

# CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Joe Carrotta for NYU Langone Health

A genetically modified pig heart suspended in solution ahead of xenotransplantation at NYU Langone Health on July 6, 2022, in New York City.

## Modified pig hearts functional in ventilated deceased humans

BY NEIL OSTERWEIL  
*MDedge News*

A team of surgeons successfully transplanted genetically engineered pig hearts into two recently deceased people whose bodies were being maintained on ventilatory support – not in the hope of restoring life, but as a proof-of-concept experiment in xenotransplantation that could eventually help to ease the critical shortage of donor organs.

The surgeries were performed on June 16 and July 6, 2022, using porcine hearts from animals genetically engineered to prevent organ rejection and promote adaptive immunity by human recipients

“From the very beginning our goal was to be able to create a model where we actually mimicked what is now done clinically in human

transplantation, without utilizing unapproved devices or techniques or medications,” said Nader Moazami, MD, surgical director of heart transplantation and chief of the division of heart and lung transplantation and mechanical circulatory support at NYU Langone Health, New York. Through 72 hours of postoperative monitoring “we evaluated the heart for functionality and the heart function was completely normal with excellent contractility,” he said at a press briefing announcing early results of the experimental program.

He acknowledged that for the first of the two procedures some surgical modification of the pig heart was required, primarily because of size differences between the donor and recipient.

“Nevertheless, we learned a tremendous amount from the first operation, and when that

**PIG HEARTS** // continued on page 6

## Anxiety in COPD: Consequential, but often overlooked

BY CHRISTINE KILGORE  
*MDedge News*

Anand S. Iyer, MD, MSPH, frequently hears his patients with chronic obstructive pulmonary disease (COPD) express fear and hopelessness and describe panic and other symptoms of anxiety. He sees anxiety affect the course of COPD, worsening symptoms and outcomes.

“I had questions about what we are doing [to help patients], so I began looking into the role of palliative care to help patients assess and manage these complex emotional and psychological symptoms,” said Dr. Iyer, assistant professor in the division of pulmonology, allergy, and critical care medicine at the University of Alabama at Birmingham.

His research is now focused on the integration of palliative care principles in COPD care. For Dr. Iyer and others engaged in research and/or patient care, finding ways of identifying and managing anxiety in patients with COPD – and other chronic lung diseases – is a calling of growing urgency.

**COPD ANXIETY** // continued on page 7

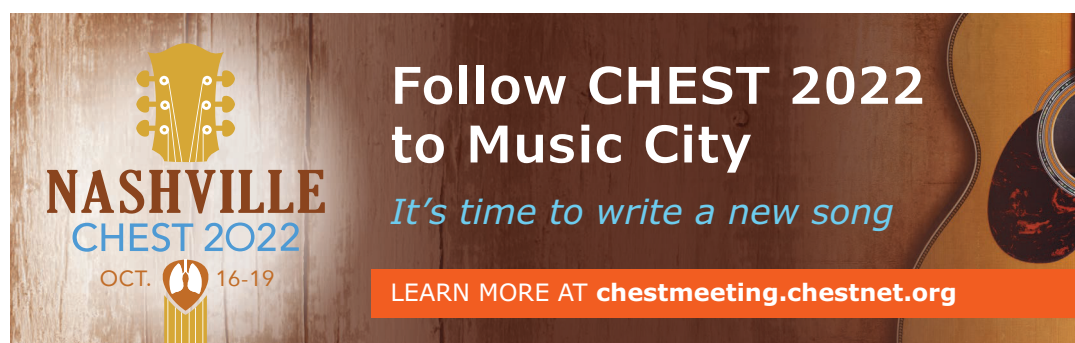
### INSIDE HIGHLIGHT



NEWS FROM CHEST

Addressing racial bias in pulse oximetry.

Page 18



**Follow CHEST 2022 to Music City**  
*It's time to write a new song*

**NASHVILLE CHEST 2022**  
OCT. 16-19

LEARN MORE AT [chestmeeting.chestnet.org](https://chestmeeting.chestnet.org)

PERMIT NO. 500  
HARRISBURG, PA  
PAID  
U.S. POSTAGE  
PRESORT STD

CHANGE SERVICE REQUESTED

CHEST PHYSICIAN  
10255 W Higgins Road,  
Suite 280  
Rosemont, IL 60018

**Nucala**   
**(mepolizumab)**  
Injection 100 mg/mL

# The targeted therapy for 4 eosinophil-driven diseases

**Severe  
eosinophilic  
asthma (SEA)**

**Chronic rhinosinusitis  
with nasal polyps  
(CRSwNP)**

**Eosinophilic  
granulomatosis with  
polyangiitis (EGPA)**

**Hypereosinophilic  
syndrome (HES)**

## **NUCALA is for the:**

- add-on maintenance treatment of patients 6+ with SEA. Not for acute bronchospasm or status asthmaticus.
- add-on maintenance treatment of CRSwNP in patients 18+ with inadequate response to nasal corticosteroids.
- treatment of adult patients with EGPA.
- treatment of patients aged 12+ with HES for ≥6 months without an identifiable non-hematologic secondary cause.

## **Important Safety Information**

### **CONTRAINDICATIONS**

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

**Please see Brief Summary of Prescribing Information for NUCALA on the following pages.**



Visit [Nucala4EOS.com](https://www.nucala4eos.com) to learn more →

## Important Safety Information (cont'd)

### WARNINGS AND PRECAUTIONS

#### Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

#### Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

#### Opportunistic Infections: Herpes Zoster

Herpes zoster infections have occurred in patients receiving NUCALA. Consider vaccination if medically appropriate.

#### Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

#### Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

### ADVERSE REACTIONS

Most common adverse reactions ( $\geq 5\%$ ) in patients receiving NUCALA:

- Severe asthma trials: headache, injection site reaction, back pain, fatigue
- CRSwNP trial: oropharyngeal pain, arthralgia
- EGPA and HES trials (300 mg of NUCALA): no additional adverse reactions were identified to those reported in severe asthma clinical trials

Systemic reactions, including hypersensitivity, occurred in clinical trials in patients receiving NUCALA. Manifestations included rash, pruritus, headache, myalgia, flushing, urticaria, erythema, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, stridor, angioedema, and multifocal skin reaction. A majority of systemic reactions were experienced the day of dosing.

### USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit [www.mothersbaby.org/asthma](https://www.mothersbaby.org/asthma).

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

Trademarks are owned by or licensed to the GSK group of companies.



©2021 GSK or licensor.  
MPLJRNA210003 December 2021  
Produced in USA.

## BRIEF SUMMARY

### NUCALA (mepolizumab) for injection, for subcutaneous use

### NUCALA (mepolizumab) injection, for subcutaneous use

The following is a brief summary only; see full prescribing information for complete product information.

#### 1 INDICATIONS AND USAGE

##### 1.1 Maintenance Treatment of Severe Asthma

NUCALA is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype [see Use in Specific Populations (8.4) and Clinical Studies (14.1) of full prescribing information].

##### Limitations of Use

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

##### 1.2 Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

##### 1.3 Eosinophilic Granulomatosis with Polyangiitis

NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

##### 1.4 Hypereosinophilic Syndrome

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

#### 4 CONTRAINDICATIONS

NUCALA is contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation [see Warnings and Precautions (5.1) and Description (11) of full prescribing information].

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued [see Contraindications (4)].

##### 5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

##### 5.3 Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials [see Adverse Reactions (6.1)]. Consider vaccination if medically appropriate.

##### 5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dosage, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dosage may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

##### 5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

#### 6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions [see Warnings and Precautions (5.1)]
- Opportunistic infections: herpes zoster [see Warnings and Precautions (5.3)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

##### 6.1 Clinical Trials Experience in Severe Asthma

###### Adult and Adolescent Patients Aged 12 Years and Older

A total of 1,327 patients with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT01000506; Trial 2, NCT01691521; and Trial 3, NCT01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 patients required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All patients had markers of eosinophilic airway inflammation [see Clinical Studies (14.1) of full prescribing information]. Of the patients enrolled, 59% were female, 85% were White, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 patients received NUCALA (mepolizumab 100 mg subcutaneous) for at least 24 weeks. Serious adverse events that occurred in more than 1 patient and in a greater percentage of patients receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of patients receiving placebo. The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

**Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with Severe Asthma (Trials 2 and 3)**

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

**52-Week Trial:** Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in patients receiving mepolizumab 75 mg IV compared with 2 patients in the placebo group.

**Systemic Reactions, including Hypersensitivity Reactions:** In Trials 1, 2, and 3 described above, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving NUCALA 100 mg and 3% of patients in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

**Injection Site Reactions:** Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.

**Long-term Safety:** Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

##### Pediatric Patients Aged 6 to 11 Years

The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 patients with severe asthma aged 6 to 11 years. Patients received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Patients received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for patients aged 6 to 11 years was similar to that observed in patients aged 12 years and older.

##### 6.2 Clinical Trials Experience in Chronic Rhinosinusitis with Nasal Polyps

A total of 407 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received NUCALA 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent CRSwNP with a history of prior surgery and were on nasal corticosteroids for at least 8 weeks prior to screening [see Clinical Studies (14.2) of full prescribing information]. Of the patients enrolled, 35% were female, 93% were White, and ages ranged from 18 to 82 years. Approximately 2% of patients receiving NUCALA 100 mg withdrew from study treatment due to adverse events compared with 2% of patients receiving placebo. Table 2 summarizes adverse reactions that occurred in ≥3% of NUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

**Table 2. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with CRSwNP**

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Oropharyngeal pain	8	5
Arthralgia	6	2
Abdominal Pain Upper	3	2
Diarrhea	3	2
Pyrexia	3	2
Nasal dryness	3	<1
Rash	3	<1

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps.

##### Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic [type I hypersensitivity] and other) reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and no patients in the placebo group. The manifestations of systemic allergic (type I hypersensitivity) reactions included urticaria, erythema, and rash and 1 of the 3 reactions occurred on the day of dosing. Other systemic reactions were reported by no patients in the group receiving NUCALA 100 mg and <1% of patients in the placebo group.

##### Injection Site Reactions

Injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving NUCALA 100 mg compared with <1% in patients receiving placebo.

##### 6.3 Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 patients with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment [see Clinical Studies (14.3) of full prescribing information]. Of the patients enrolled, 59% were female, 92% were White, and ages ranged from 20 to 71 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

##### Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of NUCALA and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of NUCALA and 1% of patients in the placebo group. The manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving 300 mg of NUCALA included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor. Systemic non-allergic reactions were reported by 1 (1%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of systemic non-allergic reactions reported in the group receiving 300 mg of NUCALA was angioedema. Half of the systemic reactions in patients receiving 300 mg of NUCALA (2/4) were experienced on the day of dosing.

##### Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg of NUCALA compared with 13% in patients receiving placebo.

##### 6.4 Clinical Trials Experience in Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients must have been on a stable dose of background HES therapy for the 4 weeks prior to randomization [see Clinical Studies (14.4) of full prescribing information]. Of the patients enrolled, 53% were female, 93% were White, and ages ranged from 12 to 82 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

##### Systemic Reactions, including Hypersensitivity Reactions

In the trial, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 (2%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of other systemic reaction was multifocal skin reaction experienced on the day of dosing.

(continued on next page)

## 6 ADVERSE REACTIONS (cont'd)

### Injection Site Reactions

Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

### 6.5 Immunogenicity

In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.

In patients with CRSwNP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with CRSwNP.

In patients with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with EGPA.

In adult and adolescent patients with HES receiving 300 mg of NUCALA, 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

### 6.6 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

#### Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

## 7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting [www.mothersobaby.org/asthma](http://www.mothersobaby.org/asthma).

#### Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg subcutaneous (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Clinical Considerations

**Disease-Associated Maternal and/or Embryofetal Risk:** In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

#### Data

**Animal Data:** In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5-deficient mice has been reported to be generally unaffected relative to wild-type mice.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see Use in Specific Populations (8.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

### 8.4 Pediatric Use

#### Severe Asthma

The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.

Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. [See Clinical Studies (14.1) of full prescribing information.] Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA. Of the 19 adolescents who received NUCALA, 9 received 100 mg and the mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies [see Adverse Reactions (6.1)]. Use of NUCALA in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC [see Clinical Pharmacology (12.3) of full prescribing information].

The effectiveness of NUCALA in pediatric patients aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents [see Clinical Pharmacology (12.3) of full prescribing information]. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents [see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]. The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.

#### Chronic Rhinosinusitis with Nasal Polyps

The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established.

#### Eosinophilic Granulomatosis with Polyangiitis

The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.

#### Hypereosinophilic Syndrome

The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older.

The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established.

Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT02836496) in adults and adolescents and an open-label extension study (NCT03306043). One adolescent received NUCALA during the controlled study and this patient and an additional 3 adolescents received NUCALA during the open-label extension study [see Clinical Studies (14.4) of full prescribing information]. The 1 adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

### 8.5 Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of patients aged 65 years and older that received NUCALA (n = 79) to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

## 10 OVERDOSAGE

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

### Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

### Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.

### Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

### Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting [www.mothersobaby.org/asthma](http://www.mothersobaby.org/asthma) [see Use in Specific Populations (8.1)].

Trademarks are owned by or licensed to the GSK group of companies.

### Manufactured by

GlaxoSmithKline LLC  
Philadelphia, PA 19112  
U.S. License Number 1727

### Distributed by



GlaxoSmithKline  
Research Triangle Park, NC 27709

©2021 GSK group of companies or its licensor.

Revised: 7/2021

©2021 GSK or licensor.

MPLJRNA210003 December 2021  
Produced in USA.

NCL:7BRS

experience was translated into the second operation it even performed better," he said.

Alex Reyentovich, MD, medical director of heart transplantation and director of the NYU Langone advanced heart failure program noted "there are 6 million individuals with heart failure in the United States. About 100,000 of those individuals have end-stage heart failure, and we only do about 3,500 heart transplants a year in the United States, so we have a tremendous deficiency in organs, and there are many people dying waiting for a heart."

who was not involved in the study commented that there can be unwelcome surprises even with the most rigorous infection prophylaxis protocols. "I think these are important steps, but they don't resolve the question of infectious risk. Sometimes viruses or latent infections are only manifested later," said Jay A. Fishman, MD, associate director of the Massachusetts General Hospital Transplant Center and director of the transplant infectious diseases and compromised host program at the hospital, which is in Boston.

"I think these are important steps, but as you may recall from the Maryland heart transplant experience, when porcine cytomegalovirus was activated, it was a long way into that patient's course, and so we just don't know whether something would have been reactivated later," he said in an interview.

Dr. Fishman noted that experience with xenotransplantation at the University of Maryland and other centers suggests that immunosuppressive regimens used for human-to-human transplants may not be suited for animal-to-human grafts.

The hearts were taken from pigs genetically modified with knockouts of four porcine genes to prevent rejection – including a gene for a growth hormone that would otherwise cause the heart to continue to expand in the recipient's chest – and with the addition of six human transgenes encoding for expression of proteins regulating biologic pathways that might be disrupted by incompatibilities across species.

The organ recipients were recently deceased patients who had expressed the clear wish to be organ donors but whose organs were unsuitable for transplant.

The first recipient was Lawrence Kelly, a Vietnam War veteran and welder who died from heart failure at the age of 72. "He was an organ donor, and would be so happy to know how much his contribution to this research will help people like him with this heart disease. He was a hero his whole life, and he went out a hero," said Alice Michael, Mr. Kelly's partner of 33 years, who also spoke at the briefing.

"It was, I think, one of the most incredible things to see a pig heart pounding away and beating inside the chest of a human being," said Robert A. Montgomery, MD, DPhil, director of the NYU Transplant Institute, and himself a heart transplant recipient.

