

# Julia, a young woman with TSC who develops LAM



**Los Angeles  
TSC/LAM Joint  
Conference**  
November 2, 2019

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Taylor Professor and Director  
Pulmonary, Critical Care and Sleep Medicine  
The University of Cincinnati

# Agenda

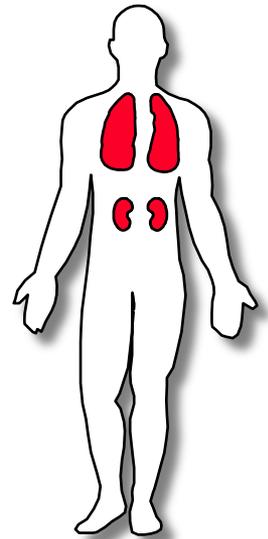
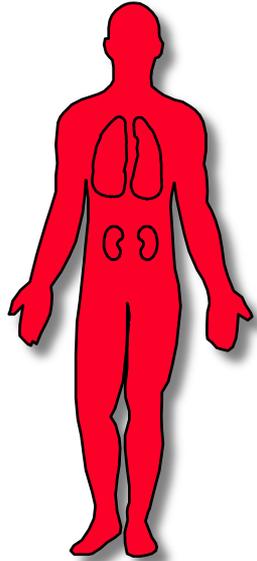
- We are going walk through the case of a fictional young lady with TSC, Julia, followed in a Tuberos Sclerosis Clinic
- We will spend a few minutes describing LAM first

# What is LAM and what causes it?

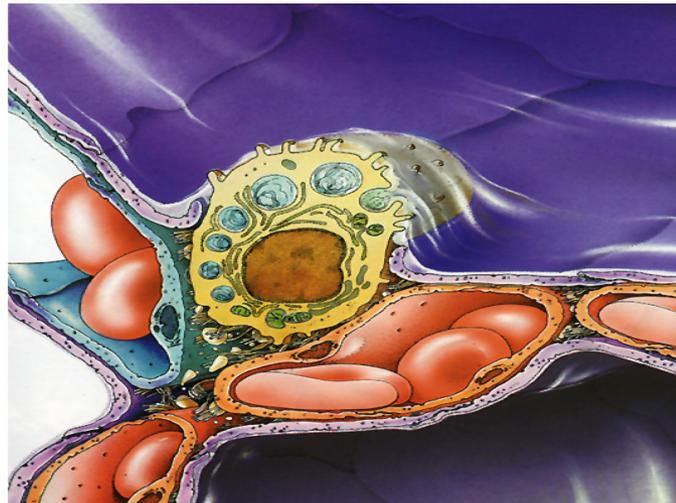
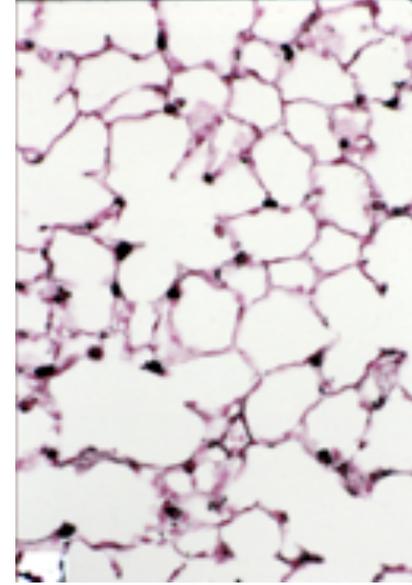
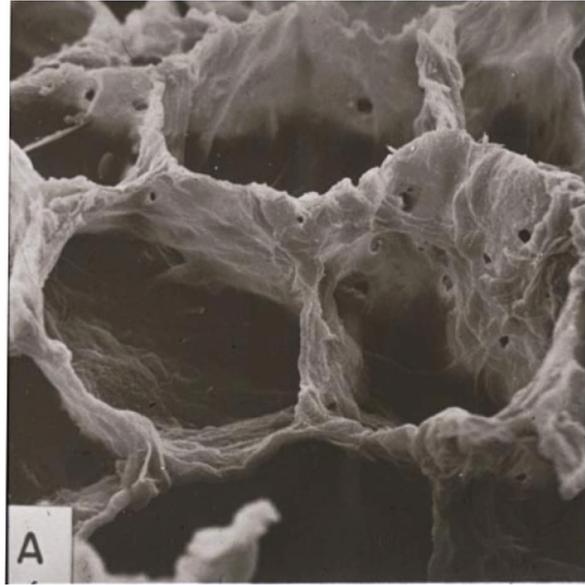
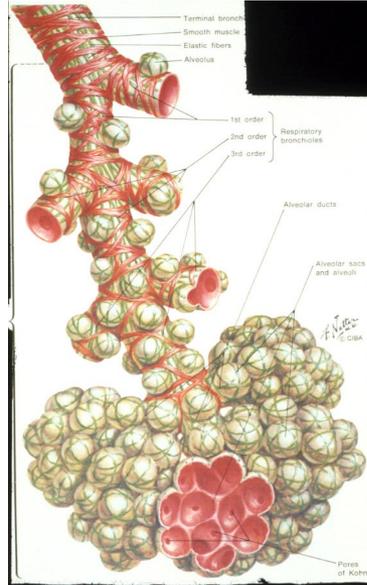
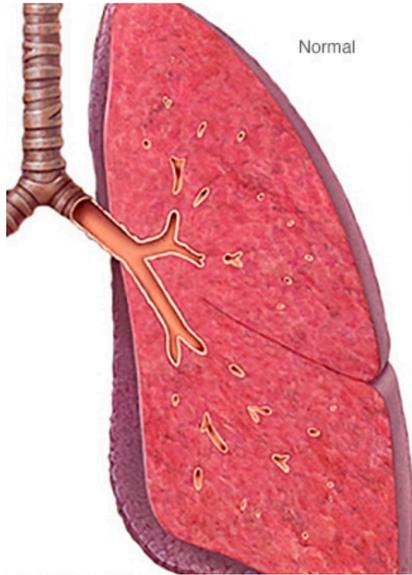
- A rare lung disease that
  - Produces holes in the lung, called cysts, which limit airflow and uptake of oxygen
  - Predominant affects females, mostly in reproductive years
    - Affects about 40% of women in the TSC Clinic, and 15-20% of those will develop symptoms at some point
    - Affects about 10% of men in TSC Clinic, who only very rarely have symptoms
  - Can occur in patients who have TSC or do not have TSC

