

Kidney manifestations in TSC: a multidisciplinary approach

Djalila Mekahli

NEPHROGENETICS

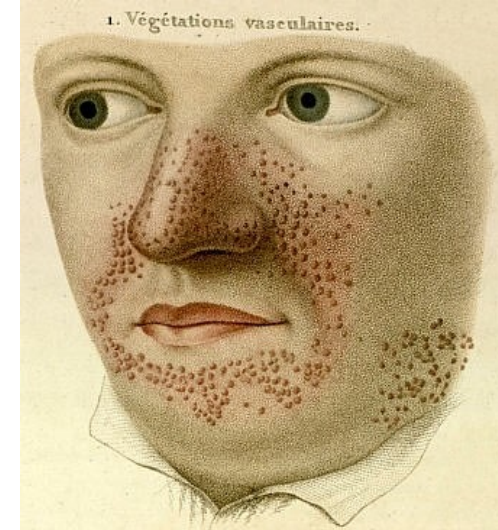
A CORNERSTONE TO OPTIMIZE CLINICAL CARE

Renal genetics symposium Ghent University Hospital

Saturday October 12, 08.30 – 13.30 | Zebra, Zebrastraat 32, 9000 Ghent

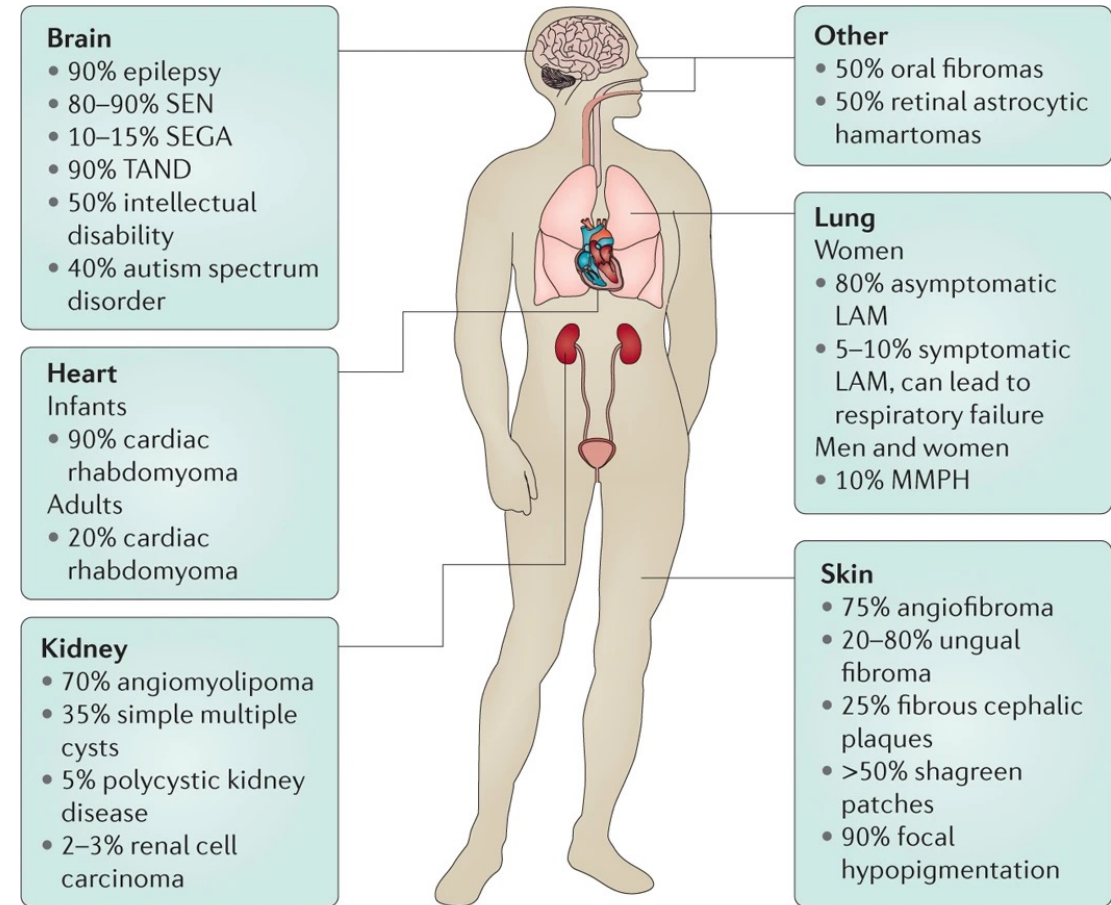
Tuberous Sclerosis Complex (TSC) : Introduction

- 1835: Pierre Rayer « végétations vasculaires »
- 1880: Desiré Bourneville “First case “
- 1979: Gomez criteria
- 2004: modified Gomez criteria
- 2012: new diagnostic and FU recommendations
- 2021: Updated Consensus Guidelines for diagnosis of TSC



TSC : Introduction

- A rare Autosomal dominant disorder with multiple benign tumors throughout the body
- Estimated incidence: 1:6.000-10.000 live births
- Mutations of TSC1 (80%-85%) or TSC2
- Often not recognized as fewer than 40% of patients have the classical presentation
- Updated Consensus Guidelines for diagnosis of TSC (Northrup H . 2021)



Updated Consensus Guidelines for diagnosis of TSC (2021)

Diagnostic Criteria

Major Criteria	Minor Criteria
Hypomelanotic macules (≥ 3 ; at least 5 mm diameter)	“Confetti” skin lesions
Angiofibroma (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥ 2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM*	
Angiomyolipomas (≥ 2)*	

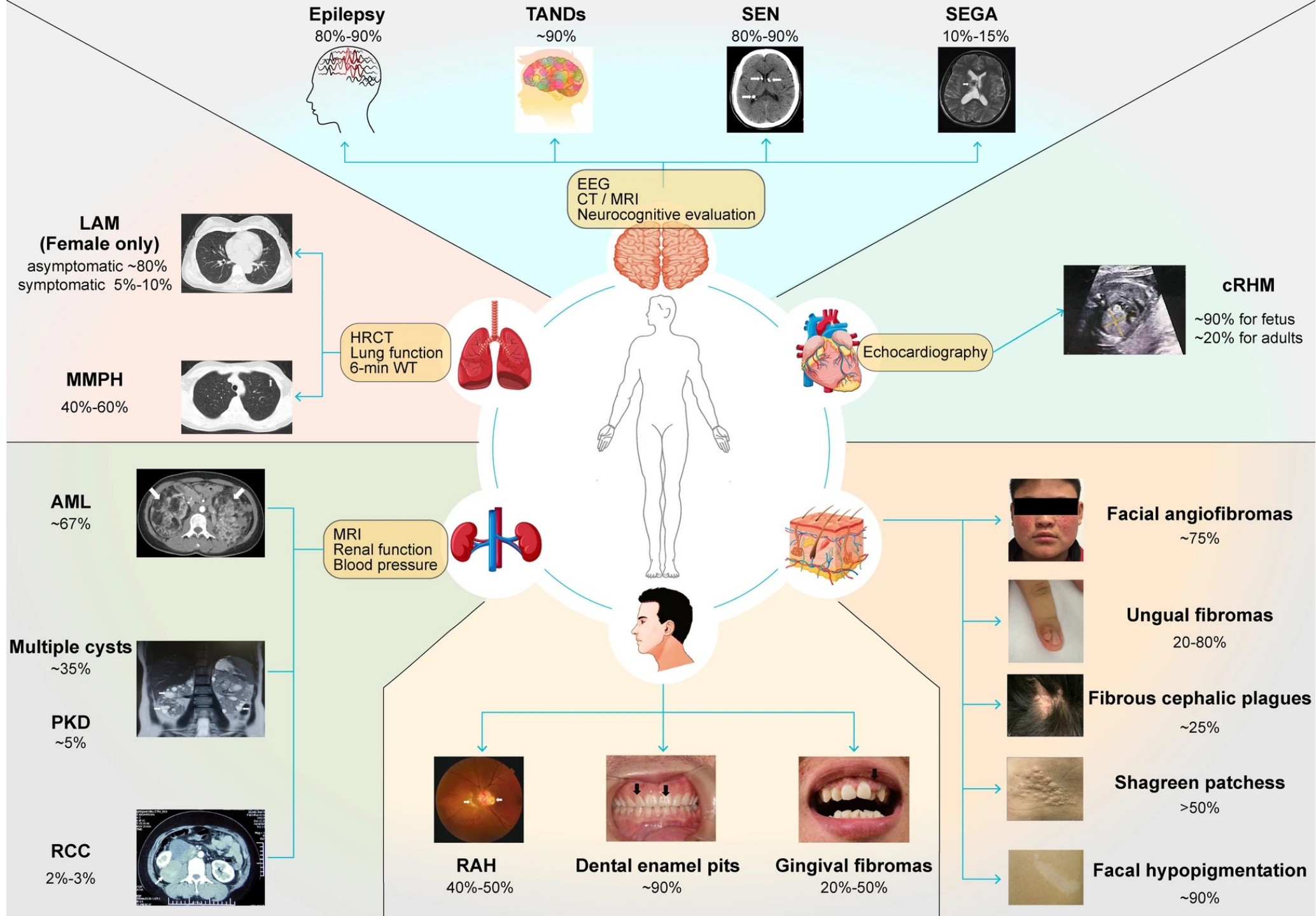
Updated Consensus Guidelines for diagnosis of TSC (2021)

