° C (–130°F). **Frozen vials stored at –25°C to –15°C and refrigerated vials (2°C to 8°C) are NOT eligible for extension.**

| Printed Expiry Date | Updated Expiry Date |
|---|---|
| August 2021 | November 2021 |
| September 2021 | December 2021 |
| October 2021 | January 2022 |
| November 2021 | February 2022 |
| December 2021 | March 2022 |
| January 2022 | April 2022 |
| February 2022 | May 2022 |

Updated expiry dates for vaccine maintained in ultra-cold storage are shown below.

The extended expiration date is effective immediately for all currently available batches that have not yet expired. **NOTE:** Expiration dates extension does NOT apply to vials dated July 2021 and earlier.

No changes have been made to the vaccine itself to enable extension of expiry dating. This change is based on stability data generated on batches manufactured over approximately the past 9 months of COVID-19 vaccine development, from the batches that supplied early clinical trials through the commercial scale batches currently in production.

Currently available vaccine will not have an updated NCD. Please refer to the current EUA Fact Sheet for information.

Additional information on Pfizer storage and handling may be found at: Administration Overview for Pfizer-BioNTech COVID-19 Vaccine|CDC. ❖

## RI improves access to hepatitis C treatment for Medicaid patients

*State removes prior auth for two medications*

WASHINGTON, DC – The National Viral Hepatitis Roundtable (NVHR) and the Center for Health Law and Policy Innovation of Harvard Law School (CHLPI) applauded Rhode Island Medicaid for removing prior authorizations for two preferred treatments for hepatitis C, effective as of August 1, 2021. Rhode Island follows in the footsteps of just seven other states that do not require prior authorization for hepatitis C treatment, including California, Indiana, Louisiana, Michigan, New York, Washington, and Wisconsin. Nearly 23,000 Rhode Island residents are estimated to be living with hepatitis C. Removing prior authorizations will increase access to the hepatitis C cure for thousands of Medicaid beneficiaries living with hepatitis C.

"I applaud Rhode Island Medicaid for removing prior authorization processes for two hepatitis C regimens. It was a collective effort that got us to this point, and a decision made in response to ongoing work from healthcare workers, people with lived experience, and advocacy coming together," said **LYNN E. TAYLOR, MD, FACP, FAASLD**, Director of HIV and Viral Hepatitis Services at CODAC Behavioral Health. "While this is a game-changing step forward towards hepatitis C elimination, we must continue to break down remaining barriers and discriminatory practices. Prior authorizations for direct-acting antivirals needed for patients with contraindications to the two Medicaid-preferred treatments remain in place, as do prior authorizations and high copay costs for individuals with commercial insurance." Taylor's organization, a non-profit based in Cranston, RI, provides outpatient treatment for Opioid Use Disorder across seven community-based locations and programming at the Rhode Island Department of Corrections.

"It is encouraging to see Rhode Island follow the lead of numerous other states to remove prior authorization requirements for hepatitis C treatments patients," said **PHIL WATERS**, Staff Attorney at CHLPI. "We encourage all payors and providers to immediately implement the new policies to help improve public health outcomes, especially amid the ongoing coronavirus pandemic."

The latest removal of prior authorizations for two preferred hepatitis C treatments has consequently increased Rhode Island's Hepatitis C: State of Medicaid Access score to A+. ❖

## RIDOH launches Drug Overdose Surveillance Data Hub

With drug overdose deaths increasing both nationally and in Rhode Island, the Rhode Island Department of Health (RIDOH) has launched a new Rhode Island Drug Overdose Surveillance Data Hub to increase access to information about the overdose epidemic.

The Rhode Island Drug Overdose Data Hub was formally released in July during a meeting of Governor Dan McKee's Overdose Prevention and Intervention Task Force. The hub can be accessed at: Health.ri.gov/od-datahub.

The hub has expanded public access to five overdose surveillance systems, and offers a closer look at detailed, municipal, county, and statewide trends. Featured surveillance systems include emergency department visits, emergency medical service runs, overdose fatalities from the RIDOH's Office of the State Medical Examiners and the State Unintentional Drug Overdose Reporting System, and prescribing data for the Rhode Island Prescription Drug Monitoring Program.

