

Screening for Lymphangioleiomyomatosis by High-Resolution Computed Tomography in Young, Nonsmoking Women Presenting with Spontaneous Pneumothorax Is Cost-Effective

Jared T. Hagaman¹, Daniel P. Schauer², Francis X. McCormack¹, and Brent W. Kinder¹

¹Division of Pulmonary, Critical Care, and Sleep Medicine and ²Division of General Internal Medicine, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio

Rationale: Women with pulmonary lymphangioleiomyomatosis (LAM) who present with a sentinel spontaneous pneumothorax (SPTX) will experience an average of 2.5 additional pneumothoraces. The diagnosis of LAM is typically delayed until after the second pneumothorax.

Objectives: We hypothesized that targeted screening of an LAM-enriched population of nonsmoking women between the ages of 25 and 54 years, who present with a sentinel pneumothorax indicated by high-resolution computed tomography (HRCT), will facilitate early identification, definitive therapy, and improved quality of life for patients with LAM.

Methods: We constructed a Markov state-transition model to assess the cost-effectiveness of screening. Rates of SPTX and prevalence of LAM in populations stratified by age, sex, and smoking status were derived from the literature. Costs of testing and treatment were extracted from 2007 Medicare data. We compared a strategy based on HRCT screening followed by pleurodesis for patients with LAM, versus no HRCT screening.

Measurements and Main Results: The prevalence of LAM in nonsmoking women, between the ages of 25 and 54 years, with SPTX is estimated at 5% on the basis of the available literature. In our base case analysis, screening for LAM by HRCT is the most cost-effective strategy, with a marginal cost-effectiveness ratio of \$32,980 per quality-adjusted life-year gained. Sensitivity analysis showed that HRCT screening remains cost-effective for groups in which the prevalence of LAM in the population subset screened is greater than 2.5%.

Conclusions: Screening for LAM by HRCT in nonsmoking women age 25–54 that present with SPTX is cost-effective. Physicians are advised to screen for LAM by HRCT in this population.

Keywords: pneumothorax; lymphangioleiomyomatosis; high-resolution computed tomography; cost-effectiveness; decision analysis

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease that classically affects women of reproductive age (1, 2). LAM occurs in 30% of patients with tuberous sclerosis (3–5), and also sporadically (s-LAM) in women without tuberous sclerosis. Smooth muscle infiltration and cystic destruction of the lung lead to progressive dyspnea and respiratory failure (6, 7). Owing to the uncommon nature of the disease (approximately 1–3 cases per million) (7) and the nonspecific nature of symptoms, the diagnosis of LAM is often delayed for several years into the disease process (8). Typical chest high-resolution computed tomography (HRCT) findings associated with LAM include reticular parenchymal opacities and thin-walled, 2- to 5-mm cysts, often in a diffuse distribution. Pleural effusion and retrocural

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with lymphangioleiomyomatosis (LAM) often present with spontaneous pneumothorax as the initial manifestation of the disease. The diagnosis of LAM is often delayed for several years into the disease course.

What This Study Adds to the Field

Performing high-resolution computed tomography to screen for LAM in young and middle-aged nonsmoking women who present with spontaneous pneumothorax is cost-effective.

lymphadenopathy are also often reported (9). Although the “gold standard” for diagnosis is thoracoscopic lung biopsy, in the appropriate clinical setting and with characteristic imaging features the diagnosis can be made by HRCT alone (7, 10, 11).

Spontaneous pneumothorax is a major cause of morbidity in patients with LAM (12). Indeed, 70% of patients with LAM have a pneumothorax at some point in their disease course, and pneumothorax is the presenting manifestation in 55% (13). Those with spontaneous pneumothorax are likely to experience one or more recurrences; the average number of lifetime pneumothoraces in a woman presenting with a sentinel pneumothorax is 3.5 (13). The morbidity and added cost from hospitalizations and complications associated with pneumothorax, in addition to the psychological effects from fear of recurrent pneumothorax and/or sudden respiratory death, can be debilitating for patients with LAM (14). Surgical and chemical pleurodesis has been shown to be effective in reducing the occurrence of recurrent pneumothorax (13). Identification of LAM in women who present with spontaneous pneumothorax might allow for earlier diagnosis and interventions to reduce the likelihood of recurrent pneumothorax. The LAM Foundation, a patient advocacy foundation, recommends HRCT screening for all nonsmoking women presenting with spontaneous pneumothorax (15). However, spontaneous pneumothorax is a relatively common occurrence in the population at large. In order for screening for LAM to be cost-effective, screening must be restricted to a smaller, LAM-enriched population, such as nonsmoking women of an appropriate age range presenting with spontaneous pneumothorax. Data to support this position are lacking, however, and primary care providers and emergency medicine physicians in the United States are more likely to treat spontaneous pneumothorax conservatively, without HRCT, pleurodesis, or biopsy (16). Information regarding the cost-effectiveness of screening might encourage appropriately aggressive screening and thereby improve outcomes. In addition to early

(Received in original form October 15, 2009; accepted in final form February 17, 2010)

Correspondence and requests for reprints should be addressed to Brent W. Kinder, M.D., 231 Albert Sabin Way, ML 0564, Cincinnati, OH 45267. E-mail: brent.kinder@uc.edu

Am J Respir Crit Care Med Vol 181, pp 1376–1382, 2010

Originally Published in Press as DOI: 10.1164/rccm.200910-1553OC on February 18, 2010
Internet address: www.atsjournals.org

