and 2015. Significant racial and sex differences in asthma-related mortality continue to exist, with mortality being highest among African American women and lowest among non-Hispanic white men. The decrease in asthma-related mortality was consistent in both sexes and in all race groups, with the largest decrease in patients older than 65 years.

This decline in asthma-related mortality may be related to overall improvements in the diagnosis and management of asthma. However, research specifically focused on asthma in the elderly is still limited. Older adults, in general, are more likely to have higher rates of severe asthma and asthma-related hospitalization and mortality (3, 9). Yet the prevalence of asthma in adults older than 65 years remains relatively low compared with that of younger adults, which is reported to be between 4.5% and 12.7% (10). Lower prevalence in this age group is probably related to the underdiagnosis or misdiagnosis, often as chronic obstructive pulmonary disease, of asthma in older adults (11). There is also evidence that asthma in this population is phenotypically different than asthma in younger patients. Furthermore, treatment failure risk increases with age (2), placing older patients with asthma at higher risk for severe uncontrolled asthma.

Although asthma mortality has dropped by 43% since 1999, older age, female sex, and African American race continue to be associated with higher risk for asthma-related mortality. This reflects the overall complexity of the disease and the interaction of different factors that contribute to disease control. With a greater risk for severe asthma, this group of patients would benefit from targeted interventions geared toward optimizing asthma therapy and improving access to care. In general, with the world population aging, it will become increasingly important to have research focused on the pathophysiology, diagnosis, and management of asthma in older populations.

In summary, asthma-related mortality has declined in all age groups older than 15 years in the United States from 1999 to 2015. Although this decline was seen in both sexes and all races, asthma mortality continues to be higher in women compared with men, African American women in particular. Our findings suggest that improvements in the diagnosis and management of asthma have led to declines in asthma-related mortality. Following these trends in asthma mortality can help to direct focus toward at-risk populations who might benefit the most from targeted interventions. ■

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References

1. CDC. Most recent asthma data, asthma prevalence. 2016 [accessed 2018 July 27]. Available from: https://www.cdc.gov/asthma/most_recent_data.htm.
2. Dunn RM, Lehman E, Chinchilli VM, Martin RJ, Boushey HA, Israel E, *et al*.; NHLBI Asthma Clinical Research Network. Impact of age and sex on response to asthma therapy. *Am J Respir Crit Care Med* 2015; 192:551–558.
3. Zein JG, Dweik RA, Comhair SA, Bleecker ER, Moore WC, Peters SP, *et al*.; Severe Asthma Research Program. Asthma is more severe in older adults. *PLoS One* 2015;10:e0133490.
4. Zein JG, Udeh BL, Teague WG, Koroukian SM, Schlitz NK, Bleecker ER, *et al*. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011-2012. *PLoS One* 2016;11: e0157301.
5. Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. *Curr Opin Pulm Med* 2011;17:6–11.
6. Haselkorn T, Lee JH, Mink DR, Weiss ST; TENOR Study Group. Racial disparities in asthma-related health outcomes in severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2008;101: 256–263.
7. Wechsler ME, Castro M, Lehman E, Chinchilli VM, Sutherland ER, Denlinger L, *et al*. Impact of race on asthma treatment failures in the asthma clinical research network. *Am J Respir Crit Care Med* 2011; 184:1247–1253.
8. Yaqoob Z, Al-Kindi S, Zein J. 2017. Trends in asthma mortality in the United States: a population-based study. Presented at the Chest 2017 Annual Meeting. Oct 23, 2017, Glenview, IL.
9. Tsai CL, Lee WY, Hanania NA, Camargo CA, Jr. Age-related differences in clinical outcomes for acute asthma in the United States, 2006-2008. *J Allergy Clin Immunol* 2012;129:1252–1258, e1.
10. Yanez A, Cho SH, Soriano JB, Rosenwasser LJ, Rodrigo GJ, Rabe KF, *et al*. Asthma in the elderly: what we know and what we have yet to know. *World Allergy Organ J*. 2014;7:8.
11. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD; Cardiovascular Health Study Research Group. Underdiagnosis and undertreatment of asthma in the elderly. *Chest* 1999;116:603–613.