Dr. Fishman stated he had no relevant conflicts of interest. ■



JOE CARROTTA FOR NYU LANGONE HEALTH

**Nader Moazami, MD, (right) surgical director of heart transplantation at the NYU Langone Transplant Institute, and cardiothoracic physician assistant Amanda Merrifield**

To date there has been only one xenotransplant of a genetically modified pig heart into a living human recipient, David Bennett Sr., age 57. The surgery, performed at the University of Maryland in January 2022, was initially successful, with the patient able to sit up in bed a few days after the procedure, and the heart performing like a "rock star" according to transplant surgeon Bartley Griffith, MD. However, Mr. Bennett died 2 months after the procedure from compromise of the organ by an as yet undetermined cause, of which one may have been the heart's infection by porcine cytomegalovirus (CMV).

The NYU team, mindful of this potential setback, used more sensitive assays to screen the donor organs for porcine CMV, and implemented protocols to prevent and to monitor for potential zoonotic transmission of porcine endogenous retrovirus.

The procedure used a dedicated operating room and equipment that will not be used for clinical procedures, the team emphasized.

An organ transplant specialist

**CHEST PHYSICIAN IS ONLINE**

CHEST Physician is available at [chestphysician.org](http://chestphysician.org).



**Angel Coz, MD, FCCP, is Editor in Chief of CHEST Physician.**

**CHEST Physician®**  
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

**AMERICAN COLLEGE OF CHEST PHYSICIANS (CHEST)**

**EDITOR IN CHIEF**

Angel Coz, MD, FCCP

**PRESIDENT**

David Schulman, MD, MPH, FCCP

**EXECUTIVE VICE PRESIDENT & CEO**

Robert Musacchio, PhD

**PUBLISHER, CHEST**

Nicki Augustyn, CAE

**MANAGER, EDITORIAL RESOURCES**

Pamela L. Goorsky

**MANAGING EDITOR, NEWS CHANNELS**

Danielle Leber

**SECTION EDITORS**

Aaron B. Holley, MD, FCCP

*Pulmonary Perspectives®*

Daniel R. Ouellette, MD, FCCP

*Critical Care Commentary*

Michelle Cao, DO, FCCP

*Sleep Strategies*

**EDITORIAL BOARD**

Humayun Anjum, MD, FCCP

A. Christine Argento, MD, FCCP

Abbie Begnaud, MD, FCCP

David L. Bowton, MD, FCCP

Mary Cataletto, MD, FCCP

Carolyn D'Ambrosio, MD, FCCP

Mary Jo S. Farmer, MD, PhD, FCCP

Sachin Gupta, MD, FCCP

Loren Harris, MD, FCCP

Jonathan Ludmir, MD

Diego Maselli, MD, FCCP

Mangala Narasimhan, DO, FCCP

Brandon M. Seay, MD

Shyam Subramanian, MD, FCCP

Sai Venkateshlah, MD, FCCP

Corinne Young, MSN, FNP-C, FCCP

**E-mail:** [chestphysiciannews@chestnet.org](mailto:chestphysiciannews@chestnet.org)

©Copyright 2022, by the American College of Chest Physicians

**CHEST Physician**, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST Physician** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

The statements and opinions expressed in **CHEST Physician** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Frontline Medical Communications Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

**POSTMASTER:** Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Services, 10255 W Higgins Road, Suite 280, Rosemont, IL 60018-9914.

**RECIPIENT:** To change your address, contact Subscription Services at 1-800-430-5450. For paid subscriptions, single issue purchases, and missing issue claims, call Customer Service at 1-833-836-2705 or e-mail [custsvc.chph@fulcoinc.com](mailto:custsvc.chph@fulcoinc.com)

**CHEST PHYSICIAN** (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Subscription price is \$244.00 per year. Phone 973-206-3434, fax 973-206-9378.

**EDITORIAL OFFICES** 2275 Research Blvd, Suite 400, Rockville, MD 20850, 973-206-3434, fax 240-221-2548



**FRONTLINE MEDICAL COMMUNICATIONS SOCIETY PARTNERS**

**EXECUTIVE EDITOR** Kathy Scarbeck, MA

**EDITOR** Mark S. Lesney, PhD

**CREATIVE DIRECTOR** Louise A. Koenig

**DIRECTOR, PRODUCTION/MANUFACTURING**

Rebecca Slebodnik

**DIRECTOR BUSINESS DEVELOPMENT**

Anne Gilhool,

914-916-2487

[agilhool@mdedge.com](mailto:agilhool@mdedge.com)

**DIRECTOR, THE MEDJOBNETWORK**

Julian Knight

973-206-2317, cell 201-310-7063

[jknight@mdedge.com](mailto:jknight@mdedge.com)

**FRONTLINE MEDICAL COMMUNICATIONS**

**Corporate**

**VP, SALES** Mike Guire

**VP, SALES LEAD** Dino Marsella

**VP, MEMBER MARKETING** Amy Pfeiffer

**VP, SALES, STRATEGY & PARTNERSHIPS**

JoAnn Wahl

**DIRECTOR, CIRCULATION** Jared Sonners

**EXECUTIVE EDITOR** Patrick Finnegan

**VP, PROPRIETARY CONFERENCES,**

**MEDSCAPELIVE** David J. Small, MBA

More has been published about anxiety in patients with COPD than in other pulmonary conditions – and in COPD, anxiety has long been established as a prevalent comorbidity. Prevalence rates vary from about 1 in 4, to 1 in 2 or higher, depending on the instruments used and whether clinical DSM-based diagnoses are made, Dr. Iyer said.

A 2013 systematic review of 10 studies that utilized clinical interviews based on DSM criteria, for instance, found a prevalence of clinical anxiety of 10%-55% among inpatients and 13%-46% among outpatients with COPD. The results were similar, investigators said, to studies using self-report screening tools (Respiratory Care 2013;58[5]:858-66).

In the 16 years since a CHEST workshop panel on anxiety and depression in COPD reported higher prevalence rates than for other chronic diseases and detailed a host of problems and research needs (Chest. 2008;134:43S-56), investigators have more fully documented links to COPD outcomes, showing, for instance, that anxiety predicts exacerbations, hospitalizations, poorer adherence to therapies, poorer quality of life, and higher mortality.

Dr. Iyer and other experts say anxiety is still too often a neglected comorbidity. “It’s still underdiagnosed and therefore under-treated,” said Nick Hanania, MD, MS, professor of medicine and director of the Airways Clinical Research Center at Baylor College of Medicine, Houston.

The literature on optimal approaches for management remains limited, and the role of pharmacotherapy for anxiety (and depression) in the context of COPD has not been well investigated. But there have been some advances: Screening tools have been further studied, questionnaires specific to COPD have been developed, and pulmonary rehabilitation (PR) and cognitive behavioral therapy (CBT) have both been shown to be effective in decreasing anxiety.

Researchers and academic clinicians are talking, meanwhile, about how to have important conversations about anxiety with patients who have COPD and other chronic lung conditions, and how to

improve care in the face of significant health system challenges.

### Understanding anxiety in COPD

Anxiety is often intertwined with dyspnea in a bidirectional and complex relationship, but anxiety in COPD is not always acute or limited to times of acute exacerbations.

“There’s not only the acute experience of shortness of breath or a lung change episode, but there’s an anticipation that can occur, psychologically and socially,” said Lauren Garvin, PhD, of the department of psychiatry at the University of Iowa, Iowa City. Patients worry, “what if I’m short of breath in a particular situation? What if my devices fail when I’m out somewhere?”

Patients are often living “in a state of heightened surveillance of the body,” she noted, which can be exhausting and can affect functioning.

It’s also important to appreciate that anxiety is “a continuum of experience,” said Karin Hoth, PhD, associate professor of psychiatry at the medical school, whose research includes projects focusing on psychological adjustment in COPD.

“Research historically categorizes anxiety as ‘have or don’t have.’ But there’s a continuum of experience that we’re moving toward understanding and recognizing in research,” she said. “Anxiety is part of a patient’s whole experience, no matter where one falls on the continuum.”

Female sex, current smoking, greater airflow restrictions – and in some studies, younger age – have all been associated with a greater risk of anxiety in COPD. (It may well be that women receive more attention, leaving men with higher rates of undiagnosed anxiety, Dr. Hoth said.)

Dr. Iyer stresses the complex relationship between smoking – the No. 1 cause of COPD – and anxiety. Smoking has been associated in multiple studies with an increased risk of anxiety (Brain and Behavior. 2013;3[3]:302-26), he said. (A study led by Dr. Iyer found a similar frequency of anxiety symptoms in smokers with and without COPD [Journal of Psychosomatic Research. 2019;118:18-26].)

Some patients with COPD and anxiety may smoke in order to

ease their anxiety, he said, making management of anxiety an important part of the smoking cessation desired for COPD improvement.

COPD medications such as bronchodilators may cause transient symptoms of anxiety, but these are rare and short-lived, Dr. Iyer said.

### Screening tools and conversations

“It’s not just us not thinking about anxiety that’s the problem, it’s also patients thinking that it’s just the disease [causing their anxiety symptoms],” said Dr. Hanania, a member of the 2006 ACCP panel and an author of numerous papers on COPD and anxiety and depression. “There’s quite a bit of overlap between COPD symptoms and anxiety and depression symptoms, and unless you use structured questionnaires, you may not pick it up,” he said.

Screening tools include the Generalized Anxiety Disorder 7-item (GAD-7) scale, the PHQ-9 for depression and anxiety, and the longer Primary Care Evaluation of Mental Disorders (PRIME-MD). The Hospital Anxiety and Depression Scale (HADS), Dr. Iyer noted, has been well validated for use in ambulatory settings.

Validated screening tools specific to anxiety in COPD are also now an option. Abebaw M. Yohannes, PhD, MSc, FCCP, professor in the department of physical therapy at Azuza Pacific University in Orange, Calif., and the author of numerous studies on COPD and anxiety, developed one of these tools – the 10-item Anxiety Inventory for Respiratory Disease (AIR) scale – out of concern that other surveys contain overlapping somatic symptoms (Chest. 2013;144[5]:1587-96).

“We removed the physical symptoms [of anxiety] that often manifest in patients with COPD,” he said.

Dr. Iyer said screening tools can effectively “highlight which person might be dealing with high levels of anxiety symptoms that might meet a threshold of clinical significance and require collaborative or interprofessional management,” including with psychologists and psychiatrists.

They can also open the door to conversation with patients. “I’ll often bluntly ask, do you feel anxious? Do you feel scared, or hopeless about what the future holds for you?” he said. “Anxiety about the future plays a big role, and helping patients navigate the illness and understand early how it might look



Dr. Anand S. Iyer

... can ease the level of anxiety.”

Asking patients about their experiences in managing their symptoms and about their psychological and emotional well-being can help to normalize anxiety – and it can be therapeutic, said Dr. Hoth and Dr. Garvin. Asking “how it’s going with the things that really matter in [their] life” is often a good question, they said.

Patients “won’t be offended if you ask,” said Dr. Hoth. “They view their mood and [whole] well-being as part of their medical condition.”

Time is a challenge, she said, but “conversation can be done little by little, as part of a philosophy of engaging the patient around their whole functioning, even if there’s not [a need or] a route to refer just then.”

Such early and integrated conversation borrows from the palliative care model. “Palliative care is a specialty, but it can also be an approach to care,” Dr. Iyer said. He is leading a National Institutes of Health-funded study on nurse-coach-led early palliative care for older adults with COPD (clinicaltrials.gov/ct2/show/NCT05040386) and wants to see training opportunities for pulmonologists to learn basic palliative care skills that would equip them to better guide management of mild-moderate anxiety and other complex symptoms.

### Pulmonary rehabilitation

For many patients with COPD who have anxiety and/or depressive symptoms, referral for nonpharmacologic therapies such as psychotherapy, cognitive-behavioral therapy (CBT), and pulmonary rehabilitation (PR) is “one of the best things you can do,” Dr. Iyer said.

COPD ANXIETY continued on following page



Dr. Karin Hoth

# Exercise response predicts benefit from rehab

BY PAM HARRISON

MDedge News

Not all patients with chronic obstructive pulmonary disease (COPD) respond equally well to pulmonary rehabilitation (PR).

Now, physicians can better categorize which patients will do well with PR and which ones less well or not well at all based on a new system of clustering of COPD patients according to their response to exercise therapy.

“We identified four clusters of COPD patients and their response to PR in the aim to better understand PR outcome and [adapt] it to patients’ profiles and needs,” lead author Yara Al Chikhanie, MD, of the cardiopulmonary rehabilitation center Dieulefit Sante (France), and colleagues observed.

“Identification of patients likely to show smaller responses to PR may help to target patients benefiting the most and to adapt PR settings for

nonresponders to standard PR,” they suggested.

The study was published online in *Respiratory Medicine* (2022 May 1. doi: 10.1016/j.rmed.2022.106861).

## Single-center cohort

The cohort consisted of 835 patients from a single center who had been admitted to a cardiopulmonary rehabilitation center over a 6-year period from 2021 to 2017. “The PR program used in the center was the same over the 6-year period,” the authors note – consisting of a 3- to 4-week, inpatient program with activities 5 days a week.

Each day, patients attended a 25-minute aerobic training session on a cycling ergometer or a treadmill; a 30-minute low-intensity gym session; a 30-minute group walk outdoors, and 30 minutes of strength training. “We aimed to cluster patients with COPD admitted to PR based on patients’ clinical characteristics and 6-meter walk test

results (6MWT), pulse oxygen saturation (SPO<sub>2</sub>), heart rate (HR), and dyspnea,” the authors explained.

They then evaluated patient response to PR in each of these clusters based on the amount of improvement in the 6-meter walk distance (6MWD), lung function, and quality of life observed, they added.

The population consisted of seniors, equally men and women, mostly GOLD II and III patients (a measure of lung function) with a limited walking capacity, some 84% of the cohort having a 6MWD <80% predicted. The characteristics of the four identified clusters were as follows:

- **Cluster 1:** Consisted of younger men, GOLD I-II, average walkers, obese. The average 6MWD was 430 meters and patients had a large exercise HR response to PR. This cluster had a 76 meter improvement in their 6MWD, although 16% of the same cluster

still did not respond to PR.

- **Cluster 2:** Consisted of older women, GOLD II-III, who were slow walkers. This cluster had a reduced 6MWD of 362 meters, but they also had a significant 97-meter improvement in their 6MWD following PR. Some 18% were still nonresponders to PR.
- **Cluster 3:** Consisted of older men, GOLD II-III, dyspneic, slow walkers, some 32% of whom responded to PR. This cluster also had a reduced 6MWD at 388 meters, but again, they also had a significant improvement of 79 meters in their 6MWD following the introduction of PR. Some 11% were nonresponders to PR.
- **Cluster 4:** Consisted of older men, GOLD III-IV, very slow walkers, oxygen-dependent, very dyspneic. This cluster had a severely reduced 6MWD of only 290 meters with severe exercise desaturation and dyspnea, and almost all of them

REHAB continued on following page

COPD ANXIETY continued from previous page

“If patients haven’t done pulmonary rehabilitation, get them in. And if they have done it before, get them back into it again,” he emphasized. “Accredited programs give a holistic approach to improving your strength, your breathlessness, your mindset and understanding of your breathlessness, and your own levels of security.”

Studies addressing the impact of PR and CBT on anxiety have been mostly small and observational but have yielded encouraging findings. A 2017 review reported that PR and CBT were effective in the treatment of anxiety and dyspnea, in the short term, in the majority of 47 studies (*JAMA*. 2017;18[12]:1096.e1-1096.e17). And

a 2019 systematic review and meta-analysis focused on PR reported that, across 11 studies comprising 734 patients, PR conferred significant benefits for anxiety and depression compared with usual care (*Chest*. 2019;156[1]:80-91).