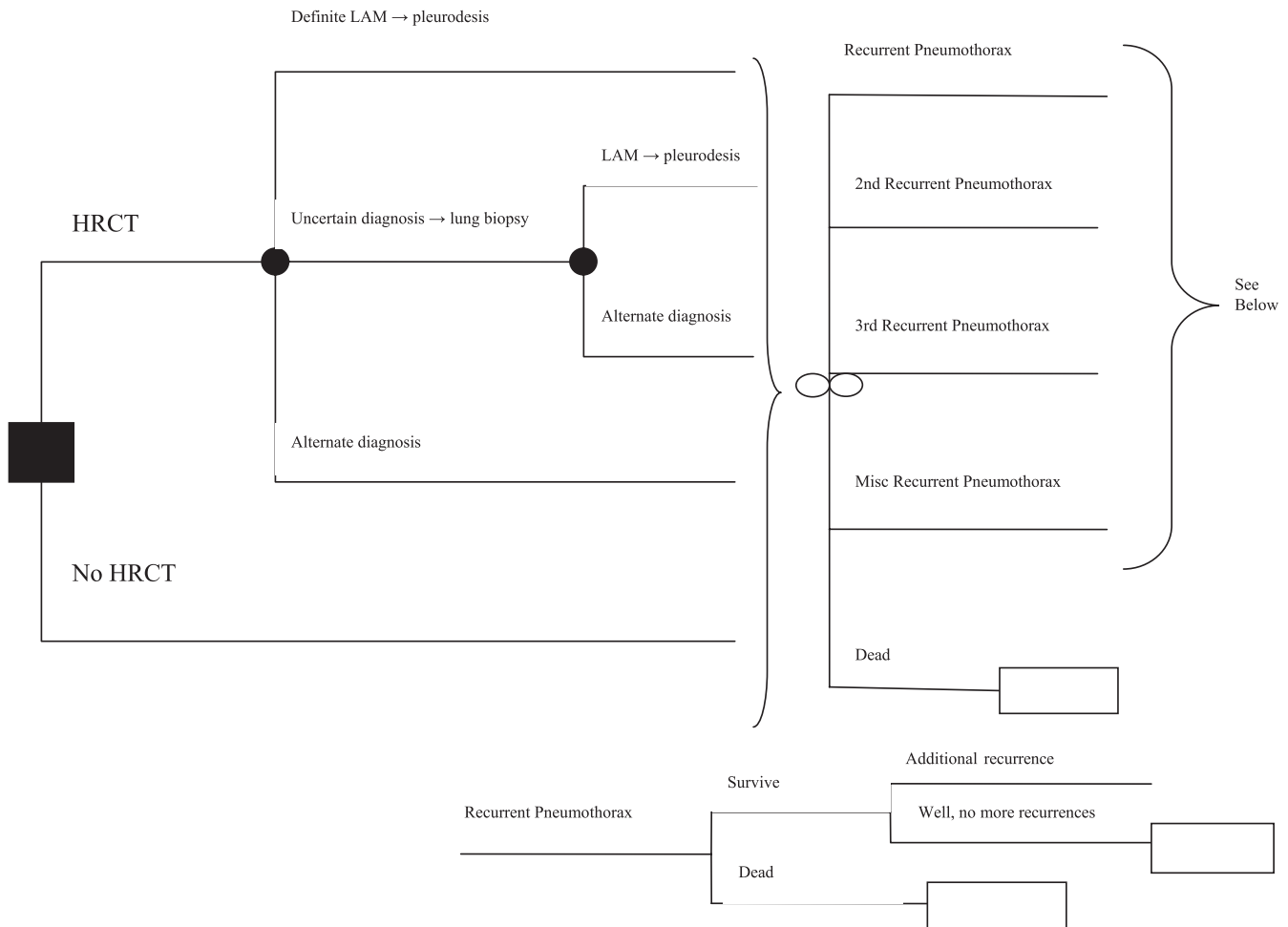


Figure 1. Simplified schematic of model. The *solid square* represents the decision node where the initial decision is made by the practicing clinician (to obtain high-resolution computed tomography [HRCT] or not). Each *solid circle* represents a chance node where the likelihood of a given outcome is defined by a probability entered into the model. Each arm of the tree ultimately ends in the Markov node (∞ symbol). In the Markov node, patients progress through various health states dictated by probabilities entered into the model. These probabilities are different, depending on how the individual entered the Markov node (e.g., a patient with lymphangioliomyomatosis [LAM] who develops pleurodesis has a lower probability of recurrent pneumothorax than a patient with LAM who did not). In each cycle (arbitrarily defined as 3 mo), patients are subjected to risk of recurrent pneumothorax or age/sex-related death. In each state, costs and quality adjustment factors are applied and tabulated. These cycles repeat until all patients are dead. Outcomes can then be compared for each strategy tested (HRCT vs. no HRCT).

identification of LAM, other cystic lung disorders could be identified early in the disease course, allowing for intervention.

Our hypothesis was that for nonsmoking women between the ages of 25 and 54 years who present with spontaneous pneumothorax, screening for LAM by HRCT is cost-effective. Some of the results of this study have been previously reported in the form of an abstract at the American Thoracic Society annual meeting, in May 2009 (17).