Peak Inspiratory Flow Rate: An Emerging Biomarker in Chronic Obstructive Pulmonary Disease

To the Editor:

The research statement by Wu and colleagues (1) representing the American Thoracic Society and NHLBI identifies fibrinogen, a measure of inflammation, as the sole biomarker in chronic obstructive pulmonary disease (COPD). I propose that peak inspiratory flow rate (PIFR) measured against the simulated resistance (*r*) (PIFRr) of a specific dry-powder inhaler (DPI) be

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considered as an "emerging biomarker" in COPD. PIFR, the maximal airflow generated during inspiration, is a physiological measure that fits the definition of a biomarker (1). A suboptimal PIFRr value (<60 L/min) can identify individuals who are more likely to experience a less than favorable response to a dry-powder bronchodilator compared with those who exhibit an optimal PIFRr (≥60 L/min). The following information follows biomarker development steps (1).

Identify an Unmet Need

According to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD), pharmacotherapy for COPD should be individualized based on the severity of symptoms and risk of exacerbations (2). However, neither the GOLD strategy nor guidelines on COPD offer specific recommendations about which of the four delivery systems to use in which types of patients to achieve clinical efficacy. Patient factors for optimal drug delivery include the patient's inspiratory flow rate, flow acceleration rate, time of inhalation, inhaled volume, and breath-hold time. For DPIs, higher inspiratory flows increase the fine particle fraction of the medication reaching the lungs. The unmet need is the ability to predict which patients are unlikely to respond optimally to a dry-powder medication (i.e., those with a suboptimal PIFRr).

DPIs are prescribed widely throughout the world to treat COPD. Each DPI has a unique internal resistance. The recommended use of dry-powder medications requires the patient to inhale "hard and fast" to create turbulent forces within the device to disaggregate the powder into fine particles (<5 μg in diameter) that are then inhaled into the lungs. PIFRr is determined by an individual's effort and respiratory muscle strength.

Intended Use Population

PIFRr is intended as a biomarker in COPD. It may also be considered for use in other patients, such as those with asthma or cystic fibrosis, who use DPIs.

Biomarker Discovery

The importance of measuring PIFRr became clear with the introduction of the sodium cromoglycate Spinhaler in 1967 and the salmeterol Diskus inhaler in 1998. In 2001, Broeders and colleagues reported PIFRr values and inhalation profiles obtained with the Diskus and Turbuhaler (3).

Analytic Validation

The In-Check DIAL (Clement Clerke International Ltd.) has been used widely in studies to measure PIFRr (4–6, 8, 9). It is portable and provides an adjustable dial to simulate different DPI resistances. Although accuracy and reliability of PIFRr have been reported in patients with COPD (4), confirmation is required in larger patient populations.

Clinical Validation

The clinical phenotype of patients with a suboptimal PIFRr includes older age, female sex, and reduced inspiratory capacity, a marker of lung hyperinflation (4). A suboptimal PIFRr is common, being reported in 19–100% of stable outpatients (six studies) and 32–52% of inpatients (three studies) before discharge after admission to the hospital for an exacerbation (4–7). These wide ranges reflect measurements with different DPI resistances in different COPD populations. Two randomized controlled trials demonstrated that patients with severe to very severe COPD and a suboptimal PIFRr against the Diskus had greater improvements in lung function with a bronchodilator delivered by nebulization compared with a DPI (8, 9).

Additional Evidence Is Needed

To establish broad clinical application of the PIFRr, additional randomized controlled trials in both inpatients and outpatients are needed. For example, to reduce readmissions, many hospitals include measurement of the PIFRr before discharging a patient after a COPD exacerbation. A non-DPI delivery system is selected if the PIFRr is suboptimal. If the evidence shows greater bronchodilation and/or reduced readmissions with a non-DPI delivery system compared with a DPI in patients with a suboptimal PIFRr, then measurement of the PIFRr can be recommended in guidelines/strategies for COPD. ■

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References

1. Wu AC, Kiley JP, Noel PJ, Amur S, Burchard EG, Clancy JP, *et al*. Current status and future opportunities in lung precision medicine research with a focus on biomarkers: an American Thoracic Society/National Heart, Lung, and Blood Institute Research Statement. *Am J Respir Crit Care Med* 2018;198: e116–e136.
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 report). 2019 [accessed 2018 Dec 30]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.
3. Broeders ME, Molema J, Vermue NA, Folgering HT. Peak inspiratory flow rate and slope of the inhalation profiles in dry powder inhalers. *Eur Respir J* 2001;18:780–783.
4. Mahler DA. Peak inspiratory flow rate as a criterion for dry powder inhaler use in chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2017;14:1103–1107.
5. Sharma G, Mahler DA, Mayorga VM, Deering KL, Harshaw O, Ganapathy V. Prevalence of low peak inspiratory flow rate at discharge in patients hospitalized for COPD exacerbation. *Chronic Obstr Pulm Dis* 2017;4: 217–224.
6. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal inspiratory flow rates are associated with chronic obstructive pulmonary disease

