only one of the studies (6). Thus, the proposed threshold serum level is based on the results obtained by a single laboratory.

Although the fundamentals of LAM have been extensively discussed, with special regard to therapeutic issues, other more general aspects concerning the practical management of the disease should be considered, such as use of bronchodilators, pulmonary rehabilitation, and indications for lung transplant. Pregnancy and air travel limitation are two further matters of great importance for the general pulmonologist and should be discussed and dealt with separately. ■

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

Sergio Harari, M.D.
Roberto Cassandro, M.D.
Olga Torre, M.D.
Ospedale San Giuseppe, MultiMedica Istituto di Ricerca e Cura a Carattere Scientifico
Milan, Italy

References

1. McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, Steagall WK, Johnson SR, Sahn SA, Ryu JH, *et al*.; ATS/JRS Committee on Lymphangioleiomyomatosis. Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med* 2016;194:748–761.
2. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, Barker AF, Chapman JT, Brantly ML, Stocks JM, *et al*.; National Institutes of Health Rare Lung Diseases Consortium; MILES Trial Group. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med* 2011;364:1595–1606.
3. Chang WY, Cane JL, Kumaran M, Lewis S, Tattersfield AE, Johnson SR. A 2-year randomised placebo-controlled trial of doxycycline for lymphangioleiomyomatosis. *Eur Respir J* 2014;43:1114–1123.
4. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Hathaway O, Moss J. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004;126:1867–1874.
5. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, *et al*. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008;358:140–151.
6. Young LR, Vandyke R, Gulleman PM, Inoue Y, Brown KK, Schmidt LS, Linehan WM, Hajjar F, Kinder BW, Trapnell BC, *et al*. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. *Chest* 2010;138:674–681.

Reply

From the Authors:

We thank Dr. Harari and colleagues for their thoughtful comments regarding the recently published American Thoracic Society/Japanese Respiratory Society (ATS/JRS) guideline document for the diagnosis and management of lymphangioleiomyomatosis (LAM) (1). We agree that there are several clinically important questions that were not addressed in this first ATS/JRS LAM Guideline publication that we hope to include in future versions.

With respect to more precisely defining thresholds for sirolimus treatment based on lung function decline or functional impairment, the committee felt the available data are insufficient to support specific spirometric ranges or cutoffs, especially given the context-specific nature of many treatment decisions in this patient population (i.e., affected by age, menopausal status, degree of disability, comorbidities, and other variables) and decided instead to provide only a rough estimate based on collective practice experiences. Although the current guidelines were focused on the decision to begin therapy with sirolimus, in future versions we hope to have sufficient data available to provide evidence-based recommendations for stopping the drug based on conversion to menopausal status, adverse events, lack of responsiveness to the drug or waning drug effect, or other reasons.

As mentioned by Harari and colleagues, there have been significant advances in our understanding of the role of mechanistic target of rapamycin inhibitors in the treatment of angiomyolipomas (AMLs) (2–4). We agree that the presence of AMLs, which are seen in approximately 30% of patients with sporadic LAM and a majority of patients with LAM (~90%) who also have tuberous sclerosis complex, frequently influence decisions regarding treatment (5). Management decisions regarding AMLs, including criteria for initiation of treatment, have been discussed in detail in the recently published tuberous sclerosis complex guidelines (6). Given the availability of this resource produced by AML experts, the ATS/JRS Committee on Lymphangioleiomyomatosis made a conscious decision to focus on the pulmonary manifestations of LAM and to avoid making recommendations for kidney manifestations of LAM, including AMLs.

With regard to the generalizability of the serum vascular endothelial growth factor D (VEGF-D) threshold of 800 pg/ml for the diagnosis of LAM, the committee carefully considered the fact that various studies had recommended slightly different optimal diagnostic cutoffs for VEGF-D. The committee made an *a priori* decision to focus on optimizing test specificity to minimize false-positive results that could lead to adverse effects and costs associated with inappropriate treatment of LAM. Although values less than 800 pg/ml had acceptable diagnostic performance characteristics with high specificities in almost all published studies (7–9), the conservatively chosen value of 800 pg/ml was associated with a specificity that approached 100% (8), and thus was chosen by the committee as the recommended threshold. The 800 pg/ml threshold has subsequently been externally validated in other cohorts with excellent test performance characteristics (10). Attention to sample processing and adherence to clinical laboratory standards, such as those in use for the College of American Pathologists/Clinical Laboratory Improvement Amendments laboratory, remain critical for VEGF-D testing, and we do not recommend making clinical decisions based on test results from laboratories that do not follow such procedures.

We agree that the use of bronchodilators, benefits of pulmonary rehabilitation, risk associated with pregnancy and air travel, and referral criteria for lung transplantation are important issues that merit inclusion in clinical practice guidelines regarding LAM. The charge to the committee for this first document, however, was to develop evidence-based guidelines for only three to four key questions, especially those for which impactful new data had become available since the publication of the European Respiratory Society LAM guidelines (11). The committee felt that the above mentioned

Originally Published in Press as DOI: 10.1164/rccm.201702-0417LE on March 13, 2017

questions had been adequately addressed in that comprehensive document and did not urgently require updating in this first publication.

