Consensus Statement for the Diagnosis, Management and Surveillance of Patients with Tuberous Sclerosis Complex in Bulgaria

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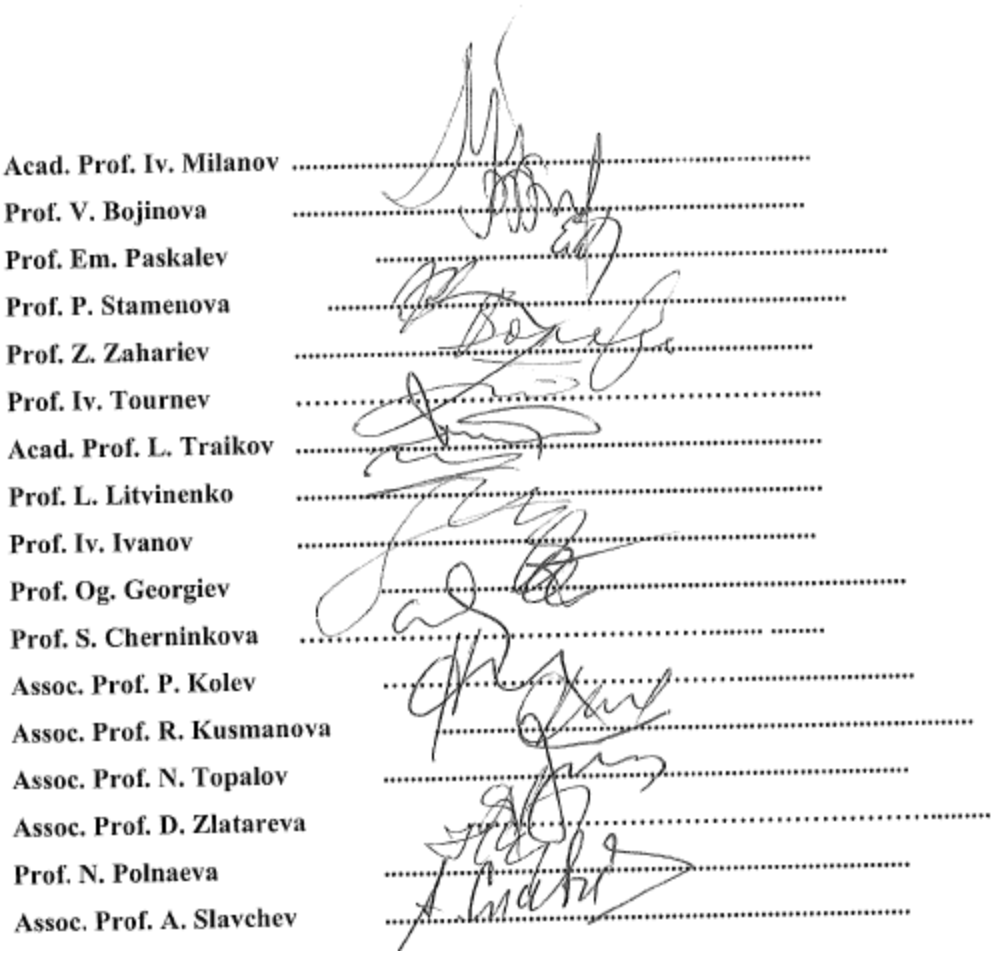
At the initiative of the Bulgarian Society of Neurology,
the Bulgarian Society of Child Neurology, Psychiatry and Psychology of Development,
the Bulgarian Society of Nephrology

Today 07.03.2019 we undersigned specialist have agreed on the consensus about diagnostics, treatment and follow up of patients with Tuberous Sclerosis Complex



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Abbreviations

AMLs – Angiomyolipoma

IEP – Individual educational program

LAM – Pulmonary lymphangioleiomyomatosis

MRI – Magnetic resonance imaging

TAND – Tuberous sclerosis complex-associated neuropsychiatric disorders

SEGA – Subependymal giant cell astrocytoma

SEN – Subependymal nodule

ACTH – Adrenocorticotropic hormone

AED – Antiepileptic drugs

BRV – brivaracetam

CBZ – carbamazepine

CZP – clonazepam

ESM – ethosuximide

ESL – eslicarbazepine

GBP – gabapentin

LCM – lacosamide

LEV– levetiracetam

LTG – lamotrigine

OxCBZ – oxcarbazepine

PB – phenobarbital

PGB – pregabalin

PHT– phenytoin

RTG – retigabine

TGB – tiagabine

TPM – topiramat

TSC – Tuberous Sclerosis Complex

VGB –vigabatrin

VPA – valproate

Contents

I. Epidemiology of Tuberous Sclerosis Complex (TSC)

II. Clinical presentation of TSC

1. Skin lesions
2. Neurological brain involvement
3. Kidney
4. Heart
5. Lung

III. Diagnosis of Tuberous Sclerosis Complex. Current diagnostic criteria

IV. Pharmacological and surgical management of TSC

V. Algorithm for surveillance and management of TSC patients

1. Surveillance and management recommendations for individuals with newly suspected or newly diagnosed TSC

2. Ongoing surveillance and management recommendations for individuals previously diagnosed with TSC

3. Coordination of care and other clinical considerations in patients with TSC

Tuberous Sclerosis Complex (TSC) is characterized by multiorgan involvement that can affect the brain, heart, skin, kidneys, lungs and liver, with a predisposition to formation of benign tumors. The clinical manifestations of the disease are highly diverse in regard to both organ system involvement and severity, with some more prevalent during infancy and others more likely to affect individuals as adults. Many manifestations can be life-threatening and appropriate surveillance and management is necessary to limit morbidity and mortality in this disease. Appropriate management is also crucial for optimal quality of life of affected individuals and requires coordination of care among medical specialties.