Dr. Yohannes, Dr. Hanania, and colleagues recently reported on 734 patients with clinically stable COPD who completed a community-based

8-week PR program of 2 hours a week: 1 hour of exercise and 1 hour of education, the latter of which covered anxiety, panic management, and relaxation.

Patients who had severe dyspnea and comorbid anxiety and depression prior to PR – one-third of the group compared with 20% having anxiety alone and 5% having depression alone – had the most significant improvements in dys-

pnea scores and anxiety and depression scores (*Respir Med*. Apr 9. doi: 10.1016/j.rmed.2022.106850.)

The problem is, pulmonary rehabilitation is under-reimbursed and not widely accessible. It’s logistically challenging for patients to attend therapy 2-3 times a week.

And according to a recently published study by Dr. Yohannes, Dr. Hanania, and colleagues, patients with more anxiety and dyspnea may be at higher risk of dropping out (*Respir Med*. 2022 Jan 20. doi: 10.1016/j.rmed.2022.10674). Moreover, Dr. Iyer said, there is a shortage of programs that are accredited.

Telehealth may help on some of these fronts. The efficacy of real-time video PR for COPD is

being investigated in a randomized NIH trial (now in the recruitment phase) led by pulmonologist Surya P. Bhatt, MD, also at the University of Alabama at Birmingham ([www.clinicaltrials.gov/ct2/show/NCT05119556](http://www.clinicaltrials.gov/ct2/show/NCT05119556)).

Researchers also need to investigate issues of sustainability – to learn what “works best in the long run,” Dr. Iyer said.

Dr. Yohannes and Dr. Hanania

are encouraged by a recent finding that patients with COPD who completed 8 weeks of PR maintained improvements in anxiety and quality-of-life scores at 2 years. (Improvements in dyspnea and other outcomes did not persist.) (*Chest*. 2021;159[3]:967-74).

Prospective studies contrasting maintenance programs with no maintenance following PR are needed, they wrote.

## Understanding psychological interventions

Dr. Hoth and Dr. Garvin advise their pulmonologist colleagues to feel as confident as possible in describing for patients what CBT and other psychological therapies entail.

“A person [with COPD] who is

experiencing something on the continuum of anxiety might be really turning inward and [assessing] unwanted internal experiences” and accompanying thoughts, sensations, emotional impacts and behaviors, Dr. Garvin said.

Among the goals, she said, are to “make shifts around those internal experiences that might invoke some more tolerance or that might shift their relationship with the experi-

ences, or even with the diagnosis itself and all the uncertainties it carries.”

Psychological therapies can involve social support, or “breath and grounding work,” she said. “There are lots of different approaches from different providers.”

Dr. Yohannes advocates incorporating principles of CBT into

PR. “In the absence of one-on-one or group [stand-alone] CBT ... the principles are worth incorporating as part of the education piece [of PR],” he said. “CBT helps patients to refocus their attention. ... and gives them self-confidence to engage in exercise and to function a bit more in their daily activities.”

None of those interviewed for this story reported having any relevant conflicts of interest. ■



Dr. Lauren Garvin



Dr. Abebaw M. Yohannes



were on long-term oxygen therapy. Nevertheless, this cluster also had a significant, 66-meter improvement in their 6MWD. Twenty-eight percent of them were nonresponders to PR.

### Clinical practice

“The highly heterogeneous nature of the enrolled patient population reflects clinical practice,” the authors point out. For example, cluster 1 included patients with the best lung function, compared with those in clusters 2, 3, and 4 – which may be due, at least in part, to the aggravation in disease severity with age given that patients in cluster 1 were the youngest overall.

The fact that those in cluster 4 had the worst performance may also have been because of age and disease severity, the authors note, as those in cluster 4 had the highest proportion of patients on long-term oxygen therapy, again suggestive of disease severity. “Of note, these patients show the most impaired 6MWT responses despite the use of oxygen supplementation during walking,” the researchers added.

The authors also suggest that patients such as those in cluster 4 may require specific PR modalities in order to optimize their functional benefits. In contrast, those in cluster 1 had a significantly higher body mass index, compared with those in the other 3 clusters, which, interestingly enough, was not associated with more severe functional exercise impairment. The fact that older age participants, such as those in cluster 3 as well as those with high BMI in cluster 1, were both able to improve their 6MWD post-PR to the same extent as younger patients without obesity suggests that most older or overweight/obese patients can still show clinically significant improvement in 6MWD post PR, as the authors suggest.

Notably, the 6MWT was the only test available both pre- and post PR, making this an important limitation of the study, because only one aspect of the effect of PR was evaluated, omitting other physical and psychosocial benefits of PR, investigators suggest.

### Adds to the literature

Asked to comment on the findings, Sachin Gupta, MD, attending physician, pulmonary & critical care medicine, Alameda Health System, Highland Hospital, Oakland, Calif., felt that these data add to the literature in defining COPD patient profiles, helping to categorize those in whom to expect greater walk

distance improvements with PR versus those who will respond less well.

“Because 6MWD is a surrogate marker for quality of life (QOL) and mortality, further analysis in the form of a randomized controlled trial to determine long-term outcomes among the four clusters with adjustment for baseline characteristics would help determine the extent

to which certain patient clusters may respond to PR,” Dr. Gupta told this news organization in an email.

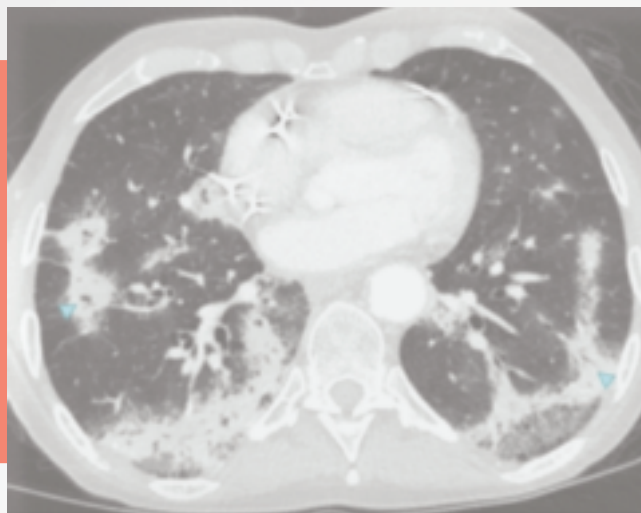
At the same time, he suggested that while patients may not experience much net benefit in their 6MWD, their QOL or mortality risk may still improve with PR. “I cannot recall a patient ever describing their experience with PR as anything

other than positive,” Dr. Gupta said.

“And as the authors [themselves] note, because PR serves to benefit patients beyond the 6MWD, I would not recommend limiting PR referrals based on the patient clusters identified,” he said.

The authors had no conflicts to declare. Dr. Gupta is an employee and shareholder at Genentech. ■

## THE PROGRESSIVE PHENOTYPE CAN DEVELOP IN PATIENTS WITH FIBROTIC ILDs REGARDLESS OF ETIOLOGY



Your **VIGILANCE** and **TIMELY INTERVENTION** can make a **DIFFERENCE**

**EXPLORE** content across the range of ILDs including signs of disease progression

**LISTEN** to ILD experts via podcasts or videos and read our latest disease state publications

Learn more about the diverse range of ILDs on Insights in ILD

[Insightsinild.com/fibroticILD/](https://Insightsinild.com/fibroticILD/)



Copyright © 2021 Boehringer Ingelheim Pharmaceuticals, Inc. All rights reserved. Printed in the U.S.A. (05/21) PC-US-120799



# Adjuvant vs. neoadjuvant? What has ASCO 2022 taught us regarding resectable NSCLC?

BY JOAN H. SCHILLER, MD

**W**e've still got some work to do before we can say with authority whether concurrent neoadjuvant chemotherapy and immunotherapy is better than concurrent adjuvant chemotherapy with immunotherapy for non-small cell lung cancer (NSCLC). While there has been some notable progress in this area, we need phase 3 trials that compare the two approaches.

Investigators reporting at the 2022 annual meeting of American Society of Clinical Oncology focused primarily on neoadjuvant treatment, which I'll address here.

In the randomized, phase 2 NADIM II clinical trial reported at the meeting, researchers expanded on the results of NADIM published in 2020 in the *Lancet Oncology* and in May 2022 in the *Journal of Clinical Oncology* (2022 May 16; doi: 10.1200/JCO.21.02660) along with Check-Mate 816 results published in the *New England Journal of Medicine* (2022 May 26; doi: 10.1056/NEJMoa2202170).

In each of these three studies, researchers compared nivolumab plus chemotherapy versus chemotherapy alone (abstract 8501) as a neoadjuvant treatment for resectable stage IIIA NSCLC. In the study reported at ASCO 2022, patients with resectable clinical stage IIIA-B (per American Joint Committee on Cancer 8th edition) NSCLC and no known EGFR/ALK alterations, were randomized to receive preoperative nivolumab plus chemotherapy (paclitaxel and carboplatin; n = 57) or chemotherapy (n = 29) alone followed by surgery.

The primary endpoint was pathological complete response (pCR); secondary endpoints included major pathological response, safety and tolerability, impact on surgical issues such as delayed or canceled surgeries or length of hospital stay, overall survival and progression free survival. The pCR rate was 36.8% in the neoadjuvant nivolumab plus chemotherapy arm and 6.9%

in the chemotherapy alone arm ( $P = .0068$ ). Twenty-five percent of patients on the nivolumab plus chemo arm had grade 3-4 adverse events, compared with 10.3% in the control arm. In addition, 93% of patients on the nivolumab plus chemo arm underwent definitive surgery whereas 69.0% of the patients on the chemo alone arm had definitive surgery. ( $P = .008$ )

## What else did we learn about neoadjuvant treatment at the meeting?

Investigators looking at the optimal number of neoadjuvant cycles (abstract 8500) found that three cycles of sintilimab (an investigational PD-1 inhibitor) produced a numerically higher major pathological response rate, compared with

two cycles (when given along with platinum-doublet chemotherapy). And, neoadjuvant chemoradiotherapy does not result in significant survival benefits when compared with neoadjuvant chemotherapy alone (abstract 8503).

Of course, when it comes to resectable NSCLC, the

goal of treatment is to increase the cure rate and improve survival. No randomized studies have reported yet on overall survival, probably because they are too immature. Instead, disease-free survival (DFS) or event-free survival (EFS) are often used as surrogate endpoints. Since none of the studies reported at ASCO reported on DFS or EFS, we need to look elsewhere. Check-Mate 816 was a phase 3 study which randomized patients with stages IB-IIIA NSCLC to receive neoadjuvant nivolumab plus platinum-based chemotherapy or neoadjuvant platinum-based chemotherapy alone, followed by resection. The median EFS was 31.6 months with nivolumab plus chemotherapy and 20.8 months with chemotherapy alone ( $P = .005$ ). The percentage of patients with a pCR was 24.0% and 2.2%, respectively ( $P < .001$ ).

We all know one has to be careful when doing cross-trial comparisons as these studies differ by the

percentage of patients with various stages of disease, the type of immunotherapy and chemotherapy used, and so on. However, I think we can agree that neoadjuvant chemoimmunotherapy results in better outcomes than chemotherapy alone.

Of course, resectable NSCLC is, by definition, resectable. And traditionally, resection is followed by adjuvant chemotherapy to eradicate micrometastases. Unfortunately, the current standard of care for completely resected early-stage NSCLC (stage I [tumor  $\geq 4$  cm] to IIIA) involves adjuvant platinum-based combination chemotherapy which results in only a modest 4%-5% improvement in survival versus observation.

Given these modest results, as in the neoadjuvant space, investigators have looked at the benefit of adding immunotherapy to adjuvant chemotherapy. One such study has been reported. IMpower 010 randomly assigned patients with completely resected stage IB (tumors  $\geq 4$  cm) to IIIA NSCLC, whose tumor cells expressed at least 1% PD-L1, to receive adjuvant atezolizumab or best supportive care after adjuvant platinum-based chemotherapy. In the stage II-III population whose tumors expressed PD-L1 on 1% or more of tumor cells, 3-year DFS rates were 60% and 48% in the atezolizumab and best supportive care arms, respectively (hazard ratio, 0.66;  $P = .0039$ ). In all patients in the stage II-III population, the 3-year DFS rates were 56% in the atezolizumab group and 49% in the best supportive care group, (HR, 0.79;  $P = .020$ ).

KEYNOTE-091, reported at the 2021 annual meeting of the European Society for Medical Oncology, randomized early-stage NSCLC patients following complete resection and adjuvant chemotherapy to pembrolizumab or placebo. Median DFS for the overall population was 53.6 months for patients in the pembro arm versus 42 months in the placebo arm (HR, 0.76;  $P = .0014$ ). Interestingly, the benefit was not seen in patients with PD-L1 with at least 50%, where the 18-month DFS rate was 71.7% in the pembro arm and 70.2% in the placebo arm (HR, 0.82;  $P = .14$ ). Although the contradictory results of PD-L1 as a biomarker is puzzling, I think we can agree that the addition of



**Dr. Joan H. Schiller:** Many questions remain. There is a clear and immediate need for predictive and prognostic biomarkers.

immunotherapy following adjuvant chemotherapy improves outcomes compared with adjuvant chemotherapy alone.

## What to do when a patient presents with resectable disease?

Cross-trial comparisons are fraught with danger. Until we have a phase 3 study comparing concurrent neoadjuvant chemo/immunotherapy with concurrent adjuvant chemo/immunotherapy, I do not think we can answer the question "which is better?" However, there are some caveats to keep in mind when deciding on which approach to recommend to our patients: First, neoadjuvant treatment requires biomarker testing to ensure the patient does not have EGFR or ALK mutations. This will necessitate a delay in the operation. Will patients be willing to wait? Will the surgeon? Or, would patients prefer to proceed with surgery while the results are pending? Yes, neoadjuvant therapy gives you information regarding the pCR rate, but does that help you in subsequent management of the patient? We do not know.

Secondly, the two adjuvant studies used adjuvant chemotherapy followed by adjuvant immunotherapy, as contrasted to the neoadjuvant study which used concurrent chemo/immunotherapy. Given the longer duration of treatment in postoperative sequential adjuvant studies, there tends to be more drop off because of patients being unwilling or unfit postoperatively

ASCO 2022 continued on following page

# Drugging the 'undruggable' in patients with NSCLC

BY JOAN H. SCHILLER, MD

Long thought to be untreatable, KRAS is one of the most difficult to treat oncogenic drivers responsible for approximately 25% of all tumors, including 68% of pancreatic tumors and 20% of all non-small cell lung cancers (NSCLC) (Signal Transduct Target Ther. 2021 Nov 15;6[1]:386).

We now have a treatment – sotorasib – for patients with locally advanced or metastatic NSCLC that is driven by a KRAS mutation (G12C). And, now, there is a second treatment – adagrasib – under study, which, according to a presentation recently made at the annual meeting of the American Society of Clinical Oncology, looks promising.

Ras is a membrane-bound regulatory protein (G protein) belonging to the family of guanosine triphosphatases (GTPases). Ras functions as a guanosine diphosphate/triphosphate binary switch by cycling between the active GTP-bound and the inactive GDP-bound states in response to extracellular stimuli. The KRAS (G12C) mutation affects the active form of KRAS and results in abnormally high concentrations of GTP-bound KRAS leading to hyperactivation of downstream oncogenic pathways and uncontrolled cell growth, specifically of ERK and MEK signaling pathways (Mol Cancer. 2018 Feb 19;17[1]:33).

