2019台灣胸腔暨重症加護醫學會夏季會

2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

TSC-LAM: 台大經驗分享

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Outlines

- TSC Integrated Clinic at National Taiwan University Hospital (NTUH)
- Pulmonary manifestations
  - Computed tomography image findings: LAM vs. MMPH
  - Genotype versus phenotype
  - Correlation between the lung and other organs
  - Pulmonary function test

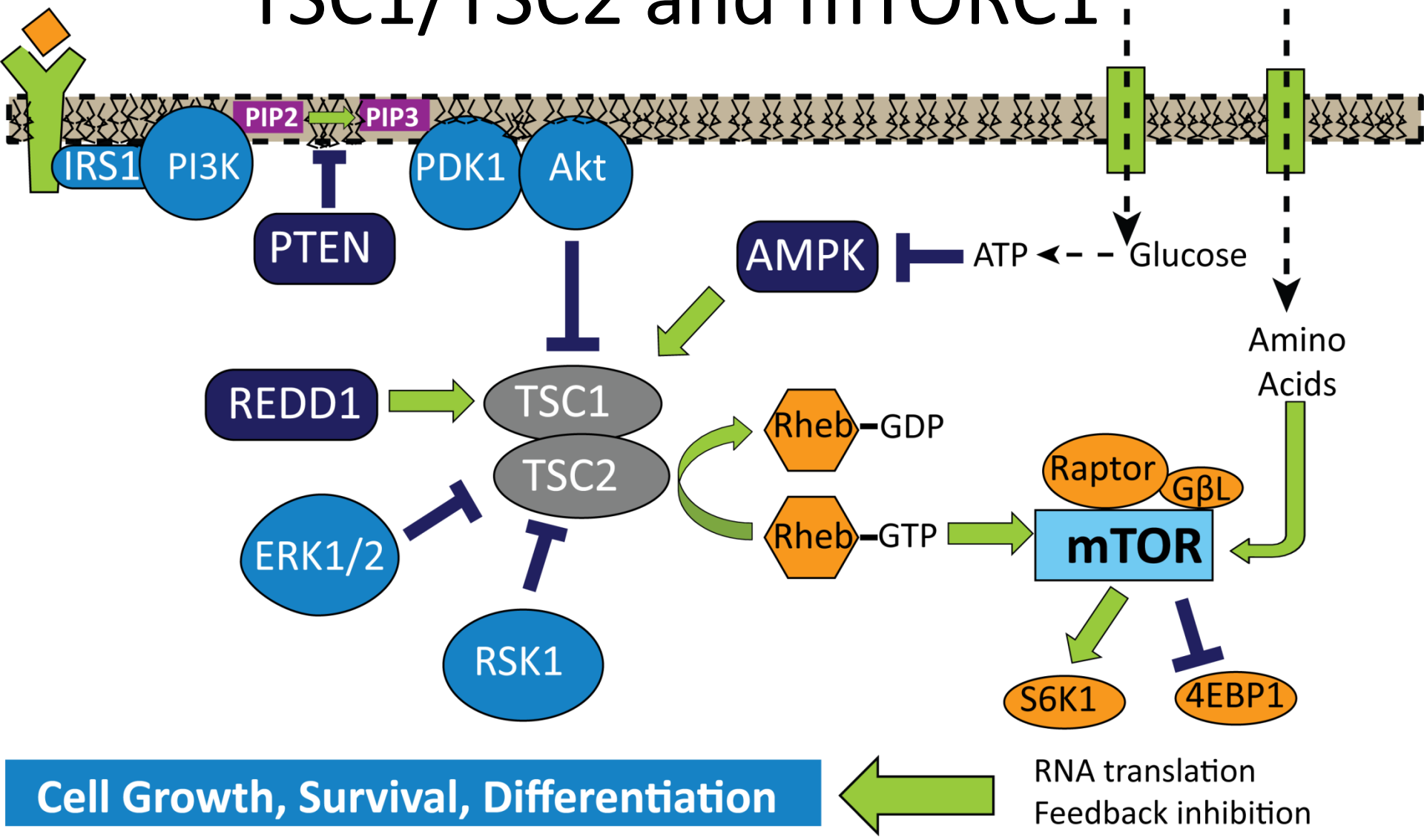
Tuberous sclerosis complex (TSC)

- Autosomal dominant genetic disorder
- Incidence of approximately 1 in 5000 to 10,000 live births
- Characterized by widespread hamartomas in the brain, heart, skin, eyes, kidney, and lung
- The affected genes are TSC1 and TSC2Most patients with TSC have epilepsy, and one-half or more have cognitive deficits and learning disabilities

Curatolo et al. Lancet. 2008;372(9639):657.

Au et al. Genet Med. 2007;9(2):88.

TSC1/TSC2 and mTORC1



Curatolo et al. Lancet 2008; 372:657.

TSC Integrated Clinic

- TSC Integrated Clinic at National Taiwan University Hospital (NTUH) since July 12th, 2010
- Monthly
- 基因醫學部陳沛隆醫師及黃愛珠遺傳諮詢師（遺傳諮詢與檢驗）
- 內科部胸腔科王鶴健醫師（監測肺部可能之淋巴管肌瘤）
- 小兒部神經科范碧娟醫師（治療癲癇，追蹤腦皮質結節、腦室管膜下結節或巨細胞星狀瘤）
- 復健部盧璐醫師（行為與發育之評估及復健）
- 泌尿部王碩盟醫師（腎臟血管肌脂肪瘤之監測與栓塞或手術治療）
- 眼科部林昭文醫師（視網膜粒狀缺陷瘤）
- 小兒部心臟科陳俊安醫師（心臟橫紋肌瘤）
- 皮膚部廖怡華醫師
- 牙科部楊湘醫師
- 影像醫學部吳志宏、黃柔瑄醫師

Diagnostic clinical criteria includes 11 major features and six minor features

1969 - 2019

- **Definite Diagnosis :**
  - ☑ **2 major features or**
  - ☑ **1 major feature + ≥2 minor features**
- Possible Diagnosis :
  - ☑ 1 major feature or
  - ☑ ≥2 minor features

Major features (主要特徵)

1.	Hypomelanotic macules (≥3, at least 5 mm in diameter) 脫色斑(≥3個,直徑至少5mm)	☐
2.	Angiofibromas (≥3) or fibrous cephalic plaque 血管纖維瘤(≥3處)或額頭斑塊	☐
3.	Ungual fibromas (≥2) 指甲纖維瘤(≥2處)	☐
4.	Shagreen patch 鯊魚皮斑	☐
5.	Multiple retinal hamartomas 多個視網膜缺陷瘤	☐
6.	Cortical dysplasias* 腦皮質發育不良*	☐
7.	Subependymal nodules 腦室管膜下結節	☐
8.	Subependymal giant cell astrocytoma 腦室管膜下巨細胞星狀瘤	☐
9.	Cardiac rhabdomyoma 心橫紋肌瘤	☐
10.	Lymphangioleiomyomatosis (LAM)** 淋巴管肌瘤增生**	☐
11.	Angiomyolipomas (≥2) [a, b, **] 血管肌脂肪瘤**(≥2)	☐

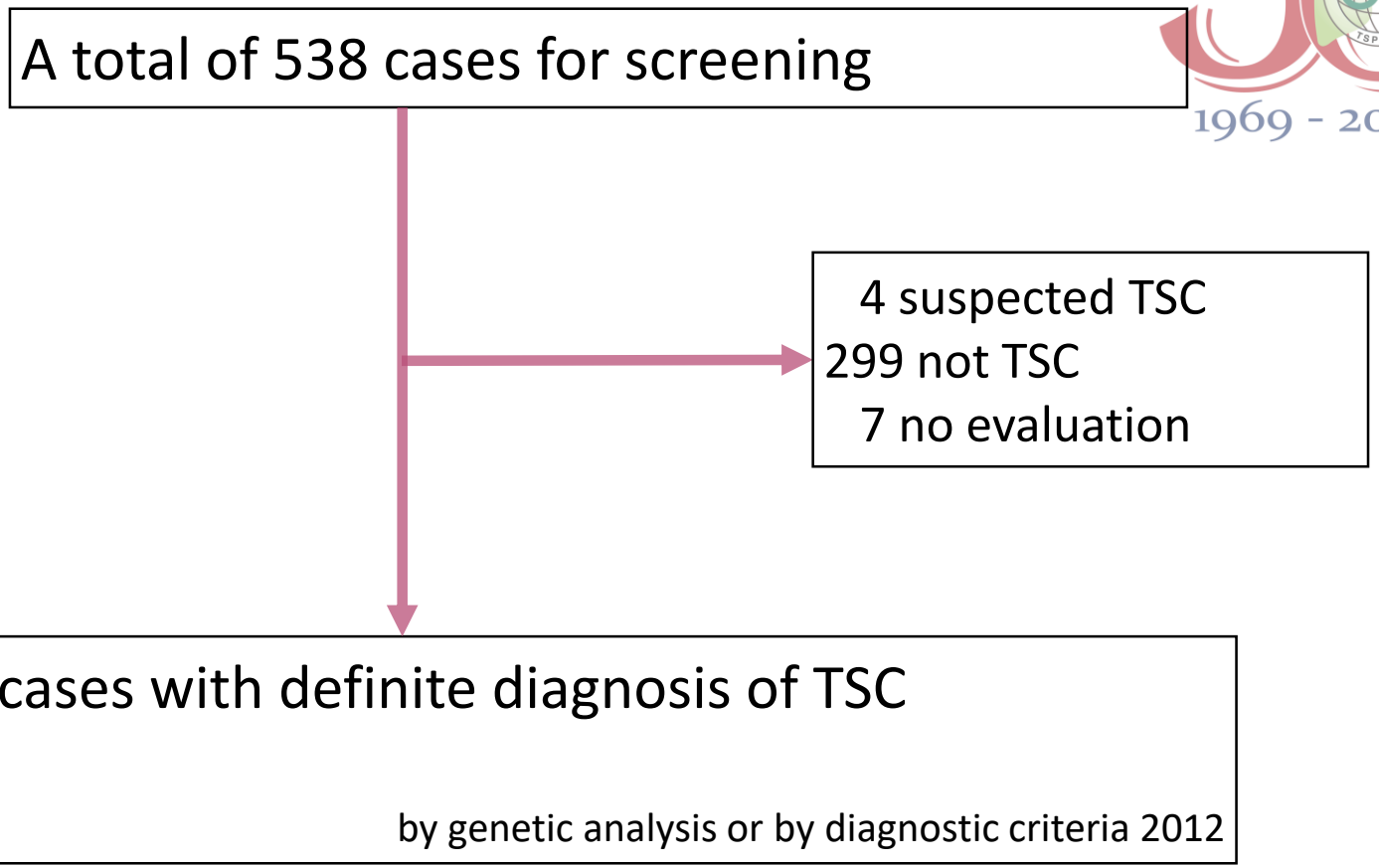
Minor features (次要特徵)

1.	"Confetti" skin lesions "斑駁樣"皮膚斑	☐
2.	Dental enamel pits (>3) 超過3個牙齒琺瑯質小孔	☐
3.	Intraoral fibromas (≥2) ≥2個口腔內纖維瘤	☐
4.	Retinal achromic patch 視網膜無色斑	☐
5.	Multiple renal cysts 多個腎囊腫	☐
6.	Nonrenal hamartomas 非腎缺陷瘤	☐

* 包含結節(tubers)和腦白質放射狀移行線 (cerebral white matter radial migration lines).

** 僅同時有LAM 和血管肌脂肪瘤兩個主要特徵，而無其他的特徵，無法構成確診TSC

From 2010 to Mar. 2019



Slide courtesy of Dr. 廖怡華

TSC 臨床診斷要件 (2012年更新版)

主要診斷要件

1.脫色斑(3, 至少直徑 ≧ 5 mm)

2.血管纖維瘤 (3) 或 頭部纖維斑

3.甲纖維瘤 (2)

4.鯊魚皮斑

5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)y
11. Angiomyolipomas (2)y

纖維錯構瘤

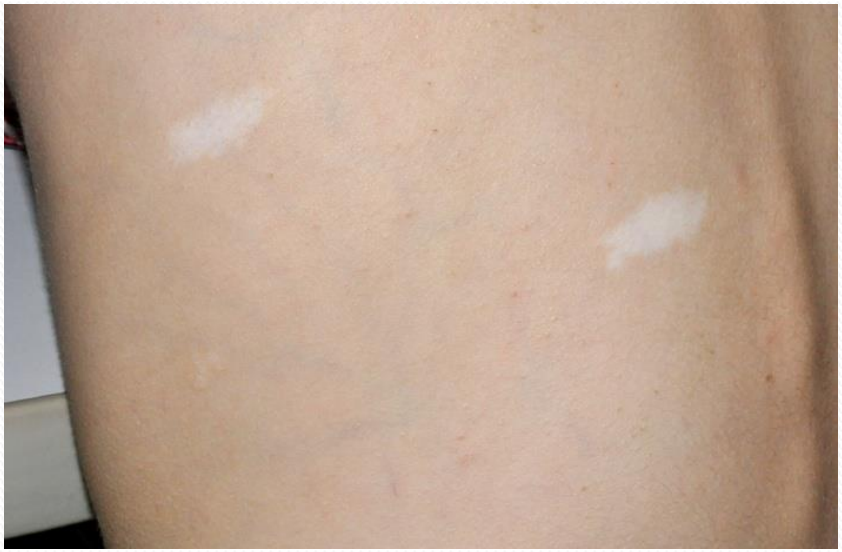
次要診斷要件

1. 五彩紙脫色斑
2. Dental enamel pits (>3)
3. Intraoral fibromas (2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with 2 minor features

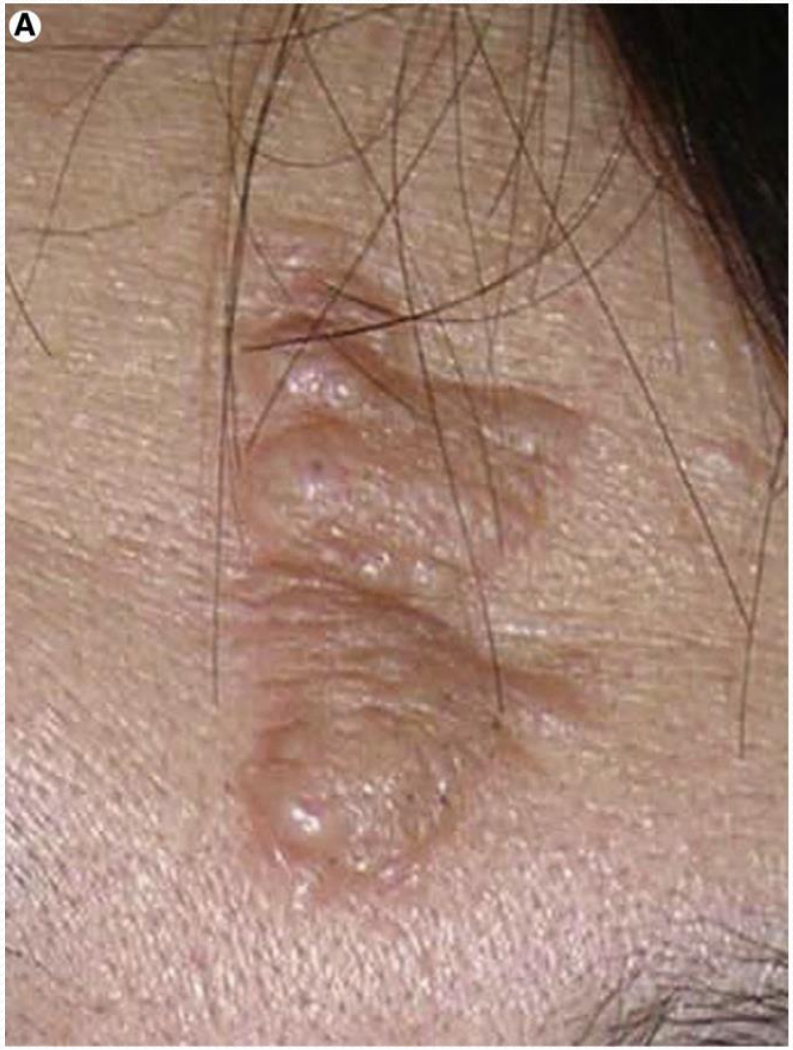
Possible diagnosis: Either one major feature or 2 minor features

Hypomelanotic macules 脫色斑

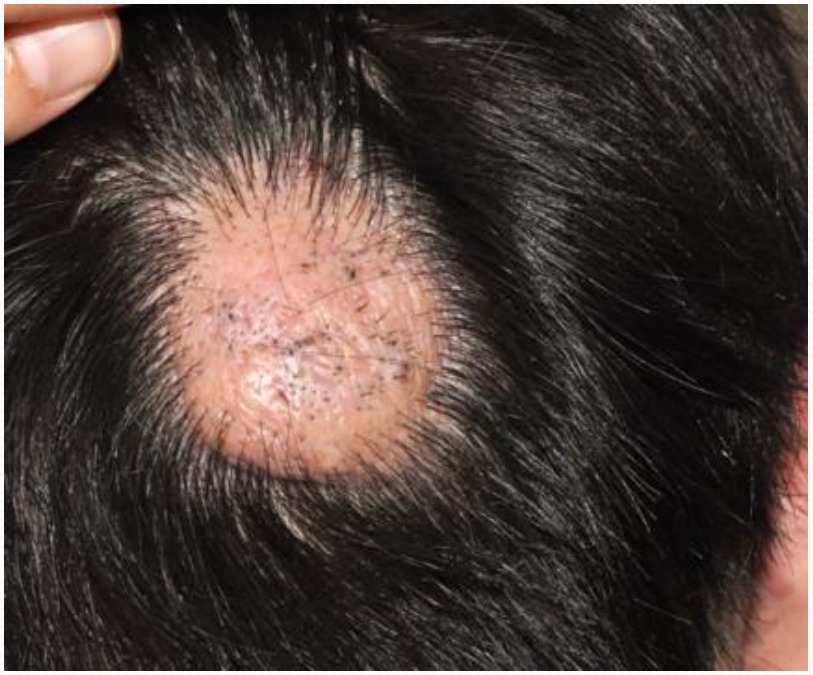


- 90%
- TSC的最早表現
- 出生或幼兒期，在成年期可能消失
- 好發於軀幹或臀部
- 1-20 個，0.5-3 cm
- 診斷要件：≧3個, 直徑≧5 mm
- **菸草葉狀**