Definite TSC: 2 major features or 1 major feature with 2 minor features.

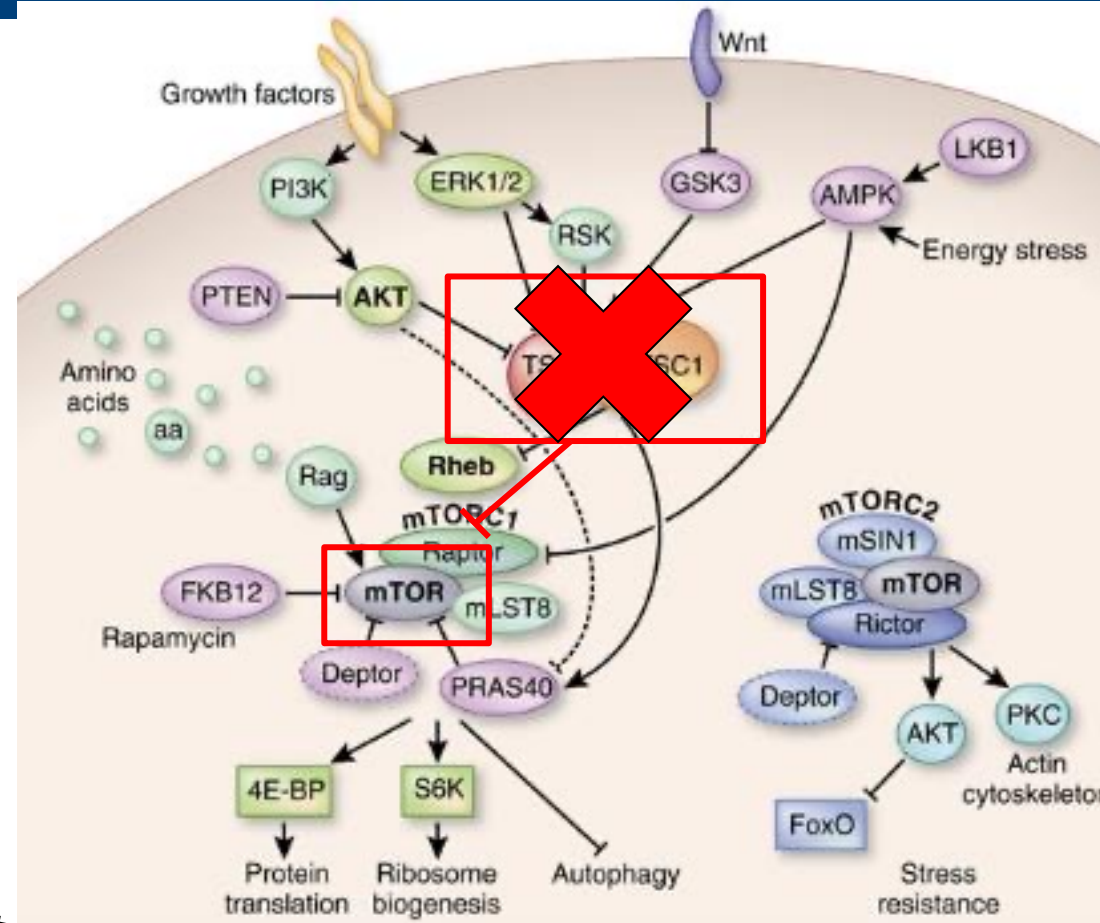
Possible TSC: either 1 major feature or ≥ 2 minor features.

Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution).

* A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.



TSC : Physiopathology



SEGA, AML

cell growth and proliferation

AML, LAM

angiogenesis and lymphangiogenesis

Cell growth and metabolism

cell metabolism and glucose uptake

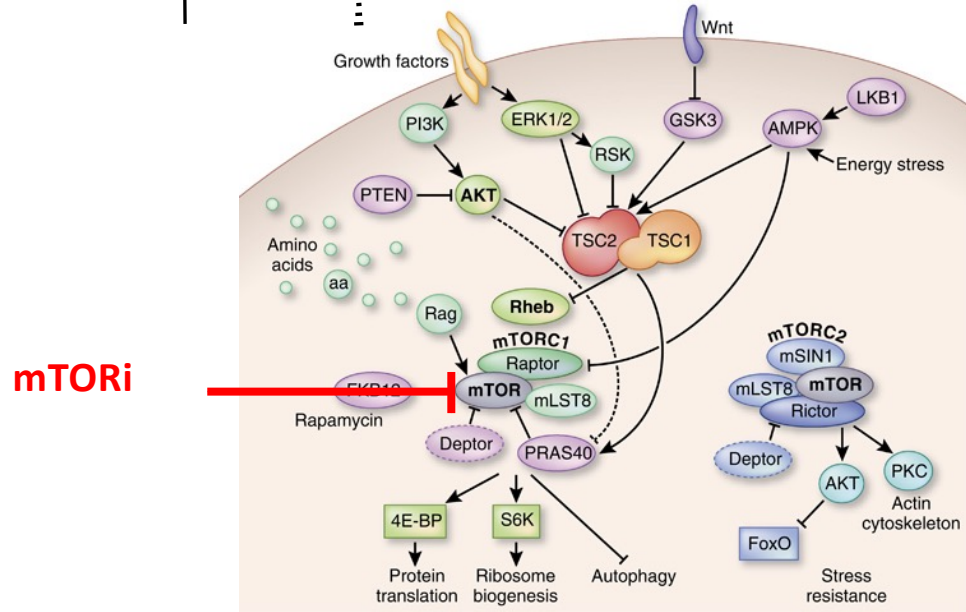
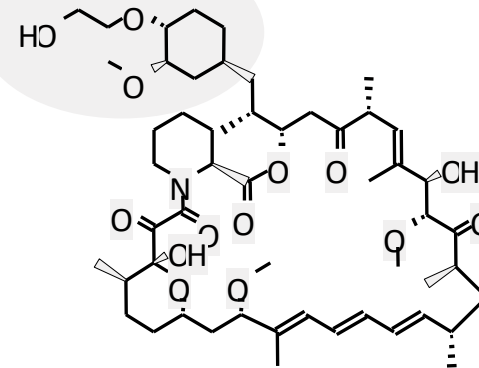
neuronal dysfunction

tubers, cortical dysplasia

cell orientation and migration

mTOR inhibitors

- RAD001 (Everolimus)