At the ASCO annual meeting in June, Spira and colleagues reported the results of cohort A of the KRYSTAL-1 study evaluating adagrasib as second-line therapy patients with advanced solid tumors harboring a KRAS (G12C) mutation. Like sotorasib, adagrasib is a KRAS

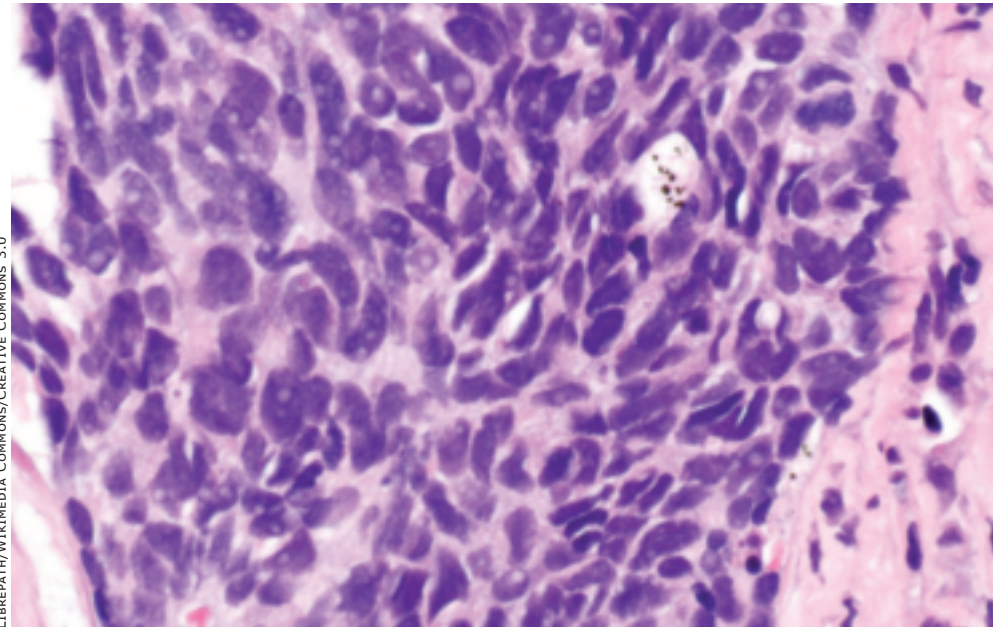
(G12C) inhibitor that irreversibly and selectively binds KRAS (G12C), locking it in its inactive state. In this study, patients had to have failed first-line chemotherapy and immunotherapy with 43% of lung cancer patients responding. The 12-month overall survival (OS) was 51%, median overall survival was 12.6 and median progression-free survival (PFS) was 6.5 months. Twenty-five patients with KRAS (G12C)-mutant NSCLC and active, untreated central nervous system metastases received adagrasib in a phase 1b cohort. The intracranial overall response rate was 31.6% and median intracranial PFS was 4.2 months. Systemic ORR was 35.0% (7/20), the disease control rate was 80.0% (16/20) and median duration of response was 9.6 months. Based on these data, a phase 3 trial evaluating adagrasib monotherapy versus docetaxel in previously treated patients with KRAS (G12C) mutant NSCLC is ongoing.

The Food and Drug Administration approval of sotorasib in 2021 was, in part, based on the results of a single-arm, phase 2, second-line study of patients who had previously received platinum-based chemotherapy and/or immunotherapy (N Engl J Med. 2021;384:2371-81). An ORR rate of 37.1% was reported with a median PFS of 6.8 months and median OS of 12.5 months leading to the FDA approval. Responses were observed across the range of baseline PD-L1 expression levels: 48% of PD-L1 negative, 39% with PD-L1 between 1%-49%, and 22% of patients with a PD-L1 of greater than 50% having a response.

The major toxicities observed in these studies were gastrointestinal

candidates. In the NADIM II trials, 9 of 29 patients on the neoadjuvant chemotherapy were not resected.

So, many questions remain. In addition to the ones we've raised, there is a clear and immediate need for predictive and prognostic biomarkers. In the NADIM II trial, PD-L1 expression was a predictive biomarker of response. The pCR rate for patients with a PD-L1 tumor expression of less than 1%, 1%-49%, and 50% or higher was 15%, 41.7%, and 61.1%, respectively. However, in KEYNOTE-091, the benefit was not seen in patients with PD-L1 of less at least 50%, where the 18-month DFS rate was



The micrograph shows H&E-stained non-small cell lung cancer cells.

(diarrhea, nausea, vomiting) and hepatic (elevated liver enzymes). About 97% of patients on adagrasib experienced any treatment-related adverse events, and 43% experienced a grade 3 or 4 treatment-related adverse event leading to dose reduction in 52% of patients, a dose interruption in 61% of patients, and a 7% discontinuation rate. About 70% of patients treated with sotorasib had a treatment-related adverse event of any grade, and 21% reported grade 3 or 4 treatment-related adverse events.

A subgroup in the KRYSTAL-1 trial reported an intracranial ORR of 32% in patients with active, untreated CNS metastases. Median overall survival has not yet reached concordance between systemic and intracranial disease control was 88%. In addition, preliminary data from two patients with untreated CNS metastases from a phase 1b cohort found cerebrospinal fluid

concentrations of adagrasib with a mean ratio of unbound brain-to-plasma concentration of 0.47, which is comparable or exceeds values for known CNS-penetrant tyrosine kinase inhibitors (Clin Cancer Res. 2022 Apr 11. doi: 10.1158/1078-0432.CCR-22-0383).

Unfortunately, KRAS (G12C) is not the only KRAS mutation out there. There are a myriad of others, such as G12V and G12D. Hopefully, we will be seeing more drugs aimed at this set of important mutations. Another question, of course, is when and if these drugs will move to the first-line setting. ■

*Dr. Schiller is a medical oncologist and founding member of Oncologists United for Climate and Health. She is a former board member of the International Association for the Study of Lung Cancer and a current board member of the Lung Cancer Research Foundation.*

ASCO 2022 continued from previous page

to receive long courses of therapy. In IMpower 010, 1,269 patients completed adjuvant chemotherapy; 1,005 were randomized, and of the 507 assigned to the atezolizumab/chemo group, only 323 completed treatment.

Finally, we must beware of using neoadjuvant chemo/immunotherapy to “down-stage” a patient. KEYNOTE-091 included patients with IIIA disease and no benefit to adjuvant chemotherapy followed by immunotherapy was found in this subgroup of patients, which leads me to wonder if these patients were appropriately selected as surgical

71.7% in the pembro arm and 70.2% in the placebo arm.

Another possible biomarker: circulating tumor DNA. In the first NADIM study, three low pretreatment levels of ctDNA were significantly associated with improved progression-free survival and overall survival (HR, 0.20 and HR, 0.07, respectively).

Although clinical response did not predict survival outcomes, undetectable ctDNA levels after neoadjuvant treatment were significantly associated with progression-free survival and overall survival (HR, 0.26 and HR, 0.04, respectively).

Similarly, in CheckMate 816,

clearance of ctDNA was associated with longer EFS in patients with ctDNA clearance than in those without ctDNA clearance in both the nivolumab/chemotherapy group (HR, 0.60) and the chemotherapy-alone group (HR, 0.63).

Hopefully, ASCO 2023 will provide more answers. ■

*Dr. Schiller is a medical oncologist and founding member of Oncologists United for Climate and Health. She is a former board member of the International Association for the Study of Lung Cancer and a current board member of the Lung Cancer Research Foundation.*

9<sup>TH</sup> ANNUAL

Irv Feldman  
TEXAS  
HOLD 'EM  
ANNUAL TOURNAMENT & CASINO NIGHT

IN PERSON | SATURDAY, AUGUST 27, 2022  
DOORS OPEN: 5:30 PM | CARDS FLY: 7 PM

FIRST PRIZE

\$10,000 seat to the 2023 World Series of Poker  
Main Event in Las Vegas

The CHEST Foundation invites you to a lively Texas  
Hold 'Em tournament, plus dining and more:

- ♠ Casino gaming
- ♠ Silent auction
- ♠ Raffle prizes
- ♠ Steak and seafood dinner
- ♠ Specialty cocktails by Tito's Vodka

Supporting improved patient access and better  
quality of life for those battling pulmonary fibrosis.

Get tickets or donate to the cause at  
[one.bidpal.net/irv](https://one.bidpal.net/irv)



GIBSONS BAR & STEAKHOUSE  
2105 SOUTH SPRING ROAD | OAK BROOK, IL 60523



PRESENTED BY



Poker partner organizations:  
Poker League of Nations, Poker Power, Chicagoland Poker Players

CRITICAL CARE

# Hospital-acquired pneumonia: Is an easy prevention being missed?

BY BRETT KELMAN, KAISER  
HEALTH NEWS

Four years ago, when Dr. Karen Giuliano went to a Boston hospital for hip replacement surgery, she was given a pale-pink bucket of toiletries issued to patients in many hospitals. Inside were tissues, bar soap, deodorant, toothpaste, and, without a doubt, the worst toothbrush she'd ever seen.

"I couldn't believe it. I got a toothbrush with no bristles," she said. "It must have not gone through the bristle machine. It was just a stick."

To most patients, a useless hospital toothbrush would be a mild inconvenience. But to Dr. Giuliano, a nursing professor at the University of Massachusetts, Amherst, it was a reminder of a pervasive "blind spot" in U.S. hospitals: the stunning consequences of unbrushed teeth.

Hospital patients not getting their teeth brushed, or not brushing their teeth themselves, is believed to be a leading cause of hundreds of thousands of cases of pneumonia a year in patients who have not been put on a ventilator. Pneumonia is among the most common infections that occur in health care facilities, and a majority of cases are nonventilator hospital-acquired pneumonia, or NVHAP, which kills up to 30% of those infected, Dr. Giuliano and other experts said.

But unlike many infections that strike within hospitals, the federal government doesn't require hospitals to report cases of NVHAP. As a result, few hospitals understand the origin of the illness, track its occurrence, or actively work to prevent it, the experts said.

Many cases of NVHAP could be avoided if hospital staffers more dutifully brushed the teeth of bedridden patients, according to a growing body of peer-reviewed research papers. Instead, many hospitals often skip teeth brushing to prioritize other tasks and provide only cheap, ineffective toothbrushes,

often unaware of the consequences, said Dr. Dian Baker, a Sacramento (Calif.) State nursing professor who has spent more than a decade studying NVHAP.

"I'll tell you that today the vast majority of the tens of thousands of nurses in hospitals have no idea that pneumonia comes from germs in the mouth," Dr. Baker said.

Pneumonia occurs when germs trigger an infection in the lungs.

Although NVHAP accounts for most of the cases that occur in hospitals, it historically has not received the same attention as pneumonia tied to ventilators, which is easier to identify and study because it occurs among a narrow subset of patients.

NVHAP, a risk for virtually all hospital patients,

is often caused by bacteria from the mouth that gathers in the scummy biofilm on unbrushed teeth and is aspirated into the lungs. Patients face a higher risk if they lie flat or remain immobile for long periods, so NVHAP can also be prevented by elevating their heads and getting them out of bed more often.

According to the National Organization for NV-HAP Prevention, which was founded in 2020, this pneumonia infects about 1 in every 100 hospital patients and kills 15%-30% of them. For those who survive, the illness often extends their hospital stay by up to 15 days and makes it much more likely they will be readmitted within a month or transferred to an intensive care unit.

John McCleary, 83, of Millinocket, Maine, contracted a likely case of NVHAP in 2008 after he fractured his ankle in a fall and spent 12 days in rehabilitation at a hospital, said his daughter, Kathy Day, a retired nurse and advocate with the Patient Safety Action Network.

Mr. McCleary recovered from the fracture but not from pneumonia. Two days after he returned home, the infection in his lungs caused him to be rushed back to the hospital, where he went into sepsis and spent weeks in treatment before

*Although NVHAP accounts for most of the cases that occur in hospitals, it historically has not received the same attention as pneumonia tied to ventilators.*



MONKEYBUSINESSIMAGES/THINKSTOCK

with patients during the coronavirus pandemic.

“We only know what’s reported,” Mr. Davis said. “Could this be the tip of the iceberg? I would say, in my opinion, probably.”

To better measure the condition, some researchers call for a standardized surveillance definition of NVHAP, which could in time open the door for the federal government to mandate reporting of cases or incentivize prevention. With increasing urgency, researchers are pushing for hospitals not to wait for the federal government to act against NVHAP.

Dr. Baker said she has spoken with hundreds of hospitals about how to prevent NVHAP, but thousands more have yet to take up the cause.

“We are not asking for some big, \$300,000 piece of equipment,” Dr. Baker said. “The two things that show the best evidence of preventing this harm are things that should be happening in standard care anyway – brushing teeth and getting patients mobilized.”

That evidence comes from a smattering of studies that show those two strategies can lead to sharp reductions in infection rates.

In California, a study at 21 Kaiser Permanente hospitals used a re-prioritization of oral care and getting

patients out of bed to reduce rates of hospital-acquired pneumonia by around 70%. At Sutter Medical Center in Sacramento, better oral care reduced NVHAP cases by a yearly average of 35%.

At Orlando Regional Medical Center in Florida, a medical unit and a surgical unit where patients received enhanced oral care reduced NVHAP rates by 85% and 56%, respectively, when compared with similar units that received normal care.

A similar study is underway at two hospitals in Illinois.

And the most compelling results come from a veterans’ hospital in Salem, Va., where a 2016 oral care pilot program reduced rates of NVHAP by 92% – saving an estimated 13 lives in just 19 months. The program, the HAPPEN Initiative, has been expanded across the Veterans Health Administration, and experts say it could serve as a model for all U.S. hospitals.

Dr. Michelle Lucatoro, a nursing official who leads HAPPEN, said the

moving to an isolation unit in a nursing home.

He died weeks later, emaciated, largely deaf, unable to eat, and often “too weak to get water through a straw,” his daughter said. After contracting pneumonia, he never walked again.

“It was an astounding assault on his body, from him being here visiting me the week before his fall, to his death just a few months later,” Ms. Day said. “And the whole thing was avoidable.”

While experts describe NVHAP as a largely ignored threat, that appears to be changing.

Last year, a group of researchers – including Dr. Giuliano and Dr. Baker, plus officials from the Centers for Disease Control and Prevention, the Veterans Health Administration, and the Joint Commission – published a “call-to-action” research paper hoping to launch “a national health care conversation about NVHAP prevention.”

The Joint Commission, a non-profit organization whose accreditation can make or break hospitals, is considering broadening the infection control standards to include more ailments, including NVHAP, said Sylvia Garcia-Houchins, its director of infection prevention and control.

Separately, ECRI, a nonprofit focused on health care safety, this year pinpointed NVHAP as one of its top patient safety concerns.

James Davis, an ECRI infection expert, said the prevalence of NVHAP, while already alarming, is likely “underestimated” and probably worsened as hospitals swelled

**A 2016 oral care pilot program reduced rates of NVHAP by 92% – saving an estimated 13 lives in just 19 months.**

**David Bowton, MD, FCCP, comments:** The studies that suggest that oral care and mobility can prevent NV-HAP were observational, used administrative data, and historic controls. These shortcomings markedly increase the uncertainty of these findings. Successful prevention of ventilator-associated pneumonia with oral care (without selective oral decontamination) has been inconsistent (Chacko R, et al. Br J Nurs. 2017;26(11):594; Klompas M, M.D., et al. Infection Control and Hospital Epidemiology. 2014;35[8]:915). However, oral care and attention to mobility are low-cost interventions with a potentially large impacts on patient-centered outcomes including delirium and return to full activity, in addition to potentially reducing antibiotic usage to treat pneumonia (Arroliga AC, et al. Respir Care. 2012;57[5]:688). I wholeheartedly agree that this area deserves much more attention and more careful examination of the specific factors that improve outcomes.



program trains nurses to most effectively brush patients’ teeth and educates patients and families on the link between oral care and preventing NVHAP. While teeth brushing may not seem to require training, Dr. Lucatoro made comparisons to how the coronavirus revealed many Americans were doing a lackluster job of another routine hygienic practice: washing their hands.