Community partners, researchers, students, and others can compare municipal-level data, such as age, sex, race, ethnicity, and incident/resident location, to county and statewide trends. People can also find municipal data reports, research publications, and request or download data.

"Rhode Island has long been a national leader in making drug overdose data accessible and available to the public. This new data hub provides an even more comprehensive resource and will be a critically important tool for harm reduction organizations, policy makers, researchers, and municipalities across the state," said **DR. BRANDON MARSHALL**, Development Team Lead for PreventOverdoseRI.org and Associate Professor of Epidemiology at Brown University School of Public Health.

The Rhode Island Drug Overdose Data Hub works together with PreventOverdoseRI.org to create a holistic view of how opioids and drug overdose are impacting the state. PreventOverdoseRI.org offers historical overdose data trends, interactive data stories, local resources, educational materials, and campaigns. The dashboard also provides resources for people who may be at risk of overdose, healthcare providers who would like to learn more about treatment, as well as concerned loved ones. Since 2015, PreventOverdoseRI.org has been an online platform for real-time data to track the progress of the Governor's Overdose Prevention Action Plan.

RIDOH's new Data Hub links directly to PreventOverdoseRI.org to ensure data visualizations on both sites are updated automatically. Improvements in the data request process have been enhanced on the website, making it easier for the public to request data directly from RIDOH's Drug Overdose Surveillance Program.

"Data is knowledge, and knowledge is power. By providing accessible data and public resources, RIDOH is putting vital tools into the hands of outreach workers and community members to do life-saving work. We are grateful for the Department of Health's commitment to supporting overdose prevention and harm reduction efforts, including the Overdose Data Hub and PORI," said **ANNAJANE YOLKEN**, Director of Programs at Project Weber/RENEW.

Increasing public access to timely, accurate data has been a focus of the Rhode Island Executive Office of Health and Human Services (EOHHS) 2020 Evidence Update for the Governor's Overdose Prevention and Intervention Task Force.

Accidental drug overdose deaths increased by 25% from 2019 to 2020 (from 308 to 384). Preliminary 2021 fatal overdose data suggest that Rhode Island remains on a similar trajectory.

Rhode Islanders experiencing a substance use or mental health crisis can get connected to immediate care by calling the 24/7 BH Link Hotline, 401-414-LINK (5465) or visiting BH Link Walk-In Triage Center at 975 Waterman Avenue in East Providence.

The Data Hub adheres to RIDOH's Small Numbers Reporting Policy to ensure confidentiality. A tutorial about the Rhode Island Drug Overdose Data Hub is available online: https://youtu.be/BPl7yk9mu58 ❖

## CODAC Behavioral Healthcare key partner in new smoking cessation effort

PROVIDENCE – CODAC Behavioral Healthcare is helping to lead a new statewide effort on tobacco cessation, especially among those in treatment for mental health and substance use disorders.

CODAC is uniquely positioned to contribute to the smoking cessation effort since it pioneered a dual substance use disorder and smoking cessation program in the early 2010s.

"CODAC has been really focused on tobacco cessation for 15 years. We were the first opioid treatment program in the country to become a tobacco-free campus. Tobacco is the only substance use disorder that will absolutely kill its users and is the leading cause of preventable deaths. Over fifty percent of the people who use tobacco will die of smoking-related conditions. However, because the fatalities are not as acute and because it's legal, there continues to be this sense of diminished risk," said **LINDA HURLEY**, President and CEO of CODAC.

In mid-July, 40 individuals representing tobacco control, behavioral health, public health, cancer control, primary providers, nonprofit organizations, and other services from across Rhode Island participated in a virtual summit hosted by SAMHA's Tobacco Cessation Leadership Center.

Other sponsors of the summit included Rhode Island's Department of Health, Rhode Island Department of Behavioral Healthcare, Developmental Disabilities and Hospitals, and the Executive Office of Health and Human Services.

