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Consensus statement

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Clinical practice recommendations for kidney involvement in tuberous sclerosis complex: a consensus statement by the ERKNet Working Group for Autosomal Dominant Structural Kidney Disorders and the ERA Genes & Kidney Working Group

Djalila Mekahli[1,2] ✉, Roman-Ulrich Müller[3,4,5], Matko Marlais[6], Tanja Wlodkowski[7], Stefanie Haeberle[7], Marta López de Argumedo[8], Carsten Bergmann[9,10], Luc Breysem[11], Carla Fladrowski[12,13], Elizabeth P. Henske[14], Peter Janssens[15], François Jouret[16,17], John Christopher Kingswood[18], Jean-Baptiste Lattouf[19], Marc Lilien[20], Geert Maleux[21], Micaela Rozenberg[13,22], Stefan Siemer[23], Olivier Devuyst[24,25], Franz Schaefer[7], David J. Kwiatkowski[26], Olivier Rouvière[27,28] & John Bissler[29,30,31] ✉

Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the presence of proliferative lesions throughout the body. Management of TSC is challenging because patients have a multifaceted systemic illness with prominent neurological and developmental impact as well as potentially severe kidney, heart and lung phenotypes; however, every organ system can be involved. Adequate care for patients with TSC requires a coordinated effort involving a multidisciplinary team of clinicians and support staff. This clinical practice recommendation was developed by nephrologists, urologists, paediatric radiologists, interventional radiologists, geneticists, pathologists, and patient and family group representatives, with a focus on TSC-associated kidney manifestations. Careful monitoring of kidney function and assessment of kidney structural lesions by imaging enable early interventions that can preserve kidney function through targeted approaches. Here, we summarize the current evidence and present recommendations for the multidisciplinary management of kidney involvement in TSC.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: djalila.mekahli@uzleuven.be; jbissler@uthsc.edu

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder affecting both fetal development and postnatal growth, with major neurological and developmental effects in most patients and tumour development in multiple organ systems. The incidence of TSC at birth[1] is of ~1 in 5,800, resulting in over one million currently affected patients worldwide[2,3]. The condition is often not recognized by most clinicians without specialist knowledge, as <40% of patients have the classic triad of facial angiofibromata, developmental delay and intractable epilepsy[4]. A systematic review identified the leading causes of mortality in patients with TSC of all ages to be epilepsy (especially status epilepticus and sudden unexpected death in epilepsy), kidney complications and complications from infections[5]. Highlighting the importance of kidney involvement, ~40% of adult patients with TSC have a low glomerular filtration rate (GFR)[6], and TSC-associated kidney disease is the most common cause of death in adults with TSC[7,8]. The exact proportion of patients with TSC who have kidney failure is unclear, partly because TSC is not always available as a diagnosis code in kidney failure databases.

TSC-associated kidney disease comprises three major phenotypes: angiomyolipomata, cystic disease and renal cell carcinoma (RCC). These phenotypes are not mutually exclusive and patients often have a combination of angiomyolipomata and cysts, or (rarely) all three phenotypes. These kidney manifestations are listed in decreasing order of frequency, such that ~70–80% of patients have angiomyolipomata, ~50% have cystic kidney disease, and a diagnosis of kidney cancer or oncocytoma is present in 3–5% of patients. TSC-associated kidney manifestations are typically gradually detected with age. Importantly, normal kidney imaging and GFR in young children do not preclude future development of kidney lesions and all patients with TSC should have regular monitoring of kidney function and imaging[9]. The median ages for the detection of cysts and angiomyolipomata are 3 years and 8–13 years, respectively. However, both cysts and angiomyolipomata can develop in the first months of life, which justifies starting kidney monitoring from the point of diagnosis[10–17]. Staging of angiomyolipomata (Table 1) and cystic burden (Table 2) can be useful to clinically describe the disease and responses to therapy.

Patients with TSC kidney involvement are at considerable risk of receiving delayed or inappropriate health care. Patient groups have emerged to support patients and families and to improve knowledge of the disease and its care. Although updated general recommendations for the diagnosis and care of TSC have been published[18], few publications explicitly provide nephrologists and urologists with information on kidney manifestations and management in TSC. Because adequate guidance for kidney care in TSC is often unavailable or difficult to access, many anecdotal reports exist of patients with TSC having unnecessary surgical procedures or nephrectomies, which worsens their risk of advanced chronic kidney disease (CKD). Moreover, the success of targeted therapeutic approaches, including mechanistic target of rapamycin complex 1 (mTORC1) inhibitor therapies for both angiomyolipomata[19,20] and, although not approved, for some forms of TSC cystic kidney disease[21], raises the expectation that kidney phenotypes in patients with TSC can be addressed to mitigate disease progression.

In this Consensus Statement, we sought to integrate the input of all physicians involved in the kidney management of patients with TSC, including nephrologists, urologists, geneticists, radiologists, interventional radiologists and pathologists, as well as patient representatives. We provide a global, systematic overview of the most current and accurate information regarding TSC-associated kidney disease. Our intent was to provide a single-source reference document for all physicians involved in the medical care of patients with TSC seeking to improve care at all ages.

Methods

Methodological support was provided by the Basque Office for Health Technology Assessment (OSTEBA) and the Basque Foundation for Health Innovation and Research (BIOEF) for this Clinical Practice Recommendation regarding the multidisciplinary management of kidney involvement in patients with TSC, which was developed over 6 months, from July 14 to December 27, 2021, in accordance with planning of the project 'ERN Guidelines: Clinical Practice Guidelines and Clinical Decision Support Tools', funded by the European Commission, DG SANTE, Tender SANTE/2018/B3/030.

Four working groups were established by the European Rare Kidney Disease Reference Network (ERKNET) to examine different clinical aspects of kidney involvement in TSC. Working group experts defined research questions, which were adapted by OSTEBA to ensure that only one intervention per question was included. The research questions were structured in four parts, according to the patient population, intervention, comparator and outcome (PICO) format. Working Group 1 analysed six research questions regarding genetic aspects of TSC; Working Group 2 analysed four research questions about comorbidities and follow-up; Working Group 3 proposed five questions related to diagnostic imaging and biopsy; and Working Group 4 addressed 16 issues related to treatment of the disease (Appendix 1, Supplementary information). The work of each working group was carried out simultaneously but independently.

Systematic evidence searches

A systematic search of evidence was conducted for all PICO questions. Meta-search engines were consulted as the first approach (Tripdatabase and Epistemonikos). Key words were identified based on the PICO framework and then translated into subject headings and free-text search terms. Depending on the clinical question as well as on practical considerations, working groups could request to limit the search based on publication language, abstract availability, publication period or publication type.

A preliminary search was conducted in one of the biomedical core databases (MEDLINE or Embase). Information specialists contacted the working groups to clarify terms and achieve a balanced search regarding specificity and sensitivity as well as to decide whether to consult systematic reviews or clinical trial databases like Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), WHO International Clinical Trials Registry Platform (ICRTP),

Table 1 | Stages of angiomyolipomata according to the number of lesions, size and impact on kidney structure

Stage	Number of lesions	Size	Morphology
0	None	NA	NA
1	1–4	<3 cm	Normal
2	>5	<3 cm	Normal
3	<5	1 lesion >3 cm	Intact
4	>5	2–4 lesions >3 cm	Intact
5	>5	>5 lesions >3 cm	Recognizable
6	>5	1 lesion >5 cm	Not recognizable

NA, not applicable. Table reprinted with permission from ref. 1, Wiley.

Table 2 | Stages and disease patterns of kidney cystic disease in patients with tuberous sclerosis complex

Disease pattern	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Polycystic	0	<2	3–6	7–10	11–20	21–30	>31
Cortical cystic	0	1–10	11–20	21–30	31–40	41–50	>51
Multicystic	0	1–10	11–20	21–30	31–40	41–50	>51
Focal cystic	0	1 ray	2 rays	3 rays	4 rays	5 rays	>5 rays
Microcystic	0	10%	20%	30%	40%	50%	>50%

The numbers in the table represent the number of cysts, number of medullary rays or the percentage of cortical involvement. Table reprinted with permission from ref. 1, Wiley.

Cochrane Central Register of Controlled Trials (CENTRAL) and European Union Clinical Trials Register (EU-CTR). Different search strategies were decided for each working group (Appendix 2, Supplementary information). The definitive literature search strategy was revised and approved by the group. For all research questions, at least two core databases (MEDLINE or Embase) were explored. In addition, to ensure adequate coverage of all aspects, a complementary search in related platforms was performed as well as a search of relevant organizations and project websites related to TSC.

Selection and synthesis of scientific evidence

Electronic records of the references retrieved by searches were stored using a reference management web application (Rayyan)[22]. For the initial screening process, at least two independent methodologists from the OSTEBA-BIOEF technical team scanned titles and abstracts from the retrieved references to exclude irrelevant publications. Next, members of ERKNet and OSTEBA-BIOEF applied the inclusion and exclusion criteria (Appendix 3, Supplementary information) that were agreed upon for each clinical question. Original articles for selected references were retrieved, and full-text screening processes were performed applying a double-blind review. Any doubts about inclusion were resolved by discussion within the review team before results of the study were considered. Studies that failed to meet the inclusion criteria after full-text screening were excluded. A list of all excluded studies, with the explicit reasons for exclusion concisely stated, was provided for each question; a PRISMA flow diagram was used to explain the selection process.

