death in adults with sleep apnea: a systematic review and meta-analysis. *JAMA* 2017;318:156–166.
15. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al*. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40:1149–1157. [Published erratum appears in *Eur Heart J* 40:1157.]
16. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, *et al*. The sleep apnea–specific pulse-rate response predicts cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* 2021;203:1546–1555.

New Diagnostics to Infer Risk in Tuberculosis
Is the Term "Latent Tuberculosis Infection" Obsolete?

Accurate diagnosis and estimation of risk in latent tuberculous infection (LTBI) remains a major clinical and global health challenge (1, 2). *Mycobacterium tuberculosis* (Mtb) infection reflects a continuum between LTBI and active tuberculosis (TB). LTBI is the most common form Mtb infection, which affects one-quarter of the world's population and kills approximately 2,000,000 people every year (3, 4). Immunocompetent individuals with LTBI have a 5–10% risk of developing active TB during their lifetime, most commonly within the first 2 years after exposure (5). Treatment of LTBI is effective in reducing the risk of developing subsequent active TB disease, but identifying patients most at risk of developing active TB and ensuring successful LTBI treatment remain significant challenges (1, 2).

Available laboratory tests for the detection of LTBI have serious diagnostic limitations, including a poor predictive value (<5%) for identifying subjects with LTBI who will actually develop active TB (1). Tuberculin skin testing and IFN-γ release assays can detect cell-mediated immune reactivity in Mtb infection. However, none of these tests can differentiate LTBI from active TB, nor can they distinguish between those who achieve subsequent bacterial clearance and/or effective infection containment from others who have silent and persistent infection at high risk to develop TB (6). Therefore, improvements in current TB diagnostics are urgently needed not only to improve both sensitivity and specificity of Mtb infection detection but also to more accurately determine the risk of progression or reactivation into active disease. Such advances in diagnostic testing could consequently improve the selection of people who would actually benefit from TB preventive therapy, thus helping to improve TB control and eradication efforts in many parts of the world (1, 2, 7).

The World Health Organization established the goal of reducing active TB and corresponding mortality by 90% and 95%, respectively, by 2035. This will be unachievable without new prevention strategies, including new diagnostic approaches for rapidly identifying infection in asymptomatic patients at the highest risk for developing active TB (1, 2, 8). Fortunately, there has been important scientific progress in recent years in our understanding of TB pathophysiology as well as in the development of new predictive diagnostics and preventive therapies (6). Among these new TB diagnostics, detection of blood RNA signatures have been validated to not only differentiate LTBI from TB but also to predict those who will likely progress to TB ("incipient TB") within 2 years (7, 9, 10). Blood-based immune profiling methods have been developed and validated to differentiate LTBI from TB, but until now, their predictive value has not been validated in adults (7, 11).

In this issue of the *Journal*, Mpande and colleagues (pp. 1556–1565) retrospectively studied antigen-specific T-cell activation markers in blood, measured with flow cytometry (FC) assays that can stratify different stages of TB infection and thus infer risk of TB progression (12). They selected a subset of available blood samples from a large prospective adolescent cohort study that were serially tested with QuantiFERON-TB Gold In-Tube (QFT) to define "recent" (QFT conversion <6 mo) and "remote" (persistent QFT+ for >1 yr) TB infection reactivity. They identified and defined the ΔHLA-DR median fluorescence intensity (MFI) biomarker as the difference in HLA-DR expression between IFN-γ+ TNF+ Mtb-specific and total CD3+ T cells (12, 13). The diagnostic performance of this composite FC biomarker was assessed by blinded prediction in test cohorts with "recent" versus "remote" TB infection reactivity. They also applied a single-cell TCR sequencing to measure the ΔHLA-DR MFI biomarker results and conducted an unblinded analysis of asymptomatic individuals with LTBI who remained healthy (nonprogressors) or who progressed to microbiologically confirmed TB disease (progressors) from a separate cohort of the same adolescent study. In the test cohorts, frequencies of Mtb-specific T cells differentiated between QFT(−) and QFT(+) individuals (area under the curve [AUC] of the receiver operating characteristic curve and 95% confidence intervals: 0.94; 0.87–1.00). ΔHLA-DR significantly differentiates between "recent" and "remote" individuals with TB infection reactivity (0.91; 0.83–1.00), "remote" TB infection reactivity and newly diagnosed TB (0.99; 0.96–1.00), and TB progressors and nonprogressors (0.75; 0.63–0.87). The authors conclude that the ΔHLA-DR biomarker can identify individuals with recent Mtb infection and those with disease progression, allowing targeted provision of preventive treatment to those at highest risk of TB (12).

