Correspondence

To Be or Not To Be a Neoplasm: What Is Lymphangioleiomyomatosis? Are We Calling It What It Really Is?

To the Editor:

As an academic pulmonologist who cares for women with lymphangioleiomyomatosis (LAM) and directs a LAM Clinic, I find it provocative to propose, as McCormack and colleagues (1) have, that LAM should be called a "low grade, destructive, metastasizing neoplasm." The idea that LAM is a neoplasm, however, is not new and has surfaced in the literature for more than two decades. Yet I am faced with a level of uneasiness and confusion with the current declaration of LAM as a cancer. The authors express their own confusion through a series of questions that conclude by suggesting that the conventional labels, "benign" or "malignant," be accompanied by the descriptive modifiers of a neoplasm. Does this make LAM a "cancer" or not if it is a destructive and metastasizing process? Does the statement, "LAM cells have growth-promoting DNA mutations, evidence of clonal origins, invasive and metastatic potential, and metabolic profiles" make LAM "entirely consistent with a neoplastic process"? Does the fact that LAM results in "remote tissue destruction, progressive respiratory failure and death or need for lung transplantation" further support LAM as a neoplastic process? I would propose that the jury is undecided. My decision is based on the fact that to date, LAM does not fulfill all eight hallmarks of cancer as described by Hanahan and Weinberg (2):

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis
7. Reprogramming energy metabolism
8. Escaping immune destruction

So, what is LAM? The answers remain unknown to this question posed in Finlay's editorial in 2008 about LAM (3): "What is it, where does it come from, and why does it grow?" Is cancer just anything that grows without control, invades locally and remotely, and causes tissue destruction? This is the National Cancer Institute definition of cancer, and in this regard, LAM almost fits the definition. Inappropriate proliferation and invasion controlled by hormones, particularly estrogens, is certainly a characteristic of LAM (4) (Figure 1). There remains a gray zone between uncontrolled proliferations and diseases like LAM, which only serves to underscore our current ignorance.

Calling it what it is, LAM remains a cystic interstitial lung process marked by uncontrolled smooth muscle proliferation (4–6). Among other examples of proliferative, nonneoplastic lung diseases are idiopathic pulmonary fibrosis (IPF) and benign metastasizing leiomyoma. IPF is a proliferative disease marked by fibroblastic foci that is not clonal and resides only in the lung. IPF is not labeled as a cancer but is certainly a destructive process. Benign metastasizing leiomyoma is associated with dissemination of cells from a primary source to the lung, but like LAM, the histologic appearance, target organ restriction, and prolonged disease course depict a benign process. It appears that our current knowledge of these "neoplasms" does not allow us to lump them together with more complex disorders such as lung cancers. Perhaps the word "controversial" taken from the LAM Foundation website best summarizes this labeling.

What is the benefit of this proposed official designation? The benefit will not lay in the minds of patients or clinicians. There is an aura and stigma about cancer that profoundly affects the psychological impact of having a disease. The authors quote the positive responses to this designation from women with LAM who participated in two separate discussions of "LAM and Cancer." What about the newly diagnosed patient? How would this affect their hope, expectations, and clinical performance?

Branding LAM as a cancer will not affect the current or future involvement of oncologists and cell and molecular biologists. Although formal trials with chemotherapeutic drugs have not been used in LAM, it is unlikely that this labeling will affect new

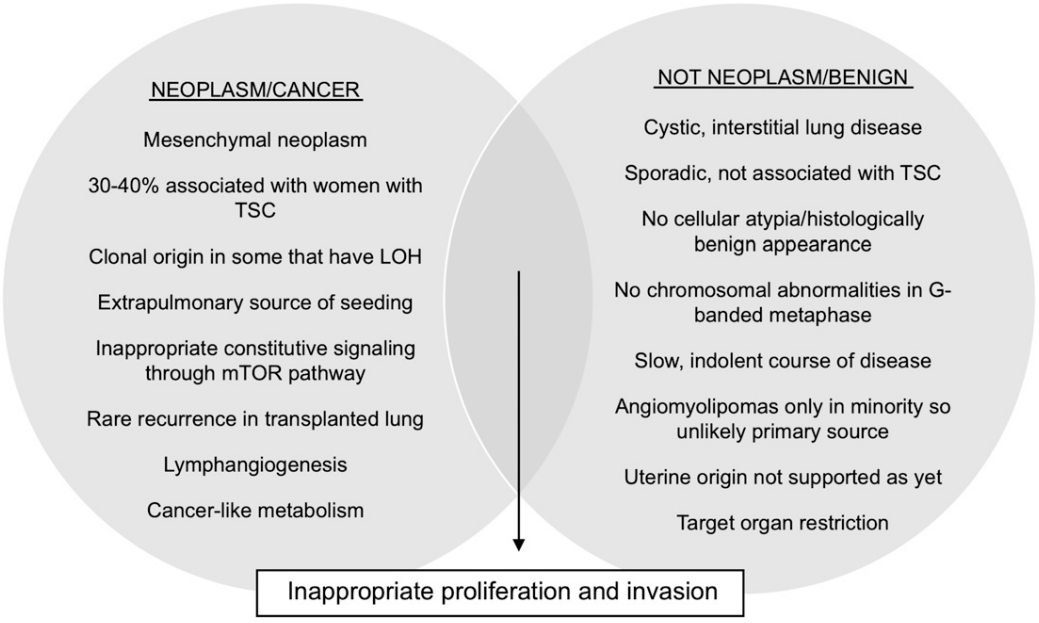

Figure 1. Is lymphangioleiomyomatosis (LAM) benign or malignant? The diagram shows the diverse features of LAM that could be argued to support one designation over the other. The only common feature between them is inappropriate proliferation and invasion. LOH = loss of heterozygosity; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

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.

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

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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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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.

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

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