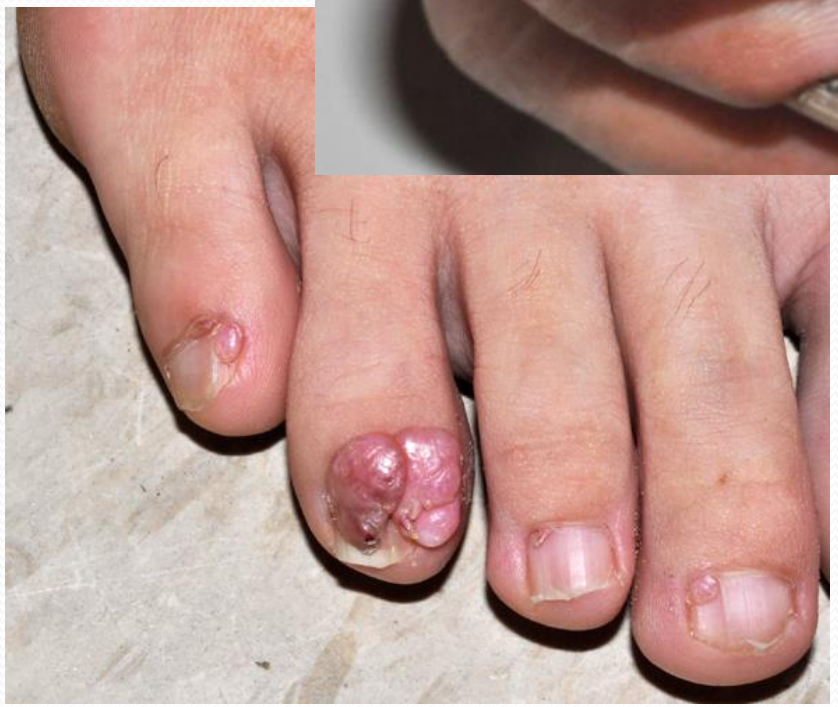
Fibrous cephalic plaque 頭部纖維斑



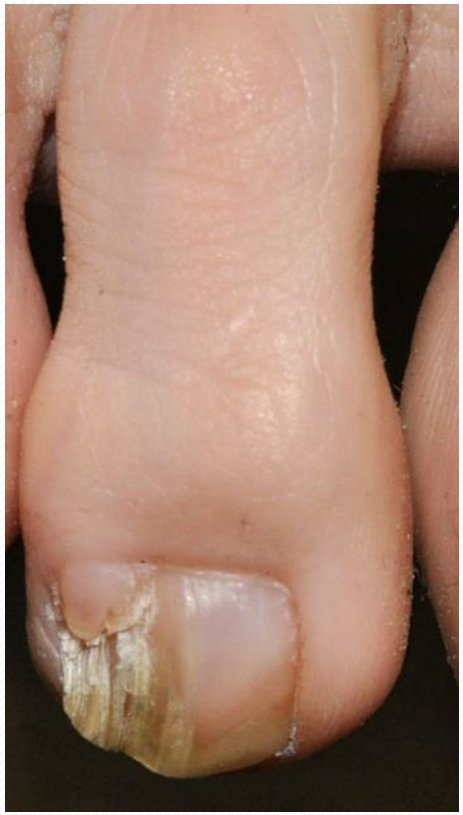
- 20-40%
- 類似臉部血管纖維瘤
- 頭皮、額頭



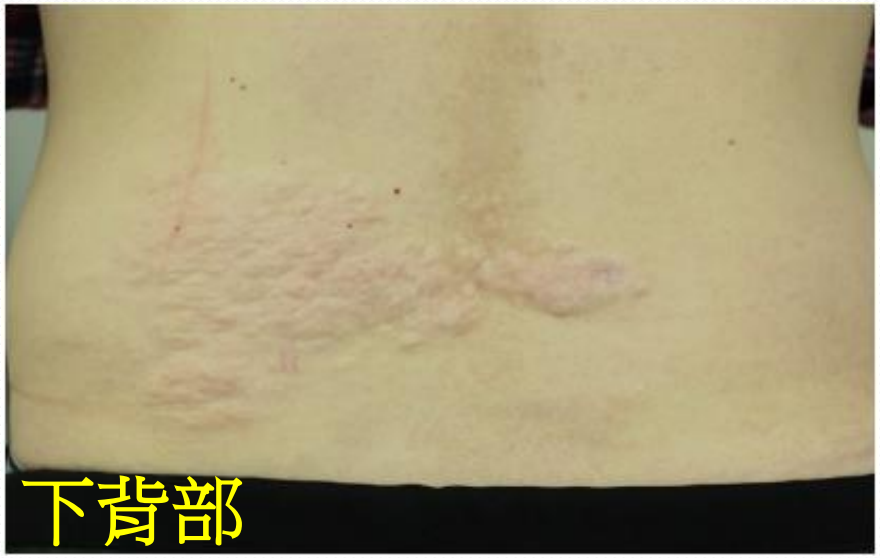
Ungual fibromas 指甲纖維瘤

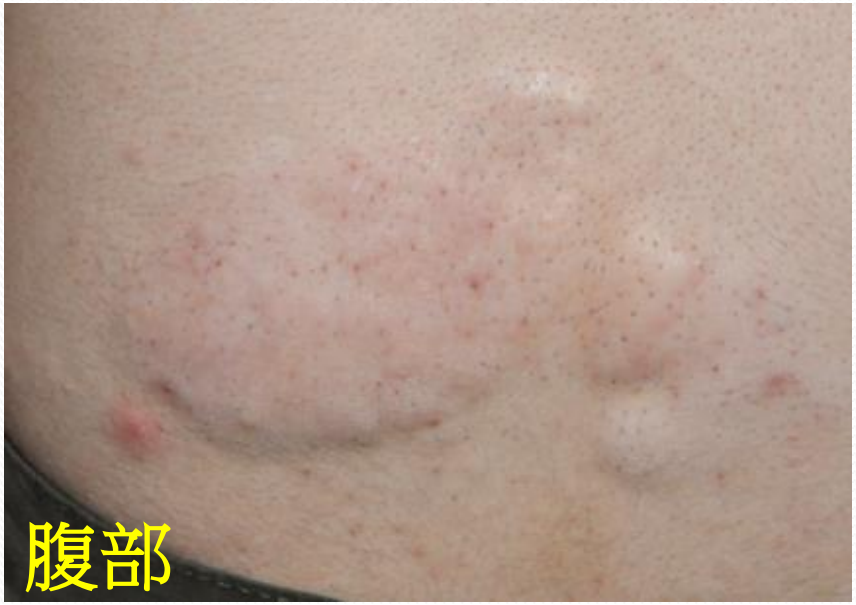


- 20-80%
- 成人期發生



Shagreen patch 鯊魚皮斑



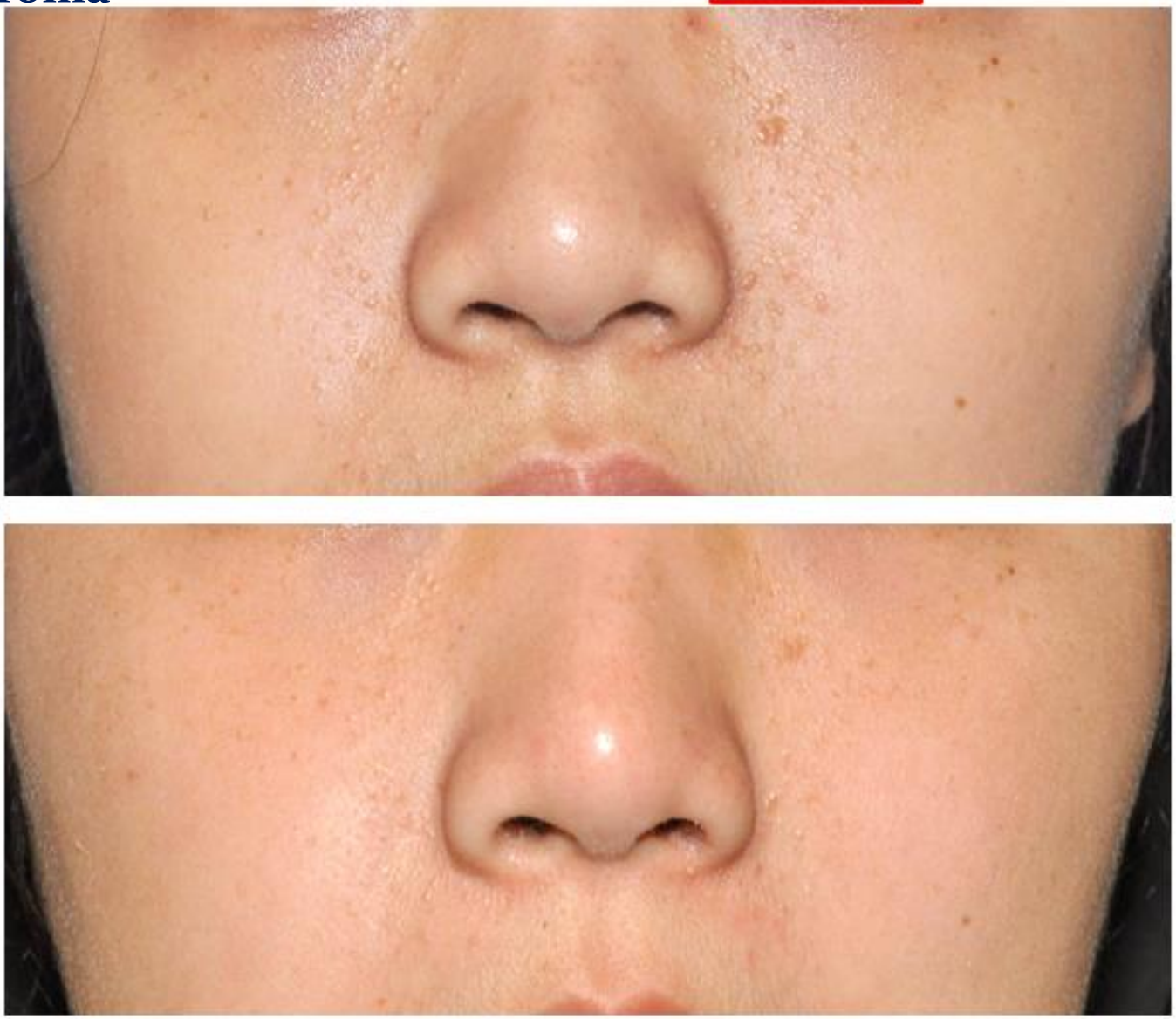


- 結締組織構成
- 下背部
- 50%
- 10歲左右發生

血管纖維瘤
Facial Angiofibroma

R + C Calcitriol

R Rapamycin



FASI 2 → 0.6 2 → 0.5

Slide courtesy of Dr.林昭文

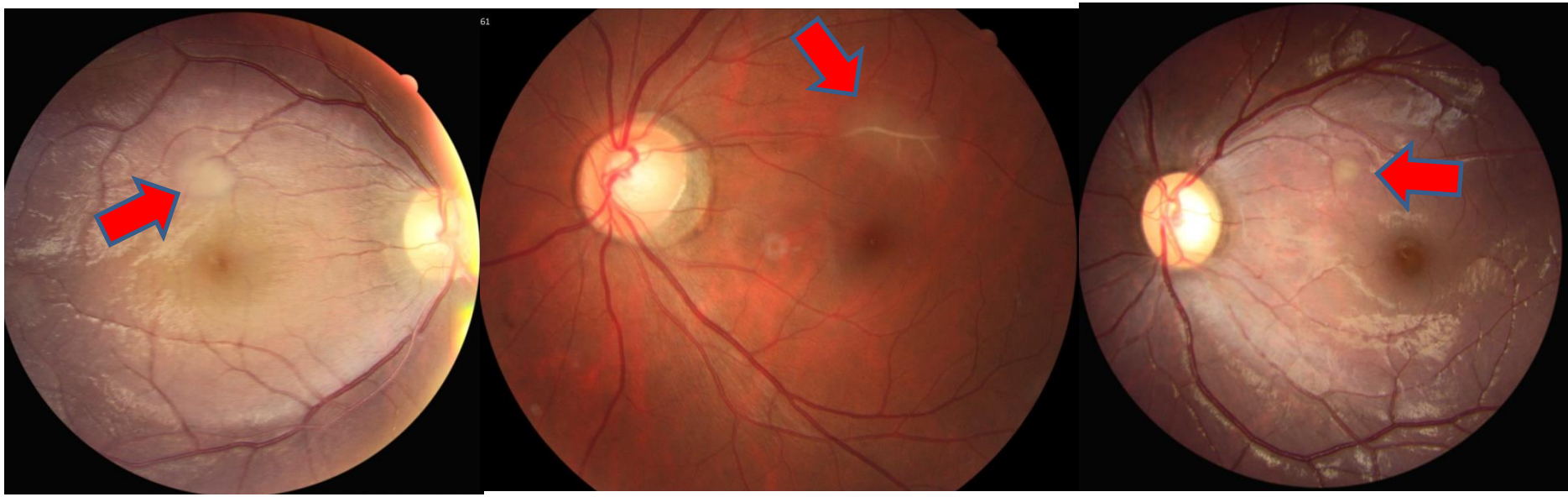
Ophthalmic manifestations in TSC

- Retinal hamartomas are the most common ocular finding
- Occur in approximately 50% of patients
  - Bilateral hamartomas occur in 30% of patients

Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81-86.

Ophthalmic manifestations in TSC

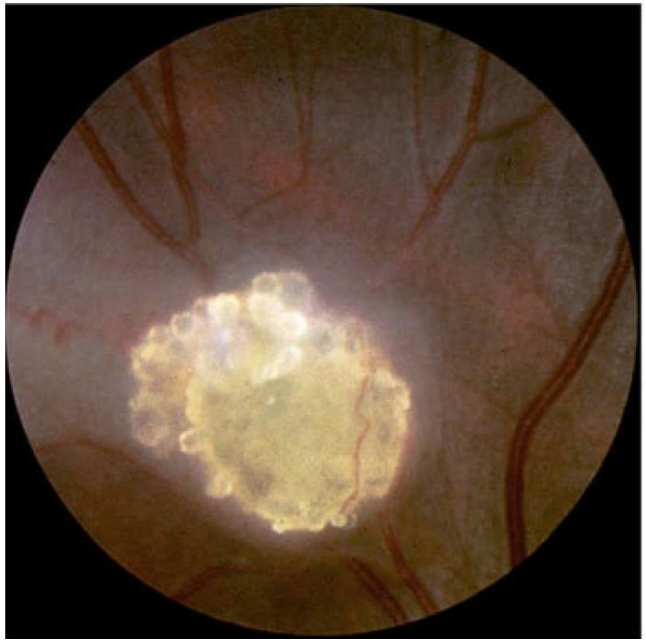
- Flat lesions are the most common type of hamartoma
- Faint in color, subtle and may be missed on examination
- Often located near the end of the arcades and are characterized by obscuration of vessels

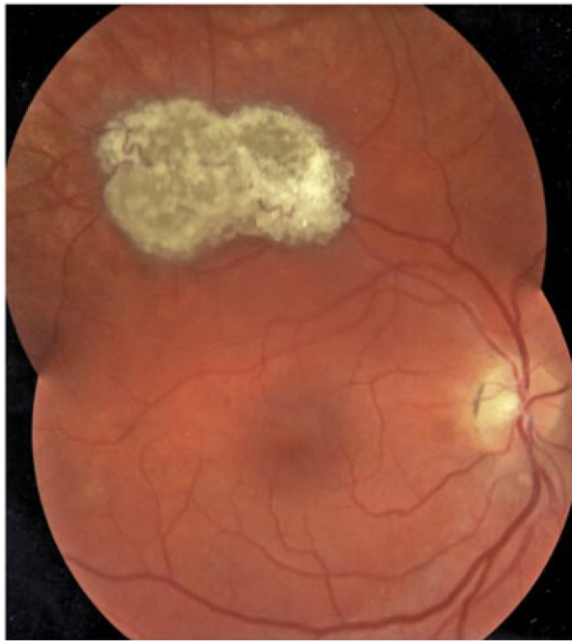


Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81-86.

Ophthalmic manifestations in TSC

- Multinodular type hamartoma: sharply demarcated, elevated, nodular lesion
- With calcifications
- Often in the posterior pole and near the disc





Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81-86.

Summary

- Retinal hamartomas are most common
- flat, nodular, and transitional type lesions
- The majority of hamartomas are non-progressive
- Lesions with subretinal fluid and progression have been reported
- Non-retinal findings: hypopigmented sectoral iris and ciliary body lesions, iris and choroid colobomas, iris and ciliary epithelium hamartomas, eyelid angiofibromas

Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81-86.