Rapamycin Causes Regression of Astrocytomas in Tuberous Sclerosis Complex

David Neal Franz, MD,^{1,2} Jennifer Leonard, MSN, FNP,^{1,2} Cynthia Tudor, MSN, PNP,^{1,2} Gail Chuck, BS,^{1,2} Marguerite Care, MD,^{1,3} Gopalan Sethuraman, PhD,⁴ Argirios Dinopoulos, MD,^{1,2} George Thomas, PhD,⁵ and Kerry R. Crone, MD^{1,6}

Everolimus Treatment of Refractory Epilepsy in Tuberous Sclerosis Complex

Darcy A. Krueger, MD, PhD,¹ Angus A. Wilfong, MD,² Katherine Holland-Bouley, MD, PhD,¹ Anne E. Anderson, MD,² Karen Agricola, CFNP,¹ Cindy Tudor, CPNP,¹ Maxwell Mays, BS,¹ Christina M. Lopez, BS,² Mi-Ok Kim, PhD,³ and David Neal Franz, MD¹

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmithorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

ORIGINAL ARTICLE

Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D., Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P., Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D., Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

Topical Rapamycin

A Novel Approach to Facial Angiofibromas in Tuberous Sclerosis

Anna K. Horne, MD, Amy L. O'Brien, MD, Joo-Mi Yoo, MD, PhD; Departments of Medicine (Dr Horne), Dermatology (Dr Horne and Yoo), and Pediatrics (Dr O'Brien and Yoo), University of Wisconsin School of Medicine and Public Health, Madison.

Pediatr Nephrol (2018) 33:101–109
DOI 10.1007/s00467-017-3806-1

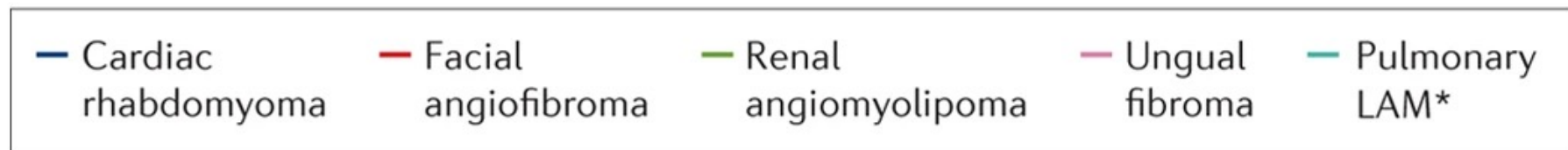
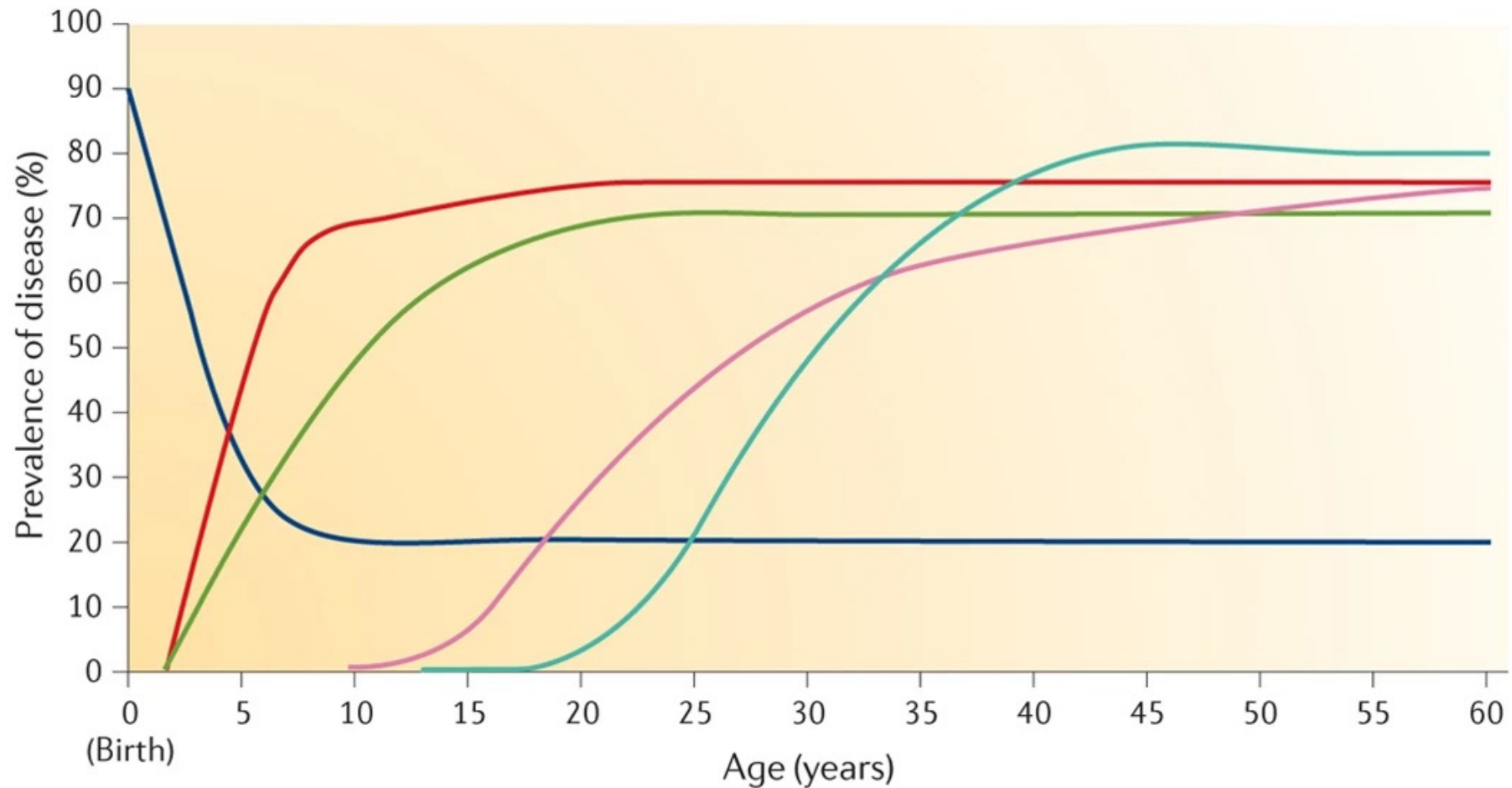