# There are two forms of LAM

- LAM in patients with TSC.
  - There is a DNA mistake in one copy of the TSC gene in every cell in the body
  - LAM and other abnormal growths occur when a mistake occurs in the other copy
  - We call this TSC-LAM
- LAM in patients who do not have TSC
  - There are mistakes in both copies of the TSC gene, but only in the affected tissues (often lung and kidney)
  - We call this sporadic LAM, or S-LAM

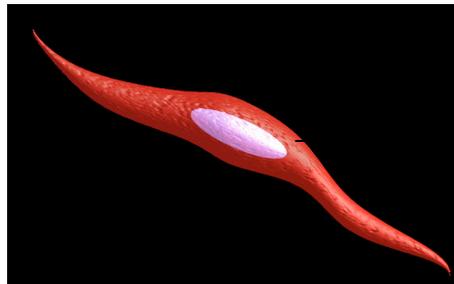
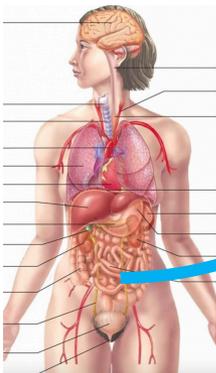
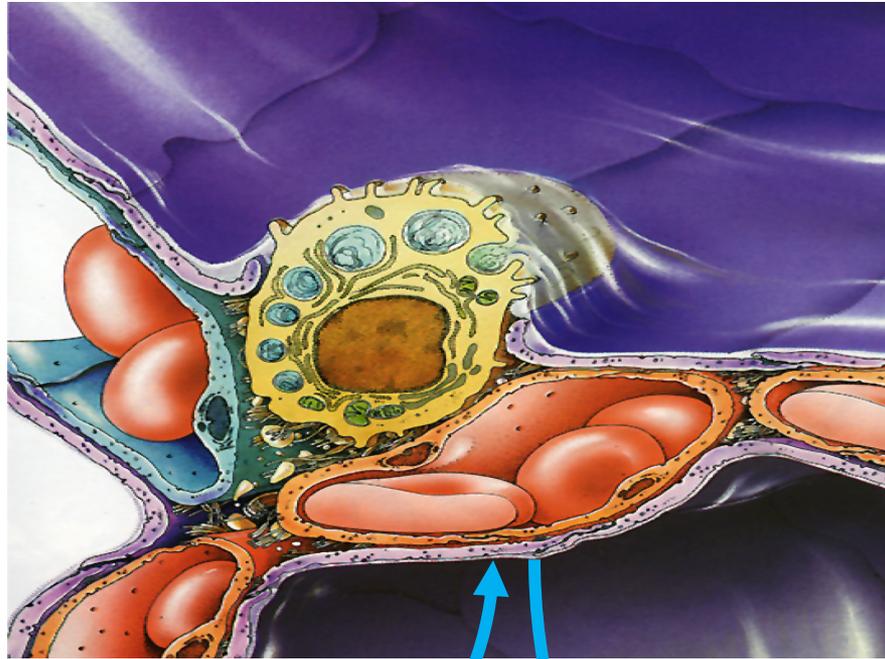
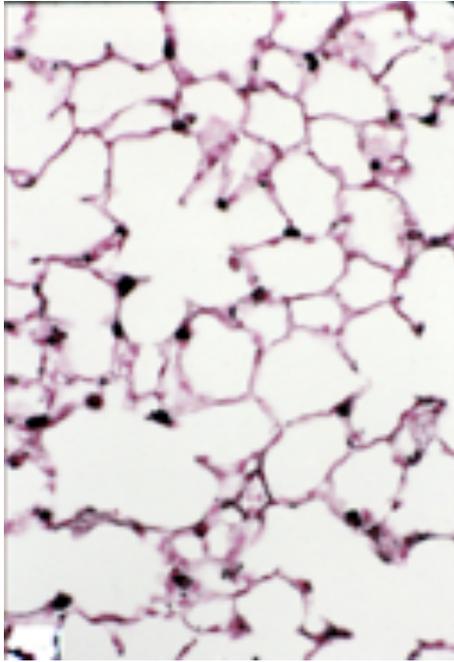


The lung is made up a trillion building blocks called cells, that have special functions and form blood vessels, airways and air sacs.