Better understanding of the genetic nature of the disease (the role of TSC1 and TSC2 genes in the regulation of cell growth and metabolism – mTOR pathway) is a main factor in modern pathogenetic treatment. mTORC1 inhibitors are used for treatment of some life-threatening TSC-related clinical manifestations, such as subependymal giant cell astrocytomas in the brain, renal angiomyolipomas and pulmonary lymphangioleiomyomatosis**.**

The multiorgan involvement in TSC patients requires a multidisciplinary approach with coordination of surveillance and care services among medical specialties from childhood to adulthood.

I. Epidemiology and etiology of TSC

Tuberose sclerosis complex is a rare genetic disorder with an autosomal dominant pattern of inheritance, with estimated incidence between 1/6000 and 1/10,000 live births (1:5800) and population prevalence rate 10 - 16: 100 000 or 1:12 500 - 1:20000.

The disease is caused by mutations in tumor suppressor genes TSC1 (9q34) and TSC2 (16 p13.3). The TSC1 gene (9q34) encodes the TSC1 protein hamartin, while TSC2 (16 p13.3) encodes synthesis of the TSC2 protein tuberin. Hamartin and tuberin function together to inhibit the mammalian target of rapamycin complex 1 (mTORC1) – a protein kinase that regulates protein synthesis, cell growth and proliferation. Their deficiency leads to dysregulation in mTOR signaling, mTORC1 overactivity and tumor growth. Hamartin and tuberin are expressed in many tissues which is the reason for the multiorgan involvement in TSC. TSC2 gene mutations are more frequent in TSC (55% to 90% of cases) and are associated with a more severe course of the disease. Although extremely rare (in about 2% of patients) TSC and autosomal dominant polycystic kidney disease (ADPKD) can co-exist in the same patient as a result of concurrent deletion of both polycystic kidney disease (PKD) 1 and TSC2 genes present on the chromosome 16p13.3.

II. Clinical presentation of TSC

There are no pathognomonic signs and symptoms in TSC. TSC with multiple organ involvement is characterized by a combination of clinical syndromes with varying prevalence of each manifestation depending on the age-related expression of the disease (Table 1).

Cardiac rhabdomyomas, neurological and cutaneous syndromes can be manifested prenatally or during the first year of life. Ophthalmological manifestations are usually detected between the ages 1 to 5 years, renal manifestations – between 5 and 10 years and pulmonary manifestations – after 18 years of age.

Table 1. Type, frequency and age of onset of clinical manifestations in tuberous slerosis

Clinical manifestations, age of onset	**Prevalence %**
Hypomelanotic macules – at birth	87 - 100
Angiofibromas – early childhood	75 - 90
Dental enamel pits – childhood	97 - 100
Cortical dysplasias – at birth	70 - 90
Epilepsy – infancy and later in life	60 - 90
Subependymal nodules (SEN) – infancy, progressive calcified tubers on CT scanning	70 - 90
Subependymal giant cell astrocytomas (SEGA) – childhood	5 - 20
Retinal hamartomas – 1 - 5 years of age	30-87
Renal and more rarely hepatic angiomyolipomas – 5 - 18 years of age	56 - 80
Ungual fibromas – 2nd decade of life	20 - 88
Cardiac rhabdomyomas – at birth	47 - 67
"Confetti" skin lesions – up to 10 years of age	3 - 58
Shagreen patches – up to 10 years of age	~50
Autism	25 - 50
Intellectual disability – early childhood	~40
Lymphangioleiomyomatosis (LAM) – 2nd – 3rd decade of life	30 - 40 of women
Fibrous cephalic and facial plaques – early childhood	20 - 40
Retinal depigmented macules	~40
Renal cysts	~20
Intraoral fibromas – 2nd decade	20 - 69

Presence of cardiac rhabdomyomas and in some cases of renal angiomyolipomas can be detected by ***prenatal*** fetal echocardiography. Early manifestations during the neonatal period and infancy include rhythm disorders associated with cardiac rhabdomyomas, skin hypomelanotic macules, and refractory epileptic encephalopathy and West syndrome.

1. Skin lesions may be a presenting sign of TSC because of their early manifestation and high frequency.

Hypomelanotic macules are observed in almost 100% of children with TSC at birth. Facial angiofibromas, gradually increasing in size, are seen in 75%-90% of patients and start to appear within the first 1–5 years of life. Later on fibrous plaques on the face and scalp may also occur (20 - 40% of patients). Skin lesions on the lower back, the so called Shagreen patches, are observed in about 50% of individuals with TSC and typically have their onset in the first decade of life (about 10 years of age). Ungual fibromas typically appear in the second decade (20 - 89%), and intraoral and gingival fibromas (20 - 69%) – during childhood. Dental enamel pits are also a diagnostic sign of TSC detected in childhood.