Slide courtesy of Dr.范碧娟

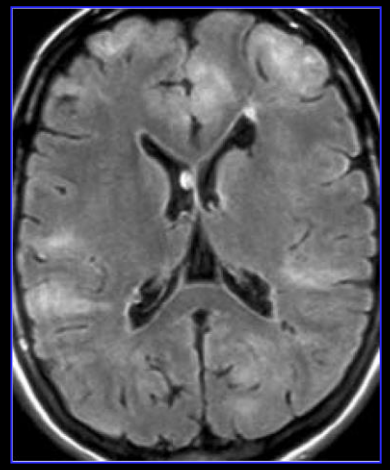
TSC Dx: major criteria

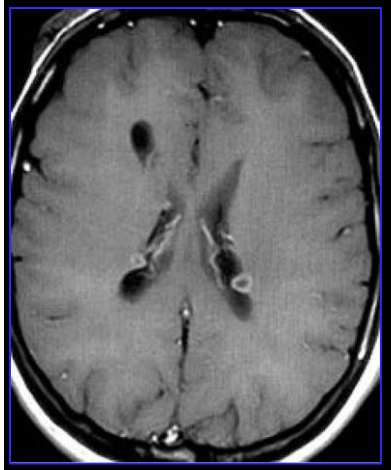
Major features (主要特徵)

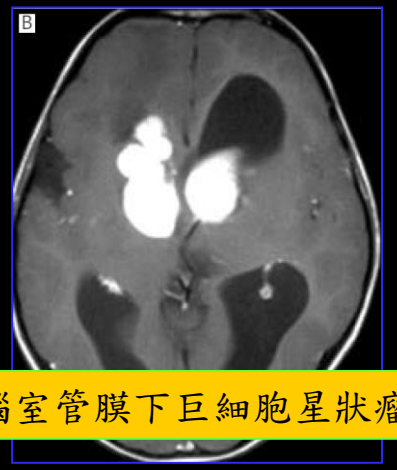
1.	Hypomelanotic macules (≥3, at least 5 mm in diameter) 脫色斑(≥3個,直徑至少5mm)	☐
2.	Angiofibromas (≥3) or fibrous cephalic plaque 血管纖維瘤(≥3處)或額頭斑塊	☐
3.	Ungual fibromas (≥2) 指甲纖維瘤(≥2處)	☐
4.	Shagreen patch 鯊魚皮斑	☐
5.	Multiple retinal hamartomas 多個視網膜缺陷瘤	☐
6.	Cortical dysplasias* 腦皮質發育不良*	☐
7.	Subependymal nodules 腦室管膜下結節 SEN	☐
8.	Subependymal giant cell astrocytoma 腦室管膜下巨細胞星狀瘤 SEGA	☐
9.	Cardiac rhabdomyoma 心橫紋肌瘤	☐
10.	Lymphangioleiomyomatosis (LAM)** 淋巴管肌瘤增生**	☐
11.	Angiomyolipomas (≥2) a, b, ** 血管肌脂肪瘤**(≥2)	☐

* 包含結節(tubers)和腦白質放射狀移行線 (cerebral white matter radial migration lines).

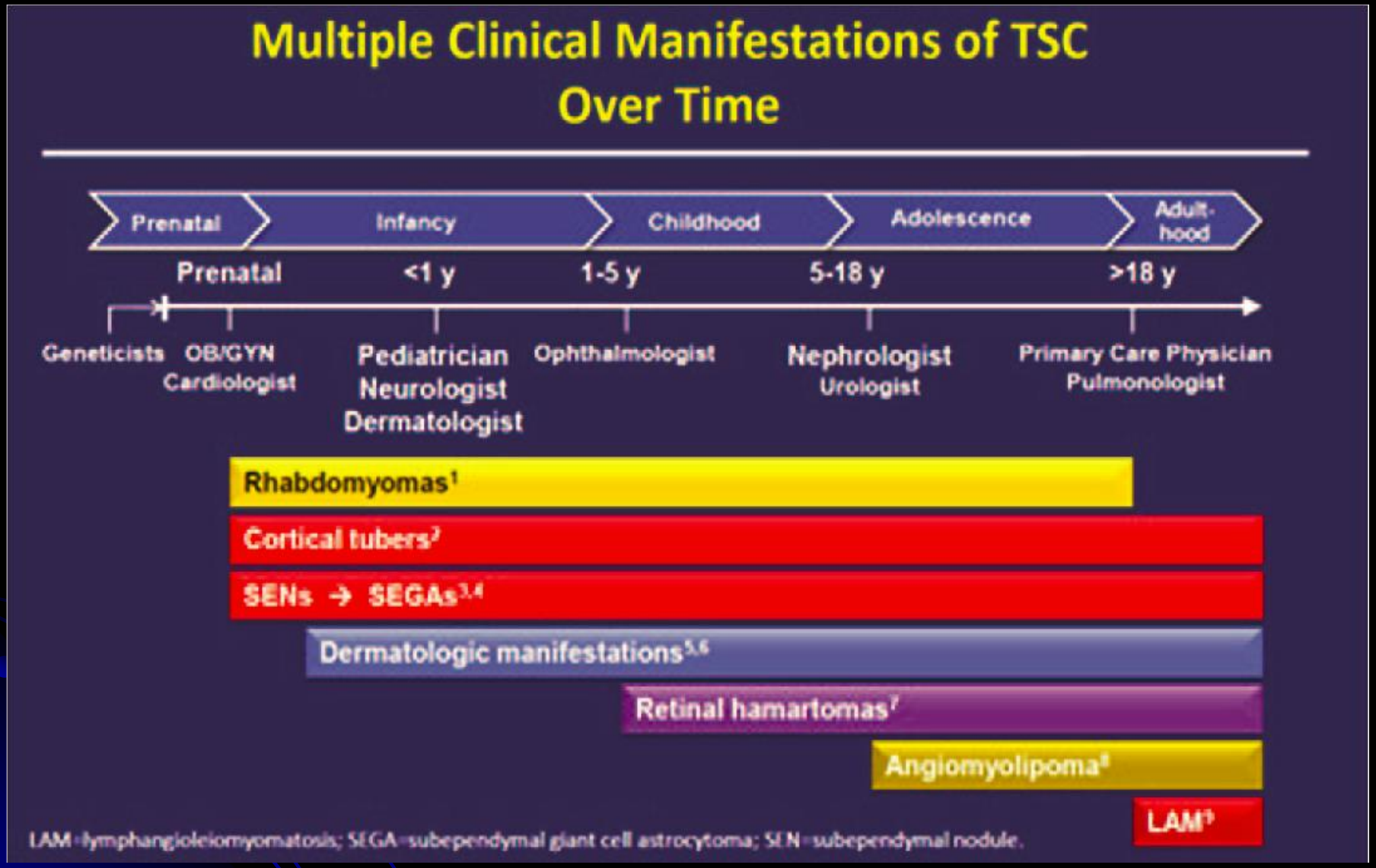
** 僅同時有LAM 和血管肌脂肪瘤兩個主要特徵，而無其他的特徵，無法構成確診TSC





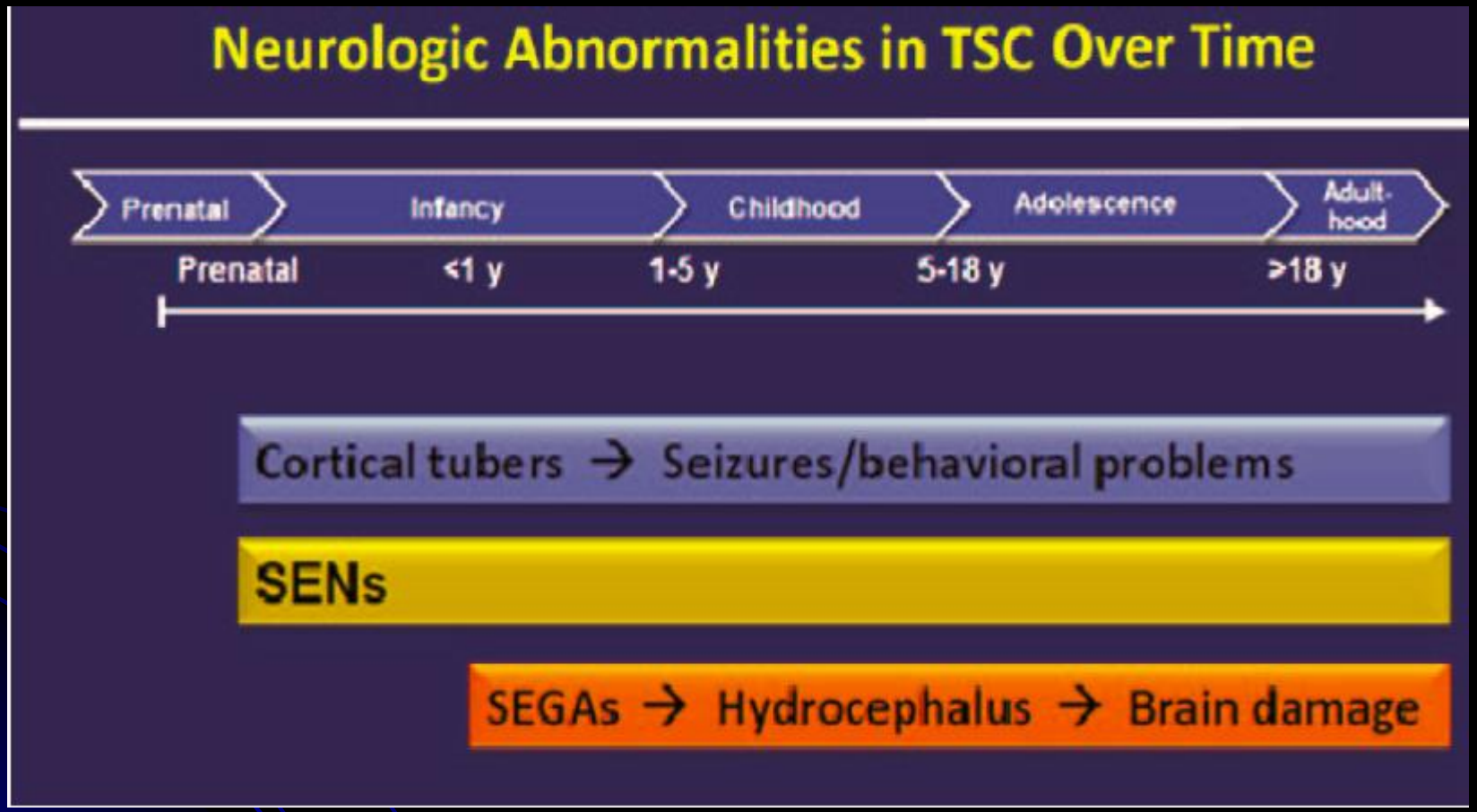


腦室管膜下巨細胞星狀瘤



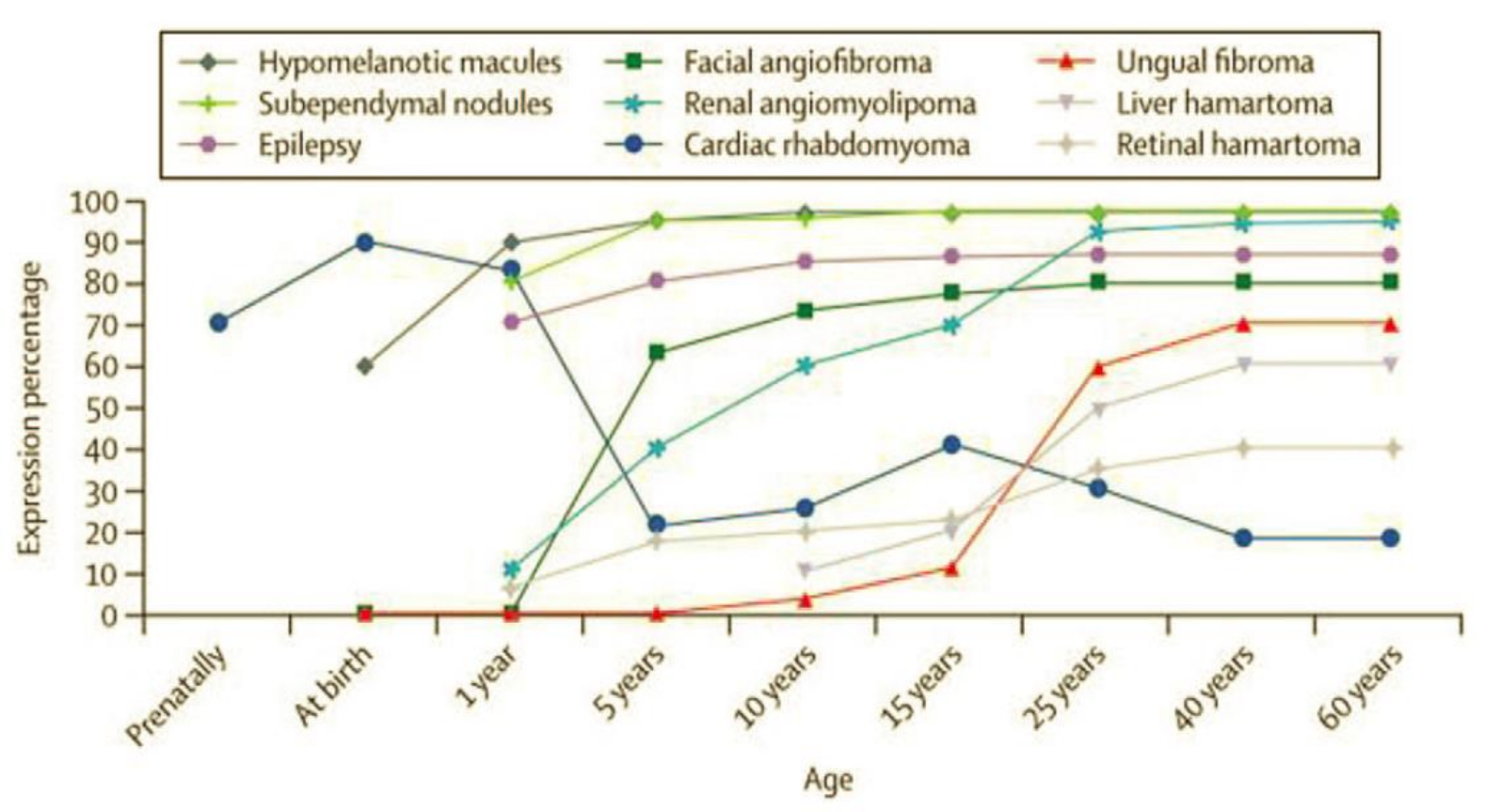
Samueli S, Wien Klin Wochenschr. 2015 Apr 10.

Age-dependent expression of neurological manifestations in TSC



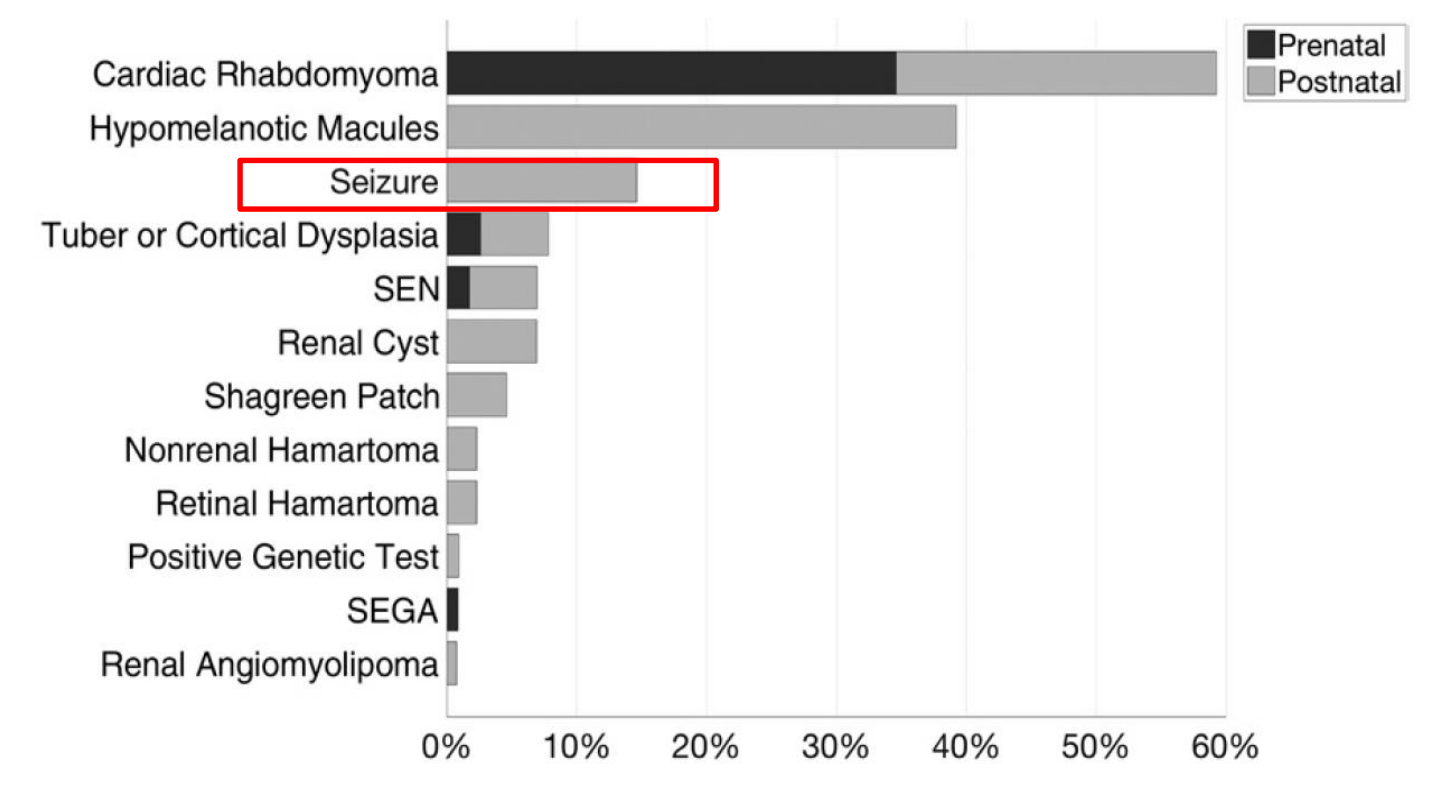
Samueli S, Wien Klin Wochenschr. 2015 Apr 10.