ORIGINAL ARTICLE

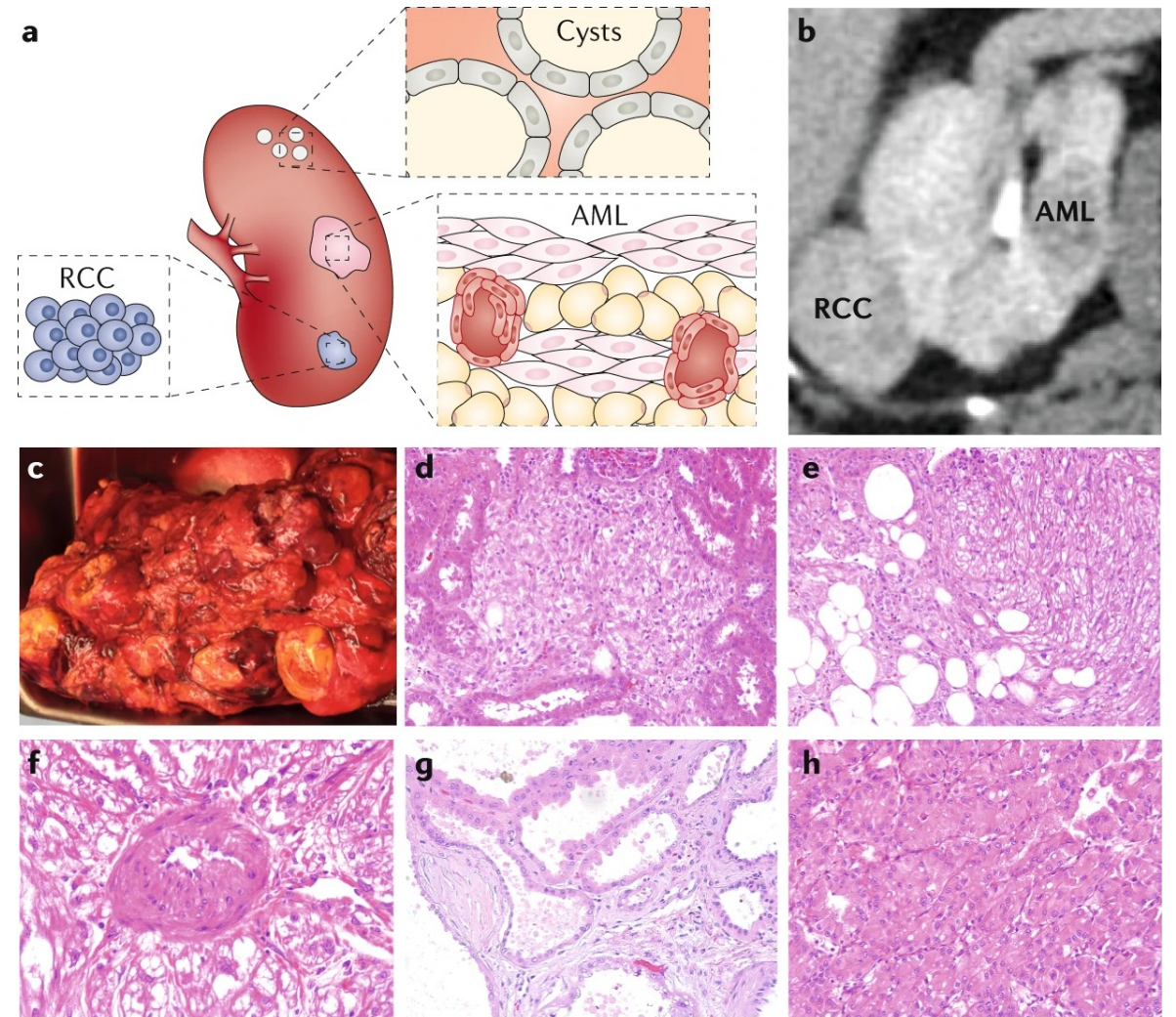
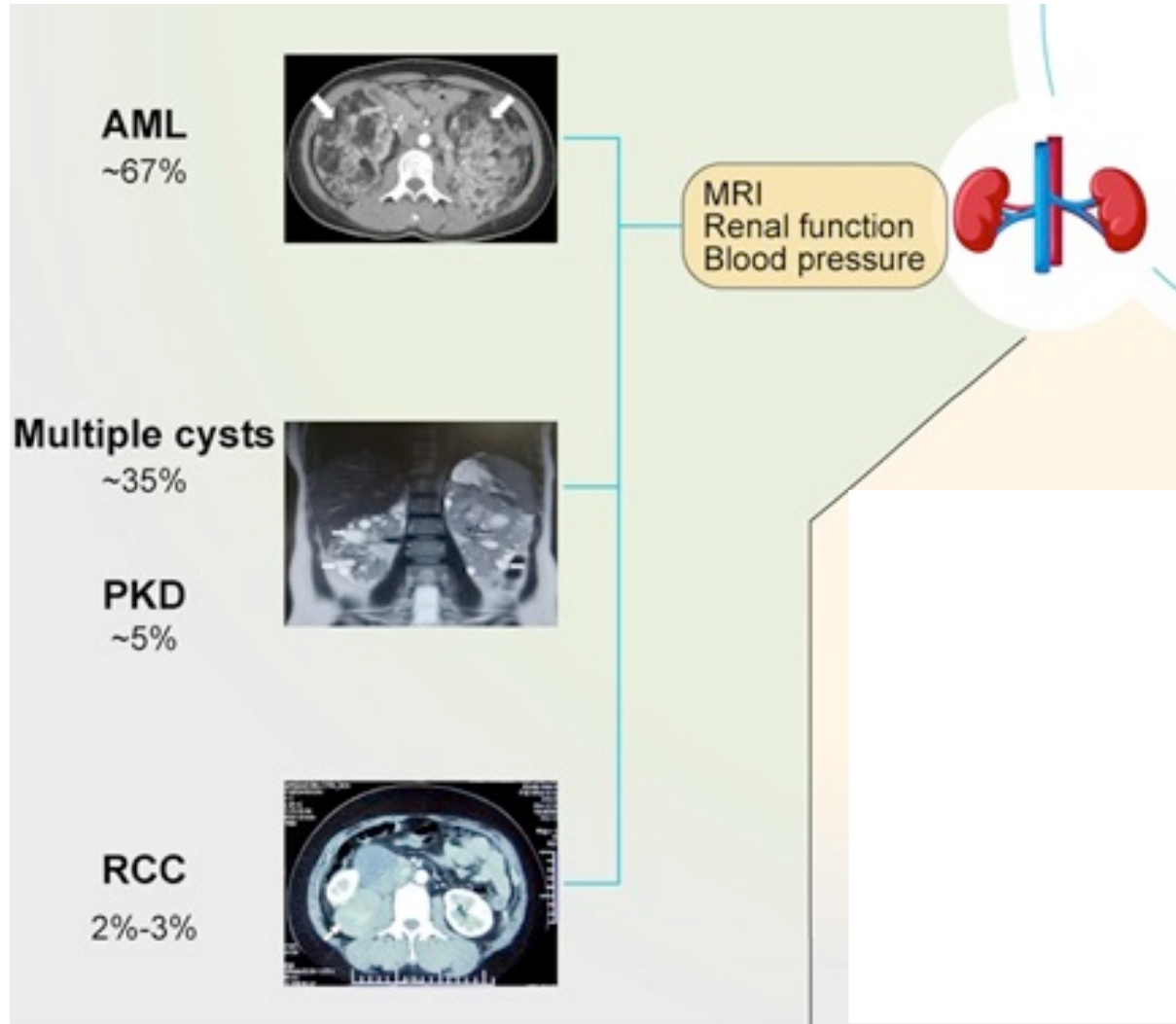
The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma

John J. Bissler¹ • David N. Franz² • Michael D. Frost³ • Elena Belousova⁴ • E. Martina Bebin⁵ • Steven Sparagana⁶ • Noah Berkowitz⁷ • Antonia Ridolfi⁸ • J. Christopher Kingswood⁹

Age-dependent clinical manifestations



TSC: Kidney manifestations



Kidney involvement in tuberous sclerosis complex (TSC)

- **TSC-associated kidney disease is the most common cause of death in adults with TSC**
- **40% of adult patients with TSC have chronic kidney disease (CKD)**
- **Lack of guidance for taking care of the kidneys in TSC**
- **Many anecdotal reports of patients with TSC having unnecessary nephrectomies enhancing their risk of serious CKD**
- **This is especially unfortunate given the success of (mTOR) inhibitor therapies**

Kidney involvement in tuberous sclerosis complex (TSC): A Clinical Practice Recommendation by the ERKNet Working Group for Autosomal Dominant Structural Kidney Disorders

- A single source reference document for all physicians involved in the medical care of patients with TSC focused on kidney involvement
- All stakeholders were involved including (pediatric)nephrologists, urologists, geneticists, (pediatric)radiologists, interventional radiologists, and pathologists; as well as patient representatives
- *PICO questions*

Working group 1: PICO questions regarding genetic aspects of TSC

Working group 2: PICO questions regarding comorbidities and follow-up

Working group 3: PICO questions regarding diagnostic imaging and biopsy

Working group 4: PICO questions regarding treatment

Box 1 | Recommendations for genetic testing of patients with TSC

Recommendation 1:

Genetic diagnosis, meaning a search for pathogenic variants in *TSC1* and *TSC2*, is recommended for all patients with TSC, both those meeting definite diagnostic criteria and those who are likely (level X, strong).