Retinal achromic patches are equivalent to skin hypopigmentations and *retinal hamartomas* – to skin hamartomas. Both are detected during ophthalmic examination.

2. Neurological brain involvement

Brain involvement is a major feature of the disease due to the presence of cortical dysplasias including cortical tubers and subependymal giant cell astrocytomas, well visualized on magnetic resonance imaging (MRI).

The most common clinical manifestations of cortical tubers are early-onset refractory epilepsy (60% - 90%), mental retardation (40%), paretic symptoms in some cases and TSC-associated neuropsychiatric disorders in about 90% of patients (autism spectrum disorders in 25-50% of patients, attention deficit/hyperactivity disorder, aggression and other behavioral problems, obsessive-compulsive disorder, psychoses). Subependymal giant cell astrocytomas, (SEGAs), seen in 5-20% of patients, can cause obstructive internal hydrocephalus. SEGAs typically arise from subependymal nodules (SEN) in the area of the foramen of Monro with diameter greater than 10 mm.

Cortical dysplasias, including cortical tubers and cerebral white matter radial migration lines, detected by magnetic resonance imaging (MRI), are caused when a group of neurons fail to migrate to the proper area of the brain during development.

The presence and type of epilepsy, mental retardation and TSC-associated neuropsychiatric disorders depend on the location and distribution of cortical tubers (malformations of cortical

development generally behaving as benign tumors). In the majority of cases epilepsy is refractory, with early onset, and may start as West syndrome and then evolve into Lennox-Gastaut syndrome or focal epilepsy. Early manifestation of West syndrome (infantile epileptic encephalopathy) is associated with problems in physical, cognitive and intellectual development. Treatment standards include combination therapy with antiepileptic drugs (Table 3).

***Subependymal nodules (SEN*)** are slow-growing benign hamartomas, typically developing along the wall of the ependymal lining of the cerebral ventricles. They are seen on CT as round periventricular calcifications, negative on MRI imaging, and are an important feature for early diagnosis of TSC.

Subependymal giant cell astrocytomas (SEGA) are benign tumors, that typically arise from subependymal nodules (SEN) in the area of the foramen of Monro in 5-20% of TSC patients. Although slow-growing, they can cause obstructive internal hydrocephalus and increased intracranial pressure. The therapeutic behavior – shunt surgery in acute hydrocephalus or conservative everolimus pharmacotherapy in SEGAs larger than 10 mm – is determined by dynamic clinical and MRI follow-up

3. Kidney

In 56-80% of TSC patients are typically found multiple and bilateral renal angiomyolipomas, seen at ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) of the abdomen, and in about 20-30% of patients are detected renal cysts.

Angiomyolipomas (AML) are benign renal tumors composed of blood vessels (angio-), smooth muscle cells (myo-) and adipose tissue (lip-) that are found in 56-80% of TSC patients. *Renal AML are multiple and bilateral* and usually asymptomatic at the beginning. However, AML tend to grow and cause pain or renal impairment. Due to aneurysms in the bloods vessels, angiomyolipomas larger than 4 cm are at risk for *hemorrhage* either spontaneously or with minimal trauma. The hemorrhage is life-threatening, with sudden onset of pain and general weakness and rapid development of severe anemia, arterial hypotension and shock.

About 20-30% of people with TSC have renal cysts and 2% may also have *autosomal dominant polycystic kidney disease* since childhood. The co-existence of polycystic kidney disease in TSC patients is a result of concurrent deletion of both polycystic kidney disease (PKD) 1 and TSC2 genes present on the chromosome 16p13.3.

Renal cysts are clinically asymptomatic but may cause renal impairment. Although very rarely (2%-3%) renal cell carcinomas and oncocytomas (benign adenomatoid hamartoma) can occur at a younger age in individuals with TSC than in the general population.

4. Heart

Cardiac rhabdomyomas are benign tumors of the heart detectable by echocardiographic examination in about 50% of TSC patients – in up to 90% of newborns and about 20% of adult patients. These tumors tend to grow during the second half of pregnancy and can be detected by fetal echocardiography after 20 weeks of gestation or postnatally. They usually regress spontaneously after birth. Cardiac rhabdomyomas can cause cavitary obstructions, cardiac arrhythmias and murmurs. Rhabdomyomas are associated with tuberous sclerosis complex diagnosis especially in the presence of family history of TSC. Rhabdosarcomas are rarely observed.

5. Lung

TSC patients with pulmonary involvement may develop a widespread pulmonary proliferation of abnormal smooth-muscle cells and cystic changes within the lung parenchyma – *lymphangioleiomyomatosis (LAM).* Recent genetic analysis has shown that the proliferative bronchiolar smooth muscle in TS-related LAM is monoclonal metastasis from a co-existing renal AML. LAM is usually diagnosed in women with TSC after 18 years of age and is initially manifested by exertional dyspnea and shortness of breath**.** LAM diagnosis requires assessment by pulmonary high-resolution computed tomography (HRCT), baseline pulmonary function testing and 6-minute walk test. Measurement of vascular endothelial growth factor D (VEGF-D) serum levels may be helpful to establish a baseline for future LAM development or progression. The presence of characteristic lung cysts on CT requires monitoring at 3-6 month intervals and pulmonary function testing. In patients with moderate-to-severe and rapidly progressing LAM, mTOR inhibitors are effective in stabilizing lung function.