Grading of recommendations

Initial recommendations were developed by members of each working group. During a face-to-face meeting, those recommendations were graded by the project leads and working group leads according to the methodology of the American Academy of Paediatrics[23]. Quality of evidence as well as the balance of potential benefits and harms were considered for the grading of recommendations as weak, moderate or strong. An additional grade of X was used for exceptional situations where validating studies could not be performed but there was a clear preponderance of benefit or harm.

TSC genetics

TSC is caused by inactivating pathogenic variants in either *TSC1* or *TSC2*. A wide spectrum of such variants has been identified, including nonsense, missense, splice, out-of-frame and in-frame insertions and deletions (Figure 1 in Appendix 4, Supplementary information) as well as larger genomic rearrangements, ranging from single exon deletions to deletion of the entire gene and some of the surrounding genomic region, and genomic inversion events[24] (Figure 2 in Appendix 4, Supplementary information). Most pathogenic variants (>90%) arise from small genetic alterations, with large genomic events occurring in *TSC2* and in *TSC1* in approximately 4.7% and 0.7% of individuals with TSC, respectively[24]. Although small pathogenic variants in each gene are widely distributed, several sites of recurrent variants have been identified in *TSC1* and *TSC2* (Figure 1 in Appendix 4, Supplementary information). These variants are typically either point mutations that occur at CpG sites, which are commonly methylated and thus prone to spontaneous mutation to thymidine through deamination of 5-methylcytosine, or indel variants occurring at short repeat sequences.

Thousands of small variants in *TSC1* and *TSC2* have been identified both in individuals with TSC and in unaffected populations (see the Human Variome Project database and the gnomAD browser). Assessment of whether such variants are pathogenic is straightforward in many cases but unclear in others. A variant is considered pathogenic if it clearly prevents protein synthesis and/or inactivates the function of TSC1 or TSC2 (ref. 25). The clinical significance of missense variants is often difficult to assess.

A pathogenic variant cannot be identified in 10–15% of children and adults diagnosed with TSC[24,26–28]. These patients typically have TSC symptoms and signs that are milder on average than those seen in other patients with TSC, and nearly all have mosaicism for a pathogenic variant in *TSC2* or, much less commonly, *TSC1* (refs. 26–29). Mosaicism is the occurrence of a genetic variant in some but not all cells of an individual and happens when a new variant occurs in an early embryonic cell but not in the fertilized egg[30]. Mosaic allele frequency typically varies across different tissues, reflecting the heterogeneous distribution of variant-containing cells. In ~18% of patients with TSC mosaicism, the pathogenic variant is not detected in blood DNA samples[26,28,29]. A diagnostic algorithm to guide the sequencing approach for the detection of TSC mosaicism in adults has been developed[31]. Many academic and commercial laboratories perform genetic analyses of *TSC1* and *TSC2* and can report varying levels of mosaicism. To our knowledge, the laboratory with the most sensitive clinically certified analysis is at the University of Alabama, which can identify and report down to 2% mosaicism. However, levels of mosaicism <2% are common in TSC[26,28,29].

TSC2–*PKD1* contiguous gene syndrome

The *TSC2* and *PKD1* genes are located directly adjacent to each other on chromosome 16, separated by only a few nucleotides at the 3′ end of each gene[32] (Figure 2 in Appendix 4, Supplementary information). Consequently, genomic deletion events in which part or all of each gene is lost can lead to the inactivation of both genes[32,33]. Approximately 50% of all patients with genomic deletions in *TSC2* also have involvement of the adjacent *PKD1* and present with early-onset polycystic kidney disease (PKD) in addition to features of TSC[32,33]. Mosaicism for these events is common and observed in ~25% of the first affected family member with a contiguous gene deletion[33].

Autosomal dominant inheritance

TSC is inherited in an autosomal dominant manner, and TSC genotypes have complete penetrance (that is, all individuals with an inherited *TSC1* or *TSC2* pathogenic variant will manifest some disease features) but disease onset and severity are variable[26]. Often, diagnosis of TSC in

one individual leads to evaluation and diagnosis in other family members who had escaped medical attention[34,35]. Although penetrance is complete, expressivity is variable, even within the same family. Several reasons might underlie this variability, including mosaicism; intrinsic variability in the number of second-hit events sustained by a patient during disease development, which is a rate-limiting step for tumour formation; and the genetic context of the patient, meaning that both common and rare variants in other genes can also affect the clinical presentation[18]. The data supporting a role for mosaicism on disease phenotype is quite clear[26–29] but, although genetic context effects are broadly considered to be important, there are currently limited data to support this.

Diagnostic genetic testing and variant classification

If possible, diagnostic genetic testing (Box 1) should be accompanied by genetic counselling before and after testing. Classification of genetic variants should follow the standards and best-practice guidelines of the American College of Medical Genetics and the Association for Clinical Genomic Science[25]. Definite pathogenic variants in *TSC1* or *TSC2* are identified in many patients but, in others, no definite mutation is identified and variants of unknown significance (VUS) in either *TSC1* or *TSC2* might be reported. VUS should not be used in clinical decision-making given the potential harm from misinterpretation of their significance, both for the proband and for any relatives identified as carriers of the VUS through cascade testing.

Mosaicism considerations in genetic counselling

Only one-third of patients diagnosed with TSC have an affected parent. Thus, most affected individuals develop the disease owing to a pathogenic *TSC1* or *TSC2* variant that has arisen de novo (that is, sporadic TSC)[18]. However, low-level mosaicism for a pathogenic variant might occur in a parent without TSC manifestations. Mosaicism for a causal *TSC1* or *TSC2* variant can be present in all tissues, especially if the mosaic allele frequency is high (>5%), but this is not always the case[26–29]; rarely, pathogenic variants might be present exclusively in germ cells. Consequently, the parent of a child with seemingly sporadic TSC might have some degree of germ cell mosaicism, which would increase their probability of having a second child with TSC. For this reason, parents of a child with sporadic TSC are advised, during genetic counselling, that the risk of TSC in subsequent pregnancies is estimated at ~1–2%. Of note, the chance of transmission of a pathogenic variant in patients with mosaicism depends on the mosaic allele frequency in germ cells, which is relatively easy to determine in male patients through sperm analysis but is not feasible in female patients.

Box 1

Recommendations for genetic testing in TSC

Recommendation 1:
Genetic diagnosis, meaning a search for pathogenic variants in *TSC1* and *TSC2*, is recommended for all patients with tuberous sclerosis complex (TSC), both those meeting definite diagnostic criteria and those who are likely to have the disease, barring financial or accessibility limitations (level X, strong).

Recommendation 2:
If no disease-causing variant is detected in a patient with definite TSC, high-sensitivity genetic analysis[a] is recommended to enable detection of a pathogenic allele with an allele frequency as low as 1% (level X, strong).

Recommendation 3:
If no *TSC2* or *PKD1* deletion is detected in a patient with definite TSC who has early-onset cystic kidney disease, high-sensitivity genetic analysis[a] is recommended to enable detection of pathogenic alleles at an allele frequency as low as 1% (level X, strong).

Recommendation 4:
We suggest that TSC gene testing should not be routinely performed in patients with isolated angiomyolipoma in the absence of other features of TSC (level D, weak).

Recommendation 5:
When a pathogenic variant is identified in a patient with TSC, expert clinical evaluation of first-degree family members is recommended (level X, strong.)

Recommendation 6:
When a pathogenic variant is identified in a patient with TSC, genetic analysis of family members without features of TSC after evaluation by an expert clinician is not routinely recommended. However, this might be a cost-effective approach in some situations (level D, weak).

Recommendation 7:
Genetic counselling is recommended for all patients with TSC who are considering having children (level X, strong).

Recommendation 8:
Genetic counselling should consider the high degree of intrafamilial variability regarding disease severity (level B, strong).

[a]We recognize that few or no clinical laboratories can detect variants with an allele frequency of below 2%.

Statement 1:
Children and adults with *TSC2* pathogenic variants can have an overall greater severity of disease, including a kidney phenotype, than those with *TSC1* pathogenic variants.

Statement 2:
Patients with combined deletion of part or all of *TSC2* and *PKD1* have a high risk of an accelerated cystic kidney disease phenotype.