Following the summit, four work groups have been established to identify existing resources and establish partnerships to effectively leverage these resources. The four groups are: Data, Education, Policy, and Systems Change, Equity, and Access. CODAC's President and CEO Linda Hurley is co-chairing the Education subcommittee and CODAC's Tobacco Program Coordinator, Carolyn James, is co-chairing the subcommittee on Systems Change, Equity, and Access.

Although smoking rates are on the decline nationally, a high number of adults and youth still smoke. In 2018, 14.6 percent of Rhode Island adults smoked and, in 2019, 4.2 percent of high school students had smoked cigarettes at least once in the past 30 days, according to CDC data. In addition, vaping has increased the popularity of tobacco use among youth. In 2019, 30.1 percent of high school students used electronic vapor products at least once in a 30-day period, according to the CDC. ❖

## Lifespan neurosurgeons perform incisionless thalamotomy

*MRI-guided focused ultrasound technology to treat patient tremors*

PROVIDENCE – Neurosurgeons at the Norman Prince Neurosciences Institute (NPNI) recently performed an incisionless thalamotomy using a novel image-guided focused ultrasound procedure to treat disabling tremors.

The procedure uses focused ultrasound energy guided by magnetic resonance imaging (MRI) to treat the brain circuit responsible for the patient's tremors. The procedure is performed while the patient is awake so their response to treatment can be assessed in real time. It is for patients with essential tremor or tremor-dominant Parkinson's disease whose tremors do not improve with medications.

During the procedure, MRI is used to target the precise location in the brain responsible for the tremor, and then an ultrasound helmet sends more than 1,000 beams of energy through the patient's skull to thermally ablate the area without damaging surrounding brain tissue. After each application of energy the patient performs tasks such as drawing a spiral to allow evaluation of the tremor improvement during the treatment. At the end of the procedure a final MRI scan is done to assess the ablation area.

"Although Essential Tremor is relatively common and often fairly mild, there is a significant number of patients for whom the condition is more severe and debilitating, impairing a wide variety of routine daily activities such as eating, writing and getting dressed," noted **WAEL ASAAD, MD, PhD**, director of the NPNI Functional Neurosurgery & Epilepsy program, and the neurosurgeon who performed the first procedure. "For those individuals who cannot find relief through medications, this procedure offers an effective, cutting-edge option without the cutting."

It is usually performed as an outpatient procedure without sedation. The single session treatment takes about 2–3 hours to complete, and after a short recovery time patients can return home. ❖

# Appointments

## Loree K. Kalliainen, MD, MA, FACS, appointed Division Chief of Hand Surgery at LPG

**LOREE K. KALLIAINEN, MD, MA, FACS**, has been appointed Division Chief of Hand Surgery in the Department of Plastic Surgery at Lifespan Physician Group (LPG).

An Associate Professor at the Alpert Medical School of Brown University in the Department of Surgery, she moved to Rhode Island in 2019 and recently completed her term as a Governor of the American Board of Plastic Surgery.

Dr. Kalliainen graduated from medical school and trained in plastic surgery at the University of Michigan. Her hand surgery training was with the combined Plastic and Orthopedic Surgery hand fellowship at the University of Virginia. In Minnesota, she obtained a Master's degree in Philosophy, focusing on ethics and epistemology.

She has worked at The Ohio State University, Regions Hospital in St. Paul, Minnesota, with an affiliation with the University of Minnesota, and at the University of North Carolina. On four occasions, she worked in New Zealand as a locum plastic surgeon and participated in the residency training program.

Her leadership roles have included being a Director of the American Board of Plastic Surgery and a board member on the American Association of Hand Surgery. She has been active in multiple national organizations, chairing committees ranging from Health Policy to Diversity. She served as Chief of Staff at Regions Hospital and has been on numerous hospital committees, primarily related to quality and safety. ❖

## Andrea McGinn appointed Associate Chief Nursing Officer at Butler

**ANDREA MCGINN, RN, MA**, has been appointed Associate Chief Nursing Officer (ACNO) for Butler Hospital.

She began her career at Butler Hospital as an Assistant Nurse Manager in Patient Assessment Services (PAS) from 2002 through 2013. When Andrea left Butler Hospital, she went on to further her psychiatric nursing experience through the clinical management of transitions of care teams for Neighborhood Health Plan of Rhode Island. She returned to Butler Hospital in 2016 as an Assistant Nurse Manager in PAS and was later appointed Nurse Director of PAS in 2020.