Prognosis for individuals with TSC depends on the severity of manifestations, which can range from skin lesions to varying grades of learning disabilities, severe intellectual disability, refractory seizures, and kidney failure.

Leading causes of death include renal disease, pulmonary lymphangioleiomyomatosis, brain tumors, and status epilepticus or bronchopneumonia in those with severe mental handicap. Renal angiomyolipomas can cause renal hemorrhages. Renal carcinomas are rarely observed. Subependymal giant cell astrocytomas may cause internal hydrocephalus. Pulmonary lymphangioleiomyomatosis is a risk factor for pneumothorax in women. Cardiac rhabdomyomas are associated with risk for the fetus during the neonatal period; rhabdosarcomas may develop later in life.

III. Diagnosis of Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a disorder that may affect nearly every organ system. It is characterized by absence of pathognomic syndrome and a combination of clinical manifestations in different organs and systems which require specialized diagnostic evaluations.

A definite diagnosis requires:

- *Accurate medical history and family history*
- *Examinations for mucocutaneous changes:* inspection of the skin for hypomelanotic macules, facial angiofibromas, fibromas of the face and scalp, Shagreen patches, ungual fibromas, inspection of the oral cavity for gingival fibromas and dental enamel pits.
- *Neuroimaging: CT* scans of the brain (for the presence of calcified subependymal nodules, cortical tubers); *MRI* of the brain is a more sensitive modality (cortical tubers, cortical dysplasias, subependymal nodules, subependymal giant cell astrocytomas).
- EEG tests in epilepsy, video EEG
- *Renal examinations*: ultrasound imaging**,** computed tomography and magnetic resonance imaging (for the presence of bilateral multiple angiomyolipomas and cysts); BP measurement of arterial hypertension, assessment of renal function by glomerular filtration rate (GFR) using CrCl estimating equations for adults or pediatric patients. An alternative method for GFR assessment is measurement of serum concentration of cystatin C.
- *Echocardiography (EchoCG) and electrocardiogram (ECG)* in infants for the presence of rhabdomyomas and arrhythmia.
- *Ophthalmic examination* – fundoscopy for retinal hamartomas and achromatic patches.
- *Lung imaging* – high-resolution chest computed tomography (HRCT) and baseline lung function testing, 6-minute walk test. Measurement of vascular endothelial growth factor D (VEGF-D) serum levels may be helpful to establish a baseline for future LAM development or progression.
- *Genetic testing* for identification of mutations in the TSC 2 or TSC 1 genes (10% to 25% of TSC patients have no mutation identified)

A definite diagnosis of Tuberous Sclerosis Complex is made on the basis of diagnostic criteria. The Tuberous Sclerosis Complex Diagnostic Criteria Update 2012 include:

A. *Genetic diagnostic criteria* – identification of either a *TSC1* or *TSC2* pathogenic mutation that inactivates the function of the TSC1 protein hamartin or the TSC2 protein tuberin is sufficient to make a definite diagnosis of TSC, but 10-25% of TSC have no mutation identified.

B. Clinical diagnostic criteria for presence of 11 major and 6 minor features:

Major features (11):

1. Hypomelanotic macules (≥3, at least 5-mm diameter);
2. Angiofibromas (≥3) or fibrous cephalic plaque;
3. Ungual fibromas (≥2)
4. Shagreen patches;
5. Multiple retinal hamartomas;
6. Cortical dysplasias (tubers and cerebral white matter radial migration lines) (≥3);
7. Subependymal nodules (SEN) (≥2);
8. Subependymal giant cell astrocytoma (SEGA);
9. Cardiac rhabdomyoma;
10. Lymphangioleiomyomatosis (LAM);
11. Angiomyolipomas (AML) (≥2).

Minor features (6):

1. "Confetti" skin lesions
2. Dental enamel pits (≥3);
3. Intraoral fibromas (≥2);
4. Retinal achromic patch;
5. Multiple renal cysts;
6. Non-renal hamartomas

Definite diagnosis: 2 major features or 1 major feature with ≥2 minor features

Possible diagnosis: Either 1 major feature or ≥2 minor features

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

IV. Management of TSC

Since TSC is a disorder with multiorgan involvement the developed algorithms for management and surveillance of TSC patients are based on a multidisciplinary approach. Therefore the evidence-based recommendations include individualized and multidisciplinary approach for management and surveillance of both newly diagnosed patients and patients with established TSC across their lifespan.