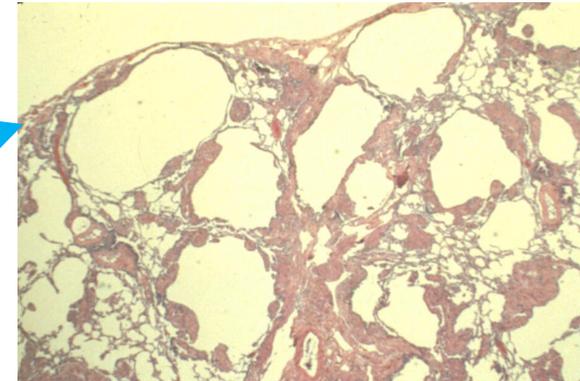


# What causes LAM

Smooth muscle-like cells with DNA mistakes arise from an unknown source, migrate to the lung, infiltrate all structures, and dissolve lung tissues, creating holes

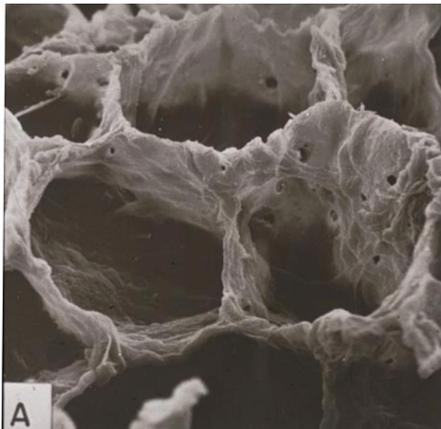
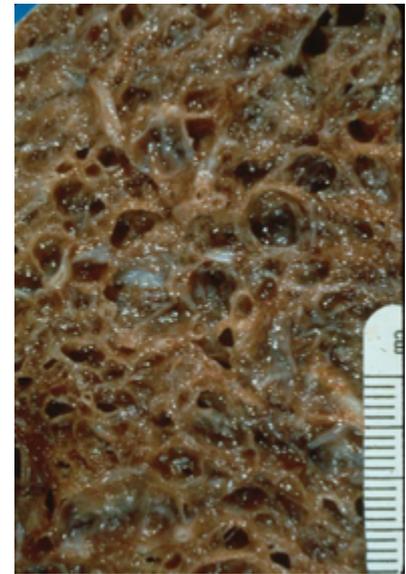


LAM smooth muscle cell



# What is LAM?

- A disorder in which the lung develops holes that replace the tiny air sacs, limiting oxygen uptake and lung function