“Sometimes we are searching for the most complicated intervention,” she said. “We are always looking for that new bypass surgery, or some

new technical equipment. And sometimes I think we fail to look at the simple things we can do in our practice to save people’s lives.” ■

*KHN (Kaiser Health News) is a national newsroom that produces in-depth journalism about health issues. Together with Policy Analysis and Polling, KHN is one of the three major operating programs at KFF (Kaiser Family Foundation). KFF is an endowed nonprofit organization providing information on health issues to the nation.*

SIMULATION COURSES 



September 8-10, 2022 | CHEST Headquarters

## Difficult Airway Management

**Confidently manage airways in critically ill patients**

**During this 3-day training, you will learn:**

- Airway management for critically ill patients using evidence-based methods and crew resource management concepts
- Systemic approaches to patient, equipment, and drug preparation before intubation
- How to perform a direct laryngoscopy in a clinical environment
- Use of videolaryngoscopes, extraglottic devices, and cricothyrotomy in difficult or failed airways

REGISTER | [chestnet.org/AirwayManagement2022](https://chestnet.org/AirwayManagement2022)

# More evidence links asthma severity to age of onset

BY RICHARD MARK KIRKNER

A recently published multinational cohort study may be the largest to date that's found the age of asthma onset is an integral factor in defining the severity of disease and the frequency of comorbidities.

"It's very simple to ask your patient: 'Did you have asthma as a child? When did your asthma start?'" coauthor Guy Brusselle, MD, a professor at the University of Ghent (Belgium), said in an interview. "You do not need expensive investigations, CT scans or proteomics or genomics; just two simple questions."

The retrospective cohort study, published in the *Journal of Allergy and Clinical Immunology: In Practice* (2022 Apr 7. doi: 10.1016/j.jaip.2022.03.019), combined national electronic health records databases from five different countries – the United Kingdom, Spain, Italy, the Netherlands, and Denmark – that included 586,436 adult asthma patients. The study divided the patients into three subtypes: childhood-onset asthma, meaning a diagnosis before age 18 (n = 81,691); adult-onset disease, defined as a diagnosis between ages 18 and 40 (n = 218,184); and late onset, defined as a diagnosis made after age 40 (n = 286,561).

Dr. Brusselle said the study found stark differences in characteristics

between the three subtypes, including an increasing risk for women with later age of onset. Across the five databases, females comprised approximately 45% of those with childhood-onset asthma, but about 60% of those with later-onset disease, Dr. Brusselle said.

As for characteristics of asthma, 7.2% of the cohort (n = 42,611) had severe asthma, but the proportion was highest in late-onset asthma, 10% versus 5% in adult onset and 3% in childhood onset. The percentage of uncontrolled asthma followed a similar trend: 8%, 6%, and 0.4% in the respective treatment groups.

The most common comorbidities were atopic disorders (31%) and overweight/obesity (50%). The prevalence of atopic disorders was highest in the childhood-onset group, 45% versus 35%, and 25% in the adult-onset and late-onset patients. However, the trend for overweight/obesity was reversed: 30%, 43%, and 61%, respectively.

"The larger differences were when late-onset asthma was compared to adult-onset asthma with respect to comorbidities," Dr. Brusselle said. "The late-onset asthma

patients more frequently had nasal polyposis."

These patients typically lose their sense of smell, as in COVID-19. However, in nasal polyposis the loss is chronic rather than transient.

Pulmonologists should be attuned to the prevalence of overweight/obesity in the late-onset group, Dr.

Brusselle said. "We know that obesity is an important risk factor for diabetes, and then obesity is also associated with gastroesophageal reflux – and we know that gastroesophageal reflux is a risk factor for asthma exacerbations."

Smaller studies have arrived at the same conclusions regarding the relationships between asthma severity and age of onset, Dr. Brusselle said. What's notable about this study is its size and the consistency of findings across different national databases.

"In childhood onset, you need to watch for different allergies – atopic dermatitis and allergic rhinitis – but in late-onset asthma, look for obesity, diabetes and reflux disease, and nasal polyposis," he said.

Sally E. Wenzel, MD, professor at the University of Pittsburgh and director of the Asthma and Environmental Lung Health Institute at

the University of Pittsburgh Medical Center, concurred that the size of this study makes it noteworthy.

"It's certainly far and away the largest study of its kind that's ever been done, and it's multinational," she said in an interview.

"Just doing a study like this with thousands and thousands of patients is a step in the right direction. That's probably what's very unique about it, to bring all of these clinical cohorts as it were together and to look at what is the relationship of the age of onset."

She also said the study is unique in how it delineates the groups by age of onset.

"In addition to this concept that there's a difference in asthma by the age that you got diagnosed with it, I think it's also important to just remember that when any physician, be they a specialist or nonspecialist, sees a patient with asthma, they should ask them when did their symptoms develop," she said.

"These are really simple questions that don't take any sophisticated training and don't take any sophisticated instruments to measure, but they can be really helpful."

GlaxoSmithKline supplied a grant for the study. Dr. Brusselle disclosed relationships with AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi, and Teva. A study coauthor is an employee of GSK. Dr. Wenzel reported no disclosures. ■

*"In childhood onset, you need to watch for different allergies – atopic dermatitis and allergic rhinitis – but in late-onset asthma, look for obesity, diabetes and reflux disease, and nasal polyposis."*

## Mepolizumab curbed corticosteroid use for severe asthma

BY HEIDI SPLETE

MDedge News

Use of mepolizumab significantly reduced the need for maintenance oral corticosteroids in adults with severe asthma, based on data from more than 800 individuals.

Many patients with severe asthma require bursts of systemic corticosteroids (SCS) or maintenance oral corticosteroids (mOCS) for disease control, but these strategies are associated with side effects that can increase the disease burden, wrote Charles Pilette, MD, of Cliniques Universitaires Saint-Luc, Brussels, and colleagues.

Previous studies have shown that the humanized, monoclonal anti-interleukin (IL)-5 antibody mepolizumab, which is approved for the treatment of severe asthma, reduced use of SCS and has shown effectiveness in less homogeneous populations, but robust, real-world data on the occurrence and magnitude of these effects are lacking, the researchers said.

In a study known as REALITI-A (J Allergy

Clin Immunol Pract. 2022 Jun 23. doi: /10.1016/j.jaip.2022.05.042), the researchers enrolled 822 adults with asthma diagnoses from 82 centers in Europe, Canada, and the United States who initiated mepolizumab at a subcutaneous dose of 100 mg.

*At 1 year, the median mOCS dose in the study population was reduced by 75%, and 64% reduced their mOCS dose by at least 50% from baseline.*

The study endpoints included daily use of oral corticosteroids at baseline and 1 year, percentage reduction in oral corticosteroid use from baseline, patients discontinuing oral corticosteroids; the primary outcome was the rate of clinically significant exacerbations (CSEs). CSEs were defined as the need for OCS for at least 3 days/parenteral administration, and/or an emergency

department or hospital admission before and after treatment.

The mean age of the trial participants was 54 years, 63% were women, and 60% were never-smokers.

The mean asthma duration was 19.7 years. Overall, a total of 319 patients (39%), used mOCS at baseline, and dose information was available for 298.

### Real-world outcomes

At 1 year, the median mOCS dose in the study population was reduced by 75%, and 64% reduced their mOCS dose by at least 50% from baseline.

In addition, the proportion of patients who discontinued daily mOCS increased from 29% during week 25-28 to 43% during week 53-56.

Overall, 80% of patients remained on mepolizumab at 1 year. Lack of efficacy and patient decision were the top two reasons for discontinuation (6% and 4%, respectively).

The primary outcome of rate of CSE decreased by

ASTHMA continued on following page

# Asthma deteriorations? Check for bronchiectasis

BY WALTER ALEXANDER

MDedge News

When asthma patients are having frequent clinical deteriorations, clinicians need to evaluate them for the presence and severity of bronchiectasis, according to the authors of a retrospective study in the *Journal of Allergy and Clinical Immunology: In Practice* (2022 Jun 8. doi: 10.1016/j.jaip.2022.05.026). While bronchiectasis is known to worsen the clinical and functional outcomes in patients with asthma, data regarding the long-term effects of bronchiectasis on the clinical course of asthma have been limited, stated corresponding author Jung-Kyu Lee, MD, division of pulmonary and critical care medicine, Seoul (Republic of Korea) National University.

Moderate to severe acute clinical deterioration risks were increased among the 251 patients (mean age 66.6 years, 77.2% men) with bronchiectasis out of 667 asthma patients included in the study. All studied patients underwent chest computed tomography and pulmonary function tests from 2013 to 2019 at two tertiary hospitals in Seoul. The primary outcome, annual incidence of moderate to severe acute exacerbations requiring additional treatment (systemic steroids, antibiotics, or both), was significantly higher in patients with bronchiectasis after a mean follow-up period of 3.96 years. Compared with patients who did not exhibit bronchiectasis, the annual rates of severe exacerbations ( $0.15 \pm 0.43$  vs.  $0.08 \pm 0.27$ ;  $P = .010$ ), moderate to severe ( $0.47 \pm 0.79$  vs.  $0.34 \pm 0.63$ ;  $P = .018$ ), and acute exacerbations during the follow-up period (49.8% vs. 39.4%;  $P = .009$ ) were all significantly higher. There was no difference in the proportion of frequent exacerbators between the two groups, however. Severe acute exacerbations leading to hospitalizations, also, were more frequent in the group with bronchiectasis.

## Risk factors explored

Significant factors conferring greater risk of severe and moderate to severe acute exacerbations in multivariable analysis included low body mass index, low baseline forced expiratory volume in 1 second (FEV<sub>1</sub>), high use of inhaled corticosteroids, high medication possession, and high neutrophil/lymphocyte ratios. The existence of bronchiectasis remained an independent risk factor for severe and moderate to severe acute exacerbations despite adjustment for all other factors. While bronchiectasis score showed no association with annual rate of acute exacerbation, progression of bronchiectasis confirmed on follow-up CT was associated with increased risks of severe and moderate to severe acute exacerbation.

Included patients had a diagnosis of asthma confirmed by variable expiratory airflow limitation with pulmonary function tests. Past histories of tuberculosis and nontuberculous mycobacterial lung disease, lower absolute and predicted values of both baseline FEV<sub>1</sub> and forced vital capacity were more common among patients with bronchiectasis.

Dividing the study population into a group that had at least one moderate to severe acute exacerbation during the follow-up period and a group that did not, the researchers identified characteristics shared by exacerbators: a greater proportion were women, they had lower forced vital capacity and lung-diffusing capacity for carbon monoxide, higher blood FVC and blood neutrophil/lymphocyte ratio, and more medication use (inhaled corticosteroids, long-acting antimuscarinic agent, leukotriene-receptor antagonist, and methylxanthine), compared with the

nonexacerbators. More bronchiectasis, more severe bronchiectasis (higher score), and more bronchiectasis progression were common among the exacerbators.

Higher acute exacerbation risks accompanied bronchiectasis, at 1.47-fold for moderate, 1.72-fold for severe, and 1.50-fold for moderate to severe exacerbations. Higher risk for severe and moderate to severe exacerbations was conferred by bronchiectasis progression, also.

The researchers pointed to contradictory effects of inhaled corticosteroid use, noting both corticosteroids' essential role in controlling airway inflammation and hyperresponsiveness, exacerbations, and lung-function decline in asthma patients and that longer or greater inhaled corticosteroid use is associated with

both clinical deterioration in asthma and bronchiectasis, and exacerbation history. For bronchiectasis, however, inhaled corticosteroid use offers no benefit while increasing susceptibility to infection and its risks through partial immunosuppression.

"Considering these contradictory effects of inhaled corticosteroid use, further research is needed regarding its risks and benefits in asthma patients with bronchiectasis, including differences in the benefit of inhaled corticosteroid use according to patient phenotype," Dr. Kim and his colleagues concluded.

## The role of corticosteroids

"One of the more important points discussed in this observational cohort study is the role of inhaled corticosteroid use in bronchiectasis," said Mary Jo Farmer, MD, PhD, director of pulmonary hypertension services, Baystate

Health, and assistant professor of medicine, University of Massachusetts – Baystate, both in Springfield, in an interview with this news organization. She cited a review finding no significant benefit versus placebo in spirometry, exacerbation rate, or sputum volume in the Cochrane Database of Systematic Reviews (2018 May 16. doi: 10.1002/14651858.CD000996.pub3/full) and another suggesting that quality of life was improved with inhaled corticosteroid use in individuals with blood eosinophils greater than 3%, compared with those not using inhaled corticosteroids or having lower eosinophil counts in the *European Respiratory Journal* (2020 May 12. doi: 10.1183/13993003.00453-2020). She cited also higher percentages (48% versus 23%) of adrenal insufficiency in bronchiectasis patients among those taking inhaled corticosteroids versus those not taking them (*Eur Respir J*. 2008. doi: 10.1183/09031936.00016908).

"According to the 2018 Cochrane review of inhaled corticosteroid treatment for non-cystic fibrosis bronchiectasis, results from most randomized, placebo-controlled trials have been disappointing in terms of effects on most endpoints such as pulmonary function and exacerbation frequency. As such, the European Respiratory Society guidelines for the management of adult bronchiectasis advise against prescribing inhaled corticosteroids to patients with bronchiectasis, unless otherwise indicated by either an asthma or chronic obstructive pulmonary disease diagnosis. Also, inhaled corticosteroid treatment in asthma and COPD is associated with common side effects such as oral candidiasis, dysphonia and, in some cases, systemic corticosteroid effects. The rate of adverse events from inhaled corticosteroid treatment of bronchiectasis, however, is largely unknown."

Dr. Lee and Dr. Farmer reported no relevant financial relationships. ■

*"Considering these contradictory effects of inhaled corticosteroid use, further research is needed regarding its risks and benefits in asthma patients with bronchiectasis."*

ASTHMA continued from previous page

a clinically significant rate ratio of 0.29 ( $P < .001$ ).

"The requirement for SCS bursts was also reduced, as observed by a decreased rate of CSEs," the researchers wrote in their discussion. The results were consistent for patients receiving lower (less than 10 mg/day) or higher (10 mg/day or more) mOCS doses at baseline, they said. No unexpected safety signals were noted during the study period.

"Furthermore, mepolizumab was associated with significant decreases in the rate of exacerbations requiring hospitalizations, or those requiring hospitalization or an ER visit, improved symptom control, and lower work productivity and activity impairment," they added.

The study findings were limited by several factors including the observational design, lack of mepolizumab comparator, and open-label data capture, the researchers noted. However,

the results were consistent with similar studies, and support the use of mepolizumab as part of the standard of care for clinically effective disease control in severe asthma patients, they concluded.

The study was funded by GlaxoSmithKline. Lead author Dr. Pilette disclosed fees for advisory boards, speaker meetings, and 42 research grants from GSK, AstraZeneca, Chiesi, Novartis, Teva, and ALK-Abello. ■

# Fatigue and sleep disturbances persist long after COVID-19

BY RICHARD MARK KIRKNER  
MDedge News

CHARLOTTE, N.C. – High percentages of patients have reported fatigue and consequential sleep disturbances long after they've had COVID-19, with Black patients and people hospitalized for COVID-19



*"It's alarming that the prevalence of both sleep disturbances and fatigue is so high."*

Dr. Pena Orbea

being the most vulnerable to lingering effects, a retrospective analysis of almost 1,000 Cleveland Clinic patients has found.

More than two-thirds of patients (67.2%) reported moderate fatigue

or worse, while more than one in five (21.8%) had severe fatigue, according to results Cinthya Pena Orbea, MD, reported at the annual meeting of Associated Professional Sleep Societies. The findings also showed that 41.5% of patients reported moderate sleep disturbances or worse, and 8% reported severe sleep disturbances.