Recommendation 2:

If no disease-causing variant is identified by genetic analysis, clinical analysis is recommended as 1% (level X, strong).

Recommendation 3:

If no *TSC2/PKD1* variant is identified by genetic analysis, clinical analysis of family members is routinely recommended (level X, strong).

Recommendation 4:

We suggest to consider having children when a pathogenic variant is identified in a patient with TSC.

Recommendation 5:

When a pathogenic variant is identified in a patient with TSC, the severity of disease is greater than that of *TSC1*-associated disease.

- Genetic diagnosis is recommended for all patients with TSC
- Expert clinical evaluation of first-degree family members is recommended when a pathogenic variant is identified in a patient with TSC
- Only one-third of patients diagnosed with TSC have an affected parent. Thus, most affected individuals are de novo, but, low-level mosaicism for a pathogenic variant might occur in a parent without TSC manifestations
- The severity of *TSC2*-associated TSC is greater than that of *TSC1*-associated disease
- Patients with combined deletion of part or all of *TSC2* and *PKD1* have a high risk of an accelerated cystic kidney disease phenotype

Genetic analysis of family members is routinely recommended (level X, strong).

We suggest to consider having children when a pathogenic variant is identified in a patient with TSC.

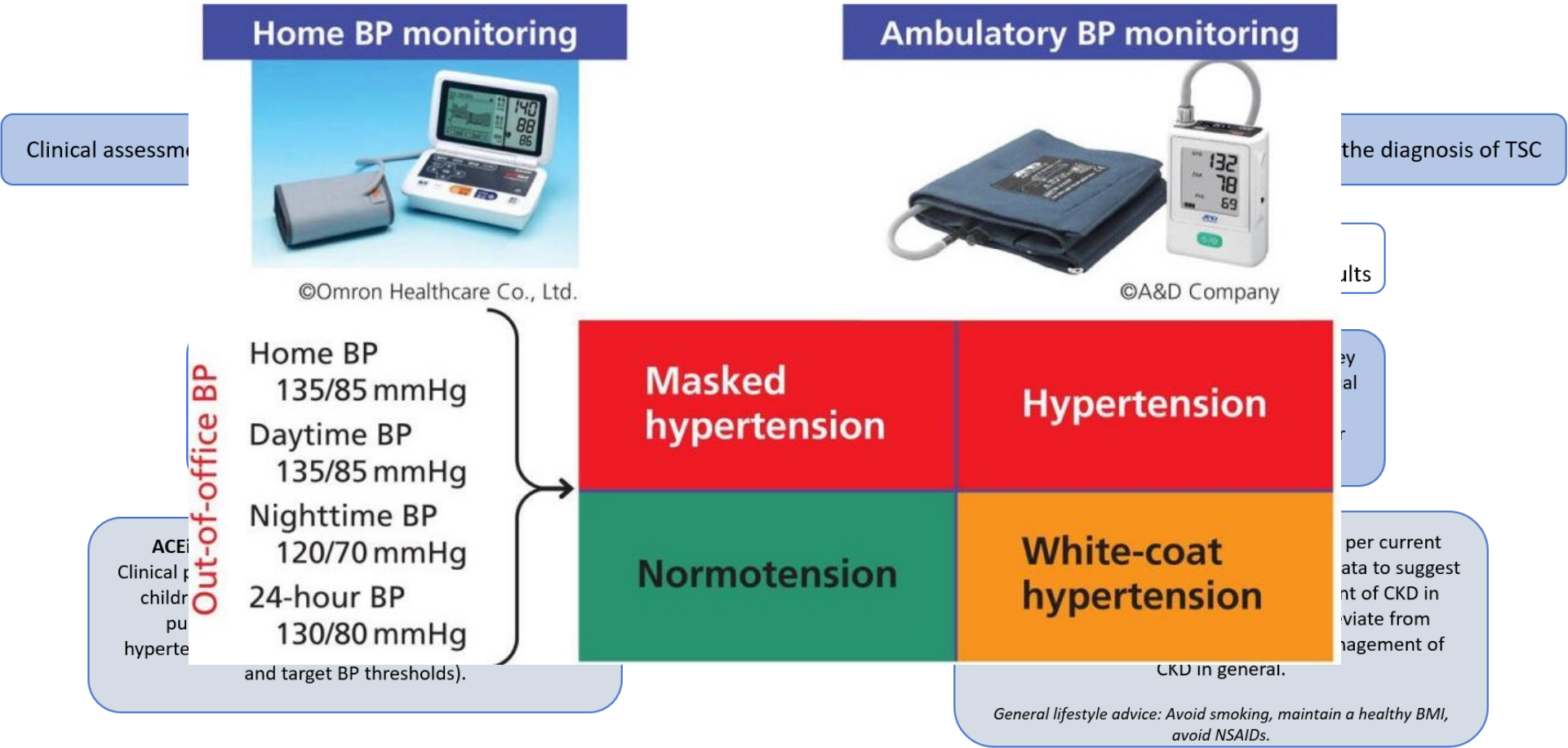
When a pathogenic variant is identified in a patient with TSC, the severity of disease is greater than that of *TSC1*-associated disease.

Patients with combined deletion of part or all of *TSC2* and *PKD1* have a high risk of having an accelerated cystic kidney disease phenotype.

Patients with combined deletion of part or all of *TSC2* and *PKD1* have a high risk of having an accelerated cystic kidney disease phenotype.

Box 2 | Recommendations for diagnosis, monitoring and treatment of hypertension in patients with TSC

