approaches and novel therapeutic avenues. Most importantly, I believe the designation will not help patients with LAM cope any better with their disease or improve survival or quality of life. The verdict on LAM as a neoplasm is undecided, the scientific evidence at present not substantial enough to support this designation, and the benefits of this labeling and its implications remain controversial.

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

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Characterization of Lymphangioleiomyomatosis as a Neoplastic Disease

To the Editor:

McCormack and colleagues offer an insightful review of the features of lymphangioleiomyomatosis (LAM) that conform to the National Cancer Institute and World Health Organization cancer criteria (1). It was somewhat surprising that the authors did not address the potential treatment implications of characterizing LAM as a neoplastic disease. Recognition of the progressive destructive nature of LAM by cells that meet the National Cancer Institute and World Health Organization cancer criteria may also impact the risk–benefit discussion of treatment options. Although sirolimus has proven benefit with respect to tumor size and lung function, long-term efficacy of this potentially toxic drug has yet to be determined (2). Nonetheless, patients and clinicians may be more inclined to accept those potential treatment toxicities as acceptable risk for a neoplastic process.

It should also be noted that clinical trials involve agents that have been developed for treatment of other types of cancer. Letrozole, an aromatase inhibitor used for breast cancer, is currently under study in a multicenter prospective trial in LAM (NCT01353209). The side-effect profile of such agents should be considered in context of the severity and progressive nature of the targeted disease.

One other issue that was not mentioned in the article is that the change in classification may result in improper referrals to oncologists for evaluation and treatment. Although this seems unlikely at first glance, a new diagnosis of a neoplasm may create some confusion. LAM is a rare disease that should be managed in subspecialty LAM Clinics, where, quite importantly, eligibility for clinical trials can be discussed (3, 4).

The proposal by the authors is timely and appropriate. Characterization of LAM as a “low-grade, destructive, metastasizing neoplasm” will facilitate the clinical decision making and consent discussions necessary to effectively treat this often devastating disease. Overall, the change in viewpoint would appear to be to the benefit of patients and providers. Their efforts to increase the recognition and understanding of LAM pathobiology should be applauded.

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Reply

From the Authors:

We thank Dr. Glassberg for her comments regarding our article (1). We acknowledge that “unease” is an expected response to paradigm shifts of all kinds. We also agree that categorizing lymphangioleiomyomatosis (LAM) as a neoplasm of low malignant potential may create anxiety among some patients, especially the newly diagnosed, despite all that the astounding progress in the oncology field has done to reduce the dread of a fresh cancer diagnosis. Patients have a right to know the facts, however, regardless of the potential responses that these facts may evoke. And the facts are that LAM is a neoplasm, LAM is due to growth-promoting DNA mutations, LAM spreads via blood and lymphatics to the lung, and LAM destroys the target organ. Although there was no “declaration of LAM as a cancer” in the essay, or insistence that it be presented to patients as such, we believe that these facts identify LAM as a cancer, albeit a low-grade malignancy, by any reasonable scientific definition of the word. We acknowledge that the cancer definitions that are commonly applied by the lay public are a poor fit for LAM, and that each physician must decide individually how to present these complex concepts to patients. These discussions will not occur in a vacuum. The LAM community has in place a series of mechanisms to enhance patient education and understanding, with support from LAM Clinics, the LAM Foundation, and the NHLBI. Perhaps we shall have to “agree to disagree” about the potential positive impact of viewing LAM as a steroid-responsive neoplasm, including the beneficial collaborations, clarity in discussions in the lay and scientific communities, and novel approaches to therapy that may ensue. We are convinced that refinement of the pathophysiologic categorization of LAM will also lead

to better patient understanding, enhanced trial enrollment, development of molecular targeted therapies, and forward motion in the field.

We agree with Dr. Burger that recognition of LAM as a neoplastic disease will facilitate discussions with patients, including those in which the risks and benefits of various treatments are weighed. We also agree that pulmonologists are the most appropriate specialists to manage LAM patients, although we are optimistic that closer ties to the oncology community in the future will benefit the LAM community.

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Obstructive Sleep Apnea and Cancer: Is It Time to Study Organ-Specific Cancers?

To the Editor:

We read the article by Campos-Rodriguez and colleagues (1) with great interest. These investigators retrospectively analyzed data from 4,910 patients with obstructive sleep apnea (OSA) and followed them for a median of 4.5 years. After adjustment for age, gender, smoking status, body mass index, alcohol intake, type of diagnostic sleep study, and hospital of enrollment, they showed that a greater percentage of sleep spent with oxygen saturation < 90% was independently associated with an increased risk of subsequent cancer incidence. We want to express sincere gratitude to the authors, who contributed significantly to this topic. Nevertheless, we believe that some points should be mentioned.

Future research on the topic of OSA and cancer incidence should shift toward organ-specific cancers (including both basic/translational and epidemiologic research). It will be particularly pertinent to study the association between OSA and some gastrointestinal malignancies. First, OSA shares some risk factors with pancreatic adenocarcinoma (PC), such as aging, obesity, smoking, and excessive alcohol intake. Furthermore, recent evidence suggests that OSA is an independent risk factor for the development of type 2 diabetes mellitus, which may act as a risk factor for the

development of PC (2). Based on the above, it is worth studying whether OSA increases the risk for PC.

Second, OSA may be an independent (from obesity and type 2 diabetes mellitus) risk factor for the development of nonalcoholic fatty liver disease (3). Nonalcoholic fatty liver disease, in turn, is an established risk factor for the incidence of hepatocellular carcinoma (4).

Both PC and hepatocellular carcinoma carry a poor prognosis. Identifying new risk factors may improve disease prevention and its economic burden. Therefore, future research on the topic of OSA and cancer/carcinogenesis should concentrate on these particular malignancies.

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Reply

From the Authors:

We thank Drs. Mirrakhimov and Barbaryan for their interest and their comments on our article about the association between obstructive sleep apnea (OSA) and cancer incidence (1).

As stated in the article, we did not have the opportunity to investigate the association between OSA and specific cancer locations. First, even the most common cancers had a low incidence rate, so we lacked the statistical power to perform any subanalyses based on tumor subtypes, and second, this approach would need to account for specific risk factors involved in these cancers, information that is not usually available in a retrospective study. Nevertheless, we agree with Mirrakhimov and Barbaryan that the association between OSA and site-specific cancers should be assessed in future studies. The typical consequences of OSA, such as intermittent hypoxia and deranged sleep, may be involved in the development of some, but not all types of tumors. The identification of those cancers with a potential link with OSA is therefore a topic of outstanding relevance.

The question about which specific cancers should be investigated is, however, more difficult to answer. One approach would be to select those more likely to be influenced by intermittent hypoxia associated with OSA. Unfortunately, even though local hypoxia and tissue oxygenation have been recognized as playing a key role in tumor progression and growth (2), the impact of systemic or overnight hypoxia on these outcomes remains unknown. The histological type of the tumor should also be taken