The basic recommended diagnostic modality in TSC patients is magnetic resonance imaging (MRI) of the brain for detection of subcortical tubers and cortical dysplasias, present in about 90% of TSC patients, SEN (in 80%) and SEGA (in 5-20% of patients), with adequate follow-up throughout the lifetime of the patient. TSC-related neuropsychiatric disorders – autistic,

hyperkinetic and mental retardation should be assessed by EEG examination, and infantile spasms – by EEG video. MRI of the abdomen is performed to assess for the presence of angiomyolipoma and renal cysts. Evaluation of renal function, baseline pulmonary function testing and high-resolution CT scan of the lungs for detection of LAM are recommended in symptomatic males and all female patients older than 18 years. Detailed clinical dermatologic, dental and ophthalmologic evaluation as well as routine electrocardiogram should be performed in all ages.

Treatment of SEGA could be either surgical or medical with everolimus depending on the individual risk-to-benefit ratio.

Table 2. SEGA – Surgical treatment and mTOR inhibitor therapy – advantages and disadvantages

Surgical treatment		**mTOR inhibitor therapy**	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
- Prompt hydrocephalus improvement	- Possible regrowth of SEGA Complications: - Loss of vision - Permanent ventriculo-peritoneal shunt - Headache - Memory disorders - Impairment of cerebral and vascular structures - Infarctions	- Non-invasive treatment – significant reduction in SEGA volume - Helps to control hamartomas in other organs; i.e. cutaneous angiofibromas, renal angiomyo-lipomas - May improve epilepsy	- Possible regrowth of SEGA after treatment discontinuation - Drug monitoring required - Mild immune suppression - Drug interactions - Adverse drug effects (stomatitis, fever, dermatitis, diarrhea (all Grade 1 and 2, >20% of patients)

Algorithm for diagnosis, surveillance and treatment of SEGA:

Surgery/mTOR inhibitor therapy

Contrast-enhanced magnetic resonance imaging of the brain

- Acute internal hydrocephalus – surgical treatment, MRI monitoring;

- SEN in the area of the foramen of Monro <5 mm – surveillance every 12 months; in the absence of progression – surveillance interval of 1 - 3 years
- SEN in the area of the foramen of Monro ≥5 mm – surveillance every 3 - 6 months; in the absence of progression, surveillance interval of 1 - 3 years
- In case of progression over 10 mm, i.e. identification of SEGA: m-TOR inhibitor at an adequate dose
- In case of growing SEGA: dose uptitration, alternative m-TOR inhibitor, more frequent monitoring, surgery

Everolimus is licensed and approved for treatment of *renal angiomyolipomas* and a recent clinical trial has also demonstrated an effect on refractory epilepsy.

Dosing recommendations and treatment follow-up:

The dosing of everolimus should be individualised according to the body surface area (BSA) using the Dubois formula, based on weight (W; in kg) and height (H; in cm)

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Initial dose of Everolimus for treatment of SEGA - 4,5 mg/m^2

- Target concentration range of Everolimus ≥1 week after initiation – 5 and 15 ng/ml; individual assessment of efficacy and tolerability
- Gradual uptitration by 2.5 mg till adequate plasma concentration and optimal response is attained.
- Monitoring of serum concentration every 3-6 months in children and every 6-12 months in patients with stable body surface area.
- Monitoring of adverse effects: complete blood count and blood biochemistry tests are recommended for detection of:
  - Hyperglycemia
  - Dyslipidemia
  - Thrombocytopenia, Grade 2 (≥75x10^9/L), Grades 3 and 4 (<50x10^9/L)
  - Neutropenia, Grades 2,3 and 4 (≥1x10^9 /L)
  - Febrile neutropenia, Grades 2, 3, and 4 (≥1.25x10^9 /L).
  - Severe adverse reactions (Grades 2, 3 and 4) or intolerability: the dose of everolimus should be reduced or treatment temporarily discontinued
  - Adverse reactions Grade 1: no dose adjustment is required
  - Adverse reactions Grade 2: the dose should be reduced by 50% and the patient monitored for subsequent reduction

- Adverse reactions Grade 3 and 4: treatment should be discontinued
- Urine test for proteinuria

In TSC patients with West syndrome early treatment with vigabatrin or ACTH therapy is recommended, and in patients with Lennox-Gastaut syndrome or focal epilepsies – a combination therapy depending on the type of seizures and the therapeutic response (Tables 3 and 4).

Table 3. Antiepileptic drugs for treatment of epileptic syndromes and seizures (National consensus for diagnosis and treatment of epilepsy, 2019)

Type of epilepsy (syndrome) epileptic seizures	**First line** Monotherapy	**Monotherapy or polytherapy options**
Primary generalized (idiopathic/genetic) epilepsies/Generalized seizures		
Tonic-clonic seizures	CBZ,PHT,VPA	CZP, LTG, LEV, OxCBZ, PB, TGB, TPM,
Atonic seizures	VPA	LTG, CZP
Absence seizures	VPA, ESM	CZP, LTG, TPM
Myoclonic seizures	VPA	CZP, ESM, LTG, LEV, TPM, Corticosteroids
	VPA	CZP, ESM, LTG, LEV, TPM
Focal epilepsies/Focal epileptic seizures		
Focal seizures	CBZ, VPA	CZP, GBP, LCM, LTG, LEV, OxCBZ, PB, PHT, PGB,TGB, TPM, BRV
Secondary generalized seizures	CBZ, PHT, VPA	GBP, LTG, LCM, LEV, OxCBZ, PB, PHT, PGB, TGB, TPM, BRV
Idiopathic focal (Rollandic and occipital)	CBZ, VPA, OxCBZ	CZP, GBP, LTG, LEV
Epileptic encephalopathies		
West syndrome	ACTH, VPA	CZP, LTG, TPM,
Lennox-Gastaut syndrome	*LTG, TPM, VPA*	CBZ, CZP, PB, PHT, Rufinamide*
Dravet syndrome (SMEI)	*VPA,TPM*	LEV, Stiripentol*
Epileptic encephalopathy with CSWS or electrical status epilepticus during sleep (ESES)	*VPA, ESM*	LEV, benzodiazepines, corticosteroids