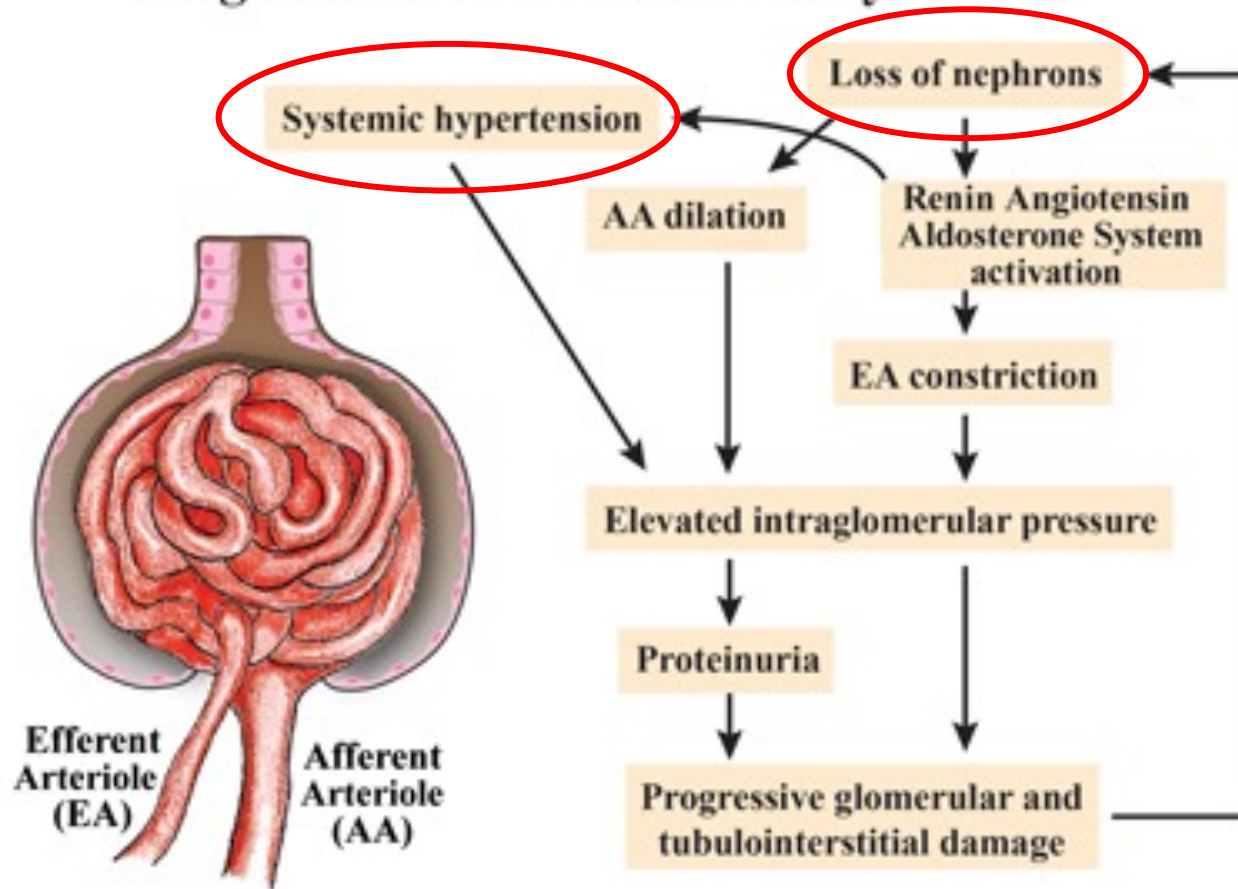
Follow-up of BP and kidney function in patients with TSC



ACEi, angiotensin-converting enzyme inhibitors; ABPM, ambulatory blood pressure monitoring; ARB, angiotensin receptor blockers; BMI, Body Mass Index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TSC, Tuberous Sclerosis Complex;

Nephron loss and Hypertension in TSC

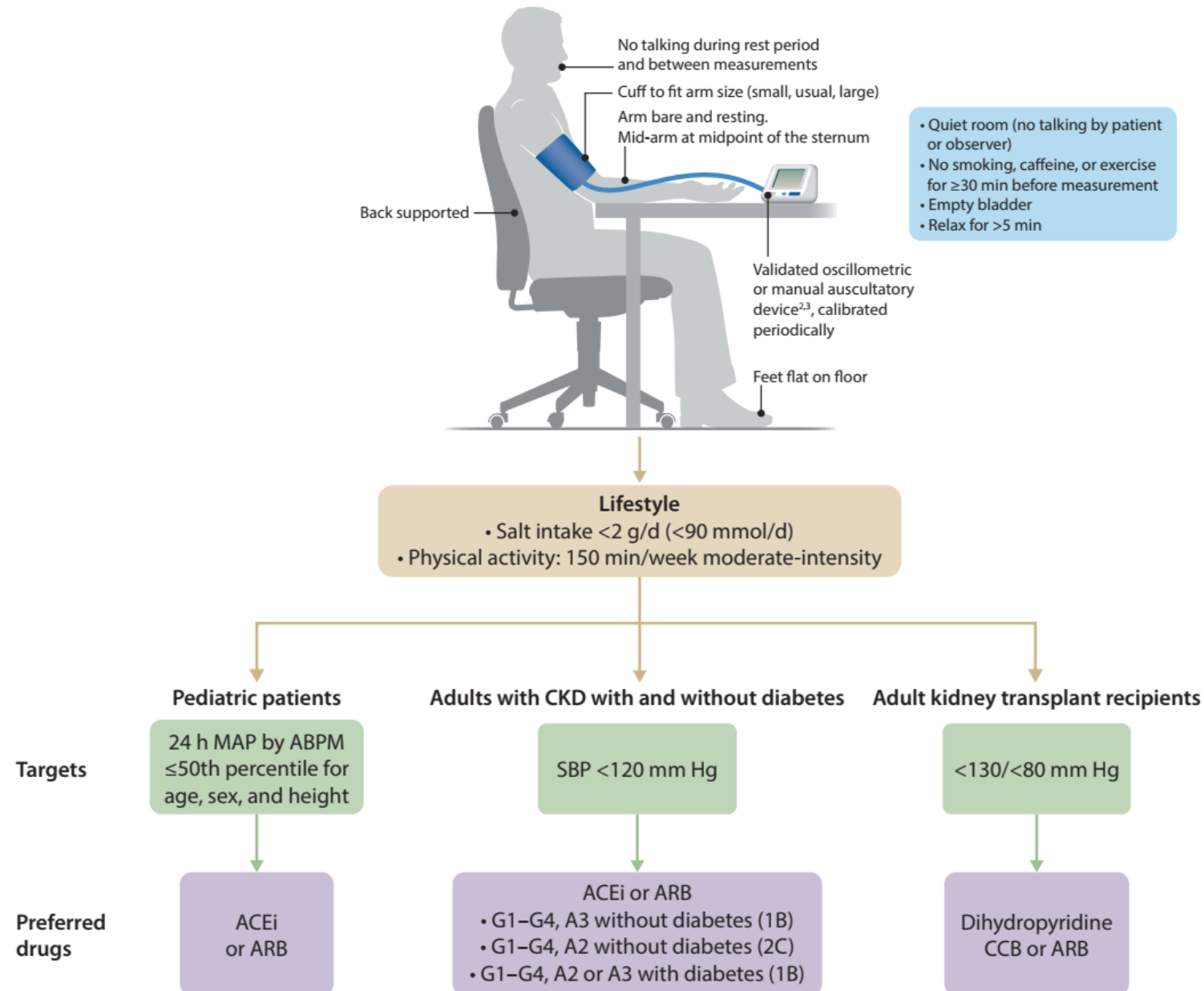
Progression of Chronic Kidney Disease



- Angiomyolipoma
- Cysts
- RCC
- Bleeding
- Embolization
- Partial/Total nephrectomy

Hypertension is one of the most important **preventable** cause of premature cardiovascular morbidity, mortality and CKD progression

Management of Hypertension in TSC according to current guidelines



Box 5 | Recommendations on kidney imaging in patients with TSC

Recommendation 1:

In children and adults with TSC, we recommend performing kidney imaging at the time of diagnosis of TSC (level B, strong).

Recommendation 2:

In children and adults with TSC, we recommend MRI as the preferred modality for detecting and monitoring kidney lesions (level B, strong).

Recommendation 3:

In children with TSC, we suggest that renal tumours is an acceptable alternative (level D, weak).

Recommendation 4:

In adults with TSC, we suggest that detecting and monitoring kidney

Recommendation 5:

In children with TSC, we suggest that MRI is performed (level D, weak).

- In children and adults with TSC, we recommend performing kidney imaging at the time of TSC diagnosis
- MRI as the preferred modality for detecting and monitoring kidney lesions, Ultrasound by expert (children) and CT are acceptable alternative
- Imaging follow-up of the kidneys at intervals of 1–3 years

the presence and type of kidney lesions, and to the presence of bleeding risk factors (Box 4) (level B, moderate).