"It's alarming that the prevalence of both sleep disturbances and fatigue is so high because we know how important these can be to patients' quality of life," Dr. Pena Orbea, a pulmonologist at the Sleep Disorders Center, Cleveland Clinic main campus, said in an interview. "Right now it's important to try and understand what are the intersections between fatigue and sleep disturbances among specific patient populations."

The study analyzed data on 962 post-COVID 19 patients who visited the Cleveland Clinic ReCOVER Clinic from February 2021 to



DIGITAL VISION/THINKSTOCK

April 2022. They completed the Patient-Reported Outcomes Measurement (PROMIS) Sleep Disturbance and PROMIS Fatigue questionnaires. The study used the label postacute sequelae of COVID-19, or PACS, to describe the post-COVID patient cohort.

"In patient-reported outcomes by sleep disturbance severity, compared with normal to mild sleep disturbance, people with moderate to severe sleep disturbance were more likely to suffer from fatigue and mood disorders," Dr. Pena Orbea said during her lecture.



*"I think we're going to be seeing the impacts of this for a very long time."*

Dr. Khosla

In the preliminary analysis, Black patients were more than three times as likely to have moderate to severe sleep disturbances, with an odds ratio of 3.42 (95% confidence interval, 1.64-7.13).

These findings indicate that clinicians should include long-term COVID-19 aftereffects in their differential diagnosis of patients with fatigue, Dr. Pena Orbea said. "What it tells us is that, whenever we see a patient in clinic, we know what the associated factors are with moderate to severe sleep disturbances," she said.

The next step for this research is "we need to truly understand the underlying mechanism of why African Americans and minority groups are suffering from more sleep disturbances in order to create targeted race-specific interventions," she said.

Pulmonologist Seema Khosla, MD, medical director at the North Dakota Center for Sleep in Fargo, concurs that any evaluation of fatigue should include a patient's COVID-19 history.

"As we try to determine if these patients have long-COVID syndrome, we need to eliminate anything that's reversible" regarding sleep problems, she said. "What I'm hoping we can do is just see if there's something there that we can fix. Maybe there's a little bit of sleep apnea. We're seeing more sleep apnea in people who do not have the classic risk factors – women, nonobesity. I think it's important even opening up the dialogue with our patients."

She added, "In the spirit of trying to give our patients the best shot at success, I think we really do need to take a step back and maybe not be so quick to dismiss anything."

Such an approach may be around a long time, Dr. Khosla said. "Even though we're tired of COVID-19 – we've seen it forever and we want it to be done – I think we're going to be seeing the impacts of this for a very long time," she said. "How do we know unless we start looking?"

Dr. Pena Orbea and Dr. Khosla have no disclosures. ■





**Join CHEST for online live sessions in August**

<b>PEDIATRIC PULMONARY MEDICINE</b> AUGUST 12-15	<b>CRITICAL CARE MEDICINE</b> AUGUST 12-15	<b>PULMONARY MEDICINE</b> AUGUST 17-20
---	---	---

Prep for your board certification exam with the experts in chest medicine board review. Leading chest medicine experts show you how to solve case-based problems during live sessions and give in-depth answers to your questions.

**12 months of unlimited access** to course materials with online live sessions in August

Course content follows the **ABIM certification exam blueprint**  
**Earn CME/MOC** for completing the course

**More than 89% of attendees** would recommend CHEST Board Review courses to colleagues

Register at [boardreview.chestnet.org](https://boardreview.chestnet.org)



# Most COVID long-haulers suffer long-term debilitating neurologic symptoms

BY MEGAN BROOKS

**M**ost COVID-19 long-haulers continue to have brain fog, fatigue, and compromised quality of life more than a year after the initial infection, results from the most extensive follow-up to date of a group of long COVID patients show.

Most patients continue to experience debilitating neurologic symptoms an average of 15 months from symptom onset, Igor Koralnik, MD, who oversees the Neuro COVID-19 Clinic at Northwestern Medicine in Chicago, said during a press briefing.

Surprisingly, in some cases, new symptoms appear that didn't exist before, including variation of heart rate and blood pressure, and gastrointestinal symptoms, indicating there may be a late appearance in dysfunction of the autonomic nervous system in those patients, Dr. Koralnik said.

The study was published online in *Annals of Clinical and Translational Neurology* (2022 May 24. doi: 10.1002/acn3.51570).

## Evolving symptoms

The investigators evaluated the evolution of neurologic symptoms in 52 adults who had mild COVID-19 symptoms and were not admitted to the hospital.

Their mean age was 43 years, 73% were women and 77% had received a COVID-19 vaccine. These patients have now been followed for between 11 and 18 months since their initial infection.

Overall, between the first and follow-up evaluations, there was no significant change in the frequency of most neurologic symptoms seen.

These symptoms including brain fog (81% vs. 71%), numbness/tingling (69% vs. 65%), headache (67% vs. 54%), dizziness (50% vs. 54%), blurred vision (34% vs. 44%), tinnitus (33% vs. 42%), and fatigue (87% vs. 81%).

The only neurologic symptoms that decreased over time were loss of taste (63% vs. 27%) and smell (58% vs. 21%).

Conversely, heart rate and blood pressure variation (35% vs. 56%) and gastrointestinal symptoms (27% vs. 48%;  $P = .04$ ) increased at follow-up evaluations.

Patients reported subjective improvements in their recovery, cognitive function and fatigue, but quality of life measures remained lower than the average population of the United States.

There was a neutral effect of COVID vaccination on long COVID symptoms – it didn't cure long COVID or make long COVID worse, which is a reason given by some long-haulers for not getting vaccinated, Dr. Koralnik told the briefing.

Therefore, “we continue to encourage our patients to get vaccinated and boosted according to the Centers for Disease Control and Prevention recommendation,” he said.

## Escape from the ‘pit of despair’

To date, the Northwestern Medicine Neuro COVID-19 Clinic has treated nearly 1,400 COVID long-haulers coming from across the United States.

Emily Caffee, a physical therapist from Wheaton, Ill., is one of them.

Speaking at the briefing, the 36-year-old described her saga and roller coaster of recovering from



*Most patients continue to experience debilitating neurologic symptoms an average of 15 months from symptom onset.*

long COVID in three acts: her initial infection, followed by a descent into a pit of physical and emotional despair, followed by her eventual escape from that pit more than 2 years later.

Following a fairly mild case of COVID, Ms. Caffee said worsening neurologic symptoms forced her to take medical leave from her very physical and cognitively demanding job.

Ms. Caffee said she experienced crushing fatigue and brain fog, as well as rapid heart rate and blood pressure changes going from sitting to standing position.

She went from being a competitive athlete to someone who could barely get off the couch or empty the dishwasher.

With the ongoing help of her medical team, she slowly returned to daily activities and eventually to work on a limited basis.

Today, Ms. Caffee says she's 90%-95% better but still she has some lingering symptoms and does not yet feel like her pre-COVID self.

It's been a very slow climb out of the pit, Ms. Caffee said.

This study has no specific funding. The authors disclosed no relevant conflicts of interest. ■

# Cancer drug reduced death risk in patients with COVID-19

BY JAY CROFT

**A**n experimental cancer drug could be promising for some people hospitalized with COVID-19, a new study shows.

The medication, called sabizabulin and given as a pill, reduced by half the risk of death among participants. It could be more effective than other drugs for those severely sick with COVID-19, *The New York Times* reports.

The manufacturer, Veru, is seeking emergency use authorization from the Food and Drug Administration. Hospitalized patients with

COVID-19 currently have only a few pharmaceutical options.

Sabizabulin blocks cells from building molecular cables that carry material from one part of a cell to another. It was created to fight cancer, because tumor cells need those cables (called microtubules) to grow quickly.

Researchers tried it against COVID-19 2 years ago, because viral replication also requires microtubules to bring pieces of new viruses together.

To participate in the small trial, patients had to be receiving oxygen or on a ventilator and at a high risk of dying from COVID-19, “with

risk factors such as hypertension, advanced age or obesity,” the *Times* reported.

A total of 134 patients received the medicine; 70 got a placebo. Among those receiving sabizabulin, 20.2% died within 2 months; 45.1% of those who took the placebo died.

One infectious disease expert told the *Times* that the high mortality rate of those on the placebo could mean the study was too small to offer conclusive results.

“The 45% mortality rate in the control group jumps out at me as rather high,” said David Boulware, MD, of the University of Minnesota. ■

## CRITICAL CARE COMMENTARY

## Addressing racial bias in pulse oximetry

BY EMILY A. HARLAN, MD, MA; DANIEL COLON HIDALGO, MD; AND THOMAS S. VALLEY, MD, MSC

**P**ulse oximetry is a vital monitoring tool in the ICU) and in pulmonary medicine. Regrettably, re-emerging data show that pulse oximeters do not accurately measure blood oxygen levels in Black patients, presumably due to their skin tone. Patients with darker skin are, therefore, more likely to experience occult hypoxemia (i.e., low arterial oxygen saturation despite a seemingly normal pulse oximetry reading). While inaccuracy of pulse oximeter measurements in patients with darker skin has been recognized for decades, recent studies have highlighted this as an ongoing problem with potentially severe consequences for Black patients and other patients of color.



Dr. Harlan

One recent study found that Black patients had almost three times the likelihood of occult hypoxemia compared with White patients (Sjoding, MW, et al. *N Engl J Med.* 2020;383[25]:2477-8).

Subsequent studies have confirmed this to be a widespread problem across various clinical settings in hundreds of hospitals (Wong AI, et al. *JAMA Netw Open.* 2021;4[11]:e2131674; Valbuena VS, et al. *Chest.* 2022;161[4]:971-8). A recent retrospective cohort study of patients with COVID-19 found that occult hypoxemia in Black and Hispanic patients was associated with delayed eligibility for potentially lifesaving COVID-19 therapies (Fawzy AF, et al. *JAMA Intern Med.* 2022; published online May 31, 2022).

Now that numerous studies have demonstrated the inaccuracy of pulse oximetry with the potential to cause harm to historically marginalized racial and ethnic groups, must we abandon the use of pulse oximetry? We would argue that pulse oximeters remain valuable tools, but for now, we must adapt our practice until better devices are widely adopted.

First, it is crucial that health

professionals are aware that pulse oximeters may underestimate the true extent of hypoxemia for all patients, but particularly for patients with darker skin. Acknowledging this device flaw is essential to avoid harm to our patients.

Second, clinicians must have heightened skepticism for seemingly normal pulse oximetry values when caring for symptomatic patients at risk of occult hypoxemia.

Until better pulse oximeters are widely available, clinicians must consider workarounds aimed at ensuring timely identification of hypoxemia in Black patients and other patients of color.

These patients may need invasive monitoring of arterial oxygenation, including arterial blood gas checks or an arterial catheter. However, invasive monitoring comes at the cost of discomfort to patients and potential complications, such as vessel or nerve damage.

Invasive monitoring of patients at risk for occult hypoxemia is not an equitable or acceptable long-term solution for this problem. As advocates for patients, clinicians and professional organizations should lobby regulatory bodies to ensure pulse oximeters are accurate for all patients.

We must also call on government leaders to move this process forward. For example, in response to efforts by the United Kingdom's Intensive Care Society, the Health Secretary of the UK, Sajid Javid, has called for a review of pulse oximeters as part of a larger review assessing structural issues in health care that lead to worse outcomes in racial and ethnic minorities (BBC News. <https://www.bbc.com/news/uk-59363544>. Published online Nov. 21, 2021).

Device companies are largely for-profit corporations with obligations to their shareholders. It seems that existing incentives are insufficient to motivate investment in less biased technology and real-world evaluations of their devices.

We previously called for buyers of pulse oximeters to change the incentives of device companies – that is, for “hospitals to commit to only

purchasing pulse oximeters that have been shown to work equally well in patients of colour.” (Hidalgo DC, et al. *Lancet Respir Med.* 2021;9[4]:E37).

And, indeed, we worry that hospitals are putting themselves at medicolegal risk by not raising their purchasing standards. Since it is now widely known that pulse oximeters are inaccurate in certain patients, could there be liability for hospitals that continue to use devices we know to be disproportionately inaccurate by race?

Device companies must commit to fixing racial bias in pulse oximeters. Change is feasible, and pulse oximeters can be redesigned to be accurate and reliable among all patients using existing technology that is decades-old.

In the 1960s and 1970s, Hewlett Packard worked with NASA to non-invasively measure oxygen saturation in astronauts (Moran-Thomas, M. *Wired.* Published online June 4, 2021. <https://www.wired.com/story/>

*Pulse oximeters may underestimate the true extent of hypoxemia for all patients, but particularly for patients with darker skin. Acknowledging this device flaw is essential to avoid harm to our patients.*

pulse-oximeters-equity). The device was designed to work for all skin tones and could be calibrated based on an individual's skin tone. However, Hewlett Packard moved away from medical devices in the 1980s, shelving their design while other companies took over the oximeter market.

Lastly, as new devices are designed, they must be proven to work for all patients. Testing should be conducted in real-world clinical settings using metrics aligned with clinical care, since we know testing in artificial environments may not

generalize to critically ill patients. Testing standards historically used by the FDA, such as only requiring device testing in a small number of non-White individuals, may miss clinically relevant hypoxemia. Non-inferiority studies are particularly susceptible to poor design or under-powering, and rigorous standards are needed from unbiased sources.

While potential solutions are currently being evaluated, the fact remains that the inaccuracy of pulse oximeters has been known for decades without any meaningful action taken to correct the problem.

As Valeria Valbuena, author of a study demonstrating inaccuracy of pulse oximetry in patients about to undergo ECMO, points out, “Using White patients as the standard in biomedical design has led to both differential care and innovation inertia for optimizing the way devices and algorithms work for patients of racial and ethnic minoritized groups” (Valbuena VS. *JAMA Intern Med.* 2022. doi: 10.1001/jamainternmed.2022.1903).

We know that hypoxemia is dangerous for our patients and that this is only one example of the long-standing systemic racism leading to harm in historically marginalized racial and ethnic groups. It is unacceptable that the devices we rely on to care for our patients are disproportionately inaccurate in non-White patients.

We hope that with increased awareness of this problem, meaningful action will be taken by device companies to ensure pulse oximeters work accurately for all patients. ■

*From the Division of Pulmonary and Critical Care, Department of Medicine and the Center for Bioethics and Social Sciences in Medicine, University of Michigan Medical School (Drs. Harlan and Valley), and the Institute for Healthcare Policy and Innovation (Dr. Valley), University of Michigan, Ann Arbor, MI; and the Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine, Aurora, CO (Dr. Colon Hidalgo).*



Dr. Valley

# A look into the CHEST 2022 Annual Meeting

*Hand-picked, can't-miss sessions from Scientific Program Committee Chairs*

BY CHEST 2022 CHAIR  
SUBANI CHANDRA, MD, FCCP,  
AND CHEST 2023 CHAIR  
ANEESA DAS, MD, FCCP

There will be more than 200 educational sessions at the upcoming CHEST 2022 Annual Meeting, covering all aspects of pulmonary medicine, including: obstructive lung disease, sleep, chest infections, pulmonary vascular disease, pulmonary procedures, interstitial lung disease, practice operations, critical care, and more.

As a sneak peek into the meeting's extensive slate of educational opportunities, Scientific Program Committee Chair for CHEST 2022, Subani Chandra, MD, FCCP, and CHEST 2023 Chair, Aneesa Das, MD, FCCP, share their can't-miss sessions for CHEST 2022.