METHODS

Model

We constructed a Markov state-transition simulation model, using data from the literature and a standard software program (Decision Maker; Boston, MA) to analyze decision trees and perform sensitivity analyses (Figure 1). In our base case analysis, we assumed a 30-year-old, nonsmoking female presented to an emergency department or primary care clinic with a spontaneous pneumothorax. We evaluated two strategies after presentation and management with simple pleural drainage or observation. The first strategy used no further diagnostic

or therapeutic intervention after initial management. The second strategy employed HRCT scanning to screen for LAM. Findings on HRCT were categorized in three ways: pathognomonic findings of LAM leading to final diagnosis, indeterminate findings requiring further evaluation, and findings leading to an alternative diagnosis. Those model subjects with CT and clinical findings that were pathognomonic for LAM proceeded to pleurodesis so as to reduce the risk of recurrent pneumothorax. Those with indeterminate findings underwent open lung biopsy to establish a diagnosis. If patients were found to have a histopathological diagnosis of LAM on open lung biopsy, pleurodesis was performed. If an alternate diagnosis was found after biopsy, and for those with an alternative diagnosis on CT, no further intervention was performed. In companion analyses, we also evaluated a strategy in which chest CT was performed only after the first recurrence of pneumothorax. When patients underwent lung biopsy or pleurodesis, we applied a short-term reduction in quality of life (QOL) associated with the procedure, and also modeled potential procedural complications and costs.

After these initial management decisions, we modeled the risk of recurrent pneumothorax. On the basis of previously published data, we assumed the risk of pneumothorax was maximal in the months immediately after the initial event, and tapered to 0 over 24 months.

After an initial recurrent pneumothorax, a loss in QOL was applied over the next 12 months, maximal over the first few months, and tapering to baseline QOL by 1 year. We made similar assumptions after all subsequent recurrent pneumothoraces. The model was designed so that any number of recurrences could occur, but the rates were structured in such a fashion so that few patients would have greater than four recurrences (consistent with clinical observation).

Given that the prevalence of angiomyolipoma in LAM is approximately 30–50% (19), abdominal imaging can often aid in the diagnosis of LAM. To explore the impact of adjunctive abdominal imaging, we constructed a model with an additional arm in which patients with cystic lung changes suggestive of, but nondiagnostic for, LAM on chest CT underwent subsequent abdominal CT to evaluate for angiomyolipoma. In the presence of cystic lung changes and angiomyolipomata, we assumed that patients with LAM could be diagnosed and then pleurodesed without antecedent open lung biopsy. This strategy was then compared with the others for cost-effectiveness.

We used a 3-month cycle length in which patients were exposed not only to recurrent pneumothorax, but also age- and sex-related death. We applied a discount rate of 3%/year by convention (18). All analyses of cost-effectiveness were conducted from the societal perspective.

Simplifying Assumptions

We made several simplifying assumptions in our model. First, we assumed that lung biopsy and pleurodesis, if indicated, would occur in the 3 months after initial presentation. Next, we treated all patients with any diagnosis other than LAM as having a clinical course subsequent to their sentinel event as being equivalent to those with primary spontaneous pneumothorax. Finally, we assumed that all patients diagnosed with LAM, either on the basis of HRCT alone or after lung biopsy, would choose to proceed with pleurodesis.

Summary of Data

LAM. LAM has an estimated prevalence in the general population of between 0.6 and 3 per million (19–22). We were specifically interested in the prevalence of LAM in women who present for medical evaluation with spontaneous pneumothorax, a population enriched for LAM (Table 1). The incidence of spontaneous pneumothorax in women is 1.2–9.8 per 100,000 per year (23–25). On the basis of the U.S. census in July 2007 (26), this equates to between 1,800 and 14,700 pneumothoraces in women per year in the United States. Sixty-eight percent of these cases are in the age range that is typical for LAM presentation (25–54 yr). The most common etiology of pneumothorax in this group is primary spontaneous pneumothorax, which occurs mostly (80%) in smokers (23). On the basis of these figures, between 245 and 2,000 spontaneous pneumothoraces occur in nonsmoking women aged 25–54 years each year in the United States. Over a 30-year period, the expected number of spontaneous pneumothoraces in this demographic would be between 7,350 and 60,000. Of the 850 U.S. patients that have been registered in the LAM Foundation Registry since 1995, the number of pneumothoraces estimated to have occurred during a three-decade period would be 2,550 (3 pneumothoraces per patient × 850 patients). We therefore predict that between 5 and 30% of all pneumothoraces in the selected demographic (nonsmoking women, age 25–54 yr) occurred in patients with LAM.

The gold standard for the diagnosis of LAM is histopathological confirmation, usually through thoracoscopic lung biopsy (27, 28). In many cases, however, the diagnosis can be made from HRCT in the

appropriate clinical context (such as a history of tuberous sclerosis, chylothorax, or angiomyolipoma) (7, 10, 11). Koyama and colleagues reported that a blinded review of HRCT scans by expert radiologists in 92 patients with unknown cystic lung disease yielded a diagnostic accuracy of 72% when compared with thoracoscopic lung biopsy (11). Another study (10) found that two expert radiologist were “confident” of the diagnosis of LAM in 79% of cases, with a sensitivity of 100% and specificity of 95%. Therefore, in our base case, we estimated that 80% of patients with LAM could be diagnosed by HRCT alone, and could be managed by pleurodesis without antecedent biopsy. Fifteen percent would be diagnosed after a suggestive HRCT led to biopsy, and 5% would be false negatives (an alternative diagnosis made). Lesur and colleagues performed CT on patients presenting with spontaneous pneumothorax, finding that more than half had findings of centrilobular emphysema, or cystic changes (29). On the basis of these findings, we assumed LAM would be excluded in 80% of patients with diseases other than LAM. Of the remaining 20%, we estimated that three quarters would go to lung biopsy and found to have an alternative diagnosis, and the rest would be false positives (those without LAM undergoing pleurodesis based on HRCT alone).

LAM often progresses to respiratory failure and/or respiratory-related death. Different groups that have examined series of patients with LAM have shown variation in survival between histological types and symptoms at presentation (30, 31). Johnson and colleagues studied a cohort of patients with LAM in the United Kingdom, and found a 10-year survival of 91% (30). Hayashida and colleagues reported that Japanese women with LAM have 5-, 10-, and 15-year survival rates of 91, 76, and 65%, respectively (20). As this Japanese study had the largest data set, and provided the longest period of follow-up, we used these figures to determine annual rates of mortality.