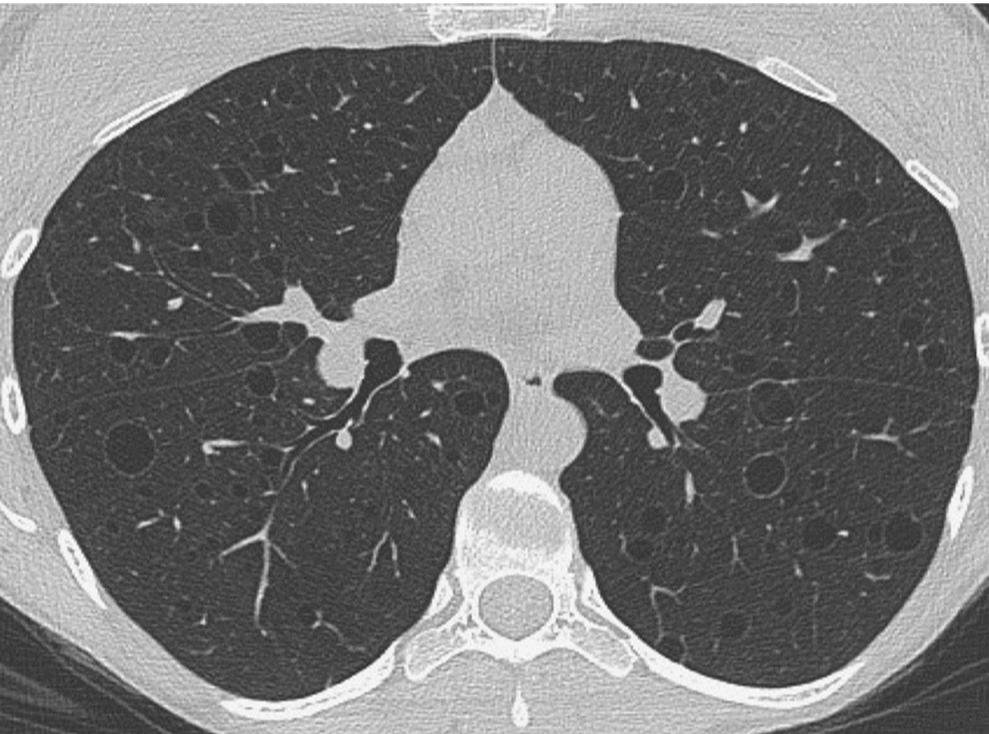
**Normal**      **LAM**



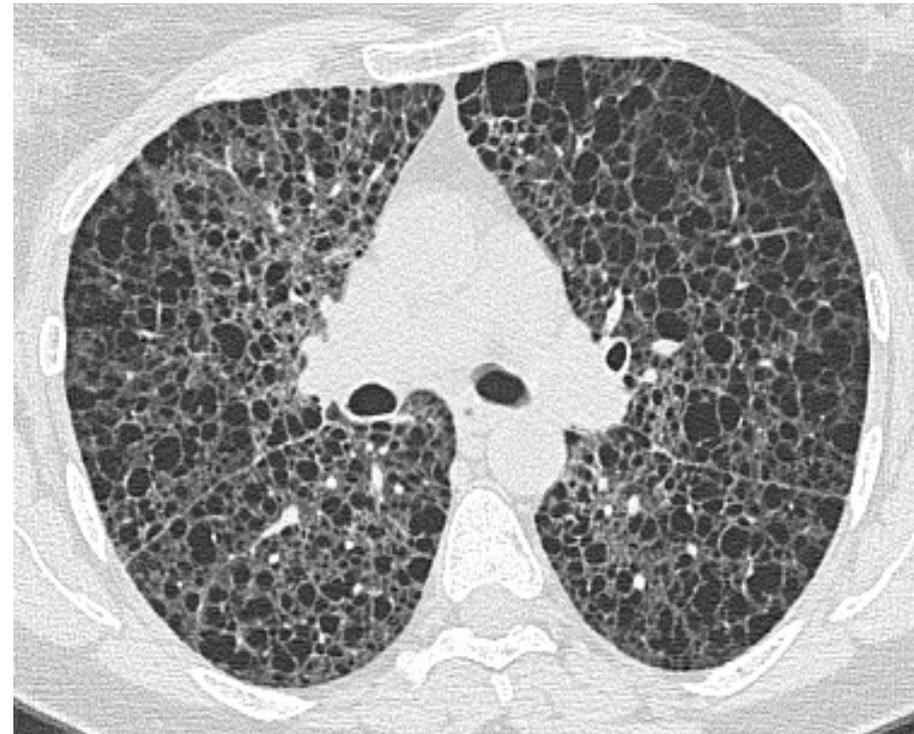
# Air filled cysts are found on the CT scan of the chest in patients with LAM

## Cyst characteristics:

- Round
- Uniform
- Thin-walled
- Diffuse distribution

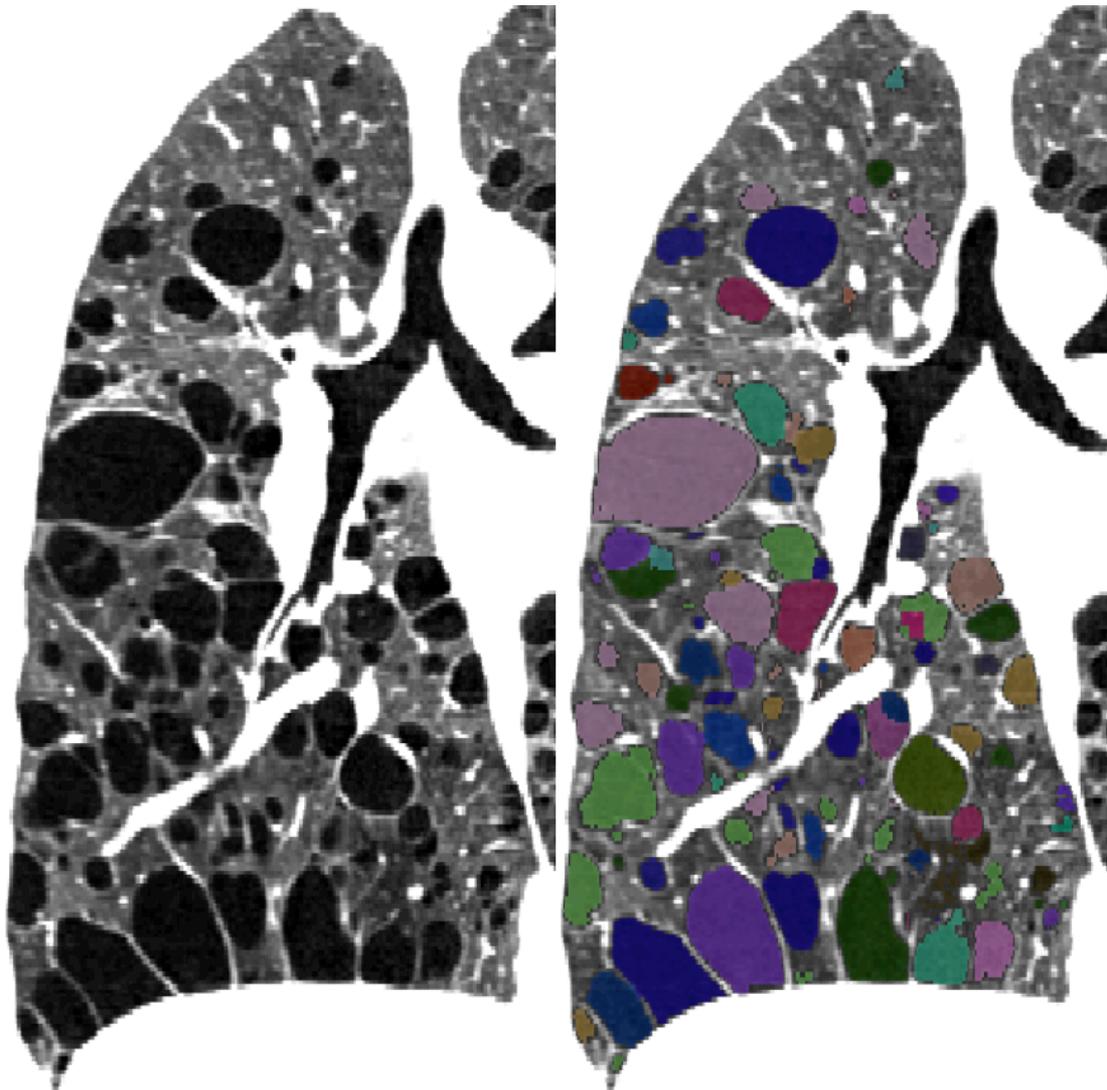


Early, mild LAM



Late stage, advanced LAM

# Coronal view of a LAM lung



# Some differences between sporadic LAM and TSC-LAM

Sporadic LAM	TSC LAM
TSC mutations only in lung and kidney	TSC mutations in all cells
Not inheritable	Can be 'inherited'
Often treated with sirolimus	Often treated with everolimus
Often discovered when shortness of breath develops or after pneumothorax	Often discovered earlier, in milder forms