We applaud the authors for this important research work with high significance for global TB control. The study was retrospective but reasonably well-designed and utilized stored blood samples from a large prospective cohort study for their training, testing, and validation study

P.E.'s research work has been supported by the National Institute of Allergy and Infectious Diseases at the NIH (AI141591) and by the CHEST Foundation. This paper's contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, Mayo Clinic, or any organization.

Originally Published in Press as DOI: 10.1164/rccm.202101-0131ED on February 17, 2021

cohorts. The study team has also published other promising RNA-based biomarkers and diagnostics to predict incipient TB, which have been validated with cohort data from other TB endemic areas in the world (9, 14). This immune profiling work is also innovative because the authors developed and validated a simplified FC method that can be applied to not only accurately detect and differentiate "recent" and "remote" TB infection reactivity but also incipient TB and active TB (12, 15). In fact, the ΔHLA-DR MFI assay has a diagnostic performance similar to the best predictive blood-RNA signatures (e.g., AUC of ∼0.75) to predict TB progressor versus nonprogressors up to 2 years (9, 12). The study limitations included bias associated with selecting participants based on sample availability and testing validation in a nonindependent study cohort. Additionally, testing methods were not the same in the validation cohort, precluding the determination of diagnostic thresholds for the ΔHLA-DR MFI assay. This study also did not include HIV-infected and other immunosuppressed subjects to further determine diagnostic accuracy in this higher risk group for TB; however, a similar FC assay has shown excellent diagnostic accuracy (AUC of 0.99) in differentiating LTBI from TB in HIV-positive individuals (11). Importantly, the ΔHLA-DR MFI method has not been validated in large groups of TB-unexposed individuals to accurately determine the specificity of this promising TB diagnostic method.

Despite these limitations, this work contributes to improving TB diagnostics by validating an Mtb antigen–specific immune profiling method that significantly raises the predictive value of the available testing methods. This novel diagnostic approach along with appropriate clinical evaluations may help further optimize treatment prevention strategies in areas of the work with experience and access to these immune profiling assays. Further validation studies of this novel immune biomarker and similar methods are needed to meet the minimum World Health Organization target product profile parameters for incipient TB in various settings and populations at risk (2, 6, 9). It is also important to determine if these new predictive TB biomarkers will return to preinfection levels after treatment completion to assess response and risk reduction, as previously suggested (16, 17). Lastly, it also remains to be seen if these new diagnostic-guided approaches for rapid disease prevention would improve TB control and eradication efforts in TB endemic and nonendemic areas.

Importantly, it was challenging to apply the broad concept and current diagnosis definition of LTBI to the study subjects with "remote" or persistent QFT(+) reactivity and the ones with "recent" QFT(+) reactivity. In this regard, we suggest changing the term "LTBI" to "TB infection reactivity," which can be applied to both postinfection immune reactivity and different stages of asymptomatic TB infection. The categories of low, high, or indeterminate risk can be added to the term "TB infection reactivity" to provide an assessment or interpretation of TB progression risk for both the available tests and the newly developed host-related TB diagnostics in the absence of a gold standard test to directly measure host bacillary burden in asymptomatic Mtb infections. This proposed terminology will enable a more individualized and risk-based diagnosis for the optimal management of the different stages of asymptomatic Mtb infection, including low-risk TB infection, high-risk or incipient TB infection, and posttreatment immune reactivity, and differentiation from subclinical TB and clinical TB. ■

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

Patricio Escalante, M.D., M.Sc.
Division of Pulmonary and Critical Care Medicine Mayo Clinic Rochester, Minnesota

John W. Wilson, M.D.
Division of Infectious Diseases Mayo Clinic Rochester, Minnesota

ORCID ID: 0000-0002-4945-1035 (P.E.).

