They show a mortality benefit of biomarker-guided antibiotic therapy in a population of patients with sepsis who are not exclusively in the ICU and have a lower predicted mortality than in ICU patients. The data also helped to define a potential mechanism for mortality benefit—the avoidance of infection-associated adverse events, particularly the prevention diarrhea and acute renal injury.

Do these new data mean that PCT-guided antibiotics should be used in all patients with sepsis? Certainly the findings are provocative, but the success of the PROGRESS trial was likely dependent on high adherence to biomarker-recommended early discontinuation of therapy in a setting where most patients received initially appropriate therapy. In hospitals in which patients with sepsis have a high rate of resistant pathogens, leading to frequent inappropriate therapy, and longer durations of therapy, this benefit may be less clear. Still, the findings are important and clearly demonstrate that in patients with sepsis, less antibiotic use can equate with more survivors. ■

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References

1. Zasowski EJ, Bassetti M, Blasi F, Goossens H, Rello J, Sotgiu G, *et al*. A systematic review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections. *Chest* 2020;158:929–938.
2. Seok H, Jeon JH, Park DW. Antimicrobial therapy and antimicrobial stewardship in sepsis. *Infect Chemother* 2020;52:19–30.
3. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, *et al*. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis* 2018;18:95–107.
4. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al*.; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;375: 463–474.
5. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, *et al*. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16: 819–827.
6. Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J* 2007;30:556–573.
7. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, *et al*. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004;363: 600–607.
8. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, *et al*. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006;174:84–93.
9. Méndez R, Menéndez R, Cillóniz C, Amara-Elori I, Amaro R, González P, *et al*. Initial inflammatory profile in community-acquired pneumonia depends on time since onset of symptoms. *Am J Respir Crit Care Med* 2018;198:370–378.
10. Pepper DJ, Sun J, Rhee C, Welsh J, Powers JH III, Danner RL, *et al*. Procalcitonin-guided antibiotic discontinuation and mortality in critically ill adults: a systematic review and meta-analysis. *Chest* 2019;155:1109–1118.
11. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, *et al*.; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis* 2011;11: 181–189.
12. Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, Panagaki A, Melachroinopoulos N, Drakou E, *et al*. Procalcitonin to reduce long-term infection-associated adverse events in sepsis: a randomized trial. *Am J Respir Crit Care Med* 2021;203: 202–210.

A New Piece to Help Solve the Interstitial Lung Disease Diagnostic Puzzle

The diagnostic journey for those with interstitial lung disease (ILD) is often complex, protracted, and overwhelming, impacting physical, emotional, and financial domains (1). A delay in diagnosis ranges between 7 months and 2 years, leading to lost time in initiating therapies to slow disease progression (1, 2). Despite significant advances over the past 20 years and the development of iterative versions of diagnostic guidelines, an "accurate" diagnosis remains elusive and delayed for many patients, likely reflecting the complexity of the pathobiology and similarity of clinical manifestations among many ILDs (3–5).

The diagnostic evaluation of patients with interstitial lung abnormalities is comprehensive, relying upon a thorough history to delineate symptoms, the course of disease, and prior environmental and pharmacologic exposures that may incite lung fibrosis, as well as prior or current medical conditions with pulmonary manifestations. A diagnostic algorithm has been