# Julia



- Julia has TSC with facial angiofibromas, subungual fibromas, bilateral angiomyolipomas, and cortical tubers, a past history of seizures and some cognitive impairment that limits her ability to contribute to the history
- She has no pulmonary symptoms and she does not smoke
- She will be 18 years old next month
- The pediatric neurologists asked me to talk to the patient and family about LAM.

# Meeting Julia and her parents

- Julia's parents have read about LAM, and they are concerned about this new health challenge.
- The first three things I typically say to families are:
  - Women with TSC frequently develop some cysts in the lung consistent with LAM
  - But the majority of women with TSC will never have symptoms due to LAM
  - And if LAM is discovered in your daughter, we have effective ways to treat it.

# Tuberous Sclerosis Guidelines

Pediatric Neurology 49 (2013) 243–254



Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: [www.elsevier.com/locate/pnu](http://www.elsevier.com/locate/pnu)



## Diagnosis

Original Article

### **Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference**

**Hope Northrup MD<sup>a,\*</sup>, Darcy A. Krueger MD PhD<sup>b</sup>, on behalf of the International Tuberous Sclerosis Complex Consensus Group**

<sup>a</sup> Division of Medical Genetics, Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas

<sup>b</sup> Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio

Pediatric Neurology 49 (2013) 255–265



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## Management

Original Article

### **Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference<sup>☆</sup>**

**Darcy A. Krueger MD PhD<sup>a,\*</sup>, Hope Northrup MD<sup>b</sup>, on behalf of the International Tuberous Sclerosis Complex Consensus Group**

<sup>a</sup> Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio

<sup>b</sup> Division of Medical Genetics, Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas

# American Thoracic Society LAM Guidelines

## AMERICAN THORACIC SOCIETY DOCUMENTS

### **Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management**

Francis X. McCormack, Nishant Gupta, Geraldine R. Finlay, Lisa R. Young, Angelo M. Taveira-DaSilva, Connie G. Glasgow, Wendy K. Steagall, Simon R. Johnson, Steven A. Sahn, Jay H. Ryu, Charlie Strange, Kuniaki Seyama, Eugene J. Sullivan, Robert M. Kotloff, Gregory P. Downey, Jeffrey T. Chapman, MeiLan K. Han, Jeanine M. D'Armiento, Yoshikazu Inoue, Elizabeth P. Henske, John J. Bissler, Thomas V. Colby, Brent W. Kinder, Kathryn A. Wikenheiser-Brokamp, Kevin K. Brown, Jean F. Cordier, Christopher Meyer, Vincent Cottin, Jan L. Brozek, Karen Smith, Kevin C. Wilson, and Joel Moss; on behalf of the ATS/JRS Committee on Lymphangioleiomyomatosis

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) AND JAPANESE RESPIRATORY SOCIETY (JRS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MAY 2016, AND BY THE JRS, MAY 2016

THIS CLINICAL PRACTICE GUIDELINE WAS ENDORSED BY THE LYMPHANGIOLEIOMYOMATOSIS FOUNDATION, MAY 2016

## AMERICAN THORACIC SOCIETY DOCUMENTS

### **Lymphangioleiomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management**

An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline

Nishant Gupta, Geraldine A. Finlay, Robert M. Kotloff, Charlie Strange, Kevin C. Wilson, Lisa R. Young, Angelo M. Taveira-DaSilva, Simon R. Johnson, Vincent Cottin, Steven A. Sahn, Jay H. Ryu, Kuniaki Seyama, Yoshikazu Inoue, Gregory P. Downey, MeiLan K. Han, Thomas V. Colby, Kathryn A. Wikenheiser-Brokamp, Christopher A. Meyer, Karen Smith, Joel Moss\*, and Francis X. McCormack\*; on behalf of the ATS Assembly on Clinical Problems

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY OCTOBER 2017 AND BY THE JAPANESE RESPIRATORY SOCIETY AUGUST 2017

# Guideline recommendations, screening for LAM

- I explain that TSC experts recommend that young women be screened for LAM at age 18, to get a sense of whether any LAM is present.
  - More than 80% of the time, there is no LAM present at this stage
  - If we find no cysts, the Guidelines recommend that she will not need another scan for 3-5 years, unless lung symptoms develop.