Her leadership has been critical during the pandemic, working with leadership to develop and maintain the safe processes necessary to keep patients and staff safe.

In her new role as an ACNO, she will continue her work in PAS and throughput, as well as her community liaison work for patient access. ❖

## Tracy Madsen, MD, named NAM American Board of Emergency Medicine Fellow

The National Academy of Medicine (NAM) has selected emergency medicine physician **TRACY MADSEN, MD, PhD, FACEP, FAHA** as the American Board of Emergency Medicine Fellow in their class of 2021 NAM Fellowships. Dr. Madsen is one of only five health professionals selected for the prestigious two-year fellowship.

The fellows will help facilitate initiatives convened by the National Academies to provide nonpartisan, scientific, and evidence-based guidance to national, state, and local policymakers, academic leaders, health care administrators, and the public. The fellows will engage part time in the NAM or the National Academies' health and science policy work, contributing to reports or other products and participating in expert study committees related to their professional interests. They will also receive a flexible research grant from the NAM.

Dr. Madsen is an emergency medicine attending physician at Rhode Island Hospital and The Miriam Hospital, and co-director of Lifespan's two stroke centers. She is also the Associate Director of The Sex And Gender In Emergency Medicine Division at Rhode Island Hospital.

She is currently conducting research funded by the National Heart, Lung, and Blood Institute, on sex and gender differences in the epidemiology, outcomes, and acute treatment of stroke.

Dr. Madsen earned her medical degree at Boston University and completed a residency in emergency medicine followed by a two-year research fellowship and a master's degree in clinical and translational research. She completed a PhD in epidemiology at the Brown University School of Public Health. ❖

## Stephanie Ramos named Director of Behavioral Health Access at Butler

**STEPHANIE RAMOS, MA, MHA**, has been appointed Director of Behavioral Health Access at Butler Hospital, responsible for onsite supervision of the patient financial counselors and oversight of the Patient Access Department, working closely with the CNE Revenue Cycle leadership team. She will continue to be responsible for Call Center operations.

She began her career at Butler Hospital as a Patient Assessment Services (PAS) intake coordinator in 1998. She also worked as a PAS clinician and bed board manager before her promotion to CNE Patient Access Manager in 2015. She has also served as Director of the Call Center since 2018. ❖

# Appointments

## Jason Graff, MD; Patricia Russo-Magno, MD, join South County Medical Group

WAKEFIELD – The South County Medical Group recently welcomed two pulmonary specialists, creating South County Health Pulmonology.

**JASON GRAFF, MD**, is board-certified in sleep medicine, critical care, and pulmonary. Most recently, Dr. Graff was Medical Director of Saint Luke's Sleep Disorders Program and Assistant Clinical Professor at the University of Missouri-Kansas City.

Dr. Graff received his medical degree from University of Oklahoma College of Medicine and completed a Residency in Internal Medicine at Banner Good Samaritan Medical Center. He completed a Fellowship in Pulmonary Disease and Critical Care Medicine at University of Missouri, Kansas City, and a Fellowship in Sleep Medicine at University of New Mexico.

**PATRICIA RUSSO-MAGNO, MD**, has expertise in pulmonary and critical care medicine, including experience in specialized areas of obstetric pulmonary care and pulmonary nodules. She is board-certified in internal medicine, pulmonary medicine, and critical care medicine.

Prior to joining South County Health, Dr. Russo-Magno provided respiratory care at Kent Hospital in Warwick and Women & Infants Hospital in Providence.

Dr. Russo-Magno earned her medical degree at Tufts University School of Medicine, Boston, MA, and completed a Residency at Rhode Island Hospital, where she also completed a Fellowship in Pulmonary and Critical Care Medicine.

### South County Health Pulmonology

Drs. Graff and Russo-Magno will provide patient care at the newly established South County Health Pulmonology practice under South County Medical Group.

