meningitis, for which 40 mg daily is administered (9). The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial demonstrated that just 6 mg daily reduced mortality in severe coronavirus disease (COVID-19) but is currently testing doses of 20 mg daily after promising results from other trials (10, 11). In addition, the intravenous route might not be necessary, given the bioavailability of oral dexamethasone, which would reduce adverse effects (e.g., phlebitis), costs, and complexity of intravenous administration (12).

In summary, as the first of its kind, the STOPPE trial has shown that it is both safe and feasible to randomize adult patients with parapneumonic effusions to steroids. Future trials are certainly indicated, but careful consideration should be given to their aim. Should we aim to prevent pleural infection development, or instead attempt to dampen inflammation in already established disease to reduce immediate symptom burden and/or improve longer-term outcomes? ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Prime Time for Proteomics in Pulmonary Arterial Hypertension Risk Assessment?

Precision-based approaches to pulmonary vascular disease have been a focus of research over the past decade (1, 2). The goal is to reclassify pulmonary hypertension (PH) in a way that more accurately aligns with pathobiology and precisely identifies patients at risk or those likely to respond to established and investigational therapeutics. One strategy to address these aims is to combine blood biomarkers and computational modeling to provide more robust and deeper phenotyping than can be achieved with clinical PH classification alone. Genomics, transcriptomics, proteomics, and metabolomics in isolation or combined in systems biology–based networks have, to date, uncovered novel insights into disease mechanisms and questioned how we clinically characterize patients (3–8). In this issue of the *Journal*, Rhodes and colleagues (pp. 1102–1111), who have been at the forefront of these efforts in pulmonary vascular disease (3, 4), build on a previous proteomics study (9) and present the largest unbiased analysis of plasma protein expression to date in idiopathic, heritable, and drug-induced pulmonary arterial hypertension (PAH) (10).

The burden that precision-based approaches in PAH bear is against established markers of disease progression and prognosis,

Supported by NIH grant R01-HL141268 (C.E.V.).

Originally Published in Press as DOI: 10.1164/rccm.202201-0040ED on February 10, 2022

such as functional class, 6-minute-walk distance, hemodynamics, and NT-proBNP (N-terminal pro–brain natriuretic peptide) levels. Newer but popular scores such as Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) and the French risk equation (11, 12) incorporate these widely available clinical measures and are used to escalate treatment. The incorporation of omics into current risk assessment tools is a natural first step toward clinical integration. In the current study, the investigators performed a rigorous, unbiased analysis of over 4,000 plasma protein targets using an aptamer-based assay in derivation and replication cohorts from the UK National PAH Cohort to identify a weighted six-protein score predictive of a composite outcome of all-cause mortality or lung transplant, independent of NT-proBNP levels and 6-minute-walk distance. This six-protein score was further validated in the French EFORT (Evaluation of Prognostic Factors and Treatment Goals in PAH) cohort, which included incident patients. The score performed well at baseline (area under the curve [AUC], 0.73; 95% confidence interval, 0.63–0.85) and follow-up (AUC, 0.84; 95% confidence interval, 0.75–0.94). The six-protein score also outperformed the previously published nine-protein score (9). The six proteins identified (polydom, peroxidasin homolog, renin, neuropilin-1, thrombospondin-2, and peroxiredoxin-4) have biologic functions that are relevant to PAH pathobiology, including stabilization of collagen scaffolds in the extracellular matrix, promotion of angiogenesis, regulation of NF-κB, and compensatory inhibition of microvascular endothelial cell proliferation. There is a large unmet need for peripherally circulating biomarkers that capture pulmonary vascular remodeling, and the authors provide a nice discussion on the identified proteins and putative mechanisms in PAH. Strong biologic plausibility, as well as the ability to accurately predict ultimate clinical endpoints such as death or transplant, is a critical first step toward validation of such a score. Of the six proteins identified, commercially available ELISAs are available for four proteins (thrombospondin-2, renin, peroxiredoxin-4, and neuropilin-1). The authors performed a sensitivity analysis to narrow the model to these proteins and demonstrated sustained accuracy to predict survival in both United Kingdom and French cohorts.