# Julia's parents have concerns about the CT

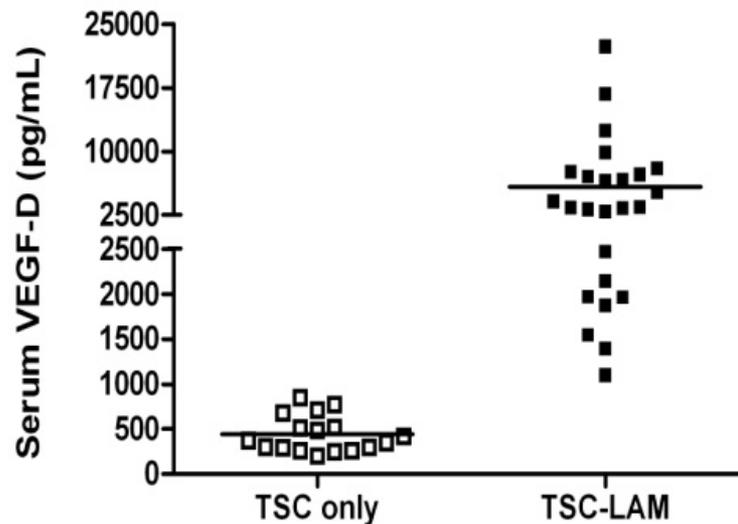
- Julia's parents ask about the radiation risk of a CT scan at her age
  - I explain that single CT exposes Julia to the same amount of radiation we all receive from a year of background radiation (cosmos, radon, rocks, etc)
  - We might be able to do a low dose radiation scan for the 5 year follow up, with about 50% less radiation

# **Julie has a normal chest CT**

- We obtain a high resolution CT scan and there are no cysts present. Julia parents are relieved.
- I tell Julia I will see her back during her annual visits to the TSC clinic, to ask about lung symptoms and measure VEGF-D in blood

# VEGF-D is elevated when cysts are present

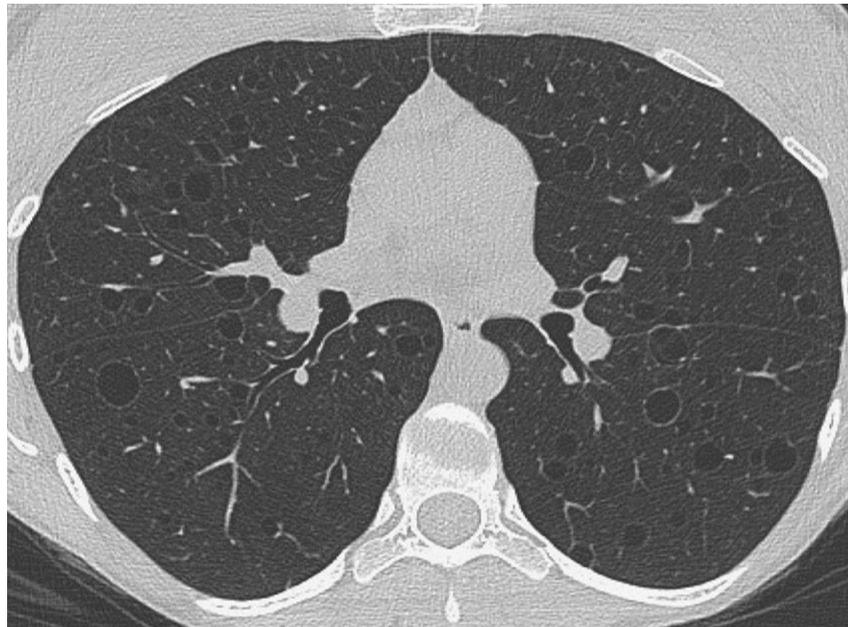
- VEGF-D is not yet proven to function well to screen for cyst development
  - We are optimistic this use will of the test will be validated, however.



TSC only = women with normal chest HRCT

# Julia now has some cysts on the scan

- I am now seeing Julia on her 23<sup>rd</sup> birthday.
- She has no lung symptoms, and she is not exposed to cigarette smoke.
- But her repeat CT shows some cysts on the CT



# **The diagnosis of LAM for Julia does not require any further testing**

- A confident diagnosis of LAM can be made based on the typical chest CT and her prior diagnosis of TSC