and all-cause readmissions. *Ann Am Thorac Soc* 2017;14: 1305–1311.
7. Broeders ME, Molema J, Hop WC, Vermue NA, Folgering HT. The course of inhalation profiles during an exacerbation of obstructive lung disease. *Respir Med* 2004;98:1173–1179.
8. Mahler DA, Waterman LA, Ward J, Gifford AH. Comparison of dry powder versus nebulized β-agonist in patients with COPD who have suboptimal peak inspiratory flow rate. *J Aerosol Med Pulm Drug Deliv* 2014;27:103–109.
9. Mahler DA, Ohar J, Barnes C, Moran E, Pendyala S, Crater G. Efficacy of revefenacin by nebulization and tiotropium by HandiHaler in subjects with COPD and suboptimal peak inspiratory flow rates (PIFR). *Chest* 2018;154(Suppl):732A–733A.

Reply to Mahler

From the Authors:

We appreciate Mahler's correspondence related to our research statement (1), the goal of which was to identify knowledge gaps that future research studies can address to efficiently translate biomarkers into clinical practice. To reach this goal, we chose to focus on example biomarkers for select lung diseases rather than create a comprehensive list of all biomarkers for all pulmonary diseases. As stated in the article, "the biomarkers discussed in this research statement are not intended to be comprehensive." Thus, we did not state or intend to imply that fibrinogen is the "sole" biomarker in chronic obstructive pulmonary disease (COPD). We agree with Mahler that the peak inspiratory flow rate is a promising COPD biomarker, and encourage studies of this and other promising biomarkers for COPD and other lung diseases. ■

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Reference

1. Wu AC, Kiley JP, Noel PJ, Amur S, Burchard EG, Clancy JP, *et al*. Current status and future opportunities in lung precision medicine research with a focus on biomarkers: an American Thoracic Society/National Heart, Lung, and Blood Institute Research Statement. *Am J Respir Crit Care Med* 2018;198:e116–e136.

Long-Term Outcomes after Prolonged Mechanical Ventilation: What of Those Cast Away?

To the Editor:

We read with interest Jubran and colleagues' article titled "Long-term outcome after prolonged mechanical ventilation: a long-term acute-care hospital study" (1). As critical-care survivorship increases, we will increasingly need to confront the issue of whether interventions made *in extremis* result in outcomes consistent with the long-term wishes of patients. Jubran and colleagues' findings that more than half of the patients in their study were detached from a ventilator by discharge from a long-term acute-care hospital, and that 85% of survivors of prolonged mechanical ventilation would choose to again undergo prolonged ventilation could potentially inform decision-making regarding prolonged mechanical ventilation. However, to apply the findings of Jubran and colleagues to patient care, it is necessary to understand the selection process by which patients were enrolled in the clinical trial on which the study was based (2).

Our interpretation of the original randomized trial's Consolidated Standards of Reporting Trials flow diagram is that 2,267 patients were screened and 316 were enrolled, and these 316 patients represent the cohort included in the current secondary observational analysis. Acknowledging the challenges of enrolling patients with prolonged mechanical ventilation in a randomized trial, we note that most patients were excluded from the trial owing to an inability or refusal to consent, and many others were excluded owing to profound neurologic deficits or a life expectancy of <3 months. We wonder if the exclusion of most long-term acute-care hospital patients—the 316 patients enrolled reflect less than 14% of the originally screened sample—introduced substantial selection bias into the estimates of ventilator liberation and patient satisfaction. We speculate that the excluded patients had disease characteristics (including an inability to participate in handgrip, maximum inspiratory pressure maneuvers, or quality-of-life and preference questionnaires) that would decrease the total proportion of patients detached from the ventilator, leading to different conclusions. Could the authors expand upon how their results should be interpreted in light of the narrow selection criteria that led patients to participate in the original trial?

Finally, we noted also that the authors invoked Daniel Kahneman's "experiencing self" and "remembering self" in the context of 85% of survivors being "willing to [again] undergo a further episode of prolonged ventilation." We wish to note that only survivors—and only those with an intact mental status, at that—are afforded the opportunity to convey a remembering self. It is impossible to ask either decedents or survivors without an intact

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