Recommendation 8:

Because of possible differences in assessing the size of kidney masses on different imaging modalities, we recommend that the growth of kidney masses be assessed using the same imaging modality (level C, strong).

Box 4 | Main reported bleeding risk factors in patients with TSC

- Presence of symptoms (flank/abdominal pain, haematuria, nausea/vomiting)
- *TSC2* pathogenic variant
- Female sex
- Age between 15 and 50
- Angiomyolipoma size >30 mm
- Presence of micro-aneurysms >5 mm
- Increased angiomyolipoma vascularity
- Angiomyolipoma exophytic growth

Box 11 | Recommendations on biopsy and management of RCC in patients with TSC

Recommendation 1:

We do not recommend routine kidney biopsy in all fat-poor lesions in children and adults with TSC (level B, strong).

Recommendation 2:

We suggest to obtain biopsies of fat-poor kidney lesions only if their growth rate is above 5

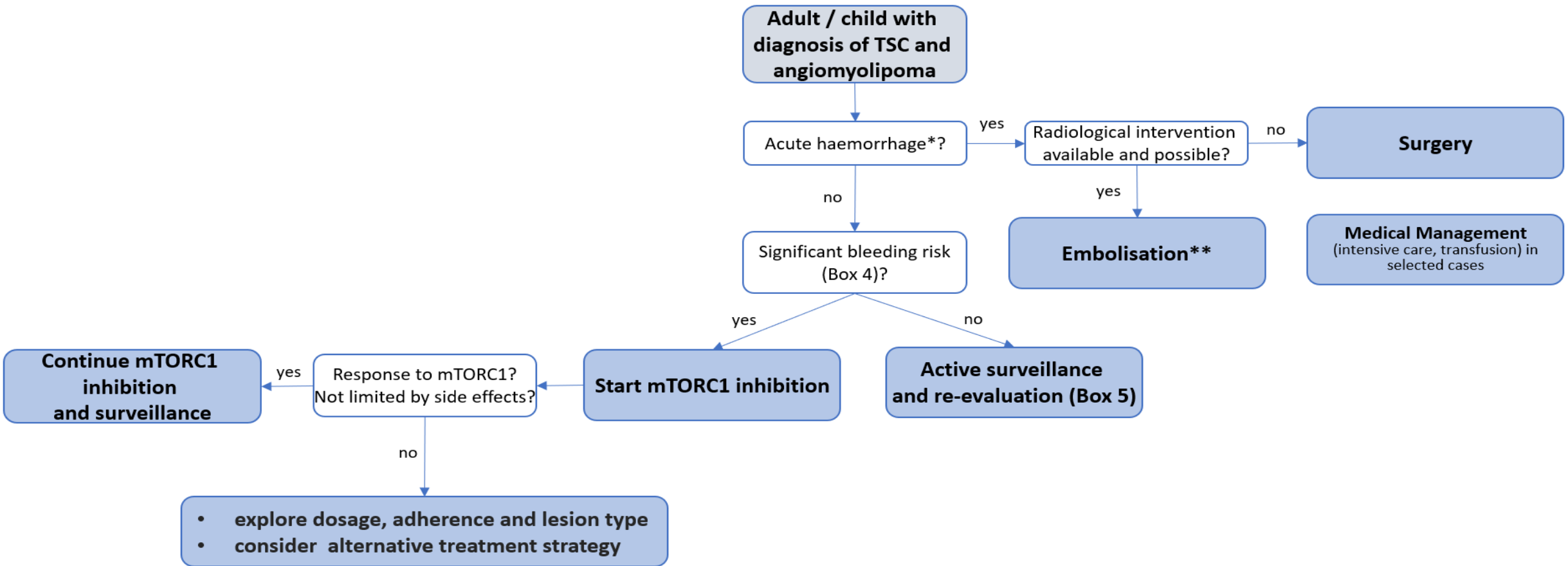
- **No routine biopsy for all the fat-poor lesions**
- **Only if their growth rate is above 5 mm/year and/or if they do not respond to mTORC1-inhibition**

We recommend to offer mTORC1 inhibition as first line treatment for fat-poor lesions requiring non-urgent treatment (level A, strong).

Statement:

Treatment strategies for histology-proven RCC in patients with TSC do not generally differ from the general population, but nephron-sparing strategies require specific attention due to the potential of developing multiple lesions and the increased risk of CKD.

Therapeutic approach to kidney angiomyolipoma in TSC



• with haemodynamic compromise or without spontaneous termination; ** in cases with moderate self-limiting bleeding medical or conservative management can be an option; for individualised treatment decisions (e.g. intermittent treatment) see chapter on dosage. mTORC1, mammalian target of rapamycin complex 1; TSC, Tuberous Sclerosis Complex.

Box 7 | Recommendations on dosage of mTORC1 inhibitors

Recommendation 1:

In adults with TSC, we suggest that 5 mg everolimus is a reasonable starting dose and further adaptation is primarily based on side effects and efficacy (level D, weak).

Recommendation 2:

In children with TSC, we suggest that 2.5mg/m² everolimus is a reasonable starting dose and further adaptation is primarily based on side effects and efficacy (level D, weak).

Recommendation 3:

We suggest that dosing schemes may require individualised adaptation (for example, intermittent treatment) (level D, weak).

Recommendation 4:

We recommend dose adjustment of mTORC1 inhibitor in cases of mild adverse events (grade 1 or 2) before discontinuing treatment (level A, strong).

Recommendation 5:

We suggest to obtain everolimus trough levels in case of safety concerns, adherence problems and lack of efficacy (level A, strong).

Recommendation 6:

We recommend not to exceed everolimus target trough levels of >15 ng/ml (level A, strong).

Statement 1:

Currently available RCTs examining the effect of everolimus on renal angiomyolipoma in patients with TSC initiated treatment at a dose of 10 mg/day (EXIST-2, adults) or 4.5 mg/m² (EXIST-1, adults and children).

Statement 2:

Sirolimus is a reasonable alternative to everolimus for mTORC1 inhibition in TSC.

Box 9 | Recommendations on duration and discontinuation of mTORC1 inhibition therapy in patients with TSC

Recommendation 1:

In cases with response to mTORC1 inhibition, we recommend to continue mTORC1 inhibition therapy for as long as the patient tolerates it (level B, strong).

Recommendation 2:

When mTORC1 inhibition therapy has been initiated in cases of typical angiomyolipoma, we recommend continuing for a minimum of 12 months before assessing for response (level B, strong).

Recommendation 3:

If there has been no response of typical angiomyolipoma to mTORC1 inhibition by 12 months we suggest to explore adherence, dosage and confirmation that the lesion is indeed a typical angiomyolipoma as well as alternative treatment options (level D, weak).

Recommendation 4:

We recommend to stop/pause mTORC1 inhibitor in patients who have active severe infection or experience significant adverse effects (grade 3 and higher) (level B, strong).

Statement:

The side effect profile of mTORC1 inhibition in TSC does not differ from the general population.

Box 8 | Definition of treatment response to mTORC1 inhibition

Typical angiomyolipoma:

- Imaging:
 - Reduction of volume or
 - Growth arrest or
 - Slowed growth based on multidisciplinary assessment (by at least radiologist, nephrologist, and urologist)
 - Absence of de-novo aneurysm formation

- Symptoms: Individual assessment with the patient if these are sufficiently controlled taking into account counselling about alternatives.