## Dr. Chandra's picks:

### Sessions on health care disparities:

- Lung Health Disparities in America: Lessons From Five Cities About Trust and Empathetic Medicine (from the work of the CHEST Foundation)
- Racial and Gender Bias in Health Care System (both as a physician and as a patient)
- The Use of Race in Pulmonary Function Testing
- Health Care Disparities in PAH
- Disparities in the Management of Lung Cancer
- Addressing Disparities in Sleep Health

### Updates on topics spanning the breadth of pulmonary, critical care, and sleep medicine:

- Updates in COVID-19 Therapeutics
- The Future of Sepsis Care
- Updates in Lung Cancer Screening: Disparities, New Guidelines, and Implementation
- Emerging Evidence in Asthma and Obstructive Sleep Apnea Overlap

### Interactive sessions:

- Pardon the Interruption sessions
- CHEST Challenge



- Rapid Fire Ultrasound

### Dr. Das's picks:

#### Pardon the Interruption 2022:

- Controversies in Sleep Medicine
- Controversies in Asthma
- Controversies in Pulmonary Vascular Disease
- Controversies in Critical Care

#### Obstructive Sleep Apnea:

- Sex-Distinct Topics and Treatments

#### When CPAP Is in Short Supply:

- Treatment Alternatives to PAP

With sessions in a variety of curriculum groups, there is something for everyone at CHEST 2022.

Scan the QR code on this page to visit the CHEST 2022 app, and see all of the sessions and special events happening at the meeting.



## Register today for CHEST 2022

CHEST 2022 is back in person, October 16-19. Join your friends and colleagues for the one-of-a-kind experience that is CHEST 2022.

### What can you expect from CHEST 2022?

- More than 300 educational sessions, including simulation and interactive learning opportunities, addressing the challenges you face in clinical practice
- Original investigation presentations with new, unpublished science
- Networking and social opportunities with experts in your field and from around the world
- New diagnostic and treatment solutions showcased in the CHEST Exhibit Hall
- CME/CE credits and MOC points for hundreds of sessions

Register | [chestmeeting.chestnet.org](https://chestmeeting.chestnet.org)

 CHEST®



## NETWORKS

# Severe asthma, supply challenges, diagnosing IPF, and more ....

## AIRWAYS DISORDERS NETWORK

### Asthma and COPD Section

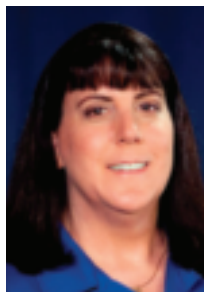
#### Go TEAM! Shared decision-making tool for patient-clinician collaboration in severe asthma

Optimal asthma management requires a patient-clinician collaboration to overcome barriers. Shared decision-making is associated with improved medication adherence in adults (Wilson, et al. *Am J Respir Crit Care Med.* 2010;181[6]:566-77) and quality of life and asthma control in children (Taylor, et al. *J Asthma.* 2018;55[6]:675-83). The Global Initiative for Asthma committee recommends a patient-clinician partnership. Activated and engaged patients play a major role in their asthma management (<https://ginasthma.org/gina-reports>). Shared decision-making discussions should include potential benefits and harms of the therapeutic options, patient's values and lifestyle preferences, and addressing concerns.

The CHEST Foundation, the Allergy and Asthma Network, and



Dr. Abbas



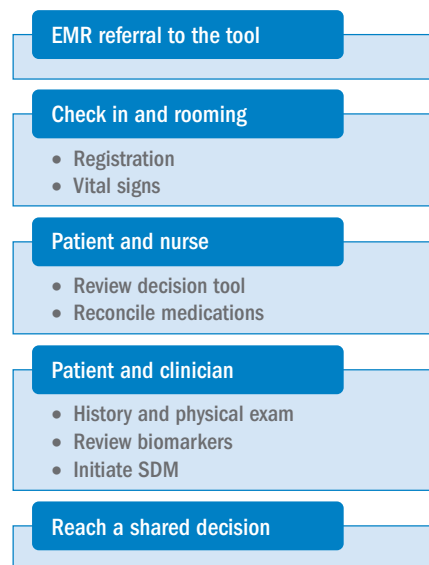
Dr. Adams

the American College of Allergy, Asthma, and Immunology developed an online shared decision-making tool for severe asthma (<https://asthma.chestnet.org/sdm-tool>).

This tool utilizes patient's values, specifics about triggers, asthma control, medication side effects, and lifestyle preferences to identify personalized management options. The tool provides information about recommended therapeutic options in simple terms, including potential benefits, possible side effects, expected treatment frequency and duration, and financial aid information. The treatment options currently explained in this tool include anti-immunoglobulin E, anti-interleukin-5, anti-interleukin-4/13, bronchial thermoplasty, long-acting

FIGURE 1

### Implementing Shared Decision-Making Tool



muscarinic antagonist, macrolides, oral corticosteroids, and standard of care.

As a team, the patient and the health care professional can use this tool during office visits to help guide management. Figure 1 shows a suggested workflow to utilize the tool in clinical practice.

Potential barriers include excess time and increased human resources. Barrier mitigation may include reviewing the tool and reconciling the medications before the clinician enters the room. With these interventions, many clinician encounters may be completed in 10 to 15 minutes.

*Farrukh Abbas, MBBS*

*Fellow-in-Training*

*Sandra G. Adams, MD, MS, FCCP*

*Member-at-Large*

## SLEEP MEDICINE NETWORK

### Home-based Mechanical Ventilation and Neuromuscular Disease Section

#### Navigating the latest device supply chain challenge: Mechanical airway clearance

Airway clearance is integral for patients with respiratory muscle weakness and is divided into cough augmentation (proximal airways) and sputum mobilizing techniques (distal airways). Cough augmentation techniques provide lung volume recruitment on the insufflation phase, in addition to

mobilization of secretions with augmentation of the peak expiratory flow rate to >160 L/min on the exhalation phase.

A mechanical insufflation-ex-sufflation (MI-E) device (T70 Cough Assist - Phillips) is now on indefinite backorder. This creates a dangerous situation for our patients requiring cough augmentation for survival. Alternative options that provide both MI-E and high frequency oscillation include two systems (Synclara Cough System - Hill-rom and the Biwaze Cough System-ABM Respiratory Care).

The Synclara can only be obtained in a direct-to-patient model, contracting with individual respiratory therapists, outside of the standard durable medical equipment model. The final MI-E model option is the VOCSYN multifunctional ventilator (ventilator, cough assist, nebulizer, oxygen concentrator, suction). This multifunction ventilator has had variable acceptance with HCPCS code E0467. If the VOCSYN is chosen, the patient cannot have been issued any component devices or have reached the 36-month cap for oxygen equipment (CR 10854 special payment rule, 42 CFR414.222).

As the supply of devices is exhausted, we will need to shift to evidence-based manual options. Manual cough augmentation can be done effectively with a bag-valve mask, using breath stacking to achieve maximal lung insufflation, optimizing the length tension relationship of elastic recoil on exhalation to increase peak cough flow (PCF).

This can be done alone but is more effective when combined with manually assisted cough (Bach JR. *Chest.* 1993;104[5]:1553-62). These interventions require training of the caregivers, using resources such as those found at [www.canventot-tawa.ca](http://www.canventot-tawa.ca).

With continued supply chain instability, manual airway clearance techniques should be considered in patients with less advanced cough impairment (PCF 160-270 L/min), to save the remaining devices for those with PCF of <160 L/min.

*Jeanette Brown, MD, PhD*

*Karin Provost, DO, PhD*

*Members-at-Large*

## DIFFUSE LUNG DISEASE & LUNG TRANSPLANT NETWORK

### Interstitial Lung Disease Section

#### Diagnosis of idiopathic pulmonary fibrosis: Is tissue still an issue?

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing disorder of unclear etiology. Per ATS/ERS/JRS/ALAT guidelines, diagnosis of IPF requires exclusion of known causes of interstitial lung disease (ILD)



Dr. Dsouza

and either the presence of a usual interstitial pneumonia (UIP) or probable UIP pattern on HRCT scan or specific combinations of HRCT scan and histopathologic patterns.

Surgical lung biopsy (SLB) is the gold standard for histopathologic diagnosis.

The recent update (Raghu, et al. *Am J Respir Crit Care Med.* 2022;205[9]:1084-92) made a conditional recommendation for transbronchial lung cryobiopsy (TBLC) as an acceptable alternative to SLB in patients with undetermined ILD. Systematic analysis revealed a diagnostic yield of 79% (85% when  $\geq 3$  sites were sampled) by TBLC compared with 90% on SLB. With consideration of this diagnostic yield vs the risk of pneumothorax, severe bleeding, and procedural mortality, TBLC is an attractive tool compared with SLB. Overall, the utility of TBLC remains limited to experienced centers due to dependence on proceduralist and pathologist skills for optimal success and more data are awaited.

No recommendation was made for or against the use of genomic classifiers (GC) for the diagnosis of UIP in patients with undetermined ILD undergoing transbronchial biopsy. Although, meta-analysis revealed a specificity of 92%, this may be driven by patient enrichment with a high probability for UIP population. GC has the potential to reduce SLB-associated risks and provide diagnostic information for multidisciplinary discussion in certain scenarios. However, limitations arise from the inability to distinguish specific ILD subtype associated with the

UIP pattern; further improvement in sensitivity and understanding of downstream consequences of false-negative results is necessary.

Kevin Dsouza, MD  
Fellow-in-Training

### THORACIC ONCOLOGY & CHEST PROCEDURES NETWORK Interventional Procedures Section Mind the gap: Improving adherence to lung cancer screening follow-up

The gap in adherence rates between a disciplined clinical trial and the heterogeneous patchwork of U.S. health care is hardly unusual, but as lung cancer remains the number one cancer killer both worldwide and in the United States, one such disparity bears closer scrutiny.

In 2011, the National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality with the implementation of low dose CT scan screening with 95% adherence to CT scan follow-up within 15 months of initial screening imaging (Aberle, et al. *N Engl J Med.* 2011;365[5]:395-409). Unfortunately, estimates of real-world adherence to lung cancer screening (LCS) follow-up fall to 51% even within an extended 18-month window (Hirsch, et al. *Ann Am Thorac Soc.* 2019;16[10]:1329-32).

Recent studies compared adherence to LCS follow-up between centralized and decentralized screening programs. Centralized programs used dedicated program coordinators and a tracking system, while decentralized programs relied on primary care providers. Patients enrolled in a centralized program had a two-fold higher likelihood of adherence when compared with those screened in

a decentralized program (Sakoda, et al. *JAMA Network Open.* 2021;4[4]:e218559). A subsequent study demonstrated adherence of 70% vs 41% among patients in centralized vs decentralized programs, respectively (Smith, et al. *Chest.* 2022;161[3]:818-25).

This gap is even more pronounced in majority-Black populations. Kunitomo and colleagues showed 33% lower odds of adherence to LCS follow-up compared with White patients (Kunitomo, et al. *Chest.* 2022;161[1]:266-75). Another study in a diverse, majority-Black patient population showed only 31% adherence to LCS follow-up at 1 year (Erkmen, et al. *Cancer Causes Control.* 2021;32[3]:291-8).

How could we close this gap? Centralized LCS programs show promise of increasing adherence to LCS follow-up. Heightened awareness of and targeted investment to mitigate racial inequities in LCS is imperative.

Jose De Cardenas MD  
John Howe, MD  
Members-at-Large



Dr. Howe

### THORACIC ONCOLOGY & CHEST PROCEDURES NETWORK Ultrasound and Chest Imaging Section

#### Advanced critical care echocardiography: A noninvasive tool for hemodynamic assessment in critically ill patients

Hemodynamic assessments in critically ill patients are important to guide accurate management; however, traditional invasive methods of

measuring cardiac output have significant limitations, including risks of infection and bleeding. Advanced critical care echocardiography (ACCE) is a feasible alternative, which can be used to provide accurate hemodynamic assessment at the point of care. ACCE can provide a multitude of hemodynamic measurements from cardiac output (CO) to right ventricular systolic pressure (RVSP) and left atrial pressure (LAP). Combinations of left ventricular function parameters, along with estimation of filling pressures, can help distinguish between types of shock. Schmidt and colleagues (*Sci Rep.* 2022;12[1]:7187) demonstrated that measurement of these indices in the majority of patients helped elucidate the cause for hemodynamic compromise. They found presence of a cardiac index (CI) < 2.5/min. m<sup>2</sup> was associated with a doubling of ICU mortality as compared with predictions based on severity of illness scores in otherwise hemodynamically stable patients. Hollenberg and colleagues (*Am J Cardiol.* 2021;153:135-39) demonstrated the feasibility of a simpler stratification using the left ventricular ejection fraction (LVEF) and CI in coronavirus disease 2019 patients with

shock, where low CI despite having a preserved LVEF was associated with worse outcomes.

Quick, reliable data are an intensivist's friend. Utilizing ACCE at the bedside adds another tool in our arsenal to provide real-time hemodynamic data that can be



Dr. Sodhi

used to manage patients in the ICU. ACCE also allows repeated measurements to determine changes based on therapeutic interventions initiated.

In recognition of the importance of ACCE as a tool for intensivists, the National Board of Echocardiography (NBE) now offers a pathway toward board certification with the Examination of Special Competence in Critical Care Echocardiography (CCEeXAM). CHEST continues to offer cutting-edge courses in ACCE, as well as a board review course for learners interested in sitting for the CCEeXAM.

Amik Sodhi, MD, FCCP  
Gul Zaidi, MD, FCCP  
Members-at-Large

## Impact factor breaks CHEST® journal's record

The journal CHEST® recently was awarded an impact factor of 10.262, the highest in its history, nearly a 10% increase over last year's metric. CHEST is ranked 6th out of 33 journals in the Critical Care category and 6th out of 63 journals in the Respiratory System category.

This new impact factor reflects the hard work of CHEST's editorial team during the heart of the COVID-19 pandemic and positions CHEST as the premier source of

clinically impactful content for pulmonary, critical care, and sleep clinicians. This year's impact factor is particularly encouraging as the American College of Chest Physicians and its flagship journal CHEST prepare to launch two new open access journals – CHEST Pulmonary and CHEST Critical Care – in early 2023.

Congratulations to all who contributed to this outstanding achievement. ■



### Challenge Yourself With CHEST SEEK™ Education

Offering a comprehensive collection of case-based questions in the pulmonary, critical care, and sleep medicine fields:

- Prepare for your ABIM exams.
- Learn more with detailed rationales written by top experts in the field.
- Earn all the CME credit and MOC points you need.
- Stay up-to-date throughout your career.
- Achieve bite-sized learning at your fingertips.

Test and improve your clinical skills in recall, interpretation, and problem-solving.

PRINT [chestnet.org/store](https://chestnet.org/store)  
DIGITAL [seeklibrary.chestnet.org](https://seeklibrary.chestnet.org)

CHEST®

## PULMONARY PERSPECTIVES®

# Robotic bronchoscopy 2022

BY JOSEPH CICENIA, MD,  
FCCP

Over the last several years, hundreds of millions of dollars have been spent on robotic bronchoscopy systems in the United States. The release of robotic scopes was made to great fanfare, translating into the market being infiltrated with these systems. With base costs in the hundreds of thousands of dollars, robotic bronchoscope systems are easily the most expensive singular capital investment in the bronchoscopy suite. I frequently get asked questions from those who have not yet made that purchase: “Should I buy a robot?” “How could I justify a new robot purchase to my hospital?” “Is the hype real?” These are complex questions to answer. Before one can answer, I think it’s best to look back on the last 2 decades of bronchoscopy for peripheral lung nodules to get a better understanding of the value proposition robotic bronchoscopes may offer.