– Antiepileptic drugs (AEDs) approved for monotherapy or adjuvant therapy: CBZ, CZP, ESM, GBP (over 12 years, monotherapy; over 3 years, polytherapy), **LTG** (over 2 years), **LEV (**over 16 years, monotherapy; over 1 month, polytherapy**), LCM** (over 4 years), **OxCBZ, PHT, PB, TPM** (over 2 years), **VPA.**

– AEDs approved for adjuvant therapy only: PGB (over 18 years); **TGB** (over 12 years), when other drug combinations have proved to be unsatisfactory of intolerable, BRV (over 16 years).

– Conventional AEDs: CBZ – carbamazepine**; CZP-**clonazepam**; ESM –** ethosuximide**, PHT –** phenytoin**; PB –** phenobarbital**; VPA–** valproate

– Novel AEDs: GBP – gabapentin**; LTG –** lamotrigine**; LCM –** lacosamide; **LEV –** levetiracetam; **OxCBZ –** oxcarbazepine; **PGB** – pregabalin**; TGB –** tiagabine**; TPM –** topiramate; Rufinamide* **–** Lennox-Gastaut syndrome; **Stiripentol* –** Dravet syndrome; **BRV –** brivaracetam

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*** Rufinamide** for treatment of Lennox-Gastaut syndrome, according to Art. 266, para 2 of the Law on medicinal products in human medicine and Art.16, para 4 of Regulation № l0/2011 on the conditions and procedures for treatment with medicinal products without marketing authorisation for the Republic of Bulgaria

* **Stiripentol** for treatment of Dravet syndrome, according to Art. 266, para 2 of the Law on medicinal products in human medicine and Art.16, para 4 of Regulation № l0/2011 on the conditions and procedures for treatment with medicinal products without marketing authorisation for the Republic of Bulgaria

****Medicinal products not registered in Bulgaria:**

Clobazam for treatment of absences, generalized tonic-clonic seizures (GTCS), Dravet syndrome and Lennox-Gastaut syndrome; **Nitrazepam** for treatment of West syndrome; **Sulthiam** for treatment of focal seizures; **Vigabatrin** for treatment of West syndrome**; Zonisamide** for treatment of focal and secondary generalized seizures in adults and children older than 6 years, myoclonic seizures, Lennox-Gastaut syndrome; **ACTH** for treatment of West syndrome.

Table 4. Types and dosages of antiepileptic drugs
(National consensus for diagnosis and treatment of epilepsy, 2019)

International Nonproprietary Name (INN)	CHILDREN		ADULTS		
	Initial daily dose (mg/kg)	**Optimal daily dose (mg/kg)**	**Initial daily dose (mg)**	**Optimal daily dose (mg)**	**Maximum daily dose (mg)**
Valproic acid	10 - 20	10 - 50	500	1000 - 2000	2100
Carbamazepine	5	10 - 30	200	600 - 1200	1600
Oxcarbazepine	10	30 - 40	300 - 600	900 - 2400	2400
Phenytoin	3 - 4	4 - 8	100	300 - 400	500
Phenobarbital	2	2-5	60	90-250	600
Clonazepam	0,01	0,01 - 0,02 up to 0,1 - 0,2	0,5	2 - 6	8
Lamotrigine	0,6 with enzyme inducers 0,15 with VPA 0,3 in mono-therapy	5-15 with enzyme inducers 5 with VPA 15 in mono-therapy	50 with enzyme inducers 12,5 with VPA 25 in mono-therapy	500-600 with enzyme inducers 300 - 400 with VPA 500 in monotherapy	700 in monotherapy
Topiramate	0,5-1,0	5-9	25	200 - 400	500
Levetiracetam	10	40	1000	2000 - 3000	3000
Tiagabine	0,1	1	5–10	60	70
Gabapentin	After 6 years of age 10-15	30-35	300	1200 - 1800-3600	3600
Pregabalin	-	-	150	450 - 600	600
Lacosamide	After 4 years of age 2 mg/kg	200-400 mg daily	100	200-400	600 mg or 10 mg/kg as monotherapy in children and adolescents with b.w. >50 kg and 8 mg/kg in

					children and adolescents with b.w. <50 kg; 400 mg as adjuvant therapy children and adolescents with b.w. >50 kg and adults
Ethosuximide	10	40	500	1500	2000
Stiripentol*	50	Up to 100	50	Up to 100	4000
Rufinamide*	Over 4 - 10 y	45	400	2400	3200
Brivaracetam	Over 16 years 50-100, divided into two equal doses	50-200 based on individual response and tolerability	50 - 100, divided into two equal doses	50-200 based on individual response and tolerability	200

V. Algorithm for Surveillance and Management of TSC patients

1. Surveillance and management recommendations for individuals with newly suspected or newly diagnosed TSC

TSC is usually first suspected in individuals when one or more clinical diagnostic criteria are identified (Table 5). The purposes of initial diagnostic studies are to confirm the diagnosis in individuals with “possible” TSC and to determine the extent of disease and organ involvement in individuals with “definite” TSC.