The practice will specialize in the respiratory system and diseases that affect it. In addition, these physicians will provide services to South County Health's Sleep Disorders Lab, diagnosing and treating a variety of sleep disorders, including sleep apnea, narcolepsy, restless leg syndrome, and insomnia. ❖

## Jose M. Rengifo, MD, named Program Chief of the Adult Partial Hospital Programs at Butler

**JOSE M. RENGIFO, MD**, has been named Program Chief of the Adult Partial Hospital Programs (Cognitive Behavioral Therapy and Women's PHP), at Butler Hospital.

Dr. Rengifo joined Butler Hospital in June 2016 as a staff psychiatrist in PAS and in the CBT PHP. He earned his medical degree at Rush Medical College and completed his residency at Cambridge Health Alliance in adult psychiatry.

Dr. Rengifo was a Clinical Fellow in Psychiatry at Harvard Medical School. He has also published on a wide variety of topics in psychiatry. He is also multi-lingual, fluent in English, French and Spanish, conversational in German, Portuguese and American Sign Language. He continues to expand his linguistic repertoire with Japanese and Mandarin Chinese.

In 2017, Dr. Rengifo was named Director of Education in PAS and has been providing supervision for medical students, Psychology residents and Psychiatry residents from the Alpert Warren Medical School of Brown University. He also supports the Psychiatry resident training program by leading various seminars and supervising residents in the Resident Continuity Clinic (RCC).

For his dedication, he was awarded the Brown Psychiatry Resident Outstanding Clinician of the Year in 2019 and the Positive Champion of Learning Environment from Brown Medical School in 2020. His educational role of supervising medical students and psychiatric residents will expand to the Partial Hospital Program. ❖

## Raymond O. Powrie, MD, named Chief Clinical Officer at CNE

**RAYMOND O. POWRIE, MD**, named Chief Clinical Officer at Care New England.

Dr. Powrie currently serves as Chief of Medicine at Women & Infants Hospital as well as Executive Chief of Medicine at Care New England.

Dr. Powrie is a Professor of Medicine at the Warren Alpert Medical School, and has multiple other responsibilities including serving as President of both of Care New England's indemnity programs. In addition, Dr. Powrie – teaming with Dr. Erica Hardy and Robin Neale – has been instrumental in leading Care New England through the COVID-19 pandemic.

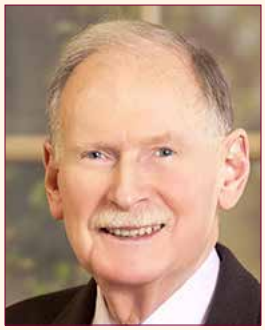
"Dr. Powrie's skills as an academic, teacher, clinician and overall leader are well recognized by everyone who has had the opportunity to work with him. His excellent communication skills and collegial approach will serve him well in this added role," said **JAMES E. FANALE, MD**, President and CEO, Care New England. ❖

# Recognition

## Karen Tashima, MD; Kwame Dapaah-Afriyie, MD; Richard Besdine, MD, honored at Miriam awards ceremony


Karen Tashima, MD


Kwame Dapaah-Afriyie, MD


Richard Besdine, MD

Infectious diseases physician **KAREN TASHIMA, MD**, who led the launch of a local clinical trial for a COVID-19 vaccine and has served on the Governor's COVID-19 Vaccine Subcommittee, has been named as the Charles C.J. Carpenter, MD, Outstanding Physician of the Year at The Miriam Hospital for 2021.

Dr. Tashima has served on the Lifespan COVID-19 Vaccine Committee and was also the principal investigator for two Gilead Remdesivir studies for moderate and severe COVID disease.

Also honored at the ceremony were **KWAME DAPAAH-AFRIYIE, MD, MBA**, and **RICHARD BESDINE, MD**.

Dr. Dapaah-Afriyie, a Professor of Medicine at The Warren Alpert Medical School of Brown University, received the Riesman Family Excellence in Teaching Award. The annual award recognizes a Miriam physician who teaches at the medical school.

He has been associated with The Miriam and Brown since beginning his residency in internal medicine in 1993. In 1997, he and his colleagues started the program for hospitalists – staff physicians who care for patients during their hospitalization. In 2004, he became the program director.