Pneumothorax and risk of recurrence. For patients with primary spontaneous pneumothorax, rates of recurrence have been shown to be as high as 30% if no preventive procedure is performed (e.g., pleurodesis), although rates are higher in women and smokers (32–34). The vast majority of recurrences occur within the first 6 months to 2 years after the initial event. After 2 years, rates of recurrence return to baseline risk. For those with at least one recurrence, few data are available on subsequent recurrences. We assumed the rate of second recurrence to be 15%, most occurring in the first 6 months to 2 years, followed by a return to baseline risk (32). Pleurodesis after the initial pneumothorax in primary spontaneous pneumothorax reduces rates of recurrence to 1.5% (32). We assumed the rate of second recurrence after pleurodesis was 0%.

In patients with LAM and pneumothorax, 70% will have an ipsilateral recurrence (13). Unlike primary spontaneous pneumothorax, risk of recurrence for patients with LAM does not decrease with time (12, 13). Of these patients with recurrence, 60% will have a third recurrence and many will have additional episodes beyond that. Pleurodesis in patients with LAM reduces the rate of recurrent pneumothorax to 32% (13).

Quality of life and life expectancy. Death is rare with primary spontaneous pneumothorax, occurring in less than 1% of patients (24, 33, 35). It is, however, associated with significant morbidity. Morimoto and colleagues have evaluated pneumothorax, and its impact on quality-adjusted life measures (36). Quality of life estimates vary from 1 (perfect health) to 0 (death) (37). After a pneumothorax, life quality is reduced by a factor of 0.37, so the quality adjustment factor is 0.63. After the second and all subsequent pneumothoraces, QOL is reduced by 0.5. This loss of QOL persists for 1 year after each

TABLE 1. PREVALENCE ESTIMATES OF LYMPHANGIOLEIOMYOMATOSIS IN PATIENTS PRESENTING WITH SPONTANEOUS PNEUMOTHORAX

Population	Number of Pneumothoraces in Population per Year	Proportion of Pneumothoraces Secondary to LAM
Women in the United States*	1,800–14,700	0.5–4.8%
Women aged 25–54 yr (68%)	1,224–12,036	0.7–6.9%
Nonsmoking women aged 25–54 yr (20%)†	979–9629	0.8–8.4%

Definition of abbreviation: LAM = lymphangioleiomyomatosis.

* Based on 1.2 to 9.8 spontaneous pneumothoraces per 100,000 women per year (23–25).

† Estimates that 85 pneumothoraces per year are secondary to LAM, and 83 of those are in nonsmokers (23).

TABLE 2. DATA USED IN MODEL

	Base Case	Values Tested in Sensitivity Analysis	Reference
Prevalence of LAM in population tested	5%	0.8–8.4%	
Probability of LAM diagnosis on HRCT alone (no biopsy required)	80%	50–100%	10, 11
Probability of LAM diagnosis after HRCT and biopsy	15%	10–40%	10, 11
Probability of negative HRCT in patients with LAM (false negative rate)	5%	1–10%	10, 11
Proportion of patients without LAM who undergo lung biopsy	15%	10–30%	10, 11
Proportion of patients without LAM who are given LAM diagnosis on HRCT alone (false positive rate)	1%	0–5%	10, 11
Proportion of patients without LAM in which LAM is ruled out on basis of HRCT alone (true negatives)	94%	90–100%	10, 11
Probability of recurrent pneumothorax in:			
Patient with diagnosis other than LAM and no pleurodesis	20%	16–52%	32
Patient with diagnosis other than LAM after undergoing pleurodesis	1.5%	0–5%	32
Patient with LAM and no pleurodesis	66%	42–90%	13
Patient with LAM after undergoing pleurodesis	32%	20–52%	13
Probability of a second recurrent pneumothorax in:			
Patient with diagnosis other than LAM and no pleurodesis	15%	10–20%	32
Patient with diagnosis other than LAM after undergoing pleurodesis	0%	0–2%	32
Patient with LAM and no pleurodesis	60%	40–80%	13
Patient with LAM after undergoing pleurodesis	6.4%	4–8%	13
Quality of Life:			
First pneumothorax (short term)	0.63	N/A	36
Recurrent pneumothorax (short term)	0.45	N/A	36
Pleurodesis (short term)	0.35	N/A	36
Thoracoscopic lung biopsy (short term)	0.35	N/A	36
LAM (QOL to diminish annually over 20-yr period)	0.60	N/A	8
Costs			
Pneumothorax*	\$10,098	\$5,000–\$15,000	
Pleurodesis†	\$20,054	\$15,000–\$25,000	
Thoracoscopic lung biopsy‡	\$20,488	\$15,000–\$25,000	

Definition of abbreviations: CPT = current procedural terminology code; DRG = diagnosis-related group code; HRCT = high-resolution computed tomography; LAM = lymphangioleiomyomatosis; N/A = not applicable; QOL = quality of life.

* DRG 95, CPT 99223, 99232 × 2, 33020 × 1, 71015 × 3.

† DRG 76, CPT 99222, 99232 × 3, 32005, 71015 × 3.

‡ DRG 76, CPT 99222, 99232 × 3, 32402, 71015 × 3.

event, and returns to baseline thereafter. In our model, we structured the quality adjustment so that QOL was lowest in the period immediately after pneumothorax and gradually returns to normal over the course of 1 year.