Baseline studies are also important in guiding treatment decisions should additional disease manifestations emerge in later years.

Table 5. Surveillance and management recommendations for patients with newly diagnosed or suspected tuberous sclerosis complex (TSC)

Organ System or Specialty Area	**Recommendation**

Genetics	• Obtain three-generation family history to assess for additional family members at risk of TSC. • Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed.
Brain	• Perform magnetic resonance imaging (MRI) of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA). • Evaluate for TSC-associated neuropsychiatric disorder (TAND). • Educate parents to recognize infantile spasms during infancy, even if none have occurred at time of first diagnosis. • Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow-up with a 24-hr video EEG to assess for subclinical seizure activity.
Kidney	• Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts. • Screen for hypertension by obtaining an accurate blood pressure. • Evaluate renal function by determination of glomerular filtration rate (GFR).
Lung	• Perform baseline pulmonary function testing (pulmonary function testing and 6-minute walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically females 18 years or older. Adult males, if symptomatic, should also undergo testing. • Provide counsel on smoking risks and estrogen use in adolescent and adult females.
Skin	• Perform a detailed clinical dermatologic inspection/exam.
Teeth	• Perform a detailed clinical dental inspection/exam.
Heart	• Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound. • Obtain an echocardiogram in pediatric patients, especially if younger than 3 yr of age. • Obtain an electrocardiogram (ECG) in all ages to assess for underlying conduction defects.

Eye	• Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal lesions and visual field deficits.

Genetics

All individuals should have a three-generation family history obtained to determine if additional family members are at risk of diagnosis. Gene testing is recommended for genetic counseling purposes or when the diagnosis of TSC is suspected or in question but cannot be clinically confirmed.

Brain

All individuals suspected of having TSC, regardless of age, should undergo magnetic resonance imaging (MRI) of the brain with and without gadolinium to assess for the presence of cortical/subcortical tubers, SEN, other types of neuronal migration defects, and SEGA. If MRI is not available, computed tomography (CT) or head ultrasound (in neonates or infants) may be used, although results are considered suboptimal compared with MRI.

Kidney

At the time of diagnosis, abdominal imaging should be obtained regardless of age. As for brain, MRI is the preferred modality for evaluation of angiomyolipomata because many can be fat-poor and hence missed when abdominal CT or ultrasound are performed. MRI of the abdomen may be combined in the same session as MRI of the brain, thereby limiting the need for multiple sessions of anesthesia if anesthesia is needed for successful MRI. MRI of the abdomen may also reveal aortic aneurysms or extrarenal hamartomas of the liver, pancreas, and other abdominal organs that also can occur in individuals with TSC. Accurate blood pressure assessment is important because of increased risk of secondary hypertension. To assess renal function at time of diagnosis, blood tests to determine glomerular filtration rate (GFR) using creatinine equations for adults or children should be performed. Alternatively, measurement of serum cystatin C concentration can be used to evaluate GFR.

Lung

To evaluate for LAM, females 18 years or older should have baseline pulmonary function testing, 6-minute walk test, and high-resolution chest computed tomography (HRCT). When possible, low-radiation protocols should be used. A serum vascular endothelial growth factor type D (VEGF-D) level may be helpful to establish a baseline for future LAM development or progression. Adolescents and adults should be counseled on

smoking risks and estrogen use (such as some oral contraceptive preparations), which can compound the impact of LAM.

Skin and teeth

All patients should undergo a detailed clinical dermatologic and dental exam at time of diagnosis to evaluate for facial angiofibromas, fibrous cephalic plaques, hypomelanotic macules or confetti lesions, ungual fibromas, shagreen patch, defects in tooth enamel, and intraoral fibroma.

Heart

In pediatric patients, especially younger than three years of age, an echocardiogram (EchoCG) and electrocardiogram (ECG) should be obtained to evaluate for rhabdomyomas and arrhythmia, respectively. In those individuals with rhabdomyomas identified via prenatal ultrasound, fetal echocardiogram may be useful to detect those individuals with high risk of heart failure after delivery.

In the absence of cardiac symptom, echocardiogram is not necessary in adults, but as conduction defects may still be present and may influence medication choice and dosing, a baseline ECG is still recommended.

Eye

A baseline ophthalmologic evaluation, including funduscopic evaluation, is recommended for all individuals diagnosed with TSC to evaluate for hamartomas and hypopigmented lesions of the retina.