Dr. Besdine received the Charles "Bud" Kahn, MD, Lifetime Leadership Award. He has devoted his career to the advancement of geriatrics. He is currently a Professor of Medicine and Health Services Policy and Practice at Brown. He retired from his position as Director of the Division of Geriatrics and Palliative Medicine in the Department of Medicine, Chief of Geriatrics for Lifespan after 20 years of service. During his career he served as the first Chief Medical Officer and Director of the Health Standards and Quality Bureau for the Health Care Financing Administration, the predecessor to the Centers for Medicare and Medicaid Services (CMS). ❖

# Event

## Rodeo luncheon for retired physicians resumes

Retired physicians happily reconvened on August 11, 2021 at the Squantum Association in East Providence after a two-year COVID-related hiatus. More than 50 physicians who practiced locally renewed friendships and met new colleagues.

**DR. ARUN SINGH** organized the event and greeted attendees prior to the buffet. **DR. CANDY DYER** and **DR. RIC CHRISTIAN** thanked Arun for his service over the last few years and will now assume future event planning.

At this time there is interest in both a spring and early fall lunch in 2022.

RODEO is an all-inclusive social gathering for all physicians who have any local connection. All are welcome. Please refer recent retirees for inclusion and invitation.

Please address any inquiries or referrals to Ric at fchistian-46@comcast.net or Candy at clesleydmd2591@gmail.com.
Also please add any comments regarding content or menu. ❖

# Obituaries

**JOSEPH BLUMEN, MD**, 88, of Newport, passed peacefully on July 25, 2021, at the Rhode Island Veterans Home in Bristol. He was 88.

Joseph was born in Brooklyn, NY, in 1933, to Dora and Elias Blumen. Along with older brothers Louis and David, the family moved to Newport soon afterwards. Dora and Elias owned and operated the Municipal Market, a small neighborhood grocery store at the corner of Bowery and Spring Streets. One of Joe's earliest memories was the way the store's plate glass window flexed and bowed during the Hurricane of 1938.

Dr. Blumen was a graduate of Rogers High School, Brown University, and Tufts University School of Medicine. In 1965, he enlisted as a Captain in the U.S. Army Medical Corps, and served as Chief of General Surgery at the 67th Evac Hospital, Qui Nhon, Vietnam, and later on the surgical staff at the U.S. Military Academy at West Point, NY.

In 1967, Joseph returned to Newport to practice as a general surgeon and primary care physician and to raise a family with Dale, his beloved wife and partner of 58 years. As a physician, he cared for generations of Aquidneck Islanders, often making house calls. As part of his holistic approach to medicine, he believed laughter was essential for health and wellbeing.

Dr. Blumen was an active member of the community. He was a Master Mason and member of St. Paul's Lodge No.14 for more than 50 years. Joseph was a long-serving member of the Planning Board for the City of Newport and a trustee of the Seamen's Church Institute. He also established the Dora and Elias Blumen Collection for the Study of Holocaust Literature at Salve Regina University.

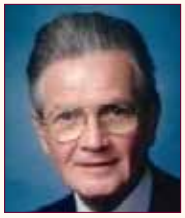
Joseph considered his family to be the most important part of his life. He is survived by his wife Dale, his children Ethan (Tracy) of Sharon, Mass., Rebecca of Newport, RI, Jonathan (Lisa) of Rutland, Mass., and Joshua (Jill) of Sharon, Mass., and his grandchildren Eli, Mira, Alexander, Maxwell, Liliana, and Violet.

Donations in Joseph's memory may be made to "The Blumen Fund" to support the Collection for the Study of Holocaust Literature at Salve Regina University. www.salve.edu. ❖

**STEPHEN PATRICK BURNS, MD, FACR**, of East Greenwich, RI, passed away peacefully on August 11, 2021. He was the loving husband of Nancy Mailhot Burns for 56 years. He graduated from Boston College in 1962 and Tufts Medical School in 1966. Following a one-year internship at St. Elizabeth Hospital in Brighton, MA, he enlisted in the US Public Health Service, Division of Indian Health Service, serving as a physician on the Standing Rock Sioux Reservation in Fort Yates, North Dakota. After 2 years of service, he entered the Radiology residency program at Boston University in 1969 and completed his training in Boston. In 1973, he accepted a position in Radiology at Kent County Memorial Hospital in Warwick, RI, where he later served as Chief of Radiology and as a member of the Special Advisory Committee. He was a Past President of the Rhode Island chapter of the American College of Radiology.