References

1. Schluger NW. Tuberculosis elimination, research, and respect for persons. *Am J Respir Crit Care Med* 2019;199:560–563.
2. Schumacher SG, Denkinger CM. Diagnostic test for incipient tuberculosis: a step forward, many more to go. *Am J Respir Crit Care Med* 2018;197:1106–1107.
3. World Health Organization. Global tuberculosis report 2020. Geneva; 2020 [accessed 2021 May 26]. Available from: https://www.who.int/tb/publications/global_report/en/.
4. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a Re-estimation using mathematical modelling. *PLoS Med* 2016;13:e1002152.
5. Behr MA, Edelstein PH, Ramakrishnan L. Is *Mycobacterium tuberculosis* infection life long? *BMJ* 2019;367:l5770.
6. Keshavjee S, Amanullah F, Cattamanchi A, Chaisson R, Dobos KM, Fox GJ, *et al*. Moving toward tuberculosis elimination. Critical issues for research in diagnostics and therapeutics for tuberculosis infection. *Am J Respir Crit Care Med* 2019;199:564–571.
7. Goletti D, Lee MR, Wang JY, Walter N, Ottenhoff THM. Update on tuberculosis biomarkers: from correlates of risk, to correlates of active disease and of cure from disease. *Respirology* 2018;23:455–466.
8. Escalante P, Theel ES. Progress towards developing a rapid triage/referral test for tuberculosis. *Clin Chem* 2020;66:995–997.
9. Gupta RK, Turner CT, Venturini C, Esmail H, Rangaka MX, Copas A, *et al*. Concise whole blood transcriptional signatures for incipient tuberculosis: a systematic review and patient-level pooled meta-analysis. *Lancet Respir Med* 2020;8:395–406.
10. Warsinske H, Vashisht R, Khatri P. Host-response-based gene signatures for tuberculosis diagnosis: a systematic comparison of 16 signatures. *PLoS Med* 2019;16:e1002786.
11. Riou C, Berkowitz N, Goliath R, Burgers WA, Wilkinson RJ. Analysis of the phenotype of *Mycobacterium tuberculosis*-specific CD4+ T cells to discriminate latent from active tuberculosis in HIV-uninfected and HIV-infected individuals. *Front Immunol* 2017;8:968.
12. Mpande CAM, Musvosvi M, Rozot V, Mosito B, Reid TD, Schreuder C, *et al*. Antigen-specific T-cell activation distinguishes between recent and remote tuberculosis infection. *Am J Respir Crit Care Med* 2021;203:1556–1565.
13. Mpande CAM, Rozot V, Mosito B, Musvosvi M, Dintwe OB, Bilek N, *et al*.; ACS Study Group. Immune profiling of *Mycobacterium tuberculosis*-specific T cells in recent and remote infection. *EBioMedicine* 2020;64:103233.
14. Penn-Nicholson A, Mbandi SK, Thompson E, Mendelsohn SC, Suliman S, Chegou NN, *et al*.; Adolescent Cohort Study team; GC6-74 Consortium; SATVI Clinical and Laboratory Team; ScreenTB Consortium; AE-TBC Consortium; RePORT Brazil Team; Peruvian Household Contacts Cohort Team; CAPRISA IMPRESS team. RISK6, a 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response. *Sci Rep* 2020;10:8629.
15. Musvosvi M, Duffy D, Filander E, Africa H, Mabwe S, Jaxa L, *et al*. T-cell biomarkers for diagnosis of tuberculosis: candidate evaluation by a simple whole blood assay for clinical translation. *Eur Respir J* 2018;51:1800153.
16. Escalante P, Arias-Guillén M, Palacios Gutiérrez JJ. New research strategies in latent tuberculosis infection. *Arch Bronconeumol* [online ahead of print] 16 Mar 2020; DOI: 10.1016/j.arbres.2020.01.024.
17. Escalante P, Peikert T, Van Keulen VP, Erskine CL, Bornhorst CL, Andrist BR, *et al*. Combinatorial immunoprofiling in latent tuberculosis infection. toward better risk stratification. *Am J Respir Crit Care Med* 2015;192:605–617.