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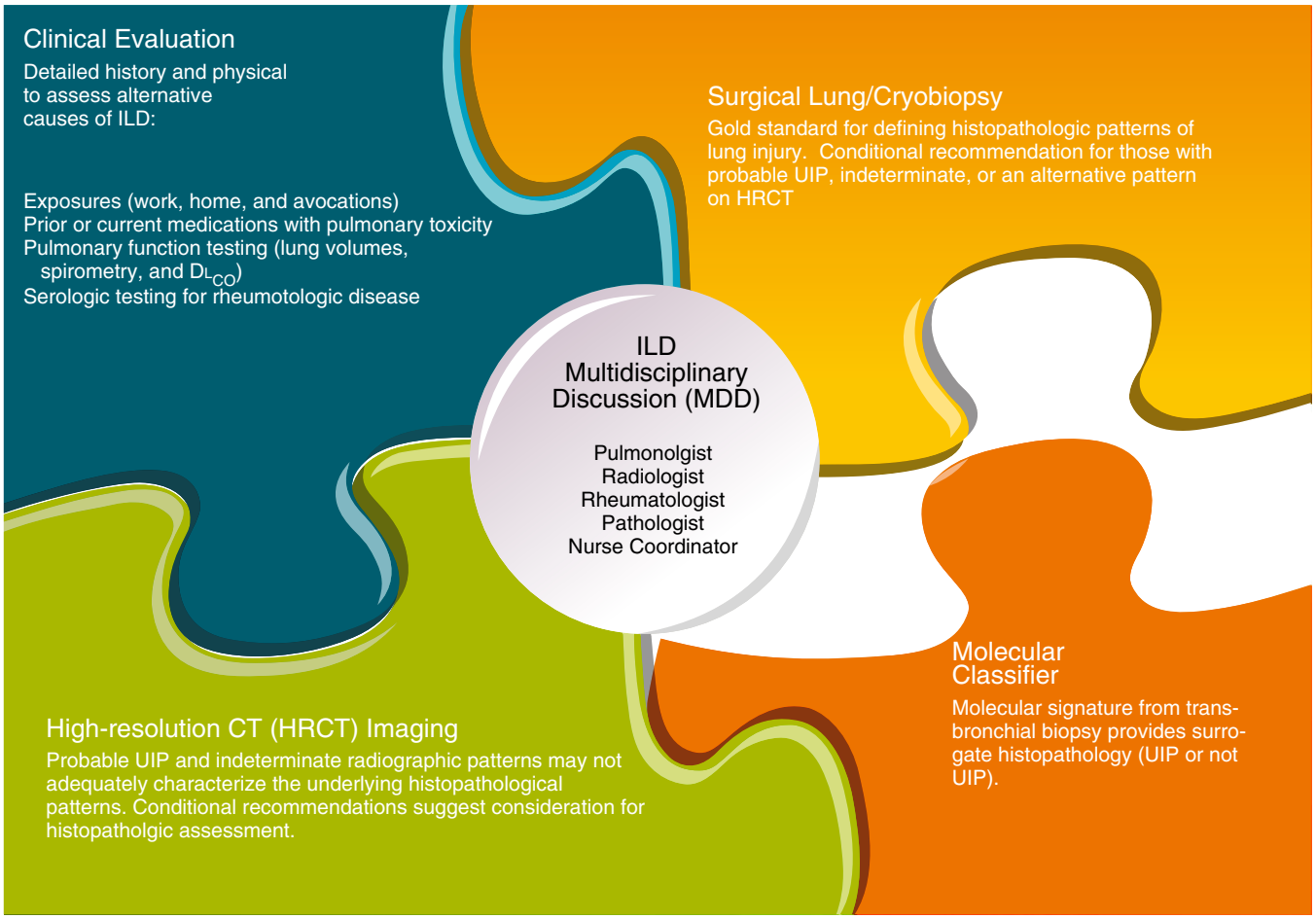

Figure 1. The ILD "diagnostic puzzle" incorporates several different lines of data to establish a confident diagnosis. The genomic classifier for UIP appears to be a piece that may replace histopathology in many cases and hopefully will allow for a more safe and rapid diagnostic process. HRCT = high-resolution computed tomography; ILD = interstitial lung disease; MDD = multidisciplinary discussion; UIP = usual interstitial pneumonia.

established with high-resolution computed tomography (HRCT) scan as a key element, which has a sensitivity >95% for the detection of ILD and allows for a degree of correlation between the radiographic pattern with predicted histopathologic correlates (e.g., usual interstitial pneumonia [UIP], nonspecific interstitial pneumonia, organizing pneumonia). Components of data from the history, physiology, and radiology are like pieces of a puzzle. Unto themselves the pieces do not provide a distinct picture, but when placed together, these pieces may provide a more clear-cut picture and lead to a confident clinical diagnosis.

For patients with ILD in whom a confident specific diagnosis cannot be made based on their clinical and radiographic presentation, additional invasive testing is recommended to more accurately classify the ILD. Specific classification may inform on an expected disease course and associated comorbidities, as well as allow for initiation of approved therapies. Surgical lung biopsy has been the "gold standard" for diagnosis of ILD but is not without its interpretive limitations, morbidity, and mortality (6). The histopathologic pattern is not diagnostic of one disease as histopathology patterns of UIP, nonspecific interstitial pneumonia, and organizing pneumonia can be present in a variety of ILDs. As in a puzzle, this piece must be integrated with others to most accurately diagnosis patients. To augment the diagnostic accuracy, multidisciplinary discussions with experienced clinicians, radiologists, and pathologists is recommended (3, 7, 8). However, implementing this process efficiently into an operational workflow can be challenging for a busy clinical practice.

In this issue of the *Journal*, Richeldi and colleagues (pp. 211–220) report on the use of a genomic classifier (GC) of lung tissue derived from pooled transbronchial biopsies (9). Subjects with all 4 Fleischner Society radiographic patterns on HRCT were enrolled, and the GC was evaluated in its ability to discriminate a UIP or NOT UIP histopathologic pattern in comparison to surgical or cryo lung biopsies. In 96 subjects undergoing both transbronchial biopsy for GC and surgical or cryobiopsy (9), the GC identified UIP histopathology with a sensitivity of 60.3 and a specificity 92.1%. When combined with community-based HRCT scoring, the sensitivity of identifying a UIP pattern increased from 34% to 79.2% while maintaining a specificity of 90.6%. The positive predictive value was 93.3% for the UIP molecular classifier compared with the pathologic pattern. These findings support the use of the GC as an