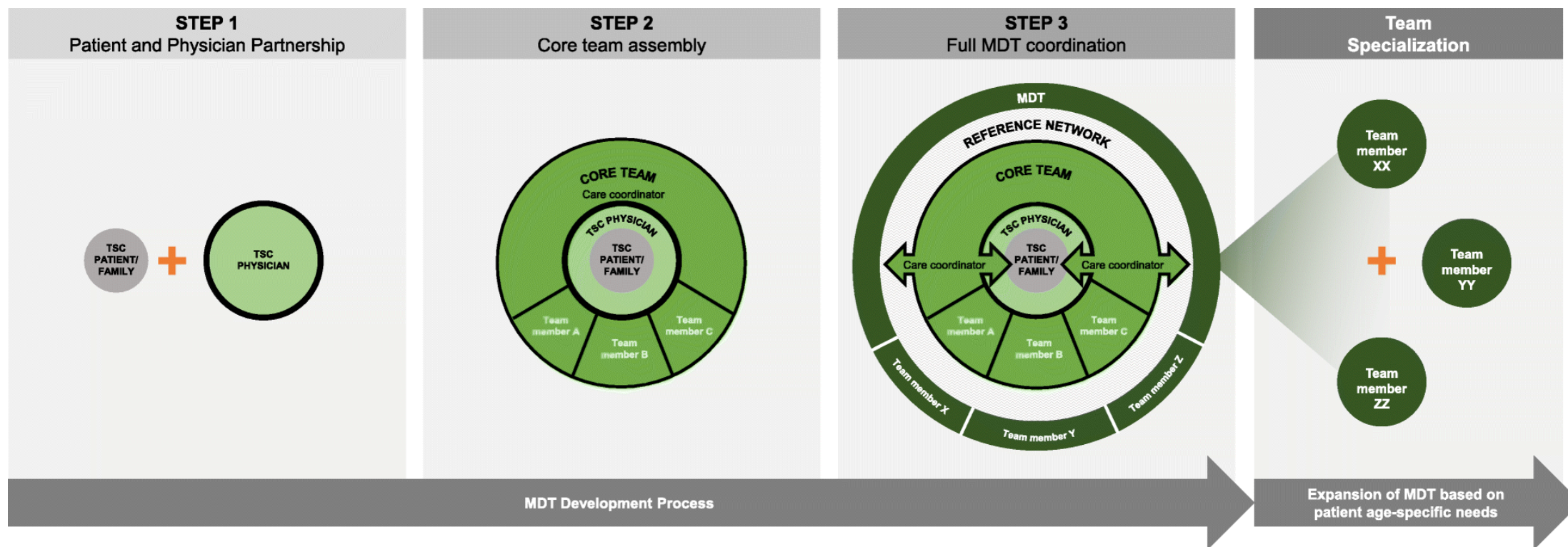
Fat-poor lesions:

- Imaging:
 - Reduction of volume or
 - Growth arrest

RESEARCH

Open Access

A step-wise approach for establishing a multidisciplinary team for the management of tuberous sclerosis complex: a Delphi consensus report



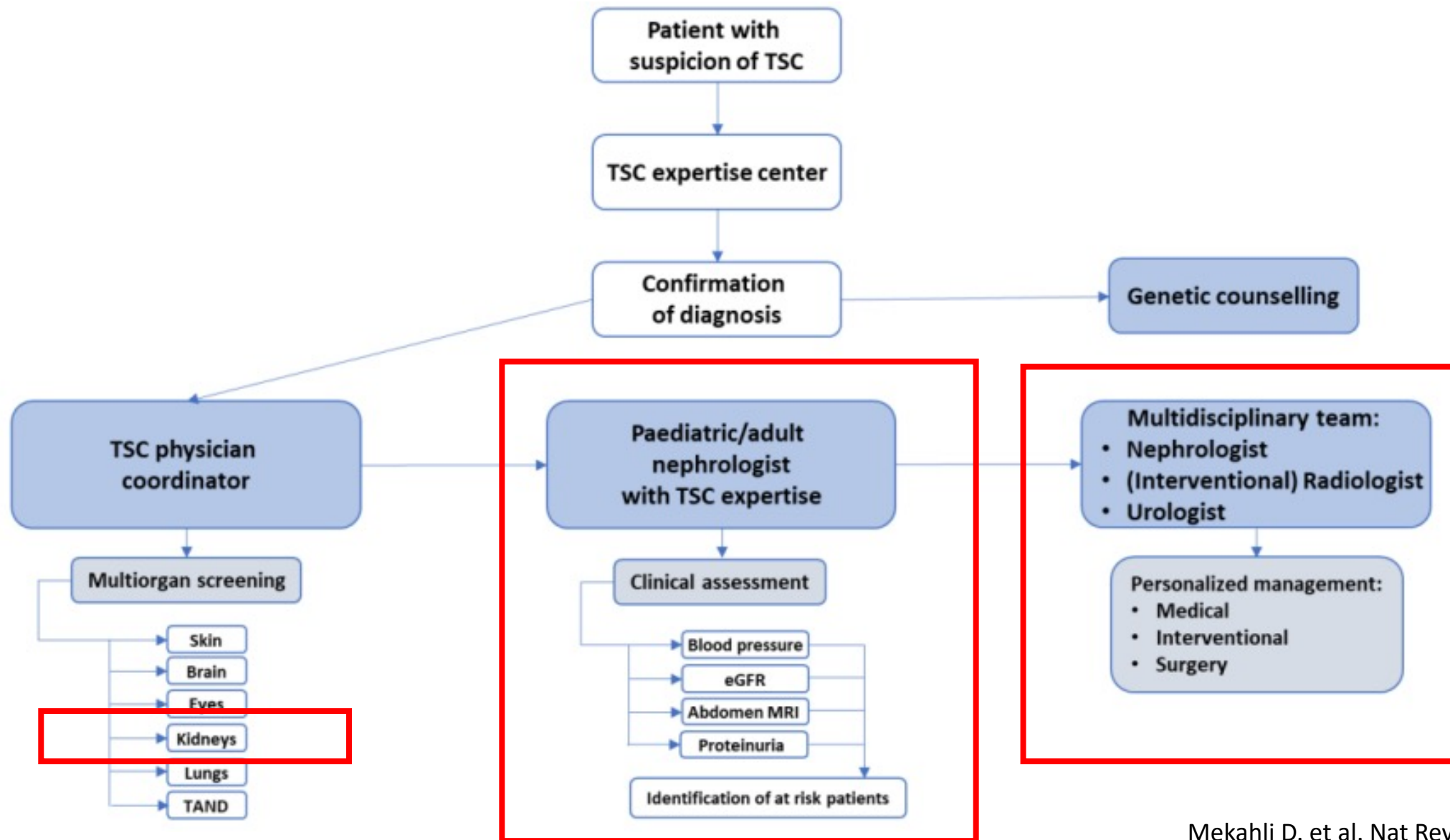
Start with a single dedicated physician who will drive the MDT development process

Organize a small core team including a care coordinator and one or more core specialists to drive the MDT process

Core team recruits members from their reference network to include physician specialists for individual patient needs

Periodically reassess and add additional specialists if needed

Multidisciplinary approach for the management of TSC



Djalila Mekahli^{1,2}; Roman-Ulrich Müller^{3,4,5}; Matko Marlais⁶; Tanja Wlodkowski⁷; Stefanie Haeberle⁷; Marta López de Argumedo⁸; Carsten Bergmann^{9,10}; Luc Breysem¹¹; Carla Fladrowski¹²; Elizabeth P. Henske¹³; Peter Janssens^{1,14}; Francois Jouret^{15,16}; Chris Kingswood¹⁷; Jean-Baptiste Lattouf¹⁸; Marc Lilien¹⁹; Geert Maleux²⁰; Micaela Rozenberg²¹; Stefan Siemer²²; Olivier Devuyst^{23,24}; Franz Schaefer⁷; David J. Kwiatkowski²⁵; Olivier Rouvière^{26,27} and John Bissler^{28,29,30}.