年齡相關之TSC臨床表現



Samueli S, Wien Klin Wochenschr. 2015 Apr 10.

Prevalence of TSC features at initial presentation



130 infants with definite TSC followed up longitudinally up to 36 m/o

Davis, PE. et al, Pediatrics 2017

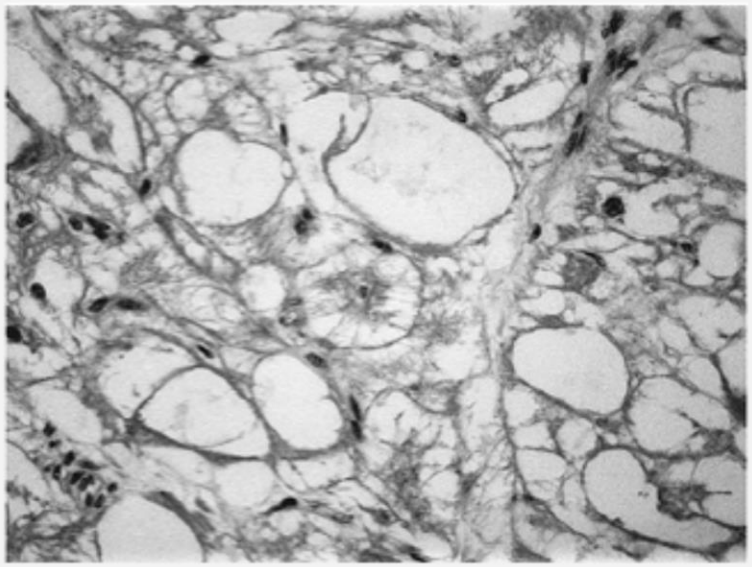
Slide courtesy of Dr.陳俊安

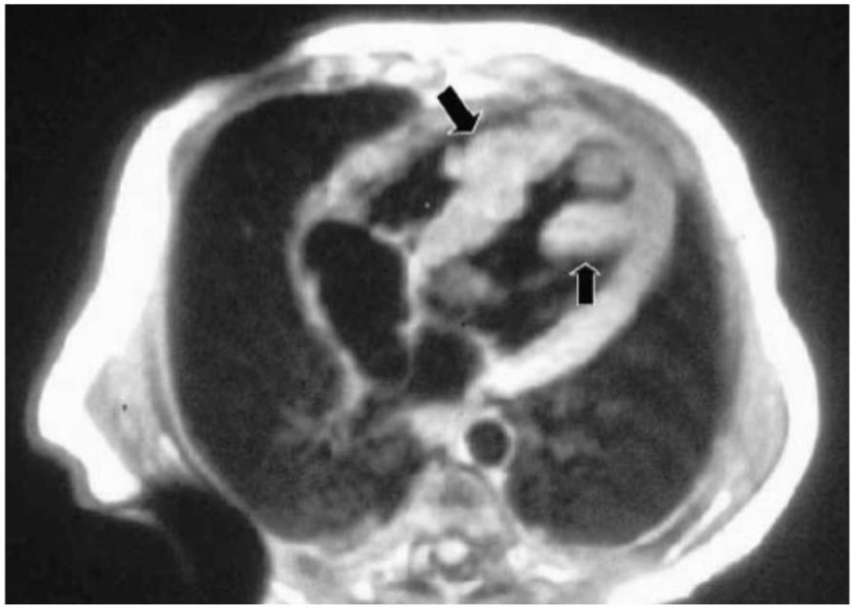
Cardiac manifestations

- Cardiac lesions in 50% of TSC[1,2]
- Cardiac rhabdomyomas
  - Multiple or single
  - Regress over time
- ECG abnormalities

1. J Pediatr 2003
2. J Am Coll Cardiol 1995

Cardiac rhabdomyomas

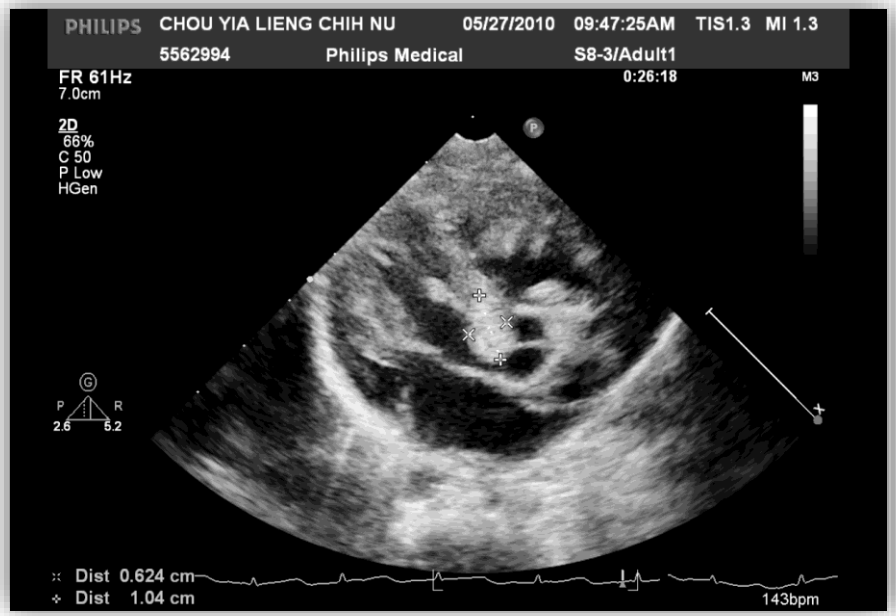


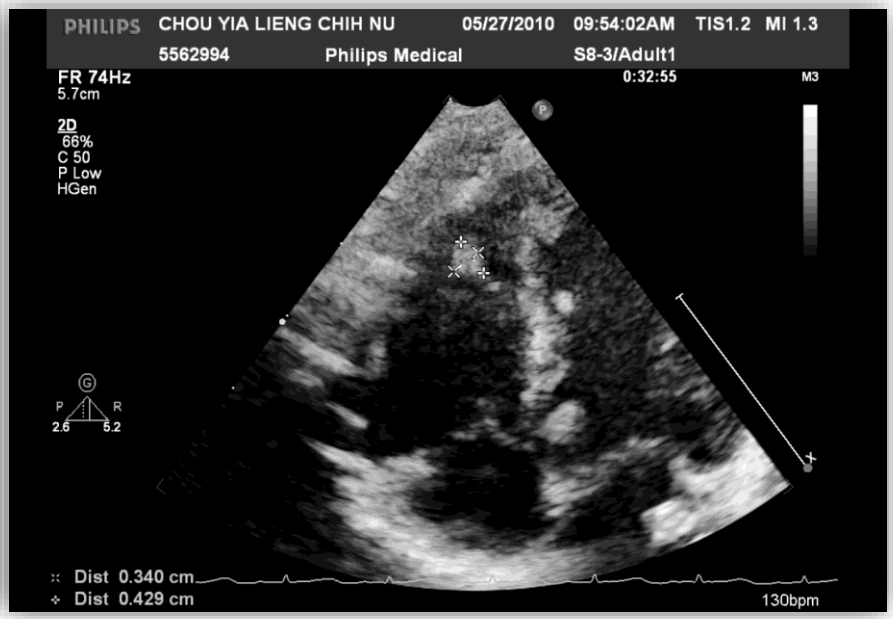


- Clear cytoplasm
- Vacuolization
- Occasional spindle cell
- Harmatoma

- Well-circumscribed
- Intramural or intracavitary
- Most commonly within ventricles

Cardiac rhabdomyomas



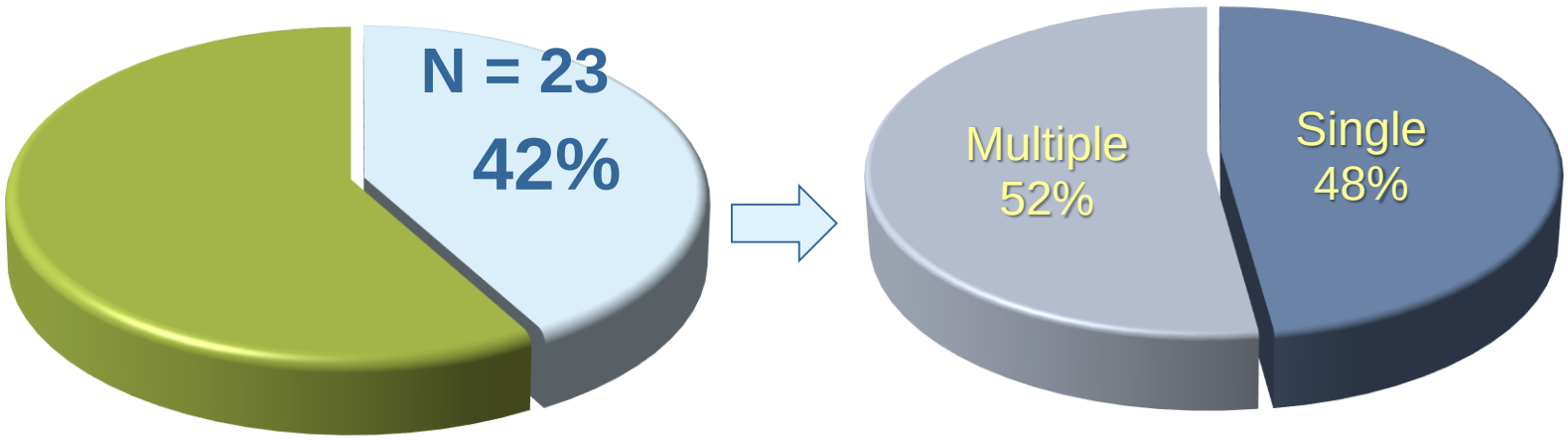


- Homogeneous, echo-bright, finely speckled pattern
- No circumscribed echolucent areas (hemorrhage)
- No interspersed, distinct, echogenic regions (calcification or fibrosis)

NTUH experiences

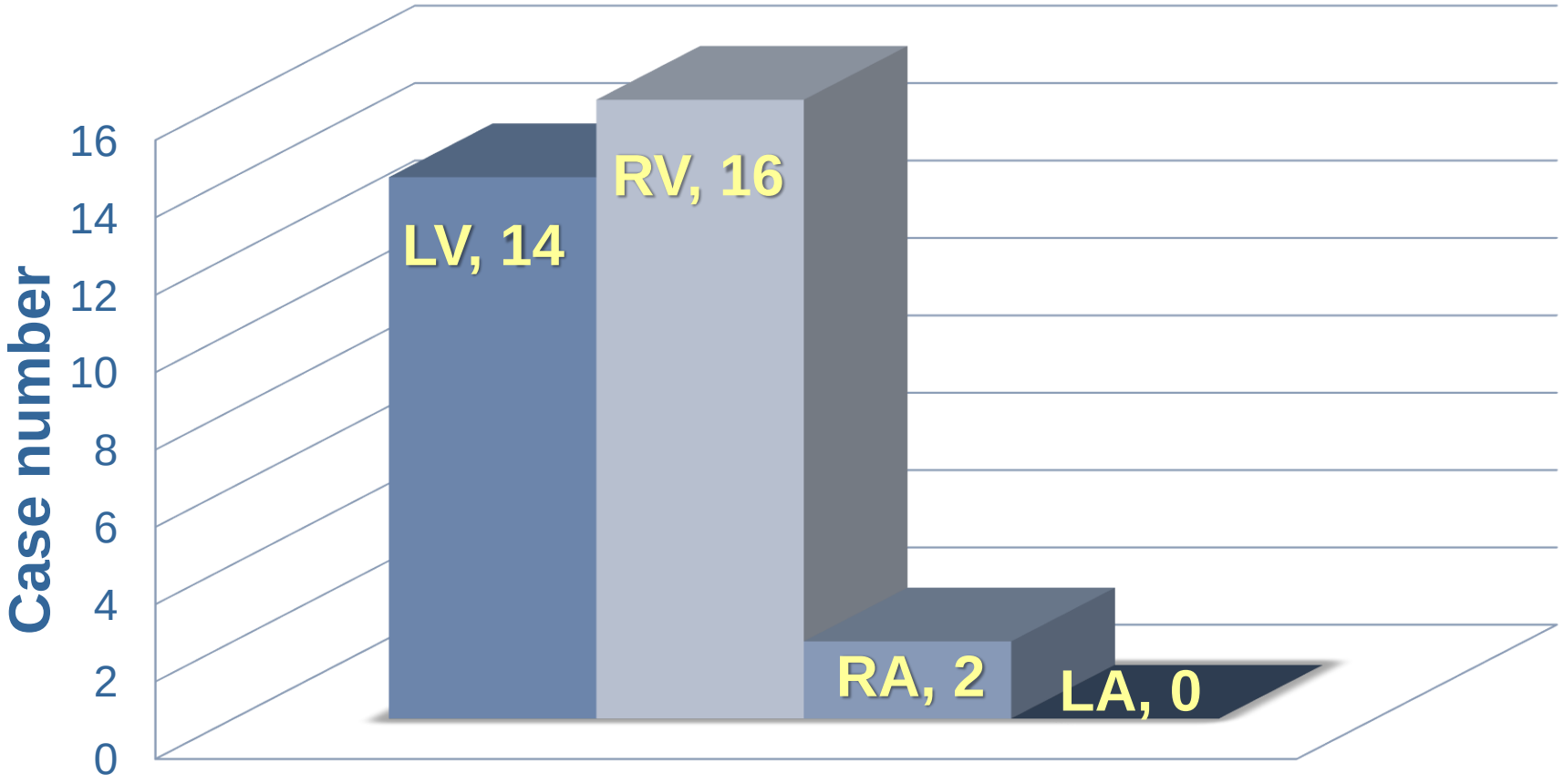
- 2010 Oct ~ 2011 Nov, joint TSC clinics
- 82 cases with clinical diagnosis of TSC
- Echocardiography was available in 55 cases
  - Male sex: 22 (40%)
  - Age: 18.0±11.9yrs (5m ~ 50 yrs)
  - All clinically asymptomatic

NTUH experiences



- Cardiac rhabdomyomas
- No rhabdomyomas

NTUH experiences



Natural course

- Prenatal diagnosis is possible
  - Increase in size until GA 32 wks[1]
- Partial or complete regression
- Surgical intervention only if
  - Hemodynamic compromise
  - Refractory malignant arrhythmias

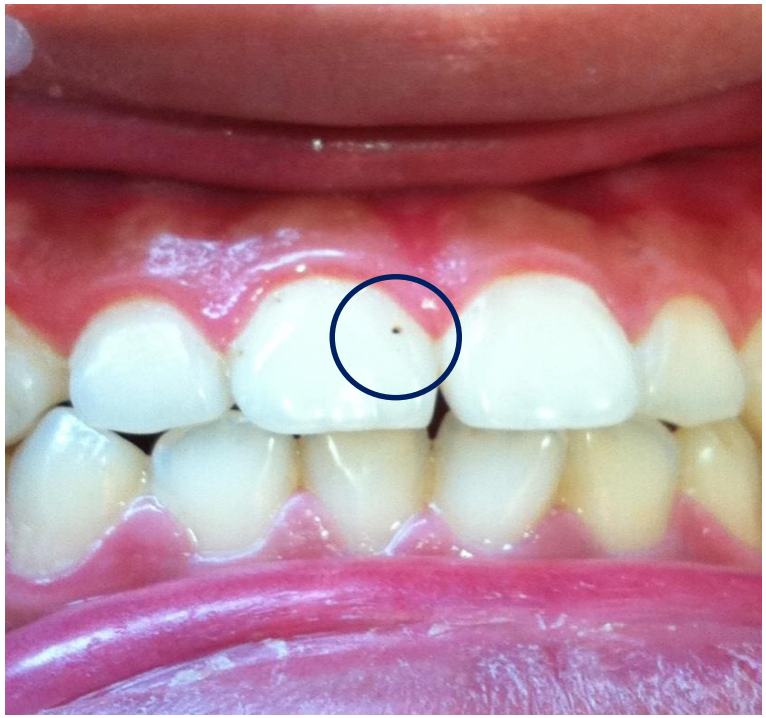
1. Pediatr Cardiol 2004

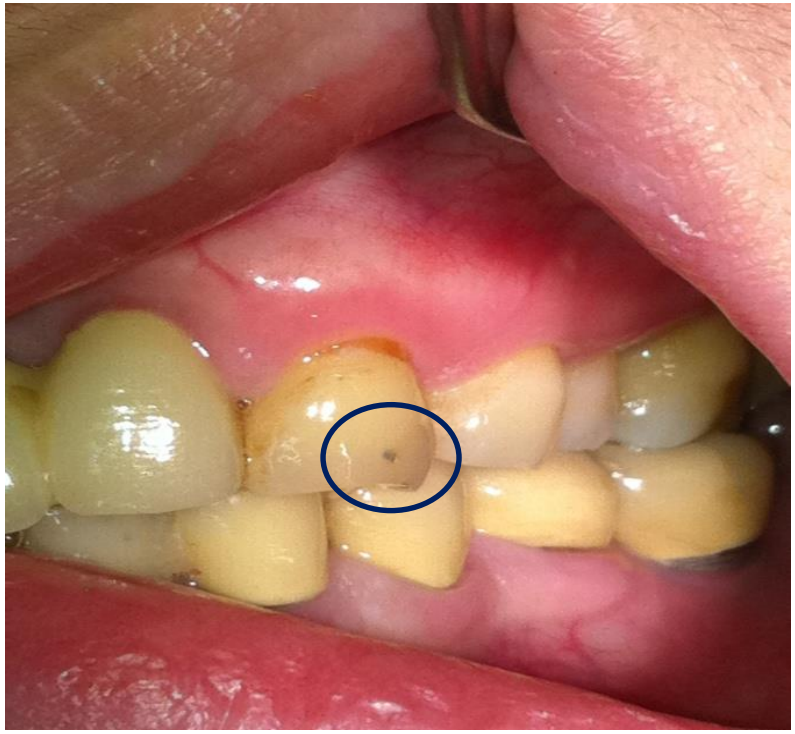
Slide courtesy of Dr.楊湘

Oral Manifestations in TSC patients

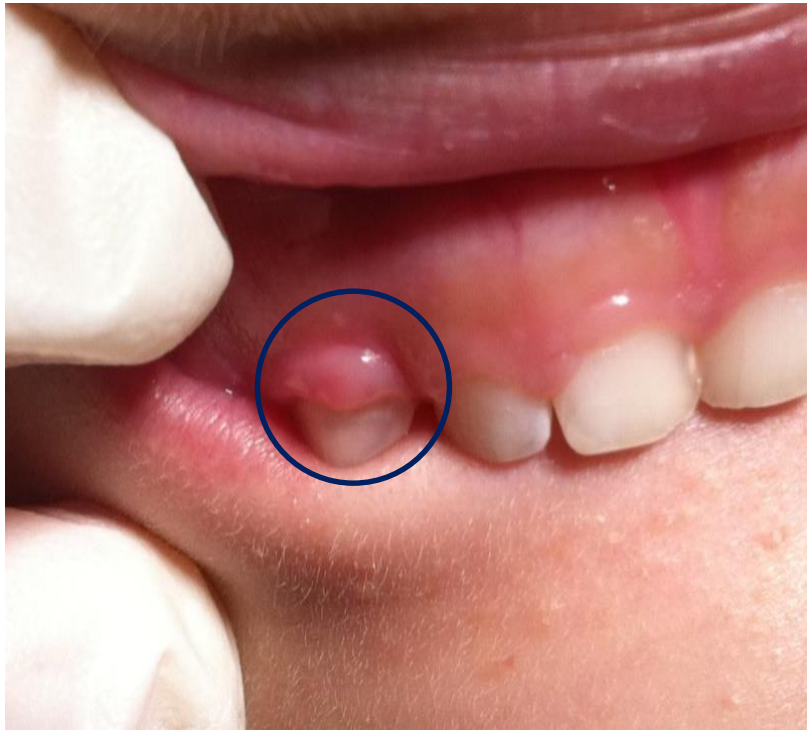
- **Enamel pit (70%-100%) (≥ 3, minor feature)**
- **Oral fibroma (36%-69%)(≥ 2, minor feature)**
- **High vault**
- **Bifid uvula**
- **Cleft lip and palate**
- **Hemangioma**
- **Macroglossia**
- **Delayed eruption**
- **Diastema between the maxillary canine and lateral incisor**
- **Multiple osteomas**