Genotype–phenotype correlations

Over the past 25 years, multiple studies showed that the severity of *TSC2*-associated TSC is greater than that of *TSC1*-associated disease[36–39]. A meta-analysis of the three largest studies[37–39] (1,039 patients in total) confirmed that neurological, kidney and skin findings are more prominent in patients with pathogenic *TSC2* variants. Furthermore, analysis of data available from the TSC Alliance Natural History Database (*TSC2* $n = 376$, *TSC1* $n = 246$) showed that multiple clinical manifestations are more severe in patients with *TSC2* variants[40,41]; this finding has been replicated in studies from Greece[42], China[43–47], Japan[48], Brazil[49], Canada[50] and Taiwan[51]. The TOSCA registry of patients with TSC from 31 countries showed that the mean age at diagnosis of angiomyolipoma was 13 years for those with *TSC2* variants ($n = 644$) and 23 years for those with *TSC1* variants ($n = 197$) and that bleeding complications were reported only in patients with *TSC2* variants[4]. This difference in severity also extends to infants and young children with TSC. The EPISTOP study found that 52% of children with *TSC1* pathogenic variants were free of seizures at age 2 years, compared with 13% for *TSC2* (ref. 11). Furthermore, the prevalence of both cortical tubers (53% versus 84%) and multiple kidney cysts (0% versus 34%) is significantly lower in patients with *TSC1* variants than in those with pathogenic *TSC2* variants. The TACERN study also found that *TSC2* pathogenic variants were associated with lower early-learning scores at age 2 years compared with *TSC1* pathogenic variants[52]. Notably, specific missense variants in *TSC1* and *TSC2* have been associated with a mild disease phenotype, including *TSC1* c.1864C>T[53], *TSC2* c.4508A>C[54], *TSC2* 1864C>T[53] and *TSC2* R905Q[55].

Genetic counselling and prenatal or pre-implantation testing

Genetic counselling is meant to provide individuals and families at risk of a genetic disorder with information on the nature, mode of inheritance and implications of that disorder to help them make informed medical and personal decisions[56]. Genetic counselling for TSC is challenging for several reasons[18], including the considerable variability in presentation, even within a family. If a mosaic or heterozygous pathogenic variant has been identified in a patient with TSC, pre-implantation genetic diagnosis is possible. Many pre-implantation genetic diagnosis options are available, and their relative merits should be discussed before pregnancy given the required advance planning. A 2022 pilot study reported on non-invasive prenatal diagnosis based on cell-free DNA analysis[57]. Prenatal diagnosis of TSC and early intervention might improve developmental and cognitive outcomes, including reducing the incidence and/or severity of epilepsy in children with TSC[58,59].

Diagnosis and monitoring of kidney involvement in TSC

Diagnosis and monitoring of hypertension

Substantial evidence from multiple observational studies and registries suggests an increased risk of hypertension in children and adults with TSC; this risk increases with age. In large studies, estimates of the prevalence of hypertension in this group vary from ~5% in children to 25% in adults overall[15,16], but some smaller studies have reported a higher prevalence (up to 40%)[60,61]. Therefore, blood pressure should be monitored at least annually in all children and adults with TSC (Box 2).

Box 2

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

Recommendation 1:
We recommend annual standardized office blood pressure assessment in children and adults with tuberous sclerosis complex (TSC) (level B, strong).

Recommendation 2:
Twenty-four-hour ambulatory blood pressure monitoring in children (≥5 years) and adults with TSC should be used to complement standardized office blood pressure readings in those with office blood pressure ≥95th percentile for age, sex and height in children, or ≥120/70 mmHg in adolescents and adults (level B, moderate).

Recommendation 3:
Home blood pressure monitoring can be an acceptable alternative to standardized in-office assessment in children and adults with TSC (level C, weak).

Recommendation 4:
We recommend the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as the first-line treatment of hypertension in children and adults with TSC unless there is a contraindication (level B, strong).

Recommendation 5:
Children and adults with TSC who are at high risk of hypertension, including those with advanced chronic kidney disease, with high-stage angiomyolipoma, or receiving treatment with adrenocorticotropic hormone or steroids for infantile spasms, should have frequent blood pressure monitoring (level C, weak).

Statement:
No data to suggest that clinical practice for the management of hypertension in children and adults with TSC should deviate from current published guidelines for the general management of hypertension. These guidelines include the threshold for starting treatment with antihypertensive medication and target blood pressure thresholds. A different clinical approach might be required for patients with *TSC2–PKD1* contiguous gene syndrome.

Treatment of hypertension

Evidence on which antihypertensive agents should be used in patients with TSC is limited but, considering the benefits of angiotensin-converting enzyme (ACE) inhibitors in CKD[62], expert opinion confirms that first-line treatment of hypertension associated with TSC should be a renin–angiotensin–aldosterone system inhibitor (that is, an ACE inhibitor or an angiotensin receptor blocker) in combination with calcium blockers or diuretics, if required. Of note, in children and adults with TSC who are receiving an mTORC1 inhibitor, reports suggest a low but increased risk of angio-oedema for those also being treated with an ACE inhibitor[63]. Some clinicians therefore advise that an angiotensin receptor blocker might be a preferable first-line treatment in these patients.

General guidelines for the management of hypertension in CKD, including thresholds for starting antihypertensive medication and targets for blood pressure, should be followed in most patients with TSC[64]. These guidelines include the European 2018 ESC/ESH guidelines for adults[65] or the 2016 ESH guidelines for children[66]; in North America, the 2017 AAP guidelines are widely accepted[67]. Although specific data for the TSC population are lacking, based on current guidelines and evidence in the general CKD population[64] (Fig. 1), we suggest that 24-h ambulatory blood pressure measurement might be helpful in patients with elevated office blood pressure values (that is, blood pressure ≥95th percentile for age, sex and height in children and ≥120/70 mmHg in adolescents and adults). Of note, an exception should be made for patients with *TSC2–PKD1* contiguous gene syndrome, as lower blood pressure targets than those recommended for the general population seemed to preserve GFR[68]. In this population, treatment should start at lower blood pressure thresholds and have lower targets. Specifically, the KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in Chronic Kidney Disease suggest that kidney benefits might be greater in autosomal dominant PKD when the systolic blood pressure target is 95–110 mmHg in adults rather than 120–130 mmHg (ref. 64).

The choice of antihypertensive agent can also be affected by the presence or absence of CKD with or without proteinuria and by lifestyle modifications. Given that large randomized controlled trials (RCTs) showed that sodium–glucose co-transporter 2 (SGLT2) inhibitors have benefits on mortality and CKD progression, we suggest that, even in the absence of specific evidence, these drugs should be considered for the TSC population.

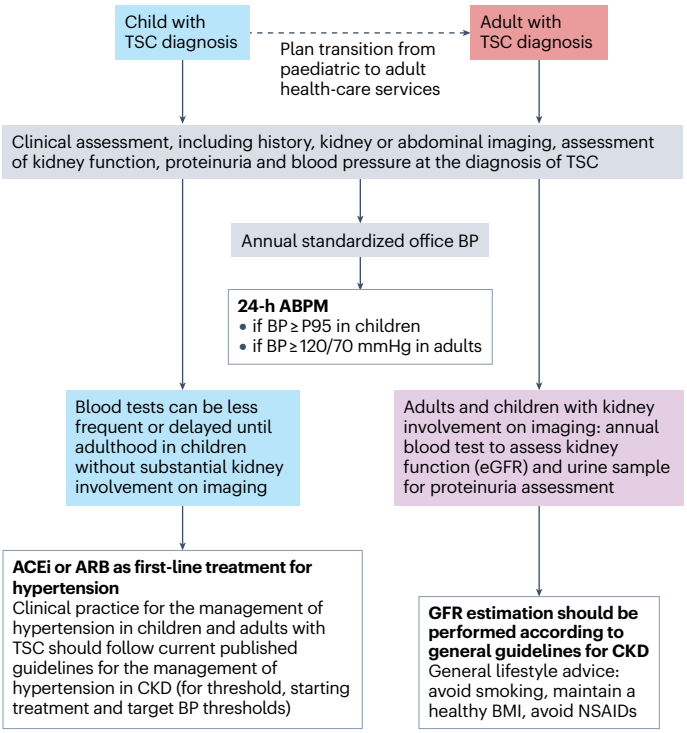

Fig. 1 | Monitoring of blood pressure and kidney function in patients with TSC. Current data suggest that the risk of hypertension rises in certain patients with tuberous sclerosis complex (TSC), including those with advanced chronic kidney disease (CKD)[61], high angiomyolipoma stage or history of embolization procedures[15]. When children and adults with TSC are undergoing general anaesthesia, blood pressure should be monitored as part of their pre-anaesthesia assessment. Of note, in infants and young children with TSC, treatment with adrenocorticotropic hormone and corticosteroids increases the risk of hypertension significantly (up to 44%)[187] and blood pressure (BP) monitoring should therefore be conducted more frequently than annually for these patients. ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; P95, 95th percentile.

Monitoring of kidney function

Kidney manifestations of TSC can present in early childhood and become increasingly common with age[16]. Compared with the general population, adults with TSC are at higher risk of developing progressive CKD[69,70]. In some cases, this CKD progression occurs without overt kidney involvement on imaging; therefore, kidney function monitoring using cystatin C or creatinine as well as urinary protein levels is advised in all adults with TSC (Box 3). Although children can have kidney lesions during early childhood, the risk of CKD detectable through blood tests (that is, through raised serum creatinine levels) is extremely low[60,71]. Therefore, in children without kidney involvement on imaging, estimated GFR (eGFR) monitoring can be reasonably deferred until adulthood. Of note, in patients with low muscle mass owing to severe neurological complications, standard creatinine-based equations can overestimate eGFR and cystatin C-based equations might be more accurate[72,73]. In cases of progressive CKD, general patient follow-up guidelines should be followed as no data suggest that children or adults with TSC should be managed differently[74]. Kidney function might need to be monitored more frequently after bleeding episodes and after embolization, until it stabilizes[75,76]. In cases of unexplained eGFR decline, attention to T2-weighted imaging for increased water in the kidney cortex or a kidney biopsy might be necessary to identify the microcystic variety of TSC kidney disease[77,78].