The intent of reducing the scope of each version of the LAM guidelines is to facilitate the development of a "living document," with frequent reassessment and updating as new data emerge. We hope to incorporate a number of additional questions, including the majority, if not all, of those raised by Harari and colleagues, in future versions of the LAM guidelines. ■

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

Francis X. McCormack, M.D.
Nishant Gupta, M.D.
The University of Cincinnati
Cincinnati, Ohio

Geraldine R. Finlay, M.D.
Tufts University
Boston, Massachusetts

Lisa R. Young, M.D.
Vanderbilt University
Nashville, Tennessee

Simon R. Johnson, M.B. B.S.
Nottingham University
Nottingham, United Kingdom

Vincent Cottin, M.D.
Université de Lyon
Lyon, France

Kevin C. Wilson, M.D.
Boston University
Boston, Massachusetts

Joel Moss, M.D., Ph.D.
National Heart, Lung, and Blood Institute
Bethesda, Maryland

For the ATS/JRS Committee on Lymphangioleiomyomatosis

ORCID IDs: 0000-0001-7168-9464 (F.X.M.); 0000-0001-9112-1315 (N.G.); 0000-0002-5591-0955 (V.C.).

References

1. McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, Steagall WK, Johnson SR, Sahn SA, Ryu JH, *et al*.; ATS/JRS Committee on Lymphangioleiomyomatosis. Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med* 2016;194:748–761.
2. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, *et al*. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008;358:140–151.
3. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, *et al*. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013;381:817–824.
4. Dabora SL, Franz DN, Ashwal S, Sagalowsky A, DiMario FJ Jr, Miles D, Cutler D, Krueger D, Uppot RN, Rabenou R, *et al*. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF- D levels decrease. *PLoS One* 2011;6:e23379.
5. Ryu JH, Moss J, Beck GJ, Lee JC, Brown KK, Chapman JT, Finlay GA, Olson EJ, Ruoss SJ, Maurer JR, *et al*.; NHLBI LAM Registry Group. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med* 2006;173:105–111.
6. Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013;49: 255–265.
7. Young LR, Inoue Y, McCormack FX. Diagnostic potential of serum VEGF-D for lymphangioleiomyomatosis. *N Engl J Med* 2008;358: 199–200.
8. Young LR, Vandyke R, Gulleman PM, Inoue Y, Brown KK, Schmidt LS, Linehan WM, Hajjar F, Kinder BW, Trapnell BC, *et al*. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. *Chest* 2010;138: 674–681.
9. Radzikowska E, Jaguś P, Skoczylas A, Sobiecka M, Chorostowska-Wynimko J, Wiatr E, Kuś J, Roszkowski-Śliż K. Role of serum vascular endothelial growth factor D in discrimination of patients with polycystic lung diseases. *Pol Arch Med Wewn* 2013;123:533–538.
10. Chang WY, Cane JL, Blakey JD, Kumaran M, Pointon KS, Johnson SR. Clinical utility of diagnostic guidelines and putative biomarkers in lymphangioleiomyomatosis. *Respir Res* 2012;13:34.
11. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, Reynaud-Gaubert M, Boehler A, Brauner M, Popper H, *et al*.; Review Panel of the ERS LAM Task Force. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J* 2010;35:14–26.

Effect of Continuous Positive Airway Pressure Therapy on Cardiovascular Outcomes: Risk Assessment

To the Editor:

Peker and colleagues determined the effects of continuous positive airway pressure (CPAP) on cardiovascular outcomes in patients with coronary artery disease suffering from nonsleepy obstructive sleep apnea (OSA) (1). The authors comparatively analyzed the data of 122 patients treated by CPAP and 122 patients not administered CPAP. The median follow-up period was 57 months, and the results revealed the absence of any significant differences in cardiovascular outcomes between the two groups. In addition, a significant cardiovascular risk reduction was observed in patients who used CPAP for 4 or more hours compared with those who used CPAP for less than 4 hours per night or who did not receive CPAP therapy at all. I have a query about their study, with special reference to the adherence time per night for CPAP therapy.

McEvoy and colleagues conducted a randomized controlled trial to evaluate the effects of CPAP therapy in patients with OSA by comparing the effects between patients who received CPAP therapy plus usual care (CPAP group) and those who received usual care alone (usual care group) (2). The mean duration of adherence to CPAP therapy was 3.3 hours per night, and there were no significant differences in cardiovascular outcomes between the two groups after a mean follow-up period of 3.7 years. Although presence/absence of sleepiness in the patients with OSA was not taken into consideration, stratification

Originally Published in Press as DOI: 10.1164/rccm.201701-0239LE on March 15, 2017