Guided bronchoscopy for lung nodules has significantly evolved over the past 2 decades, shifting diagnostic procedures from interventional radiologist to the pulmonologist. Some of these advances were based in redesigns of the bronchoscope (ultrathin bronchoscopy) or application of technology to the bronchoscope (radial EBUS, virtual bronchoscopy); but, these were not broadly applicable to the pulmonology community at large. It was not until the development of electromagnetic navigational bronchoscopy (ENB) that widespread adoption of bronchoscopy for lung nodules occurred. By and large, ENB fueled a rapid expansion of nodule bronchoscopy, mainly due to its ease of use and novel approach. Initial studies of ENB had impressive results; however, studies were criticized for having small numbers, inadequate follow-up, spurious definitions of yield, and that they were being done at highly specialized centers. The NAVIGATE trial was launched to address these criticisms among

“real world” conditions. Sponsored by Medtronic, it studied ENB (superDimension platform, v6.0 or higher) across 29 academic and medical centers in the United States, enrolling over 1,000 patients (Folch EE, et al. *J Thorac Oncol.* 2019;14[3]:445-58. Epub 2018 Nov 23), and reported a diagnostic yield of 73%.



Dr. Cicienia

This led to a drive to improve upon yield, resulting in development of new technologies specifically designed to address some of the factors thought associated with diminished yield, and, out of this, robotic bronchoscopy was born. These factors included CT scan-body registration divergence, deflection of the extended working channel (EWC) by rigid biopsy tools, and inability to accurately “aim” the EWC-biopsy tool at the nodule; these were especially problematic in nodules not associated with airways. Robotic scopes were specifically designed to reach into the peripheral lung airways similar to an EWC, but with better structural integrity and steerability. This tip integrity would resist tool-related displacement, and steerability would allow for improved targeting of nodules during the biopsy.

There are two robots approved by the FDA at the time of this writing (Auris Monarch, Intuitive Ion), with a third awaiting FDA clearance (Noah Galaxy). In general, though the engineering of the robotic scopes to improve structural tip integrity are similar, the approach to navigation and targeting vary significantly. The Monarch platform uses electromagnetic guidance, similar to other traditional ENB platforms. The Ion platform does not use ENB; instead, it uses fiberoptic shape sensing technology, which analyzes the shape and orientation of the scope to provide location information. There are potential advantages to shape sensing, the most notable being the absence of electromagnetics; this allows for use of fluoroscopy during the procedure, which otherwise would have interfered with ENB-based navigation. There are other subtle differences between the two robots.


The Monarch uses a scope-in-scope design, with a robotic scope contained within a robotic sheath; the Ion uses a single robotic scope. The Ion scope diameter is 3.5 mm, whereas the Monarch diameter is 4.4 mm; this may be a potential advantage when having to navigate through smaller airways.

So, which robot is better suited to reach peripheral nodules more consistently and accurately? I get asked this question a lot, since I have both platforms at my institution. But, answering with my own opinion based on my institution’s anecdotal experience would be irresponsible. I’m more of a “what does the data show?” person. Luckily, we do have clinical trials in both robot technologies. It should be noted here that there will likely never be a head-to-head randomized trial, so evaluating published studies with each platform is going to be the best method we have for comparison going forward, albeit an imperfect one. It should also be noted that many of the early robotic bronchoscopy trials have to be looked at with caution, as yield definitions tended not to be conservative and/or the follow-up of non-malignant was not robust. With that in mind, let’s review representative high-quality studies for each platform.

The best study to date using the Ion platform came out of Memorial Sloan Kettering Cancer Center (Kalchiem-Dekel O, et al. *Chest.* 2022;161[2];572-82). This single-site study reported on 159 nodule biopsies, with the primary outcome being diagnostic yield. The patients had 1 year of follow-up, and the definition of yield was conservative. The average lesion size was 18 mm, and nodule locations and characteristics were representative of real-world conditions. Overall diagnostic yield was 81.7%; however, it dropped to under 70% for nodules under 20 mm in size.

The largest study to date using the Monarch platform was also a single center study, this from the University of Chicago (Agrawal, et al. *Ann Thorac Surg.* 2022 Jan 17;S0003-4975(22)00042-X. Online ahead of print). This study included 124 nodules with at least 12 months of follow-up; diagnostic yield definition was conservative. Median nodule size was 20.5 mm, with distribution

PULMONARY continued on following page



**CHEST**

## 2022 COURSES

CHEST Global Headquarters | Glenview, IL

SEPTEMBER 8-10  
**Difficult Airway Management**

SEPTEMBER 15-16  
**Ultrasonography: Essentials in Critical Care**

SEPTEMBER 22-24  
**Comprehensive Bronchoscopy With Endobronchial Ultrasound**

NOVEMBER 10-11  
**Critical Care Ultrasound: Integration Into Clinical Practice**

NOVEMBER 18  
**Comprehensive Pleural Procedures With Cadavers**

NOVEMBER 19  
**Advanced Airway Management With Cadavers**

DECEMBER 1-2  
**Ultrasonography: Essentials in Critical Care**

DECEMBER 9-10  
**Extracorporeal Support for Respiratory and Cardiac Failure in Adults**

DECEMBER 6, 13, 15  
**Virtual Advanced Critical Care Echocardiography Board Review Course**

LEARN MORE AND REGISTER  
[chestnet.org/simulation](https://chestnet.org/simulation)

**Ready to Go Hands-on?**

Keep your knowledge and skill set up to date with our expert-led continuing medical education courses. Get all the relevant updates plus the irreplaceable benefits of hands-on instruction and practice. Measures designed to ensure your safety against COVID-19 will be enforced.

PULMONARY *continued from previous page*

and characteristics representative of real-world conditions. Overall accuracy was 77%, and, similar to the Ion study, dropped to under 70% when nodule size was smaller than 20 mm.

Overall, both robot studies seemed to show a modest improvement in diagnostic yield when compared with ENB, and their outcomes were overall similar. It is important to remember that these were studies of each center's first experiences with early versions of each technology; over time, the technology will continue to improve, as will operator skill and experience, and with that, perhaps improvements in yield will be seen, as well.

Interestingly, both studies evaluated target localization using radial EBUS (rEBUS), which also allowed for airway-nodule relationships to be reported. In Kalchiem-Dekel's study, 85% of cases used rEBUS to determine localization, and, of these, 91.2% of cases showed accurate localization. In Agrawal's study, rEBUS was used in all cases with a reported localization of 94%. In both, yield did not seem to be affected by airway-nodule relationships, perhaps explained by more robust tip control of the robotic scope. However, localization did not equate to yield in all cases, which brings up a very important question: Can the yield of robotic bronchoscopy be further improved with

better real-time on-board imaging, such as CBCT scanning or C-arm based tomography? Currently, there is a study using 3D technology (Cios 3D Mobile Spin) in conjunction with the Ion platform to evaluate this.

So, let's circle back to where we started. I think if you look at the totality of the data, it is clear that the robotic platforms currently offer a modest improvement in diagnostic yield over traditional ENB, with individual performances that are somewhat equivalent despite differences in design and operation. But does this improvement in yield justify the cost? Individual hospitals will have to make that decision. The capital cost and per-use price of the scope is significant, which has to be balanced against each center's current performance with non-robotic bronchoscopy.

To date, there have been over 25,000 robotic procedures performed in the United States, so enthusiasm across diverse centers is being maintained. Whether this enthusiasm is driven by yield or novelty, or both, I'm not sure. With other nonrobotic platforms having reached, or soon to reach, the market, this is a good time to be in the business of bronchoscopy. ■

*Dr. Cicenia is in the Section of Bronchoscopy at Cleveland Clinic's Respiratory Institute, Cleveland, Ohio.*

## Partnering for pulmonary fibrosis

*The CHEST Foundation raises awareness for the most common interstitial lung disease*

**O**n August 27, the CHEST Foundation and the Feldman Family Foundation will be hosting the 9th annual Irv Feldman Texas Hold 'Em Tournament & Casino Night fundraiser supporting patient access and the provision of better quality of life for patients battling the interstitial lung disease – pulmonary fibrosis.

“My dad, Irv, had pulmonary fibrosis and deeply loved to play poker. It was always a family activity, and it continued through when he got sick. We played at his kitchen table when he couldn't leave the house, and we even brought cards and chips to his hospital and rehab rooms,” said Mitch Feldman, President of the Feldman Family Foundation and member of the CHEST Foundation Board of Trustees. “During these few hours of poker play, he all but forgot about his illness and showed virtually no symptoms of the disease. In his honor, we created an event where people would come together to have fun playing poker while raising money for the disease [that] so deeply impacted our family.”

Through years of hosting the event, the Feldman family and the CHEST Foundation secured funding to develop a pulmonary fibrosis patient education resource hub that serves as a resource for those newly diagnosed and living with this disease. The Feldman Family and the CHEST Foundation continue to raise funds to support both early diagnosis and closing the gap between diagnosis and beginning treatment.

### Partnering to address gaps

Affecting around 400,000 people in the United States, ILDs are frequently misdiagnosed as more common lung diseases. Some studies show that reaching an appropriate diagnosis for rarer lung diseases can take upwards of several years.

To begin addressing the issue of delays in diagnosis, the American College of Chest Physicians (CHEST) and Three Lakes

Foundation are collaborating on a multiphase educational initiative aiming to reduce the time it takes to identify interstitial lung diseases like pulmonary fibrosis.

The initiative is called “Bridging Specialties™: Timely Diagnosis for ILD Patients” to highlight the collaboration of pulmonary and primary care medicine. A steering committee of medical experts – including pulmonologists, primary care physicians, and a nursing professional – will work to create materials that will aid in identifying and diagnosing complex lung diseases quicker.

“By having experts from both pulmonary and primary care medicine as members of the steering committee, we are bringing together the pieces of the puzzle that is a complex diagnosis,” said Bridging Specialties steering committee member and family medicine physician, Dr. William Lago. “Patients first see their family medicine or primary care clinicians and, all too often, the most complex lung diseases present in ways that are indistinguishable from more common conditions like asthma and COPD. Bringing together experts in both fields will yield the best results in creating a path to diagnosis.”

To learn more about the Bridging Specialties™: Timely Diagnosis for ILD Patients initiative and to sign up for updates, visit <https://tinyurl.com/2p92ha6r>.

For ticket and donation information to the Irv Feldman Texas Hold 'Em Tournament & Casino Night, visit the CHEST Foundation website at [foundation.chestnet.org](http://foundation.chestnet.org). ■

## This month in the journal CHEST®

### Editor's picks

**BY PETER J. MAZZONE, MD, MPH, FCCP**  
*Editor in Chief*

**Results of a Phase 2b Trial With GB001, a Prostaglandin D2 Receptor 2 Antagonist, in Moderate to Severe Eosinophilic Asthma.**  
*By Mark H. Moss, MD, et al.*

**Optimizing COPD Acute Care Patient Outcomes Using a Standardized Transition Bundle and Care Coordinator: A Randomized Clinical Trial.**  
*By Chantal E. Atwood, PhD, et al.*

**Defibrotide Therapy for SARS-CoV-2 ARDS.**  
*By David Frame, PharmD, et al.*

**Provider Perspectives on and Access to Palliative Care for Patients With Interstitial Lung**

**Disease.**  
*By Rebecca A. Gersten, MD, et al.*

**Role of Pulmonary Function in Predicting New-Onset Cardiometabolic Diseases and Cardiometabolic Multimorbidity.**  
*By Guochen Li, MD, et al.*

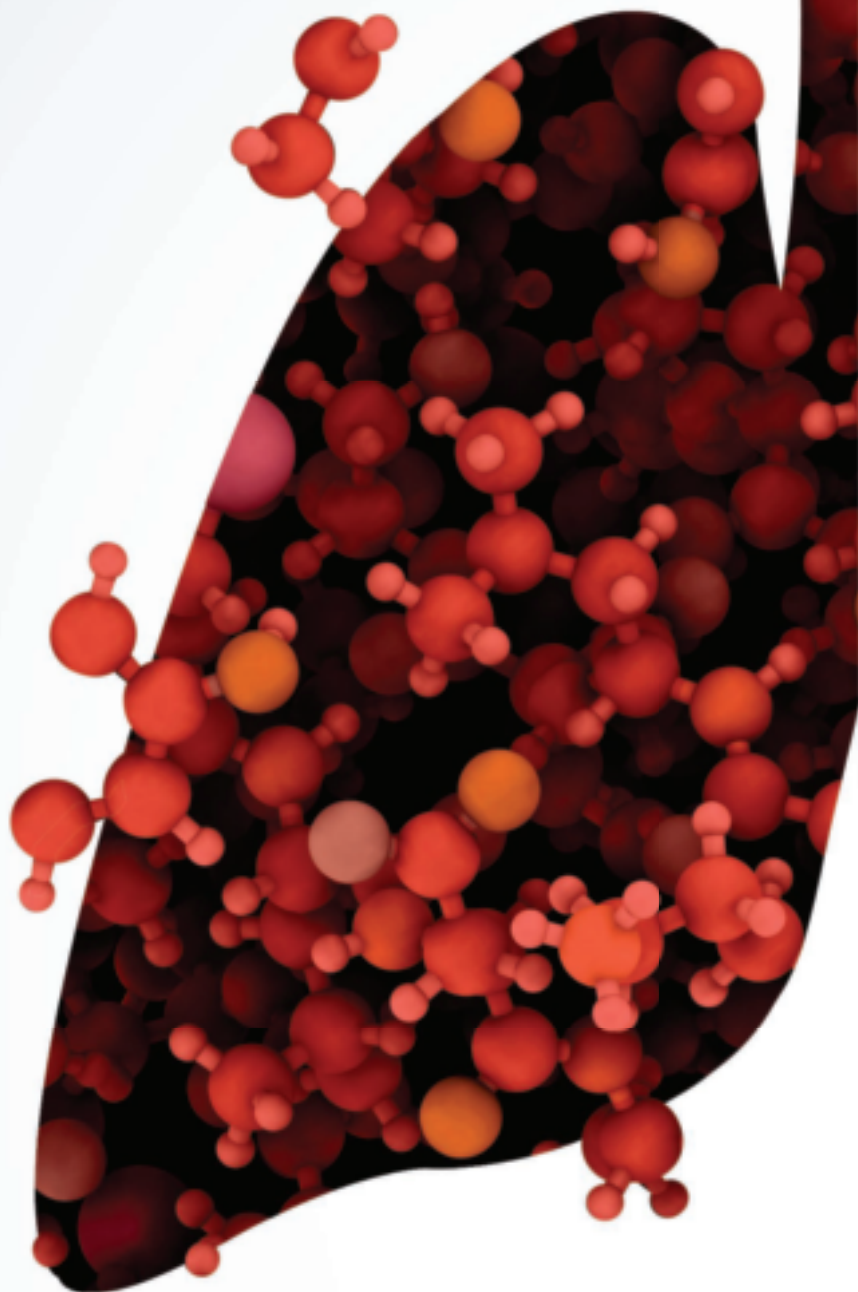
**Comparison of Full-Dose vs Moderate-Dose Systemic Thrombolysis for the Treatment of Patients With Acute Pulmonary Embolism.**  
*By Ana Jaureguizar, MD, et al.*

**Frailty in Patients With Lung Cancer: A Systematic Review and Meta-Analysis.**  
*By Klara Komici, MD, et al.*



## INDEX OF ADVERTISERS

<b>Biodesix</b> Nodify	24
<b>Boehringer Ingelheim Pharmaceuticals, Inc.</b> Corporate	9
<b>GSK</b> Nucala	2-5



Reclassify  
risk.  
Reduce  
uncertainty.

**nodifylung**<sup>®</sup>  
NODULE RISK ASSESSMENT

**nodifycdt**<sup>®</sup>  
PROTEOMIC TEST

**nodifyxl2**<sup>®</sup>  
PROTEOMIC TEST

Designed to help providers quickly and more confidently decipher the risk of malignancy of a lung nodule from a simple blood draw.

 **biodesix**<sup>®</sup>