

NEW CLINICAL TEST FOR LYMPHANGIOLEIOMYOMATOSIS (LAM)

QUANTIFICATION OF HUMAN VASCULAR ENDOTHELIAL GROWTH FACTOR D (VEGF-D) IN SERUM

Lymphangioleiomyomatosis (LAM) is a rare lung disease which affects almost exclusively women. About 80% of women with confirmed LAM have elevated serum levels of VEGF-D. Quantification of VEGF-D can be used to distinguish LAM from other cystic lung diseases with similar HRCT appearances, and thus may obviate the need for surgical lung biopsy in a significant proportion of patients with LAM who present for diagnostic evaluation.

The first blood test for a serious but often misdiagnosed lung disease, developed at Cincinnati Children's Hospital Medical Center and the University of Cincinnati in conjunction with the Australian company Circadian Technologies Ltd (ASX:CIR), is now available for clinical use.

The new test helps diagnose Lymphangioleiomyomatosis (LAM), a lung disease that causes shortness of breath and lung collapse. It affects mostly women, often striking during child-bearing years. LAM occurs in a rare sporadic form in about 5 per million persons, but also develops in approximately 40% of women with Tuberous Sclerosis Complex (TSC). These estimates, when compared to registries of known LAM patients around the world, suggest that at least 250,000 women are undiagnosed and unaware they have LAM.

Serum VEGF-D was recently validated by Cincinnati Children's as a clinical test, using Circadian's VEGF-D technology, following the discovery that high levels of vascular endothelial growth factor-D (VEGF-D) are diagnostic for LAM in

women with cystic lung disease on chest CT scan. A study reporting the diagnostic link between LAM and VEGF-D was published in the Aug. 10th, 2010 edition of *Chest* by a team of scientists led by Lisa Young, MD, director of the Pediatric Rare Lung Diseases Program at Cincinnati Children's and Frank McCormack, MD, director of the Division of Pulmonary, Critical Care and Sleep Medicine at the University of Cincinnati. "We are optimistic that serum VEGF-D will join the ranks of diagnostic tests for lung disease, reduce the need for surgical lung biopsy and allow for intervention and trial recruitment earlier in the disease course," says McCormack, who also serves as scientific director of the LAM Foundation.

In a cross sectional study, serum VEGF-D was highly associated with the presence of LAM in women with TSC. Both the TSC Consensus Committee (Roach *et al.*, 1999) and European Respiratory Society (Johnson *et al.*, *Eur Respir J* 2010; 35) recommend that women with TSC should have a high resolution computerized tomography (HRCT) scan of the chest upon reaching maturity, age 14–26. "A test which predicts the presence of LAM in women with TSC could potentially reduce the need for serial CT scanning to detect LAM, and limit the lifetime radiation exposure of these patients," said Dr. Young.

In a recent multicenter trial, serum VEGF-D levels were found to decrease in response to treatment with sirolimus. This University of Cincinnati and Cincinnati Children's based study, which also demonstrated that sirolimus stabilizes lung function and improves some measures of functional performance and quality of life in LAM, was published in the March 16th, 2011 online edition of



The New England Journal of Medicine. Additional research is underway to determine if serum VEGF-D has utility as a biomarker of disease severity, progression or treatment response, and as a screening test for LAM in females with TSC.

The new LAM diagnostic test complies with CAP/CLIA regulations established by the College of American Pathologists.

Doctors in the U.S. can order this test through the Translational Trials Development and Support Laboratory at Cincinnati Children's.

<http://www.cincinnatichildrens.org/ttdsl>.

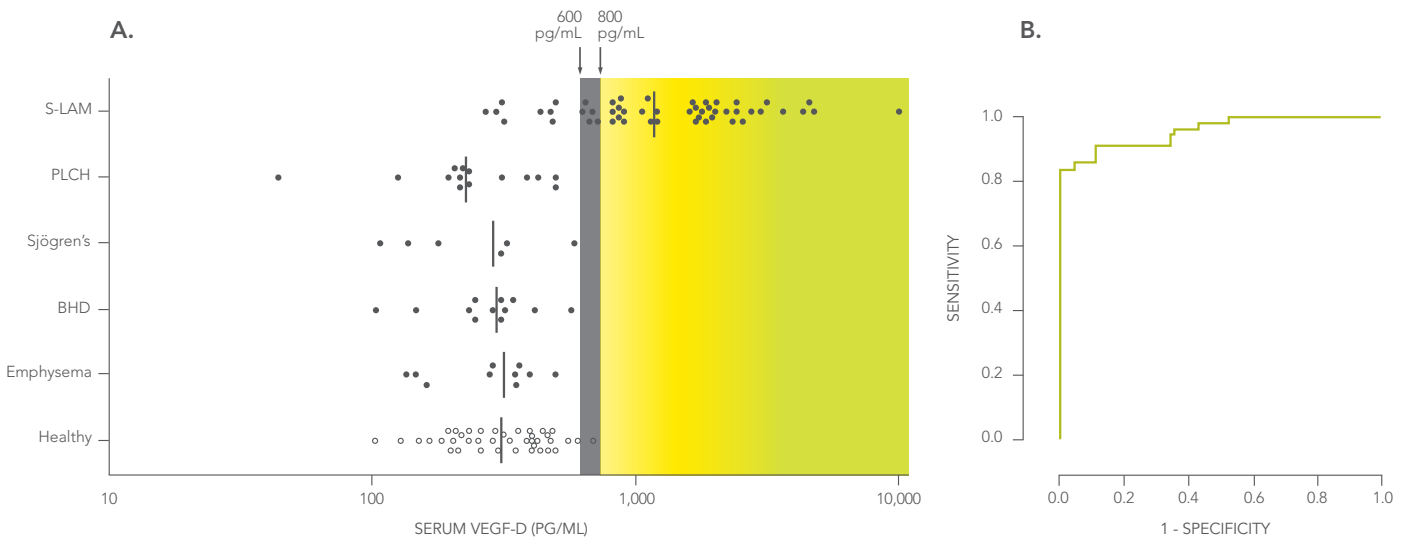
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FIGURE 1.