Following the start of mTORC1 inhibitor therapy, most kidney angiomyolipomata shrink within the first 12 months and then remain stable[20]. However, one study[79] reported that mTORC1 inhibitors did not prevent CKD progression in a minority of patients with impaired kidney function (eGFR <30 ml/min/1.73 m^2). Of note, mTORC1 inhibitor therapy can lead to or exacerbate proteinuria, which should therefore be monitored before starting this treatment. Moreover, eGFR and proteinuria should be assessed every 3–12 months in patients receiving an mTORC1 inhibitor[79]. No evidence suggests that the investigation or treatment approach should be different for patients with TSC treated with an mTORC1 inhibitor compared with other patients with CKD[80].

Children with TSC and kidney cysts might have polyuria owing to a urine-concentrating defect, placing them at risk of nocturnal enuresis[81].

However, owing to the theoretical risk of kidney cyst progression with vasopressin analogues (for example, desmopressin) reported in other cystic kidney diseases[82], we advise against the use of these agents to manage nocturnal enuresis in children with TSC.

No data suggest that kidney stones, kidney cyst complications[83–85] or urinary tract infections should be managed differently in children and adults with TSC compared with the general population. Children with TSC might have additional risk factors for kidney stone formation, including but not limited to the use of topiramate or a ketogenic diet for the treatment of epilepsy, and immobility in patients with severe neurological involvement[86]. These patients might benefit from biochemical monitoring of urine to detect an increased risk of kidney stone formation.

TSC2–PKD1 contiguous gene syndrome

An extensive kidney cystic phenotype is indicative of *TSC2–PKD1* contiguous gene syndrome but diagnosis is confirmed by genetic testing. The genotype determines the rate of disease progression, including very severe manifestations in childhood[87,88]. Onset of cysts with rapid growth at an early age should alert clinicians and prompt early and multidisciplinary management at both clinical and radiological levels, with increased monitoring of blood pressure and kidney function.

Imaging and biopsy

Methods for kidney imaging in TSC

Kidney imaging aims to detect, characterize and monitor changes in TSC-associated tumours (angiomyolipomata, cysts and RCC), assess the risk of complications (mostly spontaneous bleeding of angiomyolipomata), and evaluate the response to therapeutic interventions (Box 4).

Angiomyolipomata are benign tumours most often characterized by the presence of intratumoural macroscopic fat. However, the amount of fat varies across tumours. Fat-poor angiomyolipomata (that is, without discernible fat on imaging) are frequent in patients with TSC and/or with lymphangioleiomyomatosis (LAM)[89–91] and can be difficult to differentiate from other solid kidney tumours[92]. Moreover,

Box 3

Recommendations for diagnosis and monitoring of kidney function in patients with TSC

Recommendation 1:
In children and adults with tuberous sclerosis complex (TSC) and kidney involvement on imaging, we recommend at least annual assessment of angiomyolipoma-related complications, including pain (using validated scales), clinical bleeding risk assessment (Box 5), blood pressure and biochemical tests to monitor kidney function (level B, moderate).

Recommendation 2:
We recommend performing annual blood and urine tests in all adults with TSC to monitor kidney function and urinary protein excretion (level B, strong).

Recommendation 3:
We suggest that, in children with TSC without kidney involvement on imaging, less frequent blood tests (or delayed until adulthood) are acceptable (level D, weak).

Recommendation 4:
In children and adults with TSC and low muscle mass (for example, patients with severe neurological involvement), standard estimated glomerular filtration rate (eGFR) formulae might provide an overestimate; therefore, we suggest cystatin C-based eGFR measurements (level C, moderate).

Recommendation 5:
In children and adults with TSC who are due to start mechanistic target of rapamycin complex 1 (mTORC1) inhibitor therapy (for any indication), blood and urine tests should be performed before the start of treatment (level B, moderate).

Recommendation 6:
In children with TSC and kidney cysts who have nocturnal enuresis, we suggest avoiding vasopressin analogues (for example, desmopressin) (level D, weak).

Recommendation 7:
Consider performing more frequent monitoring of blood pressure and kidney function in children and adults with *TSC2–PKD1* contiguous gene syndrome given the associated high risk of early kidney involvement and complications (level D, weak).

Statement 1:
GFR estimation should be performed as per current general guidelines for management of chronic kidney disease. No data suggest that clinical practice for the management of chronic kidney disease in children and adults with TSC should deviate from current published guidelines.

Statement 2:
No evidence suggests that kidney stones, kidney cyst complications or urinary tract infections should be managed differently in children and adults with TSC compared with the general population.

Statement 3:
Children and adults with *TSC2–PKD1* contiguous gene syndrome should have a full clinical, biochemical and radiological assessment of kidney involvement at diagnosis.

Box 4

Recommendations on kidney imaging in patients with TSC

Recommendation 1:
In children and adults with tuberous sclerosis complex (TSC), we recommend performing kidney imaging at the time of TSC diagnosis (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 ultrasound performed by an expert radiologist who routinely images kidney tumours is an acceptable alternative to MRI for the detection and monitoring of kidney lesions (level D, weak).

Recommendation 4:
In adults with TSC, we suggest that contrast-enhanced CT is an acceptable alternative to MRI for the detection and monitoring of kidney lesions (level D, weak).

Recommendation 5:
In children with TSC, we suggest that MRI of the kidneys should be undertaken whenever a brain MRI is performed (level D, weak).

Recommendation 6:
In children and adults with TSC, we recommend an imaging follow-up of the kidneys at intervals of 1–3 years (level B, strong).

Recommendation 7:
In children and adults with TSC, we suggest adapting the imaging follow-up frequency according to the presence and type of kidney lesions, and to the presence of bleeding risk factors (Box 5) (level B, moderate).

Recommendation 8:
Owing to possible differences in assessing the size of kidney masses with different imaging modalities, we recommend that the growth of kidney masses is assessed using the same imaging modality (level C, strong).

the vessels within angiomyolipomata are fragile because they lack a complete elastic layer; microaneurysms can therefore appear on these vessels and bleed spontaneously[93,94]. TSC-associated angiomyolipomata tend to be multiple and bilateral. In patients with *TSC2* pathogenic variants, angiomyolipomata arise at a younger age, are more prone to bleeding complications and grow faster than in those with sporadic angiomyolipomata[16,93,95]. In some advanced forms of the disease, coalescent angiomyolipomata can infiltrate the kidney parenchyma diffusely and lead to progressive CKD[15,89,94,96]. Kidney cysts in patients with TSC are usually asymptomatic and the presence of multiple cysts early in life might suggest PKD due to *TSC2–PKD1* contiguous gene syndrome.

Three modalities can be used for kidney imaging: ultrasound, CT and MRI. No study has compared their accuracy in patients with TSC. Of note, although cysts can be easily detected with all three modalities, there are differences in detection accuracy for angiomyolipomata and RCC.

Angiomyolipomata usually appear hyperechoic and homogeneous in ultrasound imaging. However, these characteristics are not pathognomonic given that up to 8% of RCCs are hyperechoic[96–98]. In addition, some fat-poor angiomyolipomata might be isoechoic and difficult to detect on ultrasound[94]. Characterization of solid kidney lesions in paediatric patients with TSC could be refined with contrast-enhanced ultrasound[99]. Importantly, ultrasound does not deliver radiation and has high accuracy in patients with small body habitus. However, ultrasound results can be dependent on the experience of the operator and ultrasound accuracy decreases in patients with large body habitus, for whom CT and MRI provide better imaging of the kidneys.

CT is useful to detect macroscopic fat that appears as an area of negative density. However, its use in the follow-up of young patients is limited owing to cumulative radiation exposure[96,97] and the need for intravenous contrast injections to ensure adequate lesion definition and assessment of intralesional microaneurysms[100]. Although the spatial resolution of MRI is lower than that of CT, it allows a multiparametric approach that can help characterize fat-poor angiomyolipomata[101,102]. Of note, similar to CT, contrast injection might be needed to better assess microaneurysms with MRI. CT and MRI also enable more precise lesion measurements than ultrasound, especially for coalescent lesions[97]. Diffuse infiltration of the kidney parenchyma by angiomyolipomata complicates lesion measurement, but serial CT or MRI

Box 5

Main reported bleeding risk factors in patients with tuberous sclerosis complex

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

Box 6

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 tuberous sclerosis complex (TSC) (level B, strong).

Recommendation 2:
We suggest obtaining biopsy samples of fat-poor kidney lesions only if their growth rate is above 5 mm/year and/or if they do not respond to mechanistic target of rapamycin complex 1 (mTORC1) inhibition (level C, weak).