LAM is associated with a progressive decline in respiratory function. On the basis of reports from the National Heart, Lung, and Blood Institute LAM Registry and others, we estimated LAM to be associated with a reduction in QOL equal to 0.02/year (8, 30). Lung biopsy and pleurodesis are also associated with a short-term reduction in QOL. In their study of spontaneous pneumothorax, Morimoto and colleagues reported QOL to be reduced by a factor of 0.65 with these procedures (36). We assumed this reduction persisted over 14 days after the procedure.

Costs. All costs are expressed in 2007 U.S. dollars. Details of the costing models are described in Table 2. The costs of adverse events included both institutional and professional services. For procedures, office visits, and hospitalizations, average Medicare reimbursement for the corresponding Current Procedural Terminology or Diagnosis-related Group codes was used as a proxy for cost. We did not formally include indirect costs, such as lost income due to absence from work during hospital stays. Costs were subjected to sensitivity analyses to determine how changes in baseline values would affect results.

Alternative strategies. We also explored the impact of several alternative but plausible strategies on the cost-effectiveness of screen-

ing: performing HRCT only after the first recurrence of pneumothorax, performing adjunctive abdominal CT after HRCT screening, and performance of open-lung biopsy and subsequent pleurodesis in tandem (at a contemporaneous time).

RESULTS

The results of the base case analysis are shown in Table 3. The strategy that employed the HRCT screening strategy was both more costly and more effective. The marginal cost-effectiveness ratio (mCER) of HRCT screening was \$32,980 per quality-adjusted life-year (QALY) gained. By convention, treatment strategies costing less than \$50,000/QALY gained are deemed to be “cost-effective” (38). We also performed the analysis on female populations with variable smoking status presenting with spontaneous pneumothorax (Figure 2). HRCT screening in these populations was more expensive, owing in part to the lower prevalence of LAM. For example, 18- to 25-year-old smokers have a far greater incidence of primary spontaneous pneumothorax than does our base case population (25- to 54-year-old nonsmokers). Therefore, the prevalence of LAM in this population is lower, and the costs of screening greater. For older

TABLE 3. RESULTS OF BASE CASE ANALYSIS*

	Cost	Effectiveness (QALY)	Marginal Cost	Marginal Effectiveness (QALY)	mCER (\$/QALY)
No screening	\$9,467	15.932			
HRCT screening	\$11,642	15.998	\$2,176	0.066	\$32,980

Definition of abbreviations: HRCT = high-resolution computed tomography; mCER = marginal cost-effectiveness ratio; QALY = quality-adjusted life years.

* Thirty-year-old, nonsmoking female, presenting with spontaneous pneumothorax.

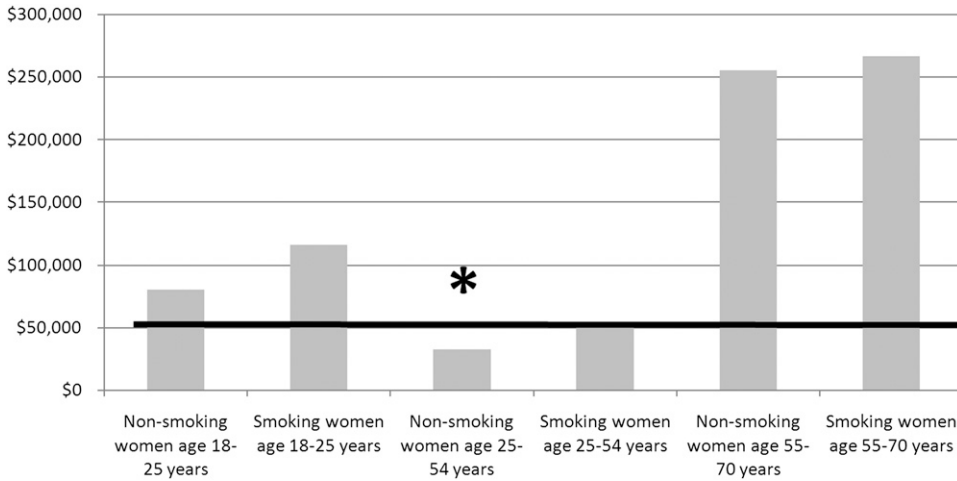


Figure 2. Marginal cost-effectiveness ratio (mCER) of high-resolution computed tomography (HRCT) screening for lymphangioleiomyomatosis (LAM) in various populations of women who present with spontaneous pneumothorax. This analysis illustrates the importance of selecting the appropriate patient population for screening by HRCT. In populations with a lower prevalence of LAM, the marginal cost-effectiveness ratio increases dramatically. By convention, treatment strategies with an mCER of less than \$50,000 per quality-adjusted life-year gained are considered to be “cost-effective.” The asterisk (*) denotes the base case.

populations, emphysema is responsible for a greater number of pneumothoraces, not only leading to a lower prevalence of LAM, but also to a higher false positive rate on HRCT. This will result in additional unnecessary lung biopsies, which diminishes the cost-effectiveness of screening.

Our initial strategy of HRCT screening after the initial pneumothorax remained the most cost-effective strategy when compared with the alternative strategies of HRCT only after the first recurrence or performing abdominal CT after HRCT. HRCT screening after the initial pneumothorax cost only an additional \$8,661/QALY gained compared with waiting until after the first recurrence, and just \$36,819/QALY gained compared with the abdominal CT arm.