Besides his wife, he is survived by his children, Stephen P. Burns, III, MD and his wife Suzanne, Kathleen B. Takata and her husband Kenn, Patricia B. Harwood and her husband Steve, and David J. Burns; and 6 grandchildren.

Steve's favorite leisure activities were music and sports, especially choral music, golf, and skiing. He participated as a member of the Narragansett Bay Barbershop Chorus for 17 years and as a member of his church choirs at Our Lady of Mercy Church in East Greenwich and St. Elizabeth Seton in Naples, FL. He was a member of the Potowomut Golf Club in East Greenwich, RI and Bears Paw Country Club in Naples, FL. After retirement, he was a dedicated volunteer at Button Hole Golf Club in Providence, a non-profit which encourages people of all backgrounds and abilities to learn the game of golf. Donations in his memory can be made to Button Hole Golf Course (buttonhole.org) or the Parkinson's Association of Southwest Florida (parkinsonassociationswfl.org). ❖



**JOHN B. LAWLOR, MD**, 95, died peacefully on August 15, 2021 at St. Elizabeth Home in East Greenwich, surrounded by his five children. He was the beloved husband of the late Virginia Hope (Daley) Lawlor, to whom he was married for 67 years before her death in 2018.

Jack graduated from LaSalle Academy and Brown University, where he was enrolled in the US Navy V-12 accelerated program as a pre-med student when doctors were needed for the World War II effort. By his graduation in 1946, the war had ended. He went on to attend medical school in Brooklyn, NY, at the Long Island College of Medicine (now SUNY Downstate College of Medicine) and interned at University Hospital of Brooklyn.

He and Hope married in 1951. As newlyweds, they lived in Charleston, SC, where Jack was a Lieutenant in the US Navy. When his active duty was complete, Hope and Jack moved to Providence, where he began his medical residency in urology at Rhode Island Hospital. They spent a year with their young family in New York City while he completed his surgical residency at Columbia Presbyterian Hospital, and returned to Rhode Island, where he joined the staff of Rhode Island Hospital. Jack spent his career there and in 1976 was named Chair of the Department of Urology, a role that included overseeing the urological training of medical students at Brown University and the hospital's medical residents. He established Urological Associates (now Brown Urology), a private partnership which grew into a group practice. He took pride in teaching the next generation of physicians, many of whom still practice in RI. Recent years included many visits to Rhode Island Hospital as a patient, and Jack was always glad to reminisce about the old days with staff he knew.

He was a man of faith who gave of his time as a Eucharistic Minister for his parish and on a medical mission to Romania

with Hope, who was a registered nurse, and a group of local surgeons. He taught English to those new to the United States. He was a lifelong learner, taking computer classes in his 80s so he could email his grandkids, forming new friendships in his 90s, and learning to play darts at his assisted living home after Hope passed away. He figured out how to Zoom with his family and watch movies on Netflix while isolated during the pandemic. He never stopped reading.

He leaves a son, John Lawlor, Jr., of East Providence, and four daughters: Peggy Lamb and her husband Tom of East Greenwich, Joanne Boehme (late husband Fred) of Juneau, AK; Betsy Lawlor of Diamond Bar, CA and Jean Lawlor of Fairhaven, MA. He is also survived by his grandchildren and great-granddaughters.

Donations in his memory may be made to Our Lady of Mercy Church, 65 Third Street, East Greenwich, RI 02818. ❖

**FRED T. "TED" PERRY, MD**, 81, of Coventry, passed away peacefully on August 11, 2021 at Miriam Hospital. He was the beloved husband of Carol L. (Anderson) Perry for 59 years.