If precision-based medicine in PAH is to reach its full potential, biomolecular risk stratification should offer improved discrimination and calibration over current clinical endpoints and risk calculators. If a blood signature reflective of ongoing pulmonary vascular remodeling reliably reclassified a patient from low to high risk, for example, it could have important implications for disease management and improve enrollment efficiency in clinical trials. More granular discrimination within intermediate-risk PAH is needed, as this group represents a significant proportion of prevalent patients; as much as 70% in some cohorts (13). The six-protein score was able to discern intermediate-risk subjects designated as low or high risk on the basis of the French risk equation. By our calculations, in low-risk subjects (those meeting at least two clinical criteria), adding the protein score reclassified 33% as high risk. This mirrors previous data demonstrating that the addition of newer endpoints (e.g., right ventricular function assessed by cardiac magnetic resonance imaging) can reclassify risk in patients when added to existing calculators (14). The addition of the six-protein score to NT-proBNP (a well-established blood marker in PAH but one that lacks specificity) alone modestly improved the AUC for transplant or death at 5 years from 0.72 (0.63–0.82) to 0.78 (0.71–0.86). The highest sensitivity and specificity cutoffs from the United Kingdom derivation cohort predicted survival with 89% sensitivity and 69% specificity in prevalent samples from the French cohort. Although this is encouraging, in high-stakes diseases such as PAH, excellent accuracy (AUC $>$ 0.9) is the goal and remains elusive even with established clinical scores.

Whether this novel protein score can be applied outside of the three subtypes of PAH studied here remains to be seen. The discovery and replication cohorts included subjects with idiopathic and heritable PAH alone; the predictive ability of the six-protein score persisted in the validation cohort that included a small number (n = 12) of subjects with drug-associated PAH. The score also held up well in two distinct geographic locations. How this score will perform with other subtypes of PAH, including PAH associated with connective tissue disease, and outside of Europe remains unstudied. Two proteins in the proposed score do not yet have commercially available assays. The ability to scale these protein scores to the bedside depends on widely available cost-effective and automated platforms to facilitate their use in "prime time." Finally, although biomolecular data may add more precise phenotypic discrimination to clinical risk assessment tools, clinical and molecular markers may have unidentified interactions, especially in this complex disease. When combined, interpretation should be done cautiously and with attention to weighting.

Rhodes and colleagues have made another important contribution to our understanding of how omics can improve our phenotyping and risk assessment for pulmonary vascular disease.

There remains a need for prospective clinical trials in which risk assessment tools are the intervention tested. Precision-based treatment regimens (with the exception of calcium channel blockers in vasoresponders) and tailored investigational drug trial eligibility for specific patients remain lofty aspirations. The six-protein score is an excellent step toward this goal for patients living with PAH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Providing Compassionate Care in the ICU

After a combined 60 years of working as intensivists, we write this editorial to reflect on our experiences caring for critically ill patients and their families, as well as caring for the interdisciplinary teams with whom we worked. In addition to our time working in the ICUs of teaching hospitals, we have also had the privilege of serving as presidents of two of the leading professional societies in critical care medicine: the American Thoracic Society (J.R.C.) and the Society of Critical Care Medicine (M.L.L.)—coincidentally in the same year. Therefore, we have insight into the strengths and limitations of educational institutions and professional societies for educating and supporting critical care clinicians in providing compassionate care in the ICU; we believe that both our educational institutions and our professional societies can do more.

Over the course of our careers, we have witnessed many advances in the understanding of critical illness pathophysiology, the technologies we use to support patients' failing organ systems, and improvements in communication and shared decision making with patients and families. Although these changes have been important, our goal now is to reflect on the foundational role of critical care clinicians' compassion and openness in our efforts to support critically ill patients, their families, and our interdisciplinary ICU colleagues, especially when facing death or life-threatening critical illness.

Being with critically ill patients at the bedside, being present and supportive with grieving and suffering family members, and at the same time being able to care for all the other critically ill patients under our care in the frenetic and complex ICU environment require a unique skill set. We believe this skill set does not receive the attention it should in the training of critical care clinicians. In this editorial, we describe five interrelated principles underlying this skill set and highlight some examples of putting these principles into practice.

The first principle is that to be compassionate to others, we must be kind to and trust ourselves. Being calm and compassionate when confronted by an angry family member upset with our care, when we are working hard to do our best, can test the patience of even the most compassionate ICU clinician. We have found that when we are kind to and trust ourselves, that compassion arises naturally. Being kind to ourselves also means practicing self-care while in the ICU and, just as important, when we are not in the ICU. There is a rising epidemic of burnout among critical care clinicians, which was present before the coronavirus disease pandemic and has been dramatically exacerbated by the pandemic (1, 2). Being able to be compassionate in our clinical work while ensuring time for self-care both in and outside of work is an essential skill for longevity as critical care clinicians. Self-care may include sleep, exercise, cultivating interests outside of medicine, and time for reflection. This important practice can be modeled for others and should become part of the culture of the ICU.

Originally Published in Press as DOI: 10.1164/rccm.202112-2787ED on February 7, 2022