Recommendation 3:
Surgical intervention must be offered for the treatment of histology-proven renal cell carcinoma in patients with TSC (level X, strong).

Recommendation 4:
We recommend offering mTORC1 inhibition as the first-line treatment for fat-poor lesions requiring non-urgent treatment (level A, strong).

Statement:
Treatment strategies for histology-proven renal cell carcinoma in patients with TSC do not generally differ from those used in the general population, but nephron-sparing strategies require specific attention owing to the potential development of multiple lesions and the increased risk of chronic kidney disease in patients with TSC.

acquired along similar planes still provides a better follow-up than ultrasound.

Overall, MRI is the preferred imaging technique to diagnose and follow-up TSC-related kidney tumours because it does not deliver ionizing radiation and has good soft tissue contrast even in the absence of contrast agents. However, the use of MRI has some limitations as it is not available in all centres and certain patient populations, including children and patients with claustrophobia or psychodevelopmental disorders, require general anaesthesia.

Risk factors for angiomyolipoma bleeding

The severity of spontaneous angiomyolipoma bleeding is highly variable and ranges from limited perirenal haematoma to life-threatening internal haemorrhage. Data on the risk factors for bleeding events in patients with TSC and kidney angiomyolipomata are very limited. No prospective studies have assessed the effect of intervention *versus* observation on the outcomes of TSC-associated angiomyolipomata bleeding. Of note, such studies might not be feasible given that the rate of spontaneous angiomyolipoma bleeding might be as low as 5% in very large cohorts of patients with TSC[16]. Consequently, bleeding risk factors have only been assessed in retrospective studies (prone to selection bias) in which most patients had sporadic angiomyolipomata. Size seems to be a major bleeding predictor (Box 5) – the average diameter of angiomyolipomata treated for bleeding was ≥70 mm in most studies[103–106]. However, many cut-off diameters have been suggested for preventive intervention: 30 mm (ref. 107), 35 mm (ref. 108), 40 mm (refs. 109,110), 50 mm (ref. 104), 60 mm (ref. 105), 73.5 mm (ref. 106) and 80 mm (refs. 103,111). This variability results from the difficulty in predicting bleeding based on size alone – not only can small (<40 mm) angiomyolipomata bleed, albeit rarely[112], but most large angiomyolipomata never bleed, even in patients with TSC[16,113,114]. Thus, the optimal size threshold for intervention depends on the number of patients one is ready to treat to prevent one bleeding event. The 30 mm threshold proposed by the Washington conference[107] corresponds to a safety strategy aimed at minimizing the risk of bleeding as much as possible.

Other reported risk factors include female sex[16], age (15–50 years)[106,113], *TSC2* pathogenic variant[16], the presence of symptoms (flank or abdominal pain, haematuria, nausea or vomiting)[109,115], the presence of microaneurysms of >5 mm within the tumour[116], increased tumour vascularity[110,117], exophytic growth[110] and high BMI[106] (Box 5). However, how these factors should be combined to improve the prediction of bleeding remains unclear. One group developed a multivariate score including symptoms at presentation, tumour size, tumour vascularity and degree of exophytic growth. All four variables were evaluated individually, and a total score was then calculated (low risk 0–6; high

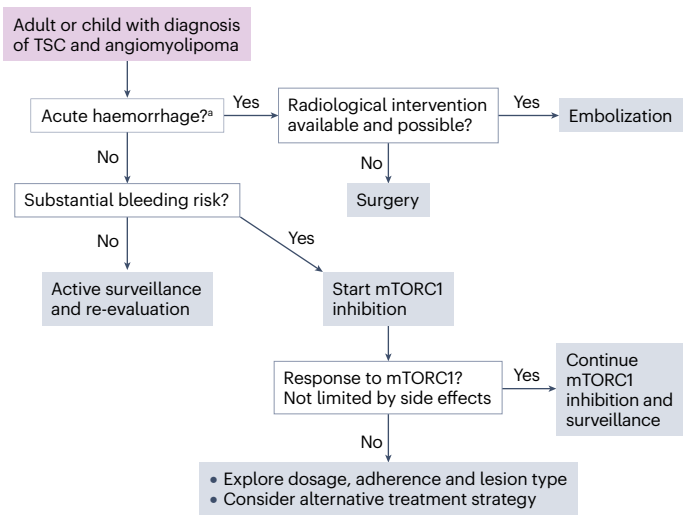

Fig. 2 | Structured approach to risk assessment and treatment of angiomyolipoma haemorrhage. In cases of acute haemorrhage of an angiomyolipoma, radiological intervention should be considered as the first-line approach. If not directly available, patient management should not be delayed and surgery should be initiated (employing a nephron-sparing approach, if possible, in the acute setting). Upon determination of substantial bleeding risk of an angiomyolipoma (Box 5), mechanistic target of rapamycin complex 1 (mTORC1) inhibition is the first-line approach. If no response to this treatment is observed or its further use is limited by side effects, reassessment and consideration of alternative strategies are required. TSC, tuberous sclerosis complex. [a]With haemodynamic compromise or without spontaneous termination; in cases of moderate self-limiting bleeding, medical (intensive care or transfusion) or conservative management might be an option.

risk 7–9), which was validated in an independent internal cohort with good results[110].

Surveys among patients and evaluation of insurance claims showed that kidney imaging surveillance is lacking or inadequate in a substantial proportion of patients with TSC[118,119]. Yet, strict kidney imaging follow-up is needed to detect patients with rapidly progressing cysts that might have contiguous gene syndrome, to monitor the risk of bleeding due to angiomyolipoma rupture and to detect rapidly growing masses that might be indicative of RCC.

Age correlates strongly with the frequency, number and size of kidney lesions in patients with TSC[15,16,120,121]. The growth rate of angiomyolipomata is slow before adolescence and accelerates thereafter, then slowing down after the age of 40 years[16,17,96,122]. These data are in line with observed bleeding complications, which occur mostly between the ages of 15 and 50 years, although bleeding risk is present at any age[15,16,113].

Risk of RCC and indication for biopsy

Cases of kidney cancer in children or adults with TSC, sometimes with the presence of multiple tumours[123–127], have prompted the hypothesis that TSC might be a risk factor for kidney malignancies. However, this view remains controversial[128]. RCC in TSC is most often of the chromophobe or chromophobe-oncocytic subtype[129,130], and multifocal RCC in two patients with RCC demonstrated the existence of distinct 'second-hit' genetic initiating events[131]. Several studies reported that the prevalence of kidney cancer is 1.4–4% in patients with TSC[128,130–132].

Box 7

Recommendations on when to initiate mTORC1 inhibition therapy in patients with TSC

Recommendation 1:
We recommend offering mechanistic target of rapamycin complex 1 (mTORC1) inhibition as first-line treatment for angiomyolipomata requiring non-urgent treatment (level A, strong).

Recommendation 2:
In children and adults with tuberous sclerosis complex (TSC), we recommend offering mTORC1 inhibition-based therapy to those with an angiomyolipoma presenting a substantial bleeding risk (Box 5) (level A, strong).

Recommendation 3:
We suggest considering mTORC1 inhibition in all children and adults with TSC and a growing angiomyolipoma of >3 cm in diameter (level D, weak).

Recommendation 4:
We suggest considering immunosuppressive regimens containing a mTORC1 inhibitor in patients with TSC after kidney transplantation based on individual assessment of TSC-associated lesions (level D, weak)

These estimations must be interpreted with care given potential selection biases, lack of histological confirmation in some reports and the presence of complex histology without definitive criteria to discriminate between RCC and angiomyolipoma.

Although advances in multiparametric MRI can help characterize kidney masses[101,102], imaging alone cannot rule out kidney cancer in the case of fat-poor solid kidney masses[91,92,97]. Because fat-poor angiomyolipomata are frequent in patients with TSC, the absence of macroscopic fat within the mass is not sufficient to indicate biopsy[89–91,96] (Box 6). The best criterium to suspect kidney cancer in patients with TSC remains the observation of rapid, sustained growth (>0.5 cm/year) at serial evaluations, although some angiomyolipomata grow rapidly[17,90,91,133]. Kidney cancers might also be present in lesions that do not respond to mTORC1 inhibitors[134].

Treatment and management

Rationale for intervention

mTORC1 inhibition is the central therapeutic option for the kidney manifestations of TSC and this pharmacological approach needs to be compared with interventional radiological and surgical procedures. Findings from several high-quality studies on mTORC1 inhibitors in TSC were pooled in a meta-analysis[135]. Data from 621 patients with TSC-related angiomyolipomata showed that mTORC1 inhibitor use reduced the nephrectomy rate over time, thereby reducing the long-term risk of CKD in this cohort[136]. Data from 99 patients with TSC in France who underwent kidney replacement therapy demonstrated the increased risk of kidney failure in patients who had a history of nephrectomy or embolization[61]. Data from 351 patients with TSC in the Netherlands also demonstrated an increased risk of CKD in patients requiring arterial embolization[15]. Combined, these data justify the preference of medical over surgical or interventional therapy where possible to minimize the risk of CKD (Fig. 2). Moreover, mTORC1 inhibition not only has an impact on the size and growth rate of TSC-associated angiomyolipomata but also on intratumoural aneurysms[137], which is an additional benefit given the important role of aneurysms in bleeding risk. Regarding cystic kidney disease in TSC, large cysts do not seem to respond to mTORC1 inhibition, although current evidence indicates some benefit in reducing the large burden of small cortical cysts as well as in microcystic and focal cystic disease[138].