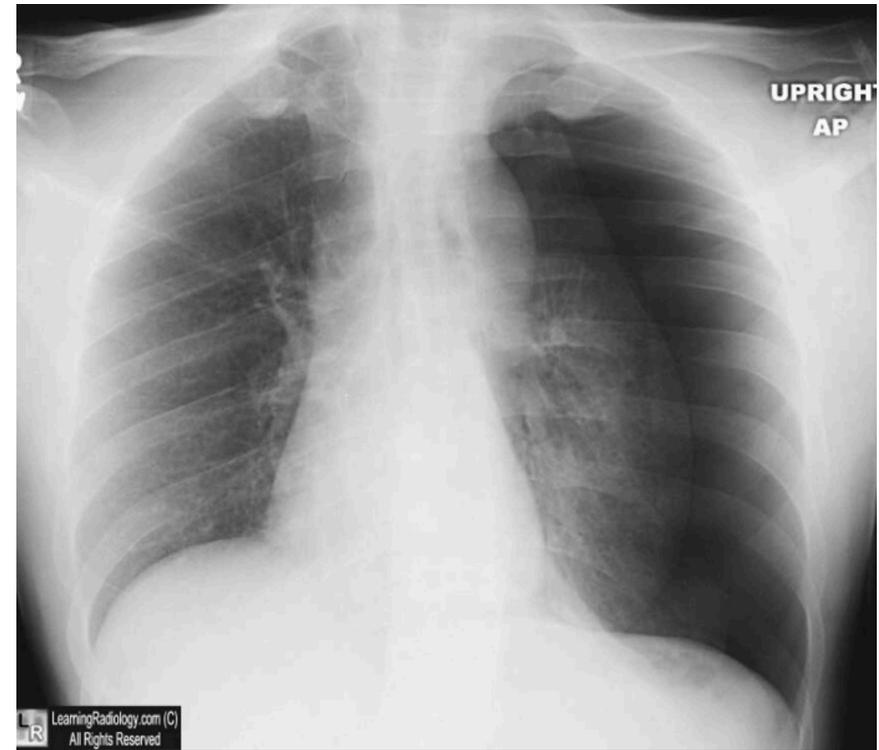
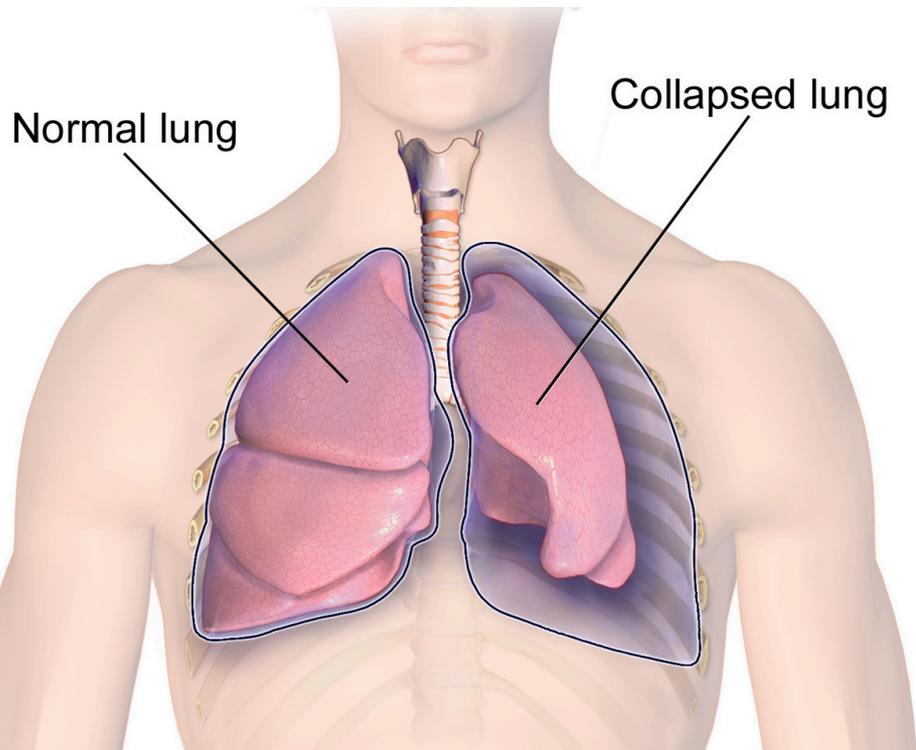
# **Julia's pulmonary function tests are normal**

- I explain that although the cyst changes are quite mild, and I don't think her pulmonary function tests (PFTs) will be abnormal, it would be a good idea to get some baseline studies.
- Julia's parents were not sure she will be able to cooperate well with the test, but she did them very well. PFTs are normal.

# **Julia has LAM and needs closer follow-up now**

- I explain that Julia does not meet criteria for treatment based on her lung findings, but that we should now follow more closely, and
  - Obtain pulmonary function tests every 6 months
  - Repeat the chest CT in 2-3 years to get an idea of whether the lung disease is progressing
  - We suggest that Julie should receive annual flu shots, and be vaccinated against pneumococcus with Prevnar and Pneumovax

# We also talk about pneumothorax, or collapsed lung, as a precaution



# Pneumothorax

- Pneumothorax occurs in up to 50% of TSC females with LAM
  - Symptoms include pleurisy and shortness of breath
- It was easily managed in most emergency rooms, by placement of a chest tube to drain the air
- Once it occurs, it is likely to recur, so the lung should be ‘glued’ up by pleurodesis
- Having pleurodesis would not exclude Julie from future lung transplant, if that was ever needed

# Julie is now 26

- Julia returns, and states that she notes some shortness of breath if she runs up the stairs.
- Her CT scan is now a bit worse, and her pulmonary function tests are now just outside the normal range (FEV1 69% predicted)
- She meets criteria to begin on mTOR inhibitor therapy, which include
  - FEV1 of less than 70% predicted
  - Rapid decline in lung function
  - Abnormal lung function other than FEV1, such as reduced diffusion or air trapping
  - Chylous effusions