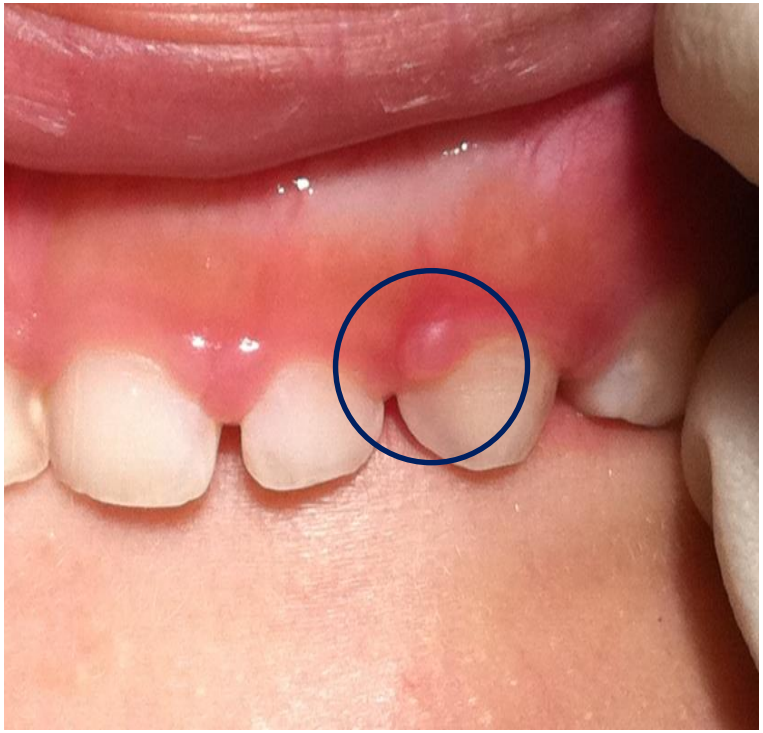
Enamel Pit (Enamel Hypoplasia)





Gingiva Fibroma





Slide courtesy of Dr.吴志宏

Renal AML

- Renal angiomyolipomas
  - TSC accounts for 20% of all AMLs
  - AML's seen in 55-75% of patient with TS
  - multiple, large, bilateral, grow and require possible hemorrhage (size, aneurysm)
  - fat may not be visible in 4.5%

2017/4/1

VOTUBIA® 獲准給付於結節性硬化症併有腎血管肌脂肪瘤(AML，Renal angiomyolipoma)

TSC-AML 健保給付規範

結節性硬化症併有腎血管肌脂肪瘤之成年病患，且需符合以下條件：

(1) 限 18 (含) 歲以上病人。

(2) 其腎血管肌脂肪瘤最長直徑已達 4cm (含) 以上且仍有持續進展之證據。

(3) 曾有發生臨床上有意義之出血或確認病灶有血管瘤 (aneurysm) 直徑 ≥5mm 者，病灶不只一處。

(4) 經腎臟或泌尿專科醫師評估無法以外科手術或動脈栓塞治療，或經動脈栓塞治療或外科手術後無效或復發者。

(5) 需經事前審查核准後使用，每次申請之療程以 6 個月為限，申請時需檢送影像檢查 (CT 或 MRI) 資料。

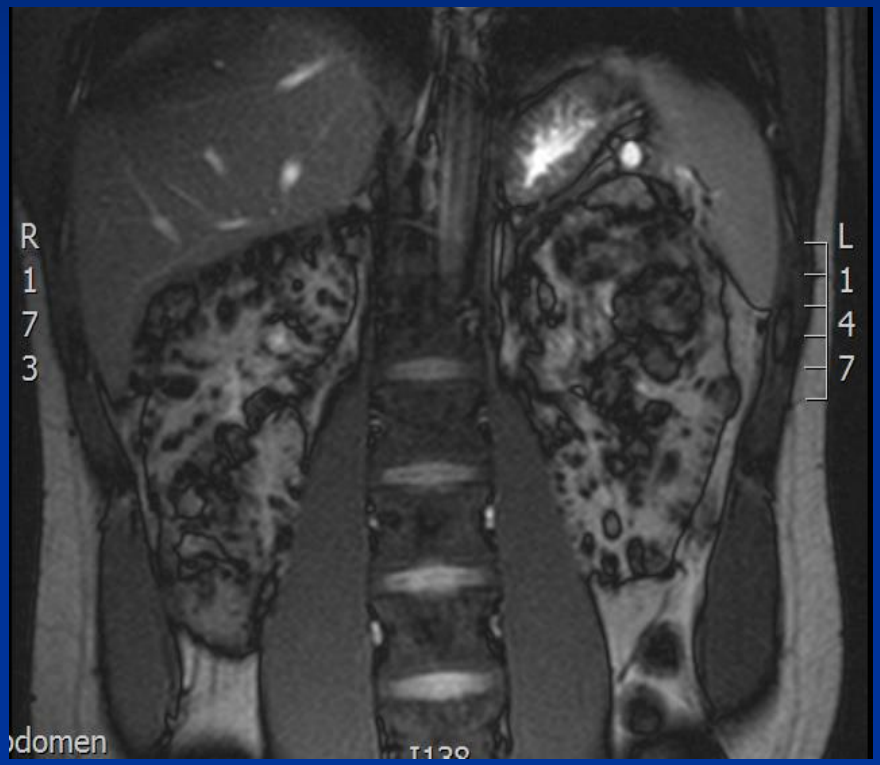
(6) 使用後需每 24 週評估一次。

(7) 申請續用時，除檢送治療前之影像資料，需檢送治療後 (第 24 週、48 週、72 週…等) 之影像檢查資料。

(8) 若腫瘤總體積較治療前降低 30% (含) 以上，且無新增直徑 1 公分以上的腫瘤或 grade 2 (含) 以上腫瘤出血併發症，始得申請續用。(註：腫瘤出血併發症分級 (grading) 定義依 Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.) 。

(9) 限每日最大劑量為 10mg。

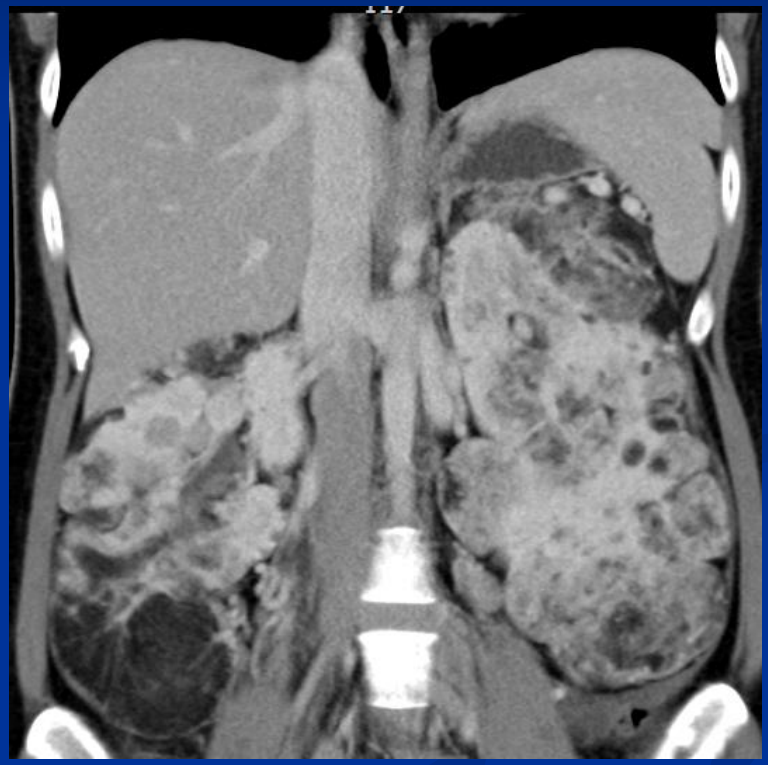
M,19y3m (class 3)



Need medical attention and Medicine is advised

>5 AML, max >4 cm, several cysts,

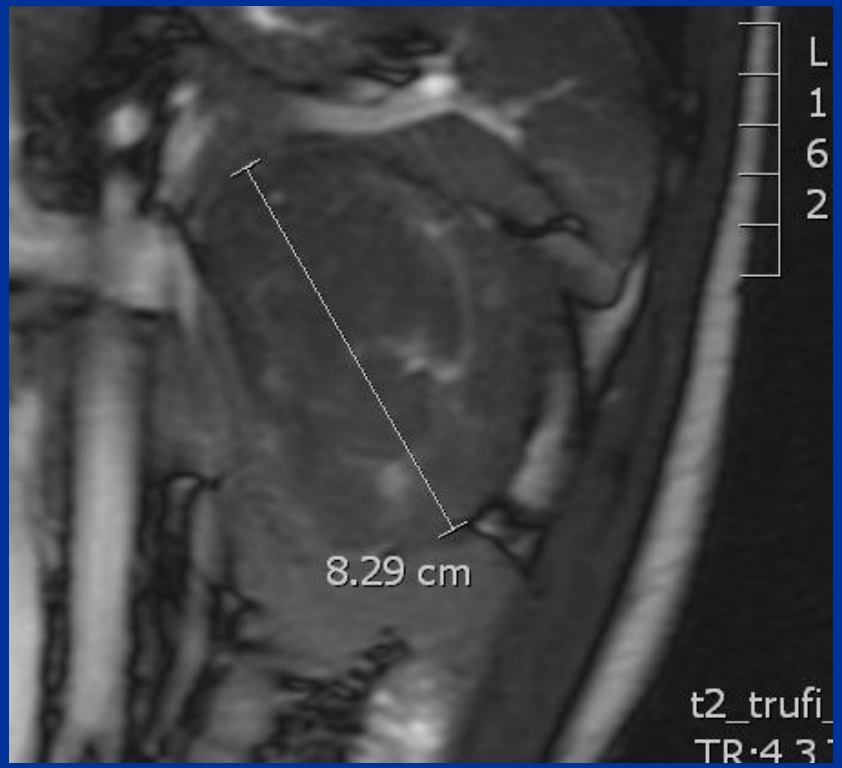
F, 34y4m, class 4



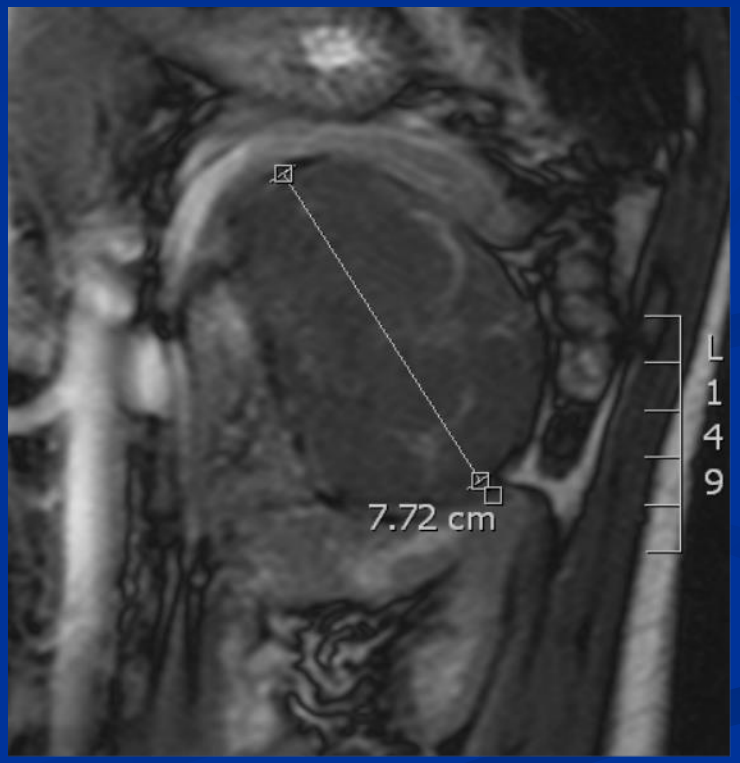
Deterioration of renal function

Treatment response >30% (everolimus)

201305



201408

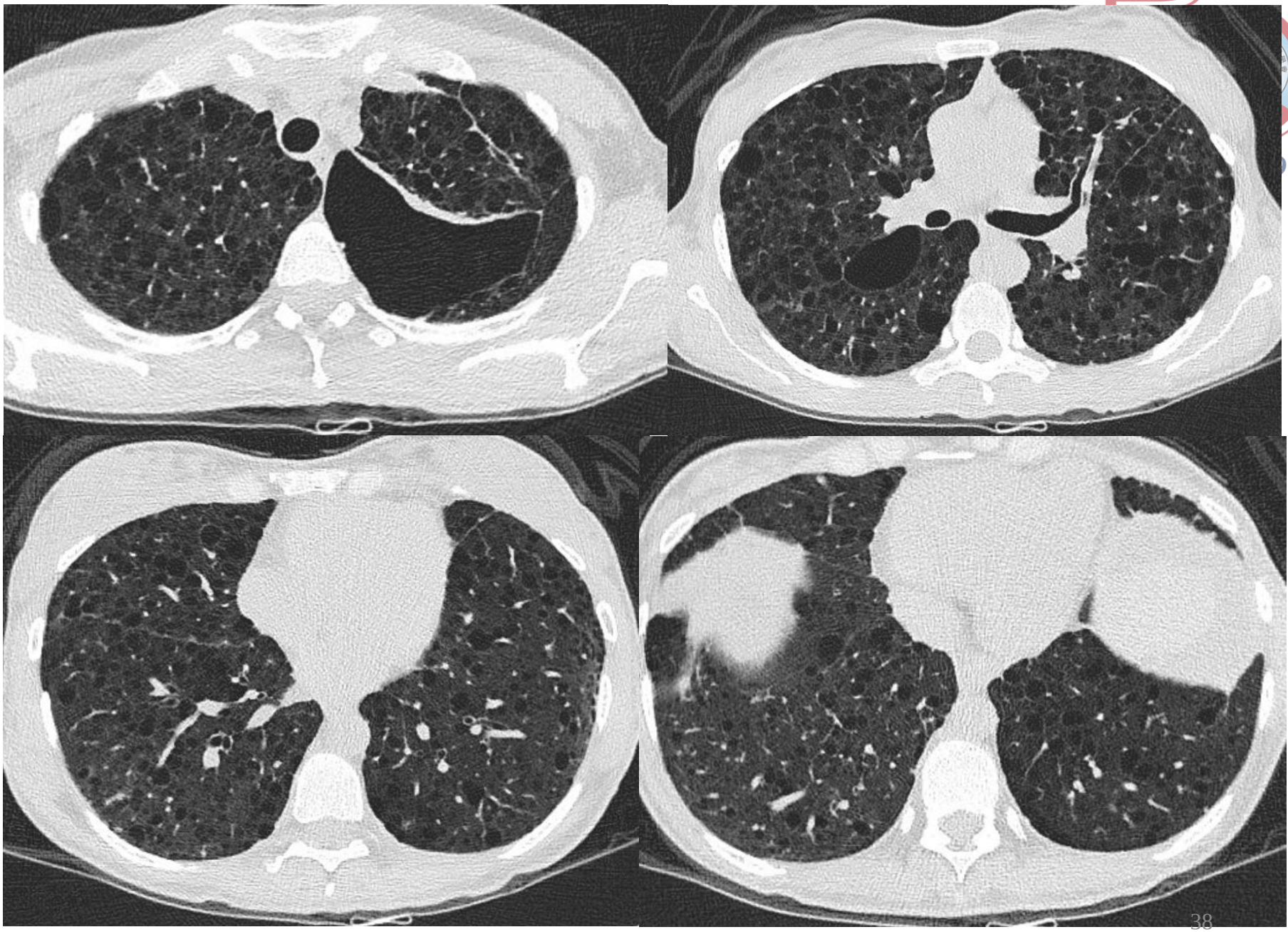


Lymphangioleiomyomatosis (LAM)

- Mutations in the tuberous sclerosis complex (TSC) genes in the smooth muscle cell proliferation
- 26-50% in TSC patients
- LAM can occur in males with TSC (10-38%)
- LAM mostly occurs among patients with *TSC2* mutations
- LAM is a late manifestation during the course of TSC
- Diagnosis of TSC-LAM at NTUH
  - Multiple (>10) thin-walled round well-defined air-filled cysts
  - Cyst size 2~30 mm
  - Cyst wall thickness barely perceptible to 2 mm

Muzykewicz et al. J Med Genet. 2009;46(7):465.