Test performance of serum VEGF-D levels in distinguishing women with Sporadic Lymphangioliomyomatosis (S-LAM) from those with other cystic lung diseases which mimic LAM.



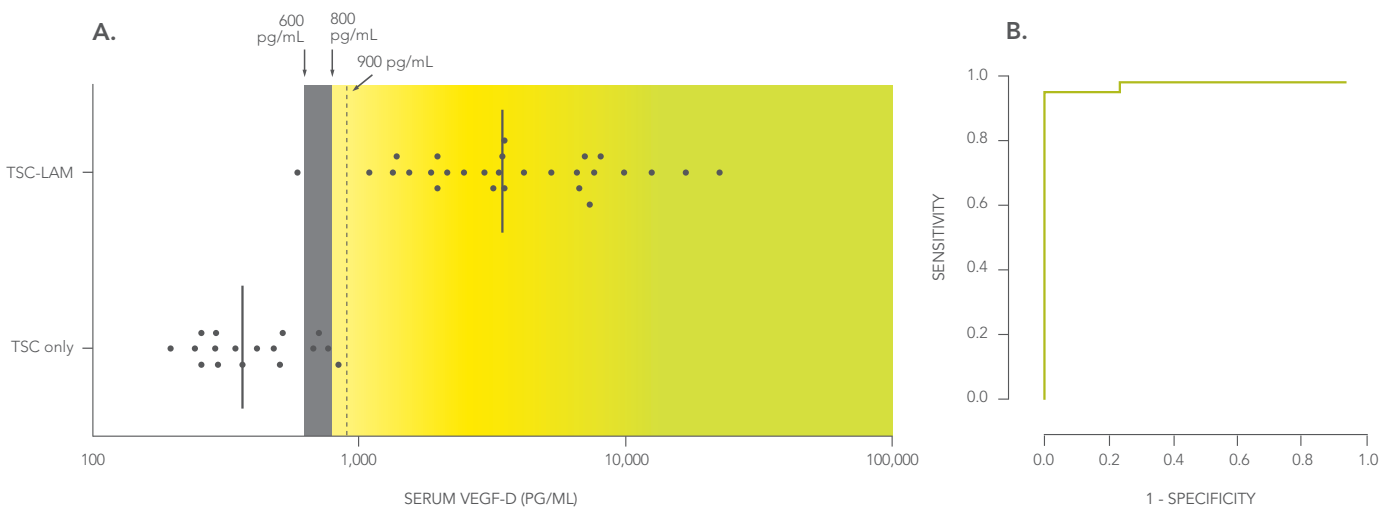
A. Serum VEGF-D levels in the combined prospective and retrospective cohorts of subjects with definite S-LAM versus female subjects with other cystic lung diseases, as proven by biopsy and/or genetic testing, and healthy volunteers. Lines denote median values for each group, and proposed cut-off values are shown.

B. ROC curve for LAM versus other cystic lung diseases. Data included are from subjects with definite sporadic LAM (n=56) in comparison to females with the other cystic lung diseases (emphysema, pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome (BHD), and Sjögren's syndrome with follicular bronchiolitis, n=44 total). Healthy volunteers are not included in this analysis. Area under the ROC curve is 0.961±0.018 (95% CI 0.923 to 0.992).

Adapted from Young LR et al. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioliomyomatosis from other diseases. *Chest* 2010 **138**(3): 674–81.

FIGURE 2.

Test performance of serum VEGF-D levels in discriminating the presence or absence of LAM in women with Tuberous Sclerosis Complex (TSC), an at-risk population.



A. Results of VEGF-D testing in women with TSC-LAM (n=28) versus women with TSC only (n=17). Women with TSC only were defined as those with the absence of cysts on chest within 18 months of VEGF-D testing. Lines denote median values for each group, and performance at proposed cut-off values is shown. Note that the dotted line indicates that a higher cut-off value of 900 pg/mL would be needed to achieve 100% specificity in this setting.

B. ROC curve for VEGF-D in women with TSC-LAM versus TSC only. Area under the ROC curve is 0.992±0.010 (95% CI 0.973 to 1.0).

Adapted from Young LR et al. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioliomyomatosis from other diseases. *Chest* 2010 **138**(3): 674–81.