# Sirolimus is an exquisitely targeted, effective treatment for LAM

The NEW ENGLAND JOURNAL of MEDICINE

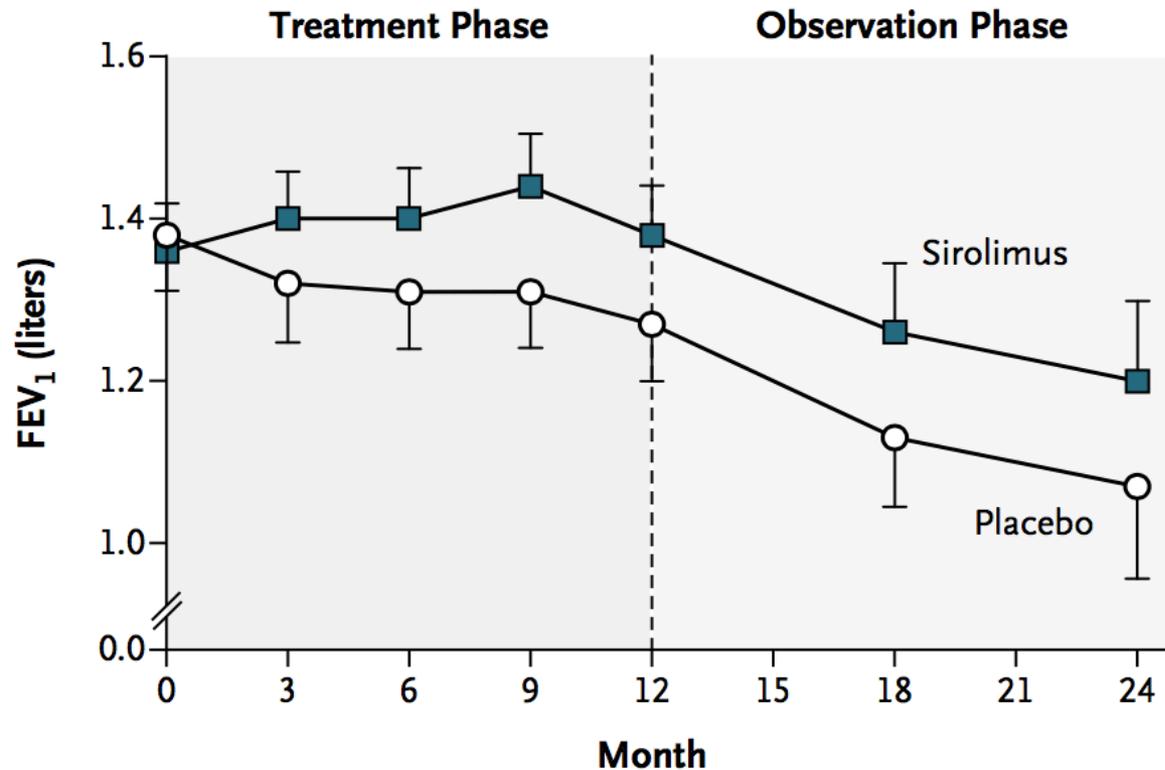
ORIGINAL ARTICLE

## Efficacy and Safety of Sirolimus in Lymphangiomyomatosis

Francis X. McCormack, M.D., Yoshikazu Inoue, M.D., Ph.D., Joel Moss, M.D., Ph.D.,  
Lianne G. Singer, M.D., Charlie Strange, M.D., Koh Nakata, M.D., Ph.D.,  
Alan F. Barker, M.D., Jeffrey T. Chapman, M.D., Mark L. Brantly, M.D.,  
James M. Stocks, M.D., Kevin K. Brown, M.D., Joseph P. Lynch, III, M.D.,  
Hilary J. Goldberg, M.D., Lisa R. Young, M.D., Brent W. Kinder, M.D.,  
Gregory P. Downey, M.D., Eugene J. Sullivan, M.D., Thomas V. Colby, M.D.,  
Roy T. McKay, Ph.D., Marsha M. Cohen, M.D., Leslie Korbee, B.S.,  
Angelo M. Taveira-DaSilva, M.D., Ph.D., Hye-Seung Lee, Ph.D.,  
Jeffrey P. Krischer, Ph.D., and Bruce C. Trapnell, M.D., for the National Institutes  
of Health Rare Lung Diseases Consortium and the MILES Trial Group\*

NEJM April 2011: 364: 1595-606

# Lung function declined by 10% on placebo, but stabilized on sirolimus.



## No. at Risk

Sirolimus	46	43	41	38	41	21	14
Placebo	43	40	42	39	34	22	13

# Julia starts on treatment

- We start Julie on mTOR inhibitors
- We choose sirolimus, because it is approved for LAM, but everolimus would also be fine
- We measure baseline safety labs, including blood counts, liver tests and cholesterol
- We measure sirolimus trough levels within a week or two of starting, then repeat safety labs and sirolimus levels monthly for a few months, then perhaps quarterly

# **I also tell Julia and her parents that:**

- sirolimus will stabilize lung function in most LAM patients
- we should measure lung function (spirometry) every 3 months or so for a while
- Julia should use sunprotection, receive the recombinant inactivated Shingles vaccine and avoid live vaccines

# What I hope for the Julia's of the future

- That we can find a way to determine which LAM patients are likely to progress, so that we can start treatment early
  - The MIDAS Registry
- That we determine if early, low dose treatment with sirolimus or everolimus can prevent progression to more advanced stages.
  - The MILED trial

# Trials

- **Completed trials**

- MILES
- RADx2201
- Doxycycline
- COLA
- The SAIL Trial
- The TRAIL Trial
- MSTLS trial
- The SOS Trial
- Imatanib trial
- The SLAM Trial

**drug**

sirolimus  
everolimus  
doxycycline  
celecoxib  
hydroxychloroquine  
letrozole  
sirolimus  
simvastatin  
gleevec  
saracatanib

**target**

mTOR pathway  
mTOR pathway  
matrix remodeling  
Cox2  
autophagy  
estrogen axis  
mTOR pathway  
apoptosis  
apoptosis  
EMT/autophagy

- **Open trials**

- MIDAS
- MILED
- RESULT

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sirolimus  
resveratrol

observation  
mTOR pathway  
apoptosis

- **Pending trials**

- Inhaled rapa
- Rapa dosing

sirolimus  
sirolimus

mTOR pathway  
mTOR pathway

# How can Julia and her family help?

- Attend a LAM or TSC clinic at least once per year
- Enroll in trials
- Donate tissue when surgery is necessary
- Help to raise funds for research

# Thank you for your attention

- Available through the LAM Foundation
  - LAM Guidelines
  - Slides from today's talks
  - Emergency room cards
  - Video library of topics
  - Guidance for
    - Vaccination
    - Sirolimus use
    - Pneumothorax management
    - etc
- Feel free to write to me
  - frank.mccormack @uc.edu