Johnson et al. Eur Respir J 2010; 35: 14–26.



Sporadic LAM vs. TSC-LAM

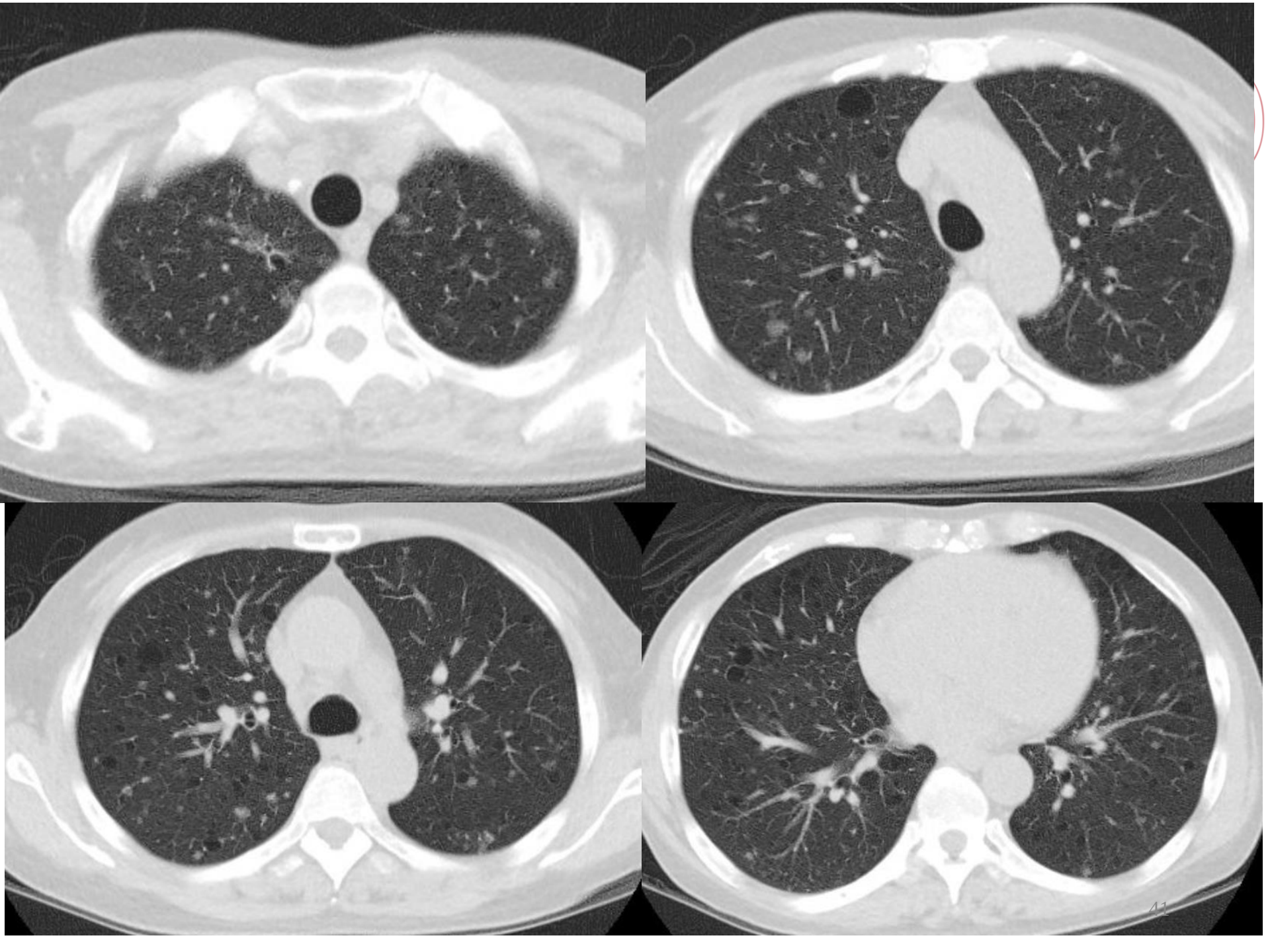
Feature	Sporadic LAM	TSC-LAM
Asymptomatic cases identified	Occasionally, >50% have respiratory symptoms	Definitely, <10% have respiratory symptoms
Gender	Female exclusively	30% in F, 10% in M
Progressive lung disease	Most	Some but not all
Pneumothorax	Yes (2/3rds)	Rare
Chylothorax	~33%	Rare
Angiomyolipomas	30-50%	70-80%
Neurologic involvement	No	Yes
mTOR inhibitors treatment considered	Yes	Yes
Lung transplant considered	Yes	Yes

Multifocal micronodular pneumocyte hyperplasia (MMPH)

- Benign proliferation of type II pneumocytes along alveolar septa caused by hyperphosphorylated mechanistic target of rapamycin (mTOR)-related proteins
- Was associated with both *TSC1* and *TSC2* mutations
- Occur in up to two-thirds of patients with TSC, with or without LAM
- Diagnosis of MMPH at NTUH
  - multiple, centrilobular solid or ground glass nodular opacities
  - size from 2 to 10 mm
  - random distribution

Maruyama et al. Pathol Int. 2001;51(8):585.

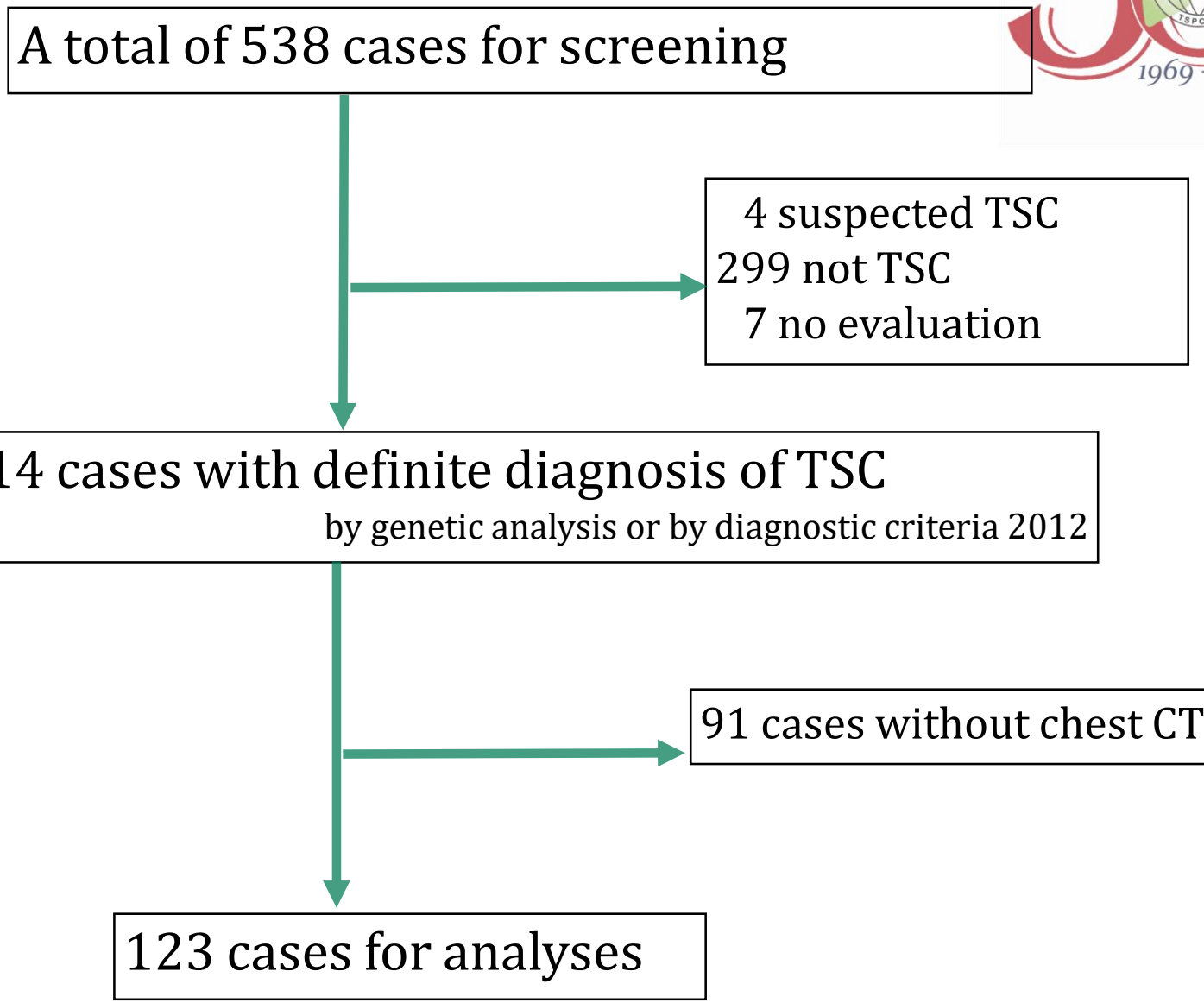
Moss et al. Am J Respir Crit Care Med. 2001;164(4):669.



In this cohort

- From 2000 to Mar 2019 at NTUH
- Inclusion criteria: TSC patients diagnosed by a next-generation sequencing (NGS)-based diagnostic pipeline or by diagnostic criteria 2012
- Data collection
  - Baseline characteristics, genotype
  - Computed tomography of chest (HRCT)
  - Pulmonary function tests before mTOR inhibitors
    - ✓ Linear mixed-effects model
  - Genotype

From 2000 to Mar. 2019



Baseline characteristics of the 123 cases

characteristics	Percentage or mean
Age	34.8 ± 13.7 (13-79)
Gender, female	78 (63.4%)
TSC1 TSC2 unclassifiable	19 (15.4%) 77 (62.6%) 14 (11.4%)
Initial Chest CT findings	
LAM + MMPH	20 (16.3%)
LAM	15 (12.2%)
MMPH	64 (52.0%)
Normal lung	24 (19.5%)

Patients with LAM or MMPH

	LAM+MMPH (n=20)	LAM (n=15)	MMPH (n=64)	Normal lung (n=24)
Gender, female	20 (100%)	14 (93.3%)	33 (51.6%)	11 (45.8%)
Age	44.0 ± 2.9	37.4 ± 3.5	33.7 ± 1.7	28.6 ± 2.1
TSC1 mutation	1 (5.0%)	1 (6.7%)	13 (20.3%)	4 (16.7%)
TSC2 mutation	17 (85.0%)	9 (60.0%)	37 (57.8%)	14 (58.3%)
unclassifiable	1 (5.0%)	3 (20.0%)	7 (10.9%)	4 (16.7%)
pneumothorax	2 (10.0%)	1(6.6%)	0	0

Patients with LAM or MMPH

	LAM+MMPH (n=20)	LAM (n=15)	MMPH (n=64)	Normal lung (n=24)
Hypomelanotic macules 脫色斑	13 (65.0%)	8 (53.3%)	31 (48.4%)	13 (54.2%)
Facial angiofibromas 臉部血管纖維瘤	4 (20.0%)	5 (33.3%)	17 (26.6%)	6 (25.0%)
Ungual fibromas 指甲纖維瘤	11 (55.0%)	4 (26.7%)	21 (32.8%)	5 (25.0%)
Shagreen patch 鯊魚皮斑	8 (40.0%)	7 (46.7%)	23 (35.9%)	6 (25.0%)

Patients with LAM or MMPH

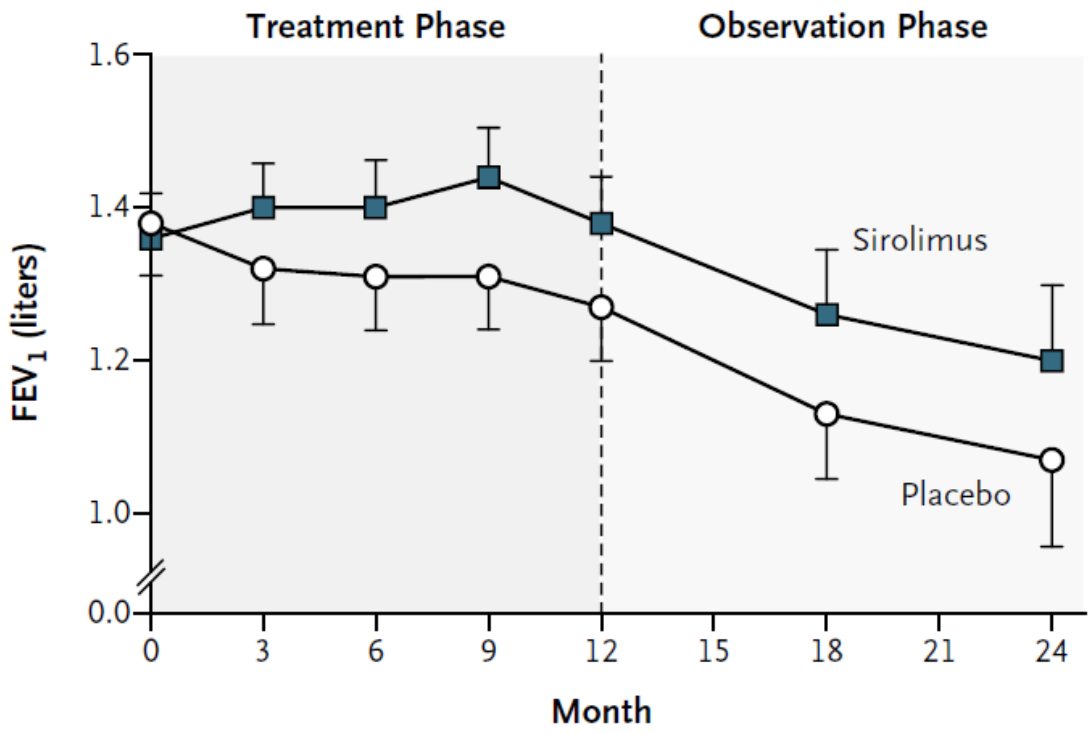
	LAM+MMPH (n=20)	LAM (n=15)	MMPH (n=64)	Normal lung (n=24)
Cortical dysplasia	13 (65.0%)	9 (60.0%)	40 (62.5%)	20 (83.3%)
Subependymal nodules	13 (65.0%)	8 (53.3%)	37 (57.8%)	16 (66.7%)
Subependymal giant cell astrocytoma	9 (45.0%)	8 (53.3%)	27 (42.2%)	16 (66.7%)
Renal Angiomyolipomas	13 (65.0%)	12 (80.0%)	31 (48.4%)	9 (37.5%)

Baseline pulmonary function test

Characteristics	LAM+MMPH (n=20)	LAM (n=15)	MMPH (n=64)	Normal lung (n=24)
FEV_1 (L) *, % pred *	2.19 ± 0.10, 85.3 ± 3.4	2.38 ± 0.16, 86.1 ± 4.5	2.97 ± 0.09, 95.1 ± 1.9	2.83 ± 0.18, 90.1 ± 3.6
FVC (L) *, % pred *	2.56 ±0.11, 87.5 ± 3.3	2.66 ±0.13, 88.3 ± 4.7	3.41 ±0.11, 97.3 ± 1.9	3.14 ±0.20, 90.6 ± 3.6
TLC (L) *, % pred *	3.99 ± 0.21, 90.1 ± 4.7	4.10 ± 0.18, 91.6 ± 3.6	4.92 ± 0.14, 101.5 ± 2.2	4.97 ± 0.33, 106.6 ± 4.9
D_{LCO} *, % pred	16.5 ± 0.9, 77.0 ± 4.9	18.1 ± 1.2, 83.5 ± 5.2	22.6 ± 0.7, 87.8 ± 1.9	22.1 ± 1.7, 82.1 ± 5.1

Change of lung function

A



No. at Risk							
Sirolimus	46	43	41	38	41	21	14
Placebo	43	40	42	39	34	22	13

McCormack et al. N Engl J Med. 2011 Apr 28;364(17):1595-606.