Results of important sensitivity analyses are shown in Figure 3. The results of our model were most affected by changes in the probability of diagnosing LAM based on HRCT findings alone, and the prevalence of LAM in the population tested. If LAM could be diagnosed by HRCT alone and biopsy avoided in 100% of cases, HRCT screening costs as little as \$15,679 per QALY gained. Conversely, when we assumed biopsy could be avoided in just 50% of cases, HRCT screening is considerably more expensive (\$178,101/QALY). Likewise, the prevalence of LAM in the population tested had a profound effect on our results. At the lowest prevalence rates tested (0.08%) screening is costly (\$85,291/QALY), whereas at higher prevalence rates (8.4%), screening cost falls well below

the cost-effectiveness threshold (\$26,570/QALY). This further emphasizes the importance of selecting the appropriate population for screening. There is considerable variability in clinical practice regarding the timing of the performance of open-lung biopsy and subsequent pleurodesis. In our base case analysis, we considered these procedures to be done successively in different settings. We also considered another scenario in which the procedures were done in tandem (one setting). This scenario would further enhance the cost-effectiveness of the HRCT screening versus the no-CT arm (\$17,179/QALY gained). As seen in Figure 3, other variables tested had a less profound impact on our results. All other variables and costs used in the model were tested in sensitivity analyses, and did not significantly impact the results of the model over a clinically plausible range (data not shown).

DISCUSSION

We have demonstrated that screening for LAM by HRCT in women presenting with spontaneous pneumothorax can be cost-effective in an appropriately selected patient population (non-smokers, age 25–54 yr). On the basis of our assumption of a prevalence of 5% in this population, 20 patients would need to be screened to identify 1 patient with LAM. Our data indicate that the benefits of early diagnosis outweigh the costs of screening these unaffected individuals. As is true for all

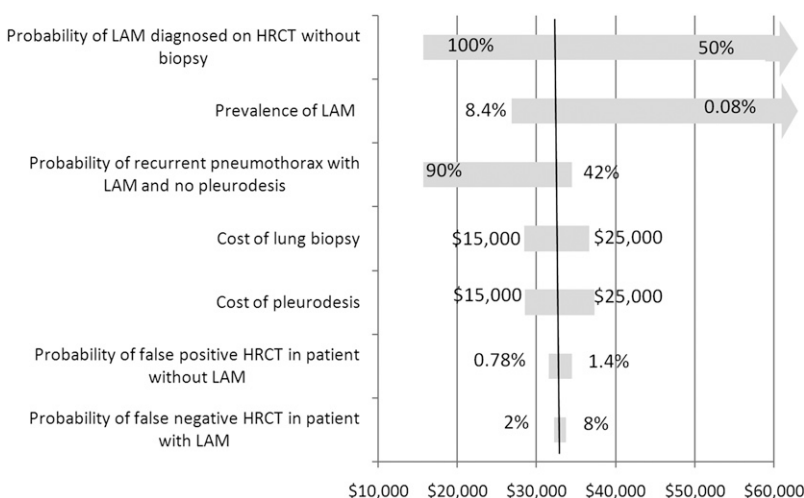


Figure 3. Tornado plot demonstrating results of important sensitivity analyses. The purpose of sensitivity analyses is to explore the effects of variations in data input on the results of the model. Data input is varied from the lowest clinically reasonable value to the highest (or 95% confidence interval), illustrating the change in results if the “base case” assumptions are invalid. The marginal cost-effectiveness ratio in dollars per quality-adjusted life-year (QALY) is shown on the x axis and ranges from \$15,000 to \$194,000/QALY. The analyses with arrows at the right end of the band indicate that the results have been truncated because we only plotted marginal cost-effectiveness ratios up to \$60,000/QALY. Values at the top, such as the probability of diagnosing lymphangioleiomyomatosis (LAM) based on high-resolution computed tomography (HRCT) alone, show a larger effect on cost-effectiveness across their confidence intervals; thus, resolving uncertainty in these measurements would improve predictions of cost-effectiveness. Uncertainty in the value of measurements (bottom) has a smaller effect on the results of the analysis.

screening tests, our results also indicate that in other populations with a lower prevalence of LAM, HRCT screening is less cost-effective. In addition, our results indicate that HRCT screening after the first pneumothorax is more cost-effective than waiting until after the first recurrence.

In our model, all benefits from early diagnosis of LAM were derived from pleurodesis, and prevention of additional spontaneous pneumothoraces. In reality, early diagnosis provides many other less tangible benefits that we did not account for in our analysis. For example, novel therapies for LAM are currently being developed and tested. The Cincinnati Angiomyolipoma Sirolimus Trial (NCT00457808) suggested that sirolimus may have a role in the treatment of LAM (39), and provided the basis for The MILES Trial (NCT00414648)—an NIH-funded, multicenter, multinational, randomized, placebo-controlled trial of sirolimus in LAM. Other therapies for LAM are also being studied (40, 41). Early diagnosis would provide greater access to such clinical trials, and add to the benefits incurred with testing. Early diagnosis will also allow patients with LAM to make informed decisions regarding air travel (42), smoking cessation, and oral contraceptive use (43). Family planning and counseling can also be provided as pregnancy can have potentially devastating effects on the health of patients with LAM (43). As many patients with LAM progress to respiratory failure and require lung transplantation (44–47), selection of agents for pleurodesis can be of great importance. An early diagnosis of LAM informs the choice of approaches to pleurodesis (such as mechanical abrasion or chemical pleurodesis rather than pleurectomy or talc pleurodesis) that have the lowest risks of perioperative bleeding at the time of transplantation (13). Given that renal angiomyolipomas are found in up to half of patients with LAM, earlier diagnosis might also aid in earlier identification of this manifestation of the disease process and related complications such as catastrophic abdominal bleeding (48, 49). Finally, support networks such as the LAM Foundation are available, and provide patients with LAM with education, support, and a mechanism to facilitate research. Although difficult to incorporate in this type of cost-effectiveness analysis, these less tangible benefits should be considered.