In patients who are haemodynamically unstable owing to TSC-related kidney complications, medical therapy will not be sufficiently fast and such patients should undergo an interventional endovascular radiological procedure or, in some cases, a surgical intervention. Moreover, in patients where medical therapy is contraindicated or has failed, surgical or radiological interventions can be considered, accepting the increased risk of CKD.

mTORC1 inhibition-based therapy

Several studies demonstrated the benefit of mTORC1 inhibition in angiomyolipomata of >3 cm in diameter[20,139]. Given that the overall angiomyolipoma burden is associated with the future risk of CKD, experts agree that using mTORC1 inhibitor preventatively before any individual lesion has become >3 cm in diameter might be beneficial in cases of rapid angiomyolipomata growth (>0.5 cm per year in diameter) and high overall angiomyolipoma burden in the kidneys (Box 7).

Fat-poor angiomyolipomata tend to respond well to mTORC1 inhibition[140]. Indeed, mTORC1 inhibitors primarily affect the highly vascularized compartments of angiomyolipomata[141–143]. The adverse effect profile of mTORC1 inhibitors is acceptable (see below). Furthermore,

Box 8

Recommendations on dosage of mTORC1 inhibitors

Recommendation 1:
In adults with tuberous sclerosis complex (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 2.5 mg/m^2 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 might require individualized adaptation (for example, intermittent treatment) (level D, weak).

Recommendation 4:
We recommend dose adjustment of mechanistic target of rapamycin complex 1 (mTORC1) inhibitors in cases of mild adverse events (grade 1 or 2) before discontinuing treatment (level A, strong).

Recommendation 5:
We suggest obtaining everolimus trough levels where safety concerns arise, adherence problems are suspected or lack of efficacy is observed (level A, strong).

Recommendation 6:
We recommend not exceeding everolimus target trough levels of >15 ng/ml (level A, strong).

Statement 1:
Currently available randomized controlled trials examined 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/m^2 (EXIST-1, adults and children).

Statement 2:
Sirolimus is a reasonable alternative to everolimus for mTORC1 inhibition in TSC.

long-term eGFR is preserved in patients with TSC treated with mTORC1 inhibitors[79] (one study reported improvement[144]) compared with surgery or interventional radiology[15,67,136].

Dosage. In the paediatric EXIST-1 RCT, which reported the impact of everolimus on angiomyolipoma in patients with TSC treated for subependymal giant cell astrocytoma[145], the initial dose was 4.5 mg/m^2/day. In EXIST-2, an RCT examining everolimus in patients with either TSC-associated or LAM-associated angiomyolipoma, everolimus was administered at a fixed dose of 10 mg/day[20]. Both trials adjusted the dose to achieve target trough levels of 5–15 ng/ml. EXIST-2 included 118 patients randomly assigned 2:1 to receive everolimus 10 mg (n = 79) or placebo (n = 39) once daily, and peak and trough concentrations of everolimus in blood remained stable over time[146]. The mean everolimus trough level in both adults (EXIST-2) and children (EXIST-1) was <10 ng/ml at all timepoints[145,147].

Several other non-randomized studies used similar dosing strategies as EXIST-1 and EXIST-2 (refs. 148–151). The dose of 10 mg in EXIST-2 was primarily chosen based on maximum tolerated dose considerations. Dose adjustments were possible based on side effects and safety. After initiating the treatment with a 10 mg dose, the EXIST-2 trial reported dose adjustments for adverse events in 48% of patients receiving everolimus. Nonetheless, the treatment efficacy remained robust, in agreement with previous data on sirolimus showing efficacy irrespective of dose or trough levels[19]. In a retrospective study of 50 adult patients with TSC, 5 mg of everolimus per day was safe and as effective in the shrinkage of angiomyolipoma as the conventional dose (10 mg of everolimus per day)[152]. The inclusion criteria for the low-dose option were kidney dysfunction (defined as serum creatinine level ≥1.5 mg/dl) or low body weight (body weight <35 kg). Taken together, therapy can be started at 10 mg/day in adults or 4.5 mg/m^2/day in children following the strategy from EXIST-2. Considering the weak relationship between trough levels and angiomyolipoma response observed[146], the ability to monitor treatment response by imaging and the observation that immediate responses are rarely required in TSC-associated angiomyolipoma, a starting dose of 5 mg per day for adults and 2.5 mg/m^2 for children seems a reasonable approach to ensure optimal adherence and minimal toxicity (Box 8). Of note, although not primarily indicated to guide dosing, trough levels can be helpful to assess adherence and avoid toxicity.

In a prospective observational cohort of 26 patients with TSC and angiomyolipoma of ≥4 cm in diameter, intermittent everolimus treatment (that is, pausing of treatment upon response and re-initiation upon documented growth) was effective for tumour control and management of adverse events. The everolimus dose was set at 10 mg once a day, and the criteria for stopping everolimus treatment were reduction of angiomyolipoma size to ≤4 cm, everolimus administration for ≥12 months or plateauing reduction of angiomyolipoma size. An abdominal CT or MRI scan was carried out every 3 months and, if the volume of the angiomyolipoma after withdrawal increased to >70% of the pretherapeutic volume, everolimus treatment was restarted at the initial dose[153]. This concept could be adopted to individualize patient treatment but most studies to date have not followed this approach.

No RCTs have assessed the use of sirolimus (also known as rapamycin) to treat kidney manifestations of TSC. However, based on the identical mode of action (mTORC1 inhibition) as well as on available data from two non-randomized studies, sirolimus might be an alternative to everolimus based on availability. In a 24-month prospective open-label, single-arm, single-centre phase II–III study, 17 patients with TSC aged >10 years presenting with at least one kidney angiomyolipoma of >2 cm in diameter were exposed to an increasing dose of rapamycin (1 mg every 2 weeks) to achieve stable plasma levels of between 4 and 8 ng/ml. According to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, all patients achieved a partial response at year 1 and all but two

Box 9

Definition of treatment response to mTORC1 inhibition

Typical angiomyolipoma:
Imaging: reduction of volume, growth arrest or slowed growth based on multidisciplinary assessment (including a radiologist, nephrologist and urologist); absence of de novo aneurysm formation.

Symptoms: individual assessment with the patient to determine if symptoms are sufficiently controlled taking into account counselling about alternative therapies and interventions.

Fat-poor lesions:
Imaging: reduction of volume or growth arrest.

had already achieved this partial response after 6 months[154]. In a 2-year multicentre phase II non-randomized, open-label trial, 16 patients with TSC with sporadic LAM and/or kidney angiomyolipoma were treated with oral sirolimus for up to 2 years. Steady-state blood levels were 3–10 ng/ml. Summated angiomyolipoma diameters decreased in all 16 patients and even by ≥30% in eight of these individuals[155].

Duration and discontinuation. The median time for angiomyolipomata to respond to mTORC1 inhibitors was ~3 months in EXIST-2 (ref. 20). Therefore, a minimal follow-up of 6 months is required before assessing the clinical and radiological response (Box 9). Furthermore, the main effect of mTORC1 inhibitors in reducing angiomyolipoma volume was observed within the first 6–12 months of exposure[19,20,148]. Therefore, lack of an effect of mTORC1 inhibition on angiomyolipoma growth after a minimal follow-up of 12 months should prompt exploration of adherence, dosage and confirmation that the lesion is indeed a typical angiomyolipoma as well as alternative treatment options (discussed below). A potential decision for discontinuation based on continued growth under therapy should also consider the evidence for beneficial effects of mTORC1 inhibition on bleeding risk[156]. Follow-up studies, including the EXIST-2 cohort, support the ongoing efficacy and safety of mTORC1 inhibitors up to 4 years after treatment initiation[156]. Most adverse events (see below) with mTORC1 inhibitors are minor and predictable[157]. Dose adjustments might be helpful considering a pragmatic risk–benefit balance[158]. Importantly, mTORC1 inhibition should be discontinued (at least temporarily) in patients who are experiencing infection or severe adverse events. Note that discontinuing mTORC1 inhibition therapy might cause re-growth of angiomyolipomata as suggested in a post hoc analysis of a subgroup of the EXIST-2 study[159]. Therefore, monitoring of angiomyolipomata through imaging remains essential after discontinuation of mTORC1 inhibition (Box 10).