alternative piece of information to histopathology to address the "ILD diagnostic puzzle" (Figure 1). This manuscript also demonstrates consistency in the performance of the GC among age, sex, and smoking subgroups. Importantly, the molecular classification of UIP is not diagnostic of a disease. It provides a molecular surrogate of the underlying lung pathology in much the same way as a "Typical UIP" radiographic pattern (11) does when integrating data into the diagnostic decision matrix. An accurate diagnosis is optimally made after putting all the other pieces of the puzzle together. For example, the molecular classifier may not distinguish UIP histopathology in patients with rheumatoid arthritis or chronic hypersensitivity pneumonitis from those with idiopathic pulmonary fibrosis; that decision remains one for the multidisciplinary discussion team.

In contrast to pursuing surgical lung biopsy, the GC has several advantages. First, its use may be more generalizable in the pulmonary community because it is not reliant on access to a thoracic surgeon and experienced pulmonary pathologists. Second, the morbidity and mortality of bronchoscopy is reduced in comparison with surgical or cryobiopsy of the lung. The utility of the information gained, the study's performance characteristics, and the safety of the procedure all appear favorable for using the GC in the population evaluated in the current study. However, it is unclear what role the molecular classifier has in subjects with an HRCT pattern with features most consistent with an alternative diagnosis. Based on our recent single-center experience, the GC did not add to IPF diagnostic confidence, when HRCT scans were indeterminate or more in keeping with an alternative diagnosis, and the multidisciplinary discussion likelihood of IPF was considered low (10). Additionally, false-negative GC results were more commonly seen when the pathology was discordant between different lobes. Inasmuch as the cutoff value for the GC is geared toward enhanced specificity, approximately 40% patients without "typical" computed tomography for UIP may require cryobiopsy- or video-assisted thoracoscopic surgery–derived lung tissue for a confident diagnosis.

As with any investigation using new technology, additional questions arise and will need to be explored in future studies. The evolution of precision medicine may expand future molecular classifiers to also include noncoding RNAs or retained introns as a result of alternative splicing. Alternatively, perhaps refinement of regions of the lung that are sampled, such as confining the biopsy sites to fibrotic regions using newer navigational or ultrasound localization techniques, may enhance the accuracy of the GC for UIP. Perhaps with further research subsequent molecular classifier versions will identify patients more likely to have rapidly progressive fibrosis or a response to a specific medication.

Our ongoing aim for any patient with ILD is an efficient, safe, and rapid evaluation with an accurate diagnosis. In doing so, the appropriate treatment and support can be provided. The Envisia GC appears to be a useful tool toward achieving this aim. ■

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References

1. Cosgrove GP, Bianchi P, Danese S, Lederer DJ. Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey. *BMC Pulm Med* 2018;18:9.
2. Snyder LD, Mosher C, Holtze CH, Lancaster LH, Flaherty KR, Noth I, *et al*. Time to diagnosis of idiopathic pulmonary fibrosis in the IPF-PRO Registry. *BMJ Open Respir Res* 2020;7:e000567.
3. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*.; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–e68.
4. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, *et al*.; American Thoracic Society; European Respiratory society; Japanese Respiratory Society; Latin American Thoracic Association. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19. [Published erratum appears in *Am J Respir Crit Care Med* 192:644.]
5. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis. Evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
6. Roden ACSB, Chung J, Danoff S, Gomez D, Hartwig M, Kheir F, *et al*. Role of surgical lung biopsy in the diagnosis of fibrotic interstitial lung diseases. 2019 [accessed 2020 Aug 12]. Available from: https://www.pulmonaryfibrosis.org/medical-community/health-provider-resources/role-of-surgical-lung-biopsy-in-ild.
7. Borie R, Kannengiesser C, Gouya L, Dupin C, Amselem S, Ba I, *et al*. Pilot experience of multidisciplinary team discussion dedicated to inherited pulmonary fibrosis. *Orphanet J Rare Dis* 2019; 14:280.
8. De Sadeleer LJ, Meert C, Yserbyt J, Slabbynck H, Verschakelen JA, Verbeken EK, *et al*. Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases: a retrospective observational study of 938 cases. *Chest* 2018;153:1416–1423.
9. Richeldi L, Scholand MB, Lynch DA, Colby TV, Myers JL, Groshong SD, *et al*. Utility of a molecular classifier as a complement to high-resolution computed tomography to identify usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021;203:211–220.
10. Kheir F, Alkhatib A, Berry GJ, Daroca P, Diethelm L, Rampolla R, *et al*. Using bronchoscopic lung cryobiopsy and a genomic classifier in the multidisciplinary diagnosis of diffuse interstitial lung diseases. *Chest* [online ahead of print] 25 May 2020; DOI: 10.1016/j.chest.2020.05.532.
11. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, *et al*. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischer Society white paper. *Lancet Respir Med* 2018;6:138–153.