Our study has several limitations. As with all analyses of this type, our model relies on previously published data. Efforts to account for potential imprecision in parameter estimates are made through sensitivity analysis. Our reliance on epidemiologic data for spontaneous pneumothorax is one such example as inaccuracies in these data could impact the validity of our estimates for the prevalence of LAM in given populations. The studies cited here, although well-conducted epidemiologic evaluations, are somewhat older and involve disparate populations (23, 24, 50). Absent the availability of direct data, this limitation cannot be eliminated. Another example of a particularly influential model assumption is the diagnostic accuracy of HRCT (combined with clinical features) for LAM. We had to rely on imperfect, but best available estimates from the literature (10, 11). An additional potential limitation of our analysis is that we assume all patients with spontaneous pneumothorax who are found to have LAM will go on to pleurodesis. This is not always congruent with the wishes of patients with LAM (14). Patients are biased toward conservative management of first pneumothoraces, and many will choose to manage the initial pneumothorax conservatively, deferring pleurodesis until after the subsequent pneumothoraces. This would certainly impact the cost-effectiveness of testing, but we believe the nontangible benefits of early diagnosis noted previously may balance this effect. Last, as we used Medicare reimbursement data as a proxy for costs, our conclusions should be tempered for international

readers, as differences in costs in different health systems may lead to different outcomes of the model.

In conclusion, through the use of decision-modeling techniques, we have shown that HRCT screening for LAM in nonsmoking women age 25–54 years who present with spontaneous pneumothorax is cost-effective. As a result, primary care providers and emergency medicine physicians treating this population are advised to consider performing HRCT in this patient population.

Conflict of Interest Statement: J.T.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.P.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.X.M. received \$1,001–\$5,000 from the Lilly Protein Advisory Board (inhaled insulin), \$1,001–\$5,000 from the Teijin Company in lecture fees, and more than \$100,001 from the Wyeth (MILES Trial) in sponsored grants; has a patent from the University of Cincinnati/Cincinnati Children's Hospital Medical Center for VEGF-D as a diagnostic for LAM (no personal benefit) and from the University of Cincinnati for collectins as antioxidants and antibacterials; B.W.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

- Hohman DW, Noghrehkar D, Ratnayake S. Lymphangioliomyomatosis: a review. *Eur J Intern Med* 2008;19:319–324.
- Hancock E, Osborne J. Lymphangioliomyomatosis: a review of the literature. *Respir Med* 2002;96:1–6.
- Franz DN. Non-neurologic manifestations of tuberous sclerosis complex. *J Child Neurol* 2004;19:690–698.
- Moss J, Avila NA, Barnes PM, Litzemberger RA, Bechtel J, Brooks PG, Hedin CJ, Hunsberger S, Kristof AS. Prevalence and clinical characteristics of lymphangioliomyomatosis (LAM) in patients with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2001; 164:669–671.
- Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioliomyomatosis in women with tuberous sclerosis complex. *Mayo Clin Proc* 2000;75:591–594.
- McCormack FX. Lymphangioliomyomatosis: a clinical update. *Chest* 2008;133:507–516.
- Johnson SR. Lymphangioliomyomatosis. *Eur Respir J* 2006;27:1056–1065.
- Ryu JH, Moss J, Beck GJ, Lee JC, Brown KK, Chapman JT, Finlay GA, Olson EJ, Ruoss SJ, Maurer JR, et al. The NHLBI Lymphangioliomyomatosis Registry: characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med* 2006;173:105–111.
- Abbott GF, Rosado-de-Christenson ML, Frazier AA, Franks TJ, Pugatch RD, Galvin JR. From the archives of the AFIP: lymphangioliomyomatosis: radiologic-pathologic correlation. *Radiographics* 2005;25:803–828.
- Bonelli FS, Hartman TE, Swensen SJ, Sherrick A. Accuracy of high-resolution CT in diagnosing lung diseases. *AJR Am J Roentgenol* 1998;170:1507–1512.
- Koyama M, Johkoh T, Honda O, Tsubamoto M, Kozuka T, Tomiyama N, Hamada S, Nakamura H, Akira M, Ichikado K, et al. Chronic cystic lung disease: diagnostic accuracy of high-resolution CT in 92 patients. *AJR Am J Roentgenol* 2003;180:827–835.
- Almoosa KF, McCormack FX, Sahn SA. Pleural disease in lymphangioliomyomatosis. *Clin Chest Med* 2006;27:355–368.
- Almoosa KF, Ryu JH, Mendez J, Huggins JT, Young LR, Sullivan EJ, Maurer J, McCormack FX, Sahn SA. Management of pneumothorax in lymphangioliomyomatosis: effects on recurrence and lung transplantation complications. *Chest* 2006;129:1274–1281.
- Young LR, Almoosa KF, Pollock-Barziv S, Coutinho M, McCormack FX, Sahn SA. Patient perspectives on management of pneumothorax in lymphangioliomyomatosis. *Chest* 2006;129:1267–1273.
- The LAM Foundation. (Accessed February 27, 2009.) Available from: <http://www.thelamfoundation.org>
- Baumann MH, Strange C, Hefner JE, Light R, Kirby TJ, Klein J, Luketich JD, Panacek EA, Sahn SA. Management of spontaneous pneumothorax: an American College of Chest Physicians delphi consensus statement. *Chest* 2001;119:590–602.
- Hagaman JT, Schauer DP, McCormack FX, Kinder BW. The cost-effectiveness of screening for lymphangioliomyomatosis with high-