Side effects. Everolimus is generally well tolerated in both adult and paediatric patients with TSC, with most adverse events being of grade 1 or 2 severity and occurring within the first 6 months[147,148]. The side effects of mTORC1 inhibition are not specific to patients with TSC. The most common grade 1 or 2 adverse events caused by mTORC1 inhibitors in patients with TSC are aphthous stomatitis, irregular menstruation, hypercholesterolaemia or hypertriglyceridaemia, urinary tract infection, hypertension, dermatitis acneiform, insomnia and interstitial lung disease[148,149]. The most common grade 3 adverse events are irregular menstruation and aphthous stomatitis[150]. Of note, the incidence of stomatitis and irregular menstruation correlates with the dosage of everolimus[152]. The impact of mTORC1 inhibitor-associated hyperlipidaemia on cardiovascular outcomes is unclear; interestingly, data from animal models suggest that sirolimus can attenuate

Box 10

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

Recommendation 1:
In cases with response to mechanistic target of rapamycin complex 1 (mTORC1) inhibition, we recommend continuing 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 the response to therapy (level B, strong).

Recommendation 3:
If a typical angiomyolipoma does not respond to mTORC1 inhibition by 12 months, we suggest exploring adherence, dosage and confirmation that the lesion is indeed a typical angiomyolipoma as well as considering alternative treatment options (level D, weak).

Recommendation 4:
We recommend stopping or pausing mTORC1 inhibitor treatment in patients with active severe infection or who experience severe adverse effects (grade ≥3) (level B, strong).

Statement:
The safety profile of mTORC1 inhibition in patients with tuberous sclerosis complex (TSC) does not differ from that in the general population.

Box 11

Recommendations on radiological and surgical intervention in patients with TSC

Recommendation 1:
Radiological or surgical interventions must be offered in case of angiomyolipoma haemorrhage with haemodynamic compromise (level X, strong).

Recommendation 2:
We suggest discussing radiological interventions, surgery or active surveillance in angiomyolipoma cases with substantial bleeding risk and a contraindication to the use of mechanistic target of rapamycin complex 1 (mTORC1) inhibitors (level D, weak).

Recommendation 3:
We suggest offering radiological interventions for the treatment of typical angiomyolipomata that do not respond to therapy with mTORC1 inhibitors (Box 8) (level D, weak).

Recommendation 4:
We recommend radiological intervention, if available on site, as the first approach in cases of angiomyolipoma bleeding requiring intervention (level X, strong).

Recommendation 5:
In angiomyolipoma at risk of bleeding requiring radiological or surgical intervention, we recommend tailoring the type of intervention considering both patient and tumour features (level C, moderate).

Recommendation 6:
We recommend steroid prophylaxis of post-embolization syndrome when embolization of an angiomyolipoma is performed (level B, strong).

Recommendation 7:
We recommend that nephrectomy should not be typically performed in patients with tuberous sclerosis complex (TSC) undergoing kidney transplantation (level X, strong).

Recommendation 8:
We suggest nephrectomy prior to kidney transplant in patients with TSC if the patient presents with large ipsilateral kidney preventing heterotopic transplantation, suspicion of concomitant malignancy, high risk of concomitant angiomyolipoma bleeding as assessed by multiple risk factors or symptomatic angiomyolipoma unresponsive to mTORC1 inhibition therapy (level D, weak).

Recommendation 9:
If surgery is considered the preferred elective approach based on multidisciplinary assessment, we recommend a nephron-sparing approach (level B, strong).

Recommendation 10:
In cases without suspected malignancy, we recommend tumour enucleation over tumour resection with a margin (level C, moderate).

Statement:
In cases of haemodynamic instability owing to ongoing bleeding after arterial embolization, radical nephrectomy might be required.

atherosclerotic plaque progression[160,161]. The FDA and EMA as well as national resources about drug safety and efficacy are useful for continuing pharmacosurveillance on the use of mTORC1 inhibitors. Nephrotoxicity has not been reported in patients with TSC exposed to everolimus, except for patients with severely compromised kidney function before treatment or patients with prior kidney intervention[20,162]. Some of these patients experienced an increase in proteinuria. The diagnostic algorithm of mTORC1 inhibitor-induced proteinuria is similar to that of the general population as described in the latest CKD guidelines by the KDIGO consortium[163]. Electrolyte, glucose and liver function monitoring is required for all patients treated with an mTORC1 inhibitor, irrespective of a TSC diagnosis.

Immunosuppressive regimens after kidney transplantation. No RCTs have examined the impact of different immunosuppressive regimens after kidney transplantation in patients with TSC[67,164]. Nonetheless, based on the effect of mTORC1 inhibition on several TSC-associated phenotypes, a regimen containing an mTORC1 inhibitor in the context of TSC-associated phenotypes known to respond to mTORC1 inhibition (for example, angiomyolipoma, subependymal giant cell astrocytoma, epilepsy, skin manifestations and LAM) should be considered[165].

Interventional radiology

In most centres, an actively bleeding angiomyolipoma of any tumour size is an accepted indication for arterial embolization owing to the minimal invasiveness of the procedure[166,167] (Fig. 2 and Box 11). However, in cases with moderate self-limiting bleeding, medical or conservative management can also be considered[168,169]. In asymptomatic angiomyolipoma, the potential benefit of arterial embolization is less clear. Expert opinion suggests preventive arterial embolization of angiomyolipoma with a threshold diameter >4 cm, especially in lesions with rich angiomatous content and distinct arterial supply[166].

Arterial embolization is less invasive than surgery and thus the first-line approach for the treatment of relevant angiomyolipoma haemorrhaging. In the decision-making process regarding surgery as an alternative to arterial embolization, several factors should be

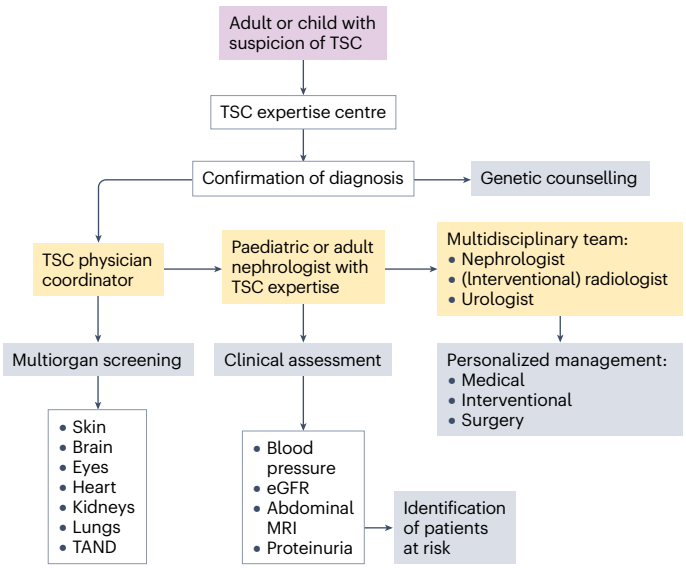

Fig. 3 | Multidisciplinary approach for the management of TSC. This algorithm depicts the optimal multidisciplinary approach for patients suspected of having tuberous sclerosis complex (TSC). This approach includes appropriate referral to an expert centre and coordination of multidisciplinary care with emphasis on kidney issues. eGFR, estimated glomerular filtration rate; TAND, TSC-associated neuropsychiatric disease.

considered: whether the blood supply allows selective arterial embolization, RENAL score[170], comorbidities and risk of general anaesthesia, number and position of lesions within the kidney, and the technical skills of the interventional radiologist performing the procedure. In particular, effective targeting of the angiomatous arteries and avoidance of non-target embolization is key to avoiding nephron loss[171]. The RENAL nephrometry score is based on five anatomical characteristics of solid renal masses — radius, exophytic or endophytic aspect, nearness to the collecting system or sinus, anterior (a) or posterior (p) location, location with respect to the polar lines, and contact with the main renal artery or vein — and is used to quantify the degree of difficulty of a surgical approach[172]. Steroid prophylaxis has been used successfully to prevent post-embolization syndrome after treatment of TSC-associated angiomyolipoma with arterial embolization[173,174]. If embolization fails or is unavailable, surgery needs to be considered.

Surgical intervention

Partial nephrectomy is feasible in populations undergoing surgery for angiomyolipoma with minimal morbidity[175]; this approach seems appropriate for cases selected by the multidisciplinary decision algorithm as it maximizes preservation of normal kidney parenchyma in patients with TSC who are at risk of kidney failure (Box 11).

In RCC, many studies have demonstrated that partial nephrectomy can prevent CKD development and ensuant morbidity and mortality. Although patients with TSC can present with angiomyolipoma and concomitant RCC[130,176], enucleation might still be appropriate. In the case of sporadic RCC, tumour enucleation, if technically possible, yields oncological results comparable to those of tumour resection with a safety margin; tumour enucleation is therefore a parenchymal-sparing therapy option even if malignancy is suspected. In practice, a combined procedure (enucleoresection) is usually conducted. Of note, resection with a margin should be considered if RCC suspicion is high, especially high-grade RCC. In cases of haemodynamic instability, attempting partial nephrectomy might be hazardous and could even compromise survival. Where main kidney arterial clamping stabilizes the patient and nephron-sparing surgery seems to be technically straightforward to perform within a reasonable time frame, partial nephrectomy might remain an option; this expert opinion is based on first principles.