Annual decline of lung function

Table 2. Effects of Sirolimus on Primary and Selected Secondary Outcome Variables during the Treatment Period.*

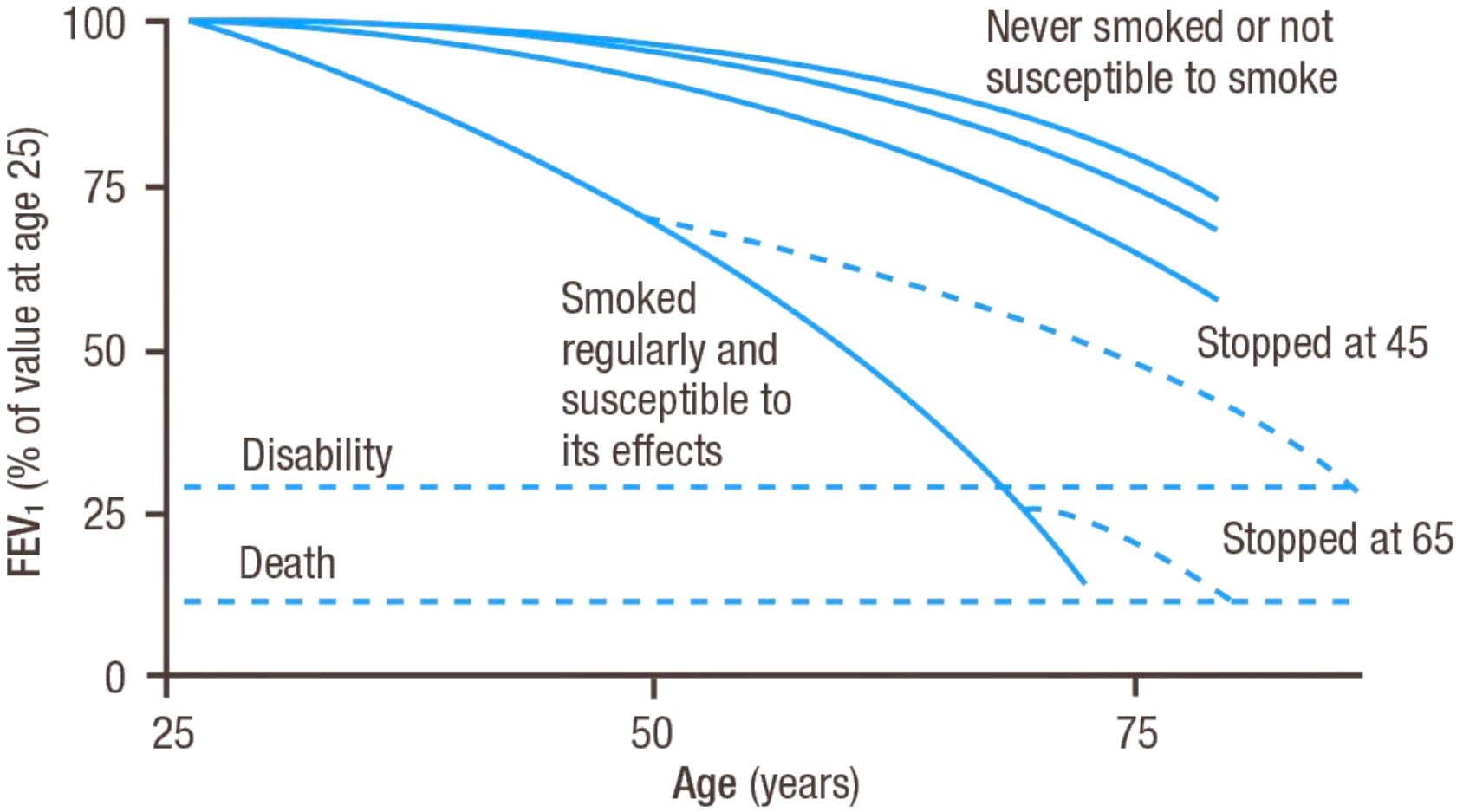
Variable	Value at 12 Months		Change from Baseline		
	Placebo (N=34)	Sirolimus (N=41)	Placebo (N=34)	Sirolimus (N=41)	P Value†
Pulmonary function					
FEV_1 (ml)	1272±414	1383±394	−134±182§	19±124	<0.001
FVC (ml)	2843±668	2780±735	−129±233§	97±260	0.001
Total lung capacity (ml)	5464±1217	4944±982	−7±650	94±504	0.65
Residual volume (ml)	2502±969	2112±617	−16 ±514	38±538	0.61
Functional residual capacity (ml)	3260±968	2912±660	−123±521	53±335	0.43
DL_{CO} (ml/mm Hg/min)	9.61±4.06	9.62±3.92	−0.62±2.89§	−0.06±1.50	0.38

	Pre-sirolimus	Post-sirolimus
Change in FEV_1 mL·year^{-1}	−105±17	−40±24
Change in FEV_1 % per year	−3.0±0.5	−1±0.8
Change in DL_{CO} mL·min^{-1}·mmHg^{-1}·year^{-1}	−0.66±0.06	−0.05±0.14#
Change in DL_{CO} % per year	−2.6±0.3	0.02±0.6#

McCormack et al. N Engl J Med. 2011 Apr 28;364(17):1595-606.

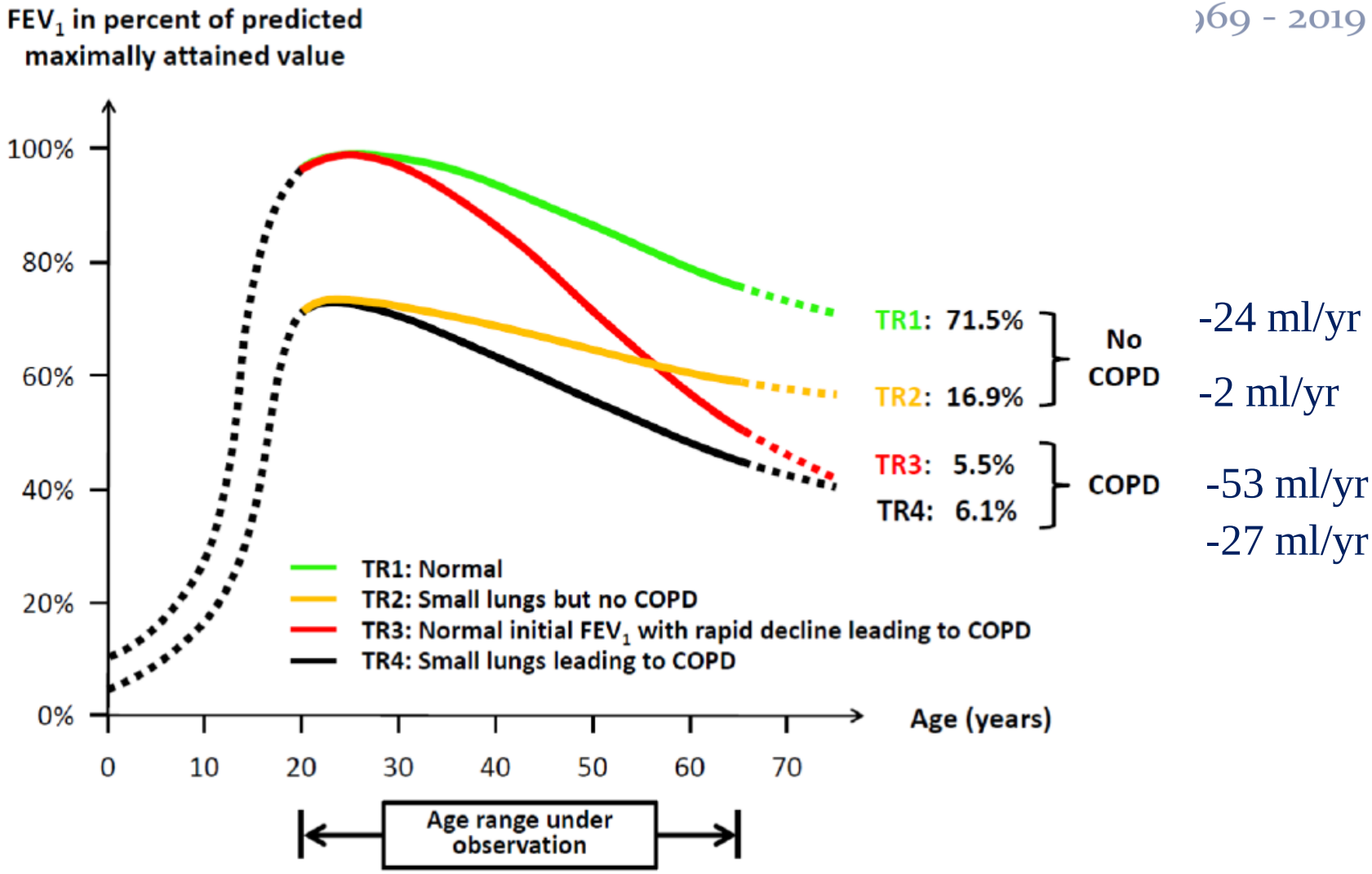
Taveira-DaSilva et al. Eur Respir J. 2018 Apr 19;51(4).

Fletcher and Peto's model



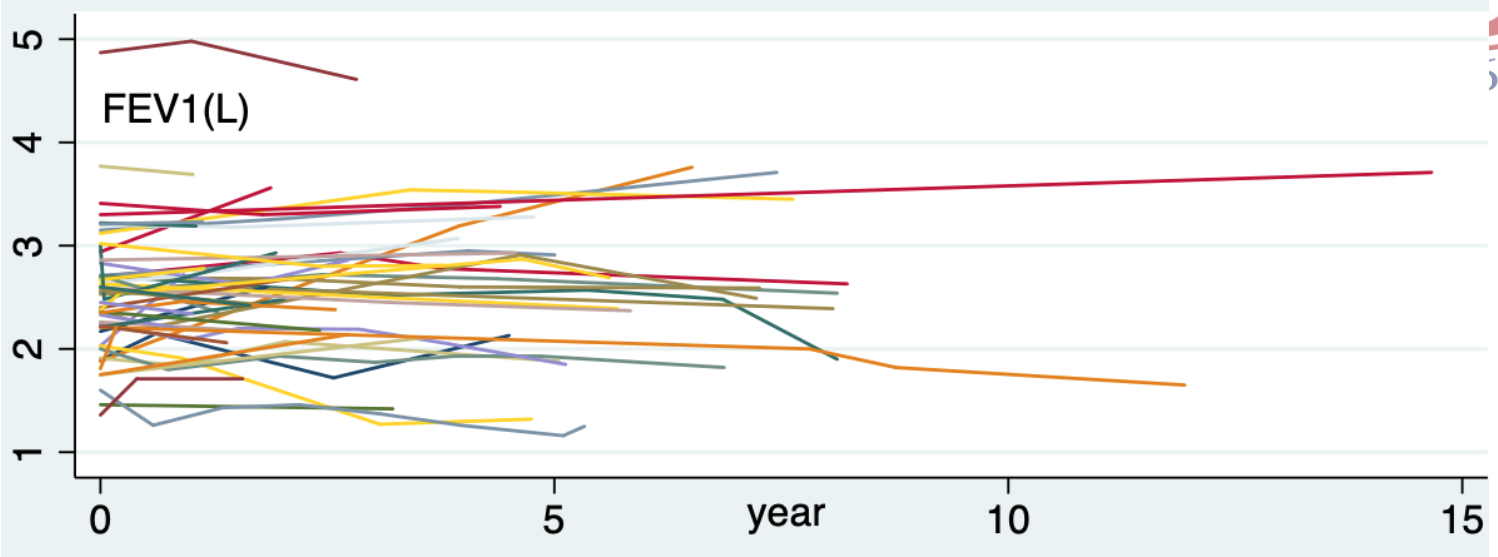
Fletcher C, Peto R. *Br Med J* 1977; 1: 1645-8.

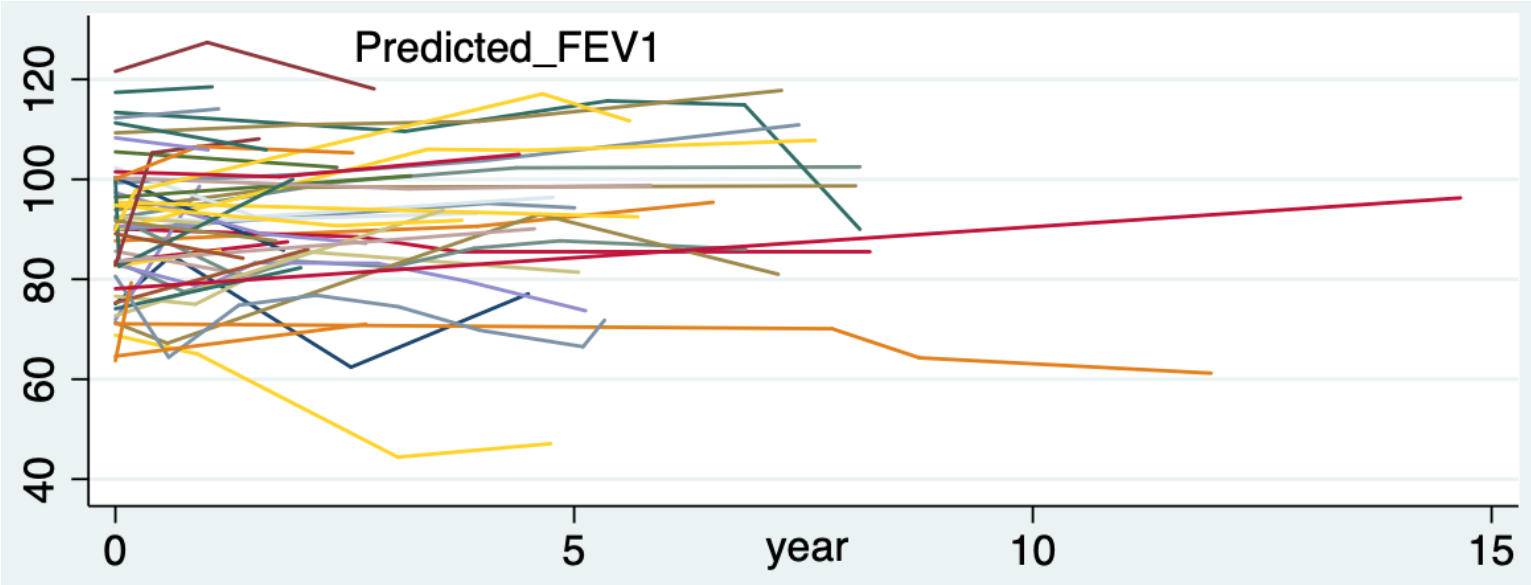
Baseline FEV1 and development of GOLD II COPD



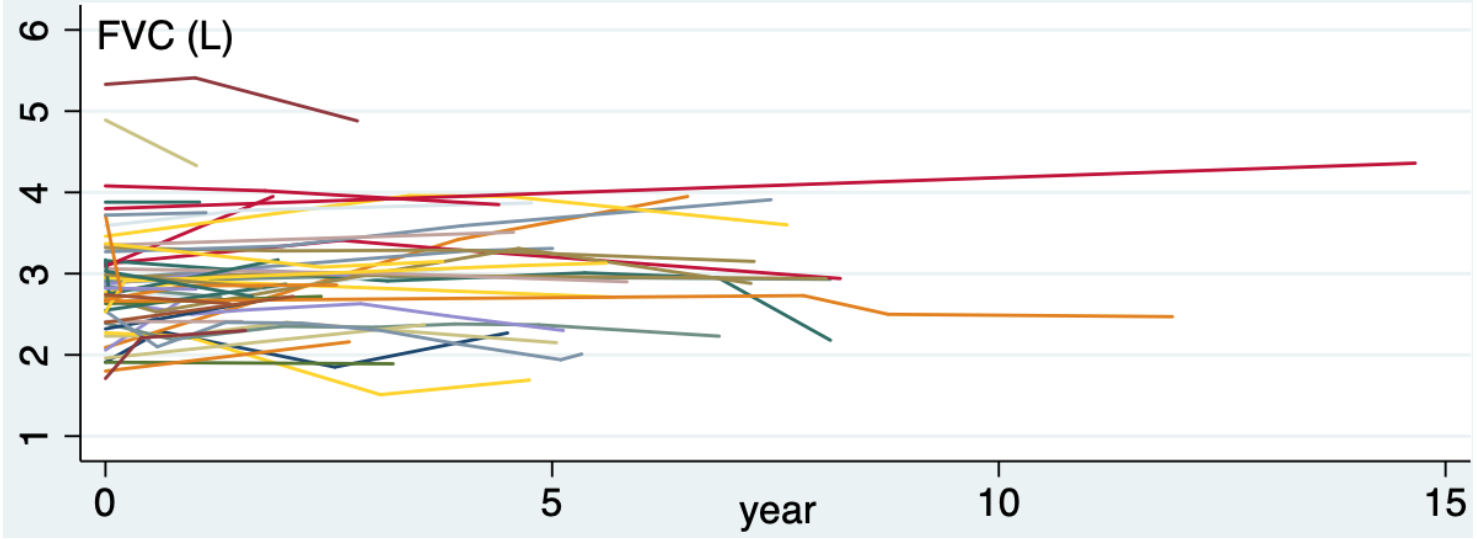
Lange et al. N Engl J Med. 2015 Jul 9;373(2):111-22.