- resolution CT in women presenting with spontaneous pneumothorax [abstract]. Presented at the American Thoracic Society International Conference, May 15–20, 2009, San Diego, CA.
18. Eisenberg JM. Clinical economics: a guide to the economic analysis of clinical practices. *JAMA* 1989;262:2879–2886.
 19. Urban T, Lazor R, Lacroinque J, Murriss M, Labrune S, Valeyre D, Cordier JF; Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Pulmonary lymphangioleiomyomatosis: a study of 69 patients. *Medicine* 1999;78:321–337.
 20. Hayashida M, Seyama K, Inoue Y, Fujimoto K, Kubo K. The epidemiology of lymphangioleiomyomatosis in Japan: a nationwide cross-sectional study of presenting features and prognostic factors. *Respirology* 2007;12:523–530.
 21. Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 1995;151:527–533.
 22. Oh YM, Mo EK, Jang SH, Yoo CG, Kim YW, Seo JW, Han SK, Im JG, Shim YS. Pulmonary lymphangioleiomyomatosis in Korea. *Thorax* 1999;54:618–621.
 23. Bense L, Eklund G, Wiman LG. Smoking and the increased risk of contracting spontaneous pneumothorax. *Chest* 1987;92:1009–1012.
 24. Gupta D, Hansell A, Nichols T, Duong T, Ayres JG, Strachan D. Epidemiology of pneumothorax in England. *Thorax* 2000;55:666–671.
 25. Melton LJ 3rd, Hepper NG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. *Am Rev Respir Dis* 1979;120:1379–1382.
 26. U.S. Census Bureau 2009 information. (Accessed February 27, 2009.) Available from: <http://www.census.gov>.
 27. Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangiomyomatosis: a review. *Am J Pathol* 1975;79:348–366.
 28. Carrington CB, Cugell DW, Gaensler EA, Marks A, Redding RA, Schaaf JT, Tomasian A. Lymphangioleiomyomatosis: physiologic-pathologic-radiologic correlations. *Am Rev Respir Dis* 1977;116:977–995.
 29. Lesur O, Delorme N, Fromaget JM, Bernadac P, Polu JM. Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. *Chest* 1990;98:341–347.
 30. Johnson SR, Whale CI, Hubbard RB, Lewis SA, Tattersfield AE. Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004;59:800–803.
 31. Matsui K, Beasley MB, Nelson WK, Barnes PM, Bechtel J, Falk R, Ferrans VJ, Moss J, Travis WD. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. *Am J Surg Pathol* 2001;25:479–484.
 32. Schramel FM, Postmus PE, Vanderschueren RG. Current aspects of spontaneous pneumothorax. *Eur Respir J* 1997;10:1372–1379.
 33. Baumann MH. Management of spontaneous pneumothorax. *Clin Chest Med* 2006;27:369–381.
 34. Sadikot RT, Greene T, Meadows K, Arnold AG. Recurrence of primary spontaneous pneumothorax. *Thorax* 1997;52:805–809.
 35. O'Rourke JP, Yee ES. Civilian spontaneous pneumothorax: treatment options and long-term results. *Chest* 1989;96:1302–1306.
 36. Morimoto T, Fukui T, Koyama H, Noguchi Y, Shimbo T. Optimal strategy for the first episode of primary spontaneous pneumothorax in young men: a decision analysis. *J Gen Intern Med* 2002;17:193–202.
 37. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care* 1996;34:702–722.
 38. Detsky AS. Using cost-effectiveness analysis to improve the efficiency of allocating funds to clinical trials. *Stat Med* 1990;9:173–184.
 39. 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.
 40. Moses MA, Harper J, Folkman J. Doxycycline treatment for lymphangioleiomyomatosis with urinary monitoring for MMPs. *N Engl J Med* 2006;354:2621–2622.
 41. Fernandez-Fernandez FJ, Buno-Ramilo B, Sesma P. Lymphangioleiomyomatosis. *Eur J Intern Med* 2009;20:e24.
 42. Pollock-BarZiv SM, Cohen MM, Downey GP, Johnson SR, Sullivan E, McCormack FX. Air travel in women with lymphangioleiomyomatosis. *Thorax* 2007;62:176–180.
 43. Oberstein EM, Fleming LE, Gomez-Marin O, Glassberg MK. Pulmonary lymphangioleiomyomatosis (LAM): examining oral contraceptive pills and the onset of disease. *J Womens Health (Larchmt)* 2003;12:81–85.
 44. Kpodonu J, Massad MG, Chaer RA, Caines A, Evans A, Snow NJ, Geha AS. The US experience with lung transplantation for pulmonary lymphangioleiomyomatosis. *J Heart Lung Transplant* 2005;24:1247–1253.
 45. Pechet TT, Meyers BF, Guthrie TJ, Battafarano RJ, Trulock EP, Cooper JD, Patterson GA. Lung transplantation for lymphangioleiomyomatosis. *J Heart Lung Transplant* 2004;23:301–308.
 46. Reynaud-Gaubert M, Mornex JF, Mal H, Treilhaud M, Dromer C, Quetant S, Leroy-Ladurie F, Guillemain R, Philit F, Dauriat G, Grenet D, Stern M. Lung transplantation for lymphangioleiomyomatosis: The French experience. *Transplantation* 2008;86:515–520.
 47. Boehler A, Speich R, Russi EW, Weder W. Lung transplantation for lymphangioleiomyomatosis. *N Engl J Med* 1996;335:1275–1280.
 48. Bissler JJ, Kingswood JC. Renal angiomyolipomata. *Kidney Int* 2004;66:924–934.
 49. Avila NA, Dwyer AJ, Rabel A, Moss J. Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: comparison of CT features. *Radiology* 2007;242:277–285.
 50. Melton LJ III, Bartleson JD. Spontaneous pneumothorax and multiple sclerosis. *Ann Neurol* 1980;7:492.