He graduated from Providence College in 1961 with Magna Cum Laude honors. He went on to attend the University of Vermont, earning his MD degree in 1966. During the Vietnam War, Ted served his country as an anesthesiologist at field hospitals in CuChi and AnKhe, achieving the rank of Captain in the United States Air Force.

Following an Anesthesia residency, he returned to Rhode Island and joined the Anesthesia Associates at Kent County Memorial Hospital. He served his patients, friends and family there for more than 20 years. As time went on, he became Chief of Anesthesia and served a term as President of the medical staff.

In 1995, he moved on to Pawtucket Memorial Hospital where he formed Anesthesia Care, Inc., serving as Chief of Anesthesia there for several years. During this time, he traveled to Honduras with Catholic Medical Missions to help provide anesthesia services to people in need. He loved his work, his patients, and teaching student nurse anesthetists.

For years, he served on the Coventry Democratic Committee and for several terms on the Coventry Zoning Board. He developed an interest in flying and became a private pilot.

He was the father of Fred Joseph "Joe" Perry (Jeff Janelle), Pamela "Pam" Anne Jackson, Patricia Lee Perry (Fred Bibeau), and James Michael "Jim" Perry (Sukanya), all of Coventry and grandfather of Ben, Teddy, Ryan, Chris, Frankie, Joshua, and Jonathan. He was the brother of William F. Perry (Charlene), of Barefoot Bay, FL, and the late Francis "Frank" J. Perry, Jr. (Elizabeth).

Memorial contributions in his memory may be made to the Orchard Lake Seminary (sscms.edu) or Lifespan Cancer Institute at RI Hospital, 593 Eddy St., APC, Providence, RI 02903. ❖

**CHARLES "CHUCK" STAUNTON, MD,** 78, of Williston, Vermont, devoted husband to Jean, and dad to Norman and Michael, died peacefully on July 26, 2021, at home, surrounded by his family.

He was the definition of a self-made man, putting himself through Blackburn College, Rensselaer Polytechnic Institute, and Albany Medical College where he received his MD. He completed a Residency in Adult Psychiatry and a Fellowship in Child and Adolescent and Psychiatry at the Menninger Foundation in Kansas. His work in Child and Adolescent Psychiatry included tenures at Bradley and Butler Hospitals in Rhode Island, teaching at Brown Medical School, and private practice and consulting in Rhode Island and Vermont.

Dr. Chuck, as he was known to so many patients, friends, kids, athletes, and colleagues, died as a result of complications from Parkinson's Disease, which he lived with and fought for the last 12 years of his life. He never once complained.

Due to ongoing COVID-19 pandemic, no service is planned at this time. Chuck's family would be honored if those who knew him would share remembrances or stories of Chuck here or by emailing them to charlesstaunton@comcast.net.

For those who wish to, Chuck's family asks that donations in his memory be made to the Michael J Fox Foundation or UVM Home Health and Hospice to support Parkinson's research, treatment, and care. ❖

**WILLIAM F. VARR, JR., MD**, 91, passed away on Aug. 5, 2021, in the peace of his home with family by his side. He was the husband of J. Lucille (St. Pierre) Varr.

Dr. Varr was a native of West Warwick and graduated from New York Medical College in 1954. He interned at S. Joseph's Hospital and completed his anesthesiology residency at Henry Ford Medical Center in Detroit. After residency he served in the US Navy as Chief of Anesthesiology at Newport Naval Hospital. After his military service he founded the anesthesiology department at Kent County Memorial Hospital where he served as Chief of Anesthesiology until his retirement.

He served as Vice President of the Rhode Island Medical Society and President of the RI Society of Anesthesiology. He was also a member of the Executive board of BCBS of RI. Civically he was president of the Sierra Club and was a member of the board of trustees at RI College.

He is survived by his three children, Dr. William F. Varr, III and his wife Victoria Morro of Somerset, MA and Newport, RI; Bradford Varr of Woonsocket and Delyse Shakespeare and her husband William of Johnston, RI. He is also survived by several grandchildren and four great-grandchildren. Donations in his memory may be made to The Providence College Fund online at https://giving.providence.edu. Remembrances may be shared at carpenterjenks.com. ❖