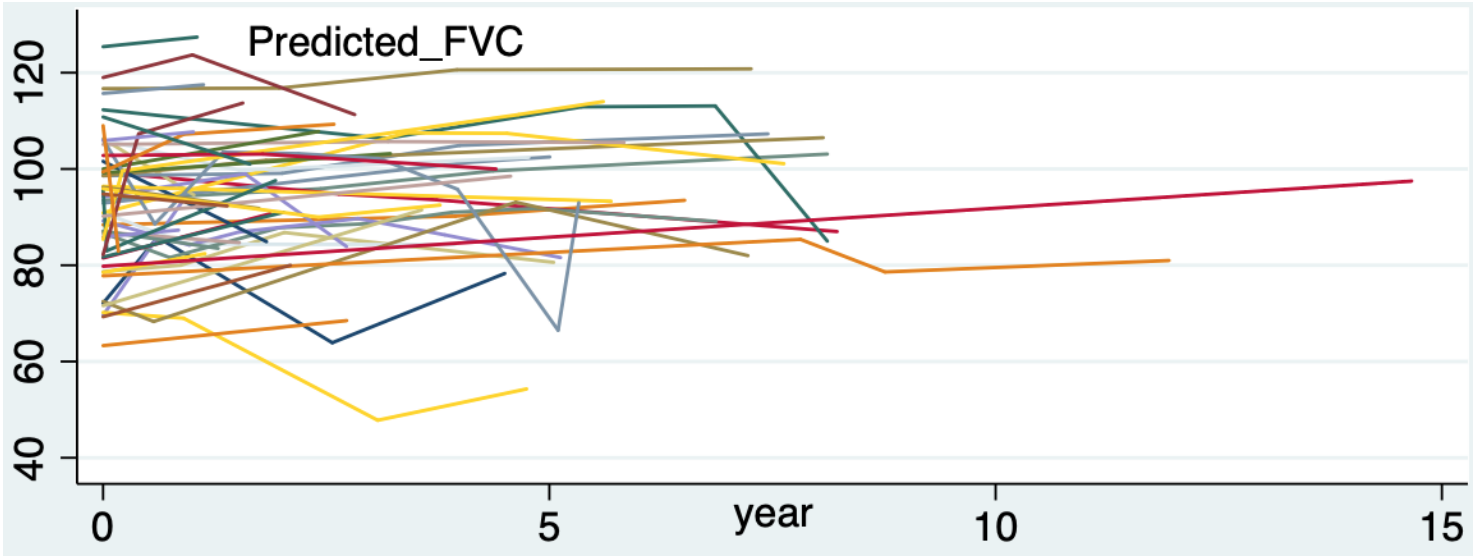
Serial line plots for FEV_1



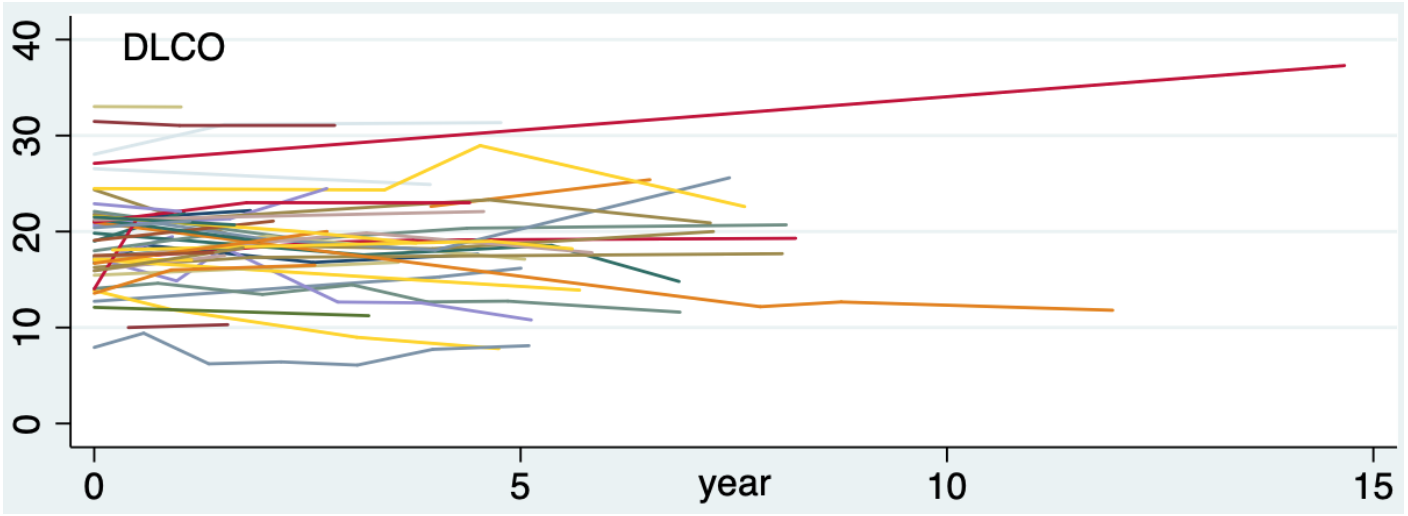


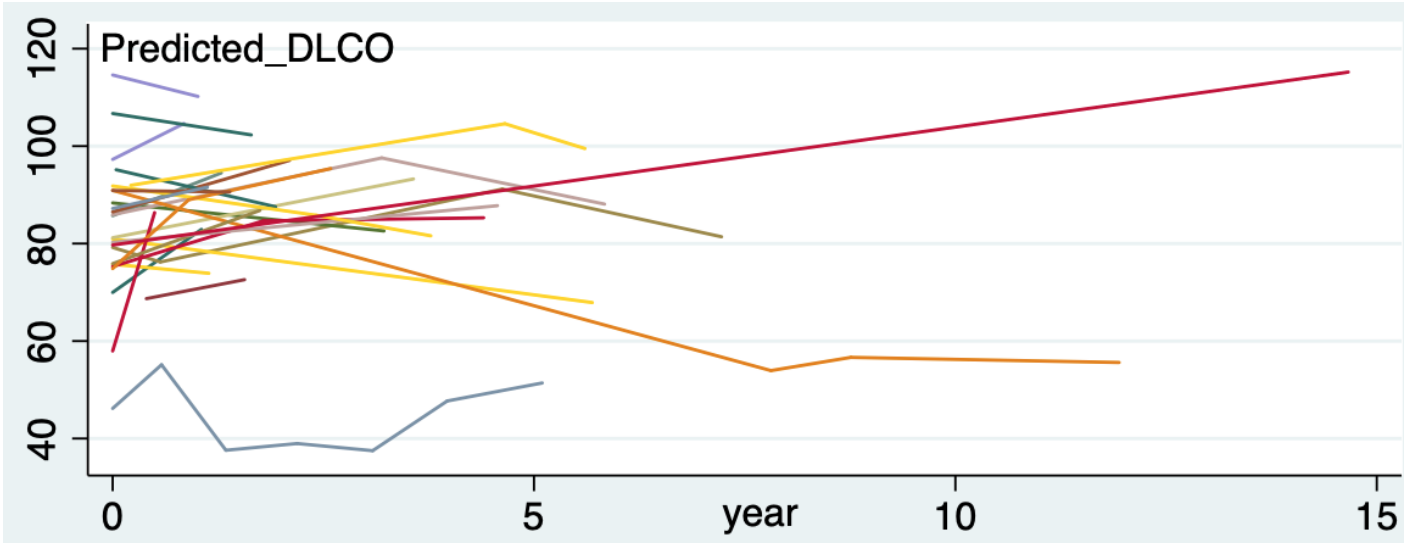
Serial line plots for FVC



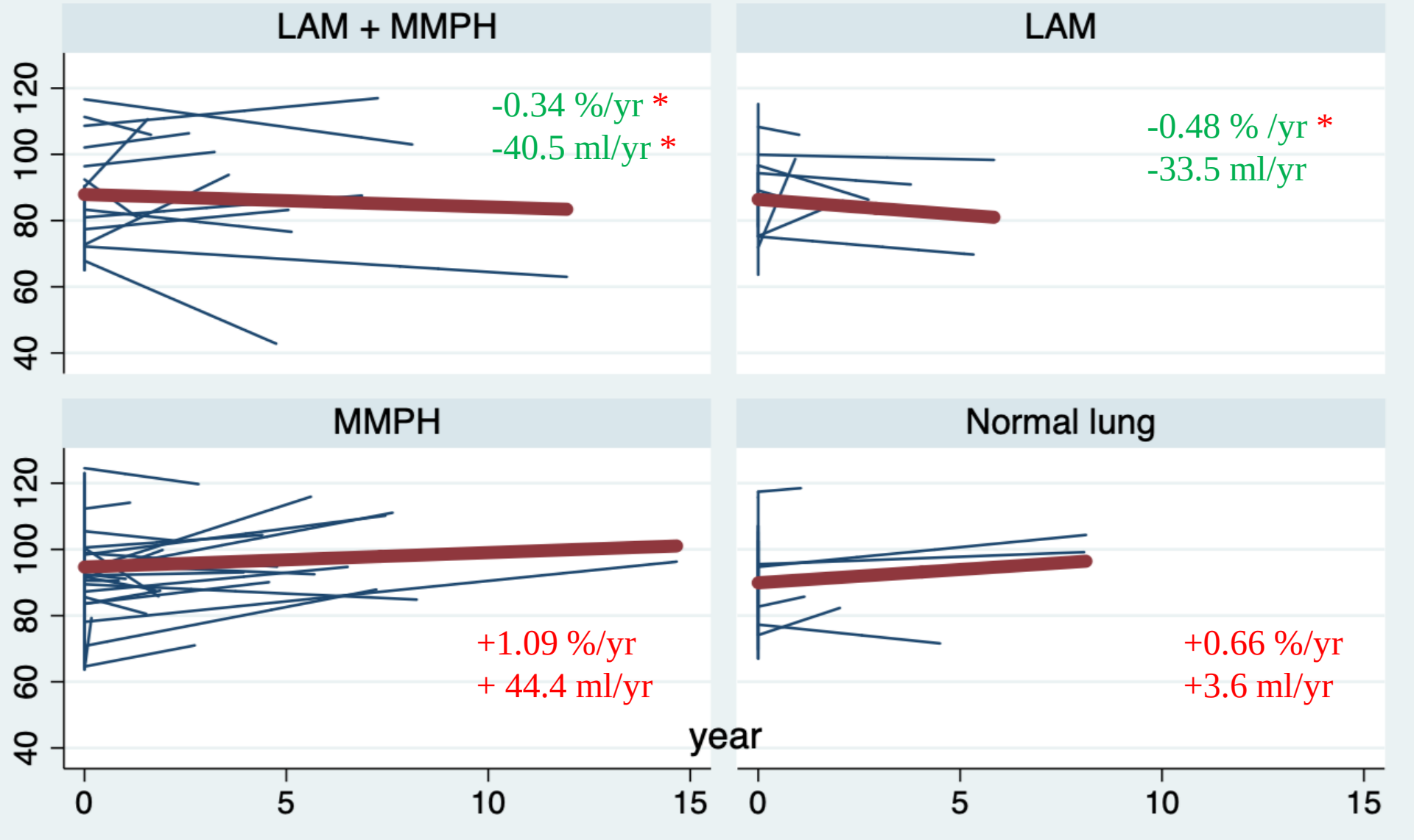


Serial line plots for D_{LCO}

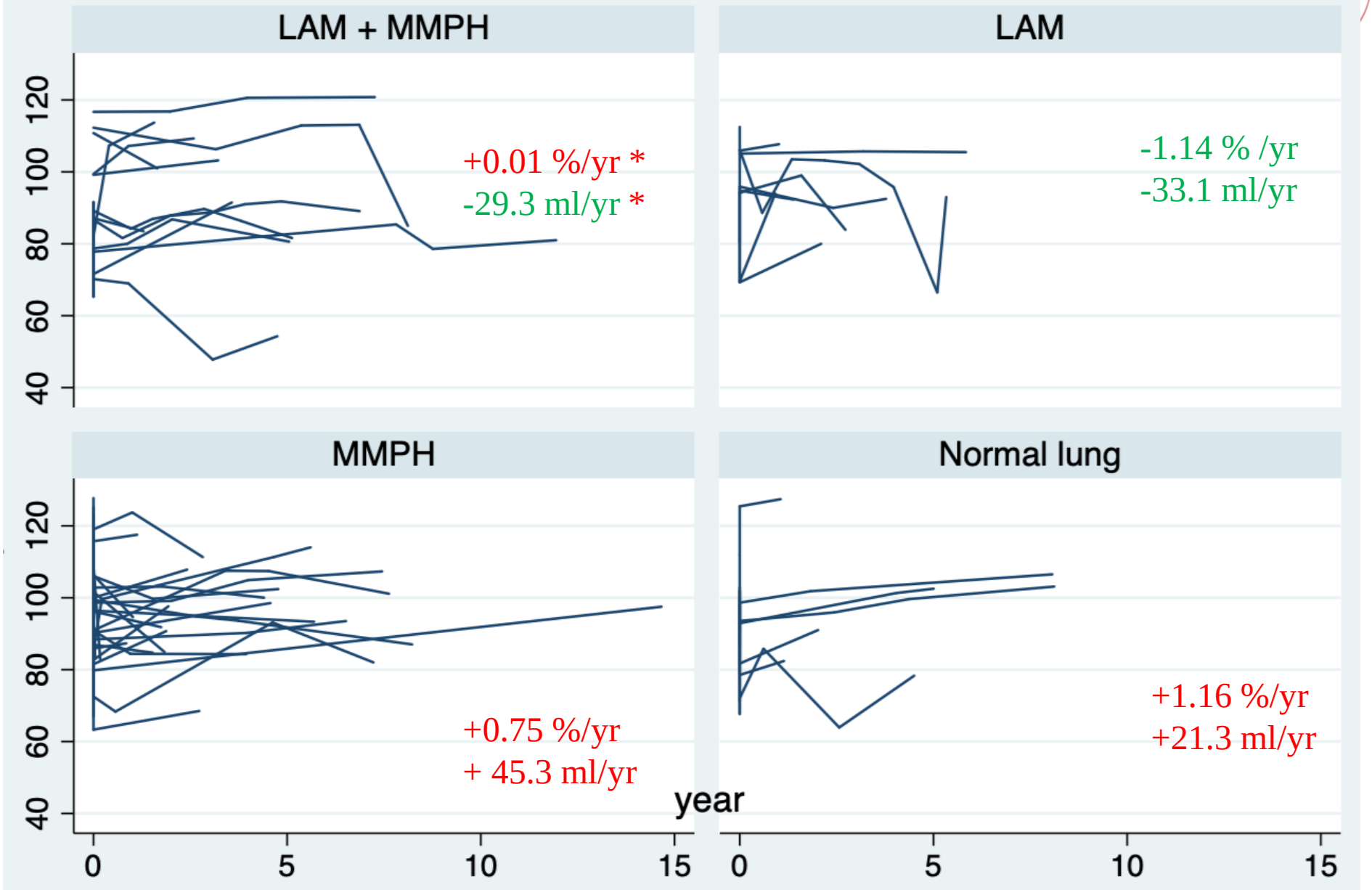




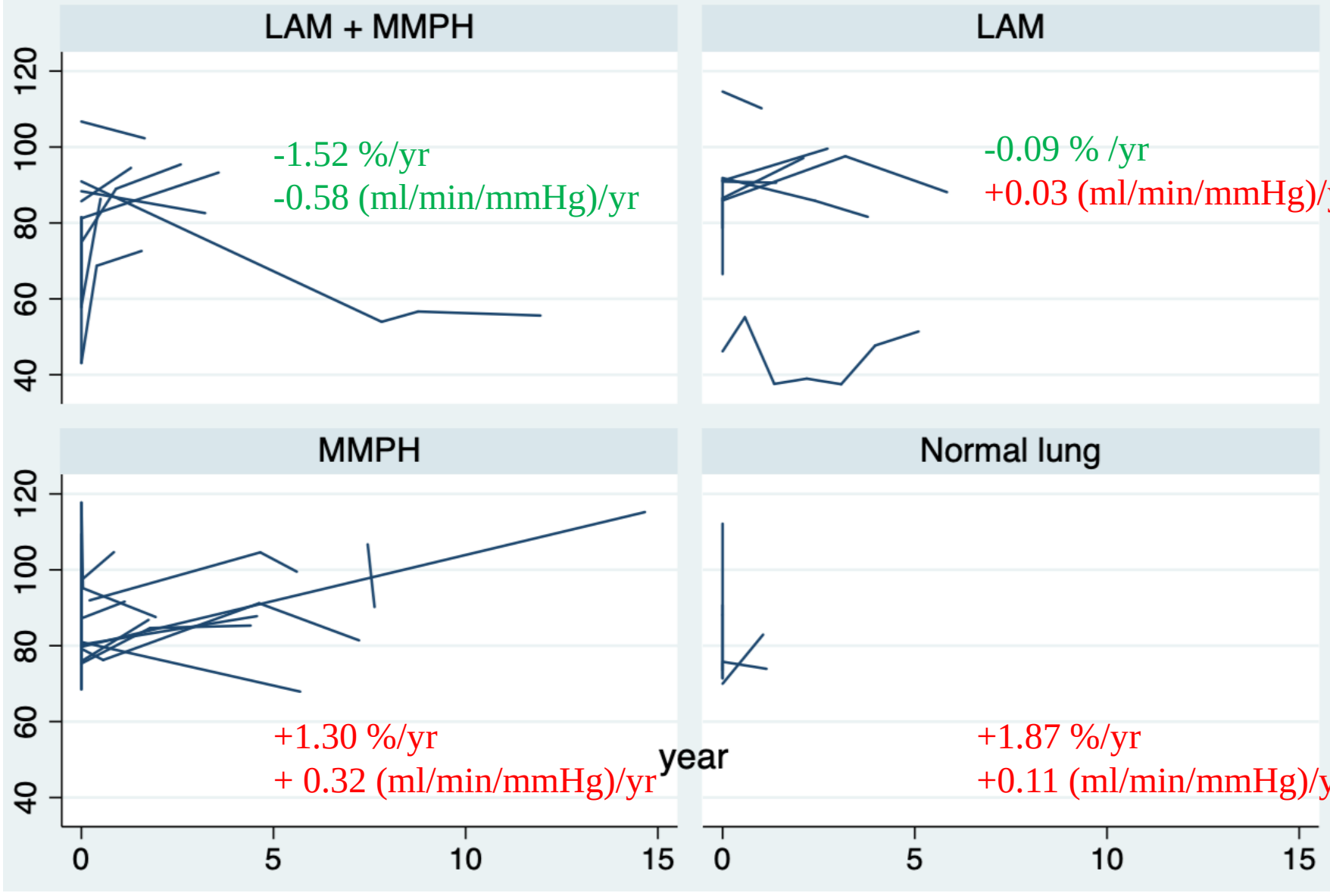
Spaghetti plot of Predicted_FEV_1



Spaghetti plot of Predicted_FVC



Spaghetti plot of Predicted_D_{LCO}



Conclusion

- In this Taiwanese cohort
- TSC with LAM, MMPH, LAM + MMPH, normal lung, all mostly occurs among patients with *TSC2* mutations
- Patient with combined LAM and MMPH had a greater average decline in FEV_1 and FVC

Many Thanks!