Nephrectomy before transplantation. Similar to patients with autosomal dominant PKD and kidney failure undergoing kidney transplantation, nephrectomy before transplantation might be warranted if the native kidney in patients with TSC occupies so much space that ipsilateral kidney transplantation is not technically feasible[83]. Of note, large contemporary cohort studies show a 1.4–2.8% major complication rate for nephrectomy[177], with blood transfusion rates as high as 9.1%, whereas the rates of haematuria and bleeding were reported at 4.2% and 5.4%, respectively, in a 2020 report on patients with TSC[16]. Whether the risks of nephrectomy are counter-balanced by the benefits of avoiding bleeding episodes is therefore unclear. Additionally, if the goal of routine nephrectomy in transplant recipients with TSC is to avoid future bleeding events after transplantation, this concern might be addressed with the routine use of an mTORC1 inhibitor after grafting[20,137].

Given the weak retrospective evidence, routine nephrectomy in patients with TSC undergoing kidney transplantation should be avoided. However, special consideration should be given to this procedure on a case-by-case basis, including in cases of suspected kidney malignancy or of an angiomyolipoma with a high risk of bleeding that cannot be treated with mTORC1 inhibitors. In this last scenario,

Box 12

Recommendations on multidisciplinary management of patients with TSC

Recommendation 1:
The diagnosis and monitoring of hypertension in children and adults with tuberous sclerosis complex (TSC) with consideration of primary and other secondary aetiologies and treatment of hypertension should be conducted by a (paediatric) nephrologist (level D, weak).

Recommendation 2:
Patients with TSC should be offered structured, multidisciplinary (kidney and other organ specialities) follow-up visits, ideally on the same day where possible (level C, moderate).

Recommendation 3:
We recommend clinical assessment, including the collection of complete relevant history, kidney or abdominal imaging, assessment of kidney function proteinuria, and blood pressure, at the diagnosis of children and adults with TSC (level B, strong).

Glossary

Cortical tubers
A developmental brain lesion in which there is loss of normal cortical architecture with large 'giant' cells and gliosis.

Enucleation
Tumour excision by blunt dissection along the natural cleavage plane between the peritumoural pseudocapsule and the kidney parenchyma. This method avoids the removal of visible kidney tissue.

Enucleoresection
Minimally invasive endoscopic procedure used to remove kidney lesions.

Expressivity
Refers to the extent and severity of tuberous sclerosis complex (TSC) symptoms and signs seen in an individual with TSC. For example, some individuals with a diagnosis of TSC have many cortical tubers, some have few and some have none.

First principles
An approach used by Aristotle where complicated problems are reduced to fundamental elements and relationships and interventions can be posited to formulate solutions.

Hyperechoic
The property of showing higher echogenicity (that is, appearing brighter on ultrasound images) than a tissue of reference.

Isoechoic
The property of showing similar echogenicity to that of a tissue of reference.

Post-embolization syndrome
An inflammatory response causing substantial fever and pain after arterial embolization.

nephrectomy might be considered a more definitive treatment compared with arterial embolization[95,178]. Bleeding risk can be assessed using multiple risk factors (Box 5).

Treatment of RCC in patients with TSC

No RCTs have examined differential therapy of TSC-associated RCC compared with sporadic RCC. Consequently, no evidence supports specific therapeutic approaches in TSC-associated RCC. Studies in sporadic RCC regarding the impact of mTOR pathway pathogenic variants, including *TSC1* and *TSC2*, on the response to mTORC1 inhibition provide no conclusive data[179–182] and studies in patients with TSC are lacking. Compared with sporadic RCC, TSC-associated RCC seems to have different histopathological patterns and a more indolent course[126,130] with only rare cases of related mortality reported to date[126,130,183]. Although these observations do not affect general treatment strategies directly, they might still be considered in individualized decision-making and patient counselling[126]. Moreover, specific emphasis on nephron-sparing strategies is required considering the multiplicity and recurrent nature of kidney tumours in TSC[126].

Multidisciplinary management

Because every organ system can be involved in TSC, care should be coordinated and delivered by a multidisciplinary team in an expert centre[184] (Fig. 3 and Box 12). Although attention can be drawn to the most affected organ system, organ involvement changes with age and engagement with the multidisciplinary team members should be fostered early. Nephrology involvement is crucial to help educate patients and their families and to enable appropriate intervention as the disease progresses. All patients with TSC-associated kidney lesions technically have CKD stage 1 (or more advanced CKD) and should be followed by a nephrologist at least annually. Such involvement of a TSC nephrologist can help guide appropriate kidney care and reduce the frequency of unnecessary surgical interventions. Such care can also increase the use of best practices[185].

Another responsibility of the multidisciplinary team is to care for the family as well as the patient. Discussing screening with family members is therefore recommended. Family members with TSC clinical features should be screened for the relevant pathogenic variant, if it is known; genetic testing has little value in family members with no clinical features of TSC. However, this opinion is subject to clinical judgement for individual patients and families.

Transition care

Another obligation of the multidisciplinary team is the creation of a plan or protocol for the transition from paediatric to adult care. This plan should include the specified age of transition, the steps in the process and the identification of health-care professionals for adult care. Medical issues and concerns change as the patient ages and can pose challenges for patients who transition to adult-oriented care[186]. Ideally, establishing a fully functional multidisciplinary TSC clinic for adults should be undertaken simultaneously with the efforts to develop a paediatric clinic or the same clinic should be used for both children and adults. The transition to adult medical care is especially challenging for adults who have a TSC-associated intellectual disability and other TSC-associated neuropsychiatric disorders. The adult clinic must be capable of handling all of those TSC-associated issues.

Conclusion

Patients with TSC are most often initially encountered in non-specialized centres where awareness of TSC-associated kidney disease development is limited. This lack of awareness can hamper optimal patient management. Many studies have investigated TSC-associated kidney disease. Here, we summarized expert recommendations on the renal management of these patients with TSC, including diagnosis and monitoring of kidney involvement, as well as available treatment options. These recommendations should inform health-care decisions for patients with TSC to reduce the disease burden and improve prognoses for this vulnerable population.

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Author contributions

All authors researched data for the article, made substantial contributions to discussions of the content, and wrote, reviewed or edited the manuscript before submission.

Competing interests

S.S. is a Proctor for Intuitive Surgical System. D.J.K. has had research contracts with Genentech, AADI, and Revolution Medicines and has been a consultant to Genentech, AADI, Guidepoint, Bridgebio and Slingshot Insights. J.B.L. receives honorarium as an advisory board

member for Novartis, Astellas, Pfizer, Roche, and Merck and is a consultant to Janssen. Bristol Myers Squibb conducts research at the centre that employs J.B.L. The other authors declare no competing interests.

Additional information

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[1]PKD Research Group, Laboratory of Ion Channel Research, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium. [2]Department of Paediatric Nephrology, University Hospitals Leuven, Leuven, Belgium. [3]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany. [4]CECAD, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany. [5]Center for Rare Diseases Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [6]UCL Great Ormond Street Institute of Child Health, University College London, London, UK. [7]Division of Paediatric Nephrology, Center for Paediatrics and Adolescent Medicine, University Hospital, Heidelberg, Germany. [8]Basque Office for Health Technology Assessment, (OSTEBA), Basque Government, Vitoria-Gasteiz, Spain. [9]Department of Medicine IV, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [10]Medizinische Genetik Mainz, Limbach Genetics, Mainz, Germany. [11]Department of Radiology, University Hospital of Leuven, Leuven, Belgium. [12]Associazione Sclerosi Tuberosa ASP, Rome, Italy. [13]European Tuberous Sclerosis Complex Association (ETSC), Oestrich-Winkel, Germany. [14]Center for LAM Research and Clinical Care, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [15]Department of Nephrology and Arterial Hypertension, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel, Brussels, Belgium. [16]Division of Nephrology, Department of Internal Medicine, University of Liège Hospital, Liège, Belgium. [17]Interdisciplinary Group of Applied Genoproteomics, Cardiovascular Sciences, University of Liège, Liège, Belgium. [18]Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Centre, St Georges University of London, London, UK. [19]Department of Surgery-Urology, CHUM-Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada. [20]Department of Paediatric Nephrology, Wilhelmina Children´s Hospital, University Medical Center Utrecht, Utrecht, The Netherlands. [21]Department of Radiology, University Hospitals Leuven, Leuven, Belgium. [22]Associação de Esclerose Tuberosa em Portugal, Lisbon, Portugal. [23]Department of Urology and Paediatric Urology, Saarland University, Homburg, Germany. [24]Department of Physiology, Mechanisms of Inherited Kidney Disorders, University of Zurich, Zurich, Switzerland. [25]Institute for Rare Diseases, Saint-Luc Academic Hospital, UC Louvain, Brussels, Belgium. [26]Cancer Genetics Laboratory, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [27]Department of Radiology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France. [28]Université Lyon 1, Lyon, France, Faculté de médecine Lyon Est, Lyon, France. [29]Department of Paediatrics, University of Tennessee Health Science Center and Le Bonheur Children's Hospital, Memphis, TN, USA. [30]Children's Foundation Research Institute (CFRI), Le Bonheur Children's Hospital, Memphis, TN, USA. [31]Paediatric Medicine Department, St. Jude Children's Research Hospital, Memphis, TN, USA.