Other

Although vascular aneurysms, gastrointestinal polyps, bone cysts, and various endocrinopathies can be associated with TSC, there is insufficient evidence to support routine evaluation at time of diagnosis unless there are clinical symptoms that warrant specific investigation.

2. Ongoing surveillance and management recommendations for individuals previously diagnosed with TSC

Once the diagnosis of TSC is established and initial diagnostic evaluations completed, continued surveillance is necessary to monitor progression of known problems or lesions and emergence of new ones (Table 6). Some manifestations begin in childhood and are less likely to be present or cause new problems in adulthood, such as cardiac rhabdomyomas or subependymal giant cell astrocytomas. In contrast, problems with LAM are typically limited to adults, and renal manifestations require significantly more monitoring and intervention in adulthood compared with childhood because of the cumulative nature of angiomyolipoma and other renal lesions. Finally, other aspects of TSC may be present throughout the entire lifespan of the individual, such as epilepsy and TAND, but specific manifestations and impact on overall health and quality of life can vary. Thus, ongoing periodic surveillance is needed after initial diagnosis for optimal care and prevention of secondary complications associated with TSC. Management of specific complications of TSC will often require input from a multidisciplinary team.

Table 6. Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

Organ System or Specialty Area	Recommendation
Genetics	• Offer genetic testing and family counseling, if not done previously, in individuals of reproductive age considering having children.
Brain	• Obtain *MRI of the brain* every 1-3 yrs. in asymptomatic TSC patients younger than age 25 years to monitor for new occurrence of SEGA. Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms. Patients with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure there is no growth. • *Surgical resection* should be performed for *acutely symptomatic SEGA.* Cerebral spinal fluid diversion (shunt) may also be necessary. • In determining the best treatment option, either surgical resection or medical treatment with mTOR inhibitors for growing but otherwise asymptomatic SEGA should be considered the complication risks,

	adverse effects, cost, length of treatment, and potential impact on TSC-associated comorbidities. • Perform screening for TSC-associated neuropsychiatric disorders (TAND) features at least annually. Perform comprehensive formal evaluation for TAND at key developmental time points: infancy (0-3 yrs.), preschool (3-6 yrs.), pre-middle school (6-9 yrs.), adolescence (12-16 yrs.), early adulthood (18-25 yrs.), and as needed thereafter. Management strategies should be based on the TAND profile of each patient and on evidence-based good practice guidelines/practice parameters for individual disorders (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder). Consider the need for an individual educational program (IEP). Sudden change in behavior should prompt medical/clinical evaluation to look for potential medical causes (e.g., seizures, renal disease). • Obtain routine EEG in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 hr or longer, is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioral changes, or other alteration in cognitive or neurological function is present. • Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropin hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies. Epilepsy surgery should be considered for medically refractory TSC patients, and is best if performed at epilepsy surgery centers.
Kidney	• Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yrs. throughout the lifetime of the patient. • Assess renal function (including determination of glomerular filtration rate [GFR]) and blood pressure at least annually. • Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to

	be avoided. Treatment with an mTOR inhibitor is the recommended first-line therapy for asymptomatic, growing angiomyolipoma larger than 2 cm in diameter. Selective embolization or kidney-sparing resection are acceptable second-line therapy for asymptomatic angiomyolipoma.
Lung	• Perform clinical screening for lymphangioleiomyomatosis (LAM) symptoms, including exertional dyspnea and shortness of breath, at each clinic visit. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk of LAM. • Obtain high-resolution computed tomography (HRCT) every 5-10 years in asymptomatic individuals at risk of LAM if there is no evidence of lung cysts on their baseline HRCT. Individuals with lung cysts detected on HRCT should have annual pulmonary function testing (pulmonary function testing and 6-min walk) and HRCT interval reduced to every 2-3 yr. • mTOR inhibitors may be used to treat LAM patients with moderate to severe lung disease or rapid progression. TSC patients with LAM are candidates for lung transplantation but TSC comorbidities may impact transplant suitability.
Skin	• Perform a detailed clinical dermatologic inspection/exam annually. • Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, laser(s), or possibly topical mTOR inhibitor.
Teeth	• Perform a detailed clinical dental inspection/exam at minimum every 6 months and panoramic radiographs by age 7 yr, if not performed previously. • Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions should be treated with surgical excision or curettage.
Heart	• Obtain an echocardiogram every 1-3 yrs. in asymptomatic pediatric patients until regression of cardiac rhabdomyomas is documented. More frequent or advanced diagnostic assessment may be required for

	symptomatic patients. • Obtain electrocardiogram (ECG) every 3-5 yrs. in asymptomatic patients of all ages to monitor for conduction defects. More frequent or advanced diagnostic assessment such as ambulatory and event monitoring may be required for symptomatic patients.
Eye	• Perform annual ophthalmologic evaluation in patients with previously identified ophthalmologic lesions or vision symptoms at the baseline evaluation. More frequent assessment, including those treated with vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise.

Genetics

Genetic testing and family counseling should be offered to individuals with TSC when they reach reproductive age, and first-degree relatives of affected individuals should be offered clinical assessment and genetic testing where a mutation has been identified in the index case.

Brain

Symptomatic SEGA or SEGA associated with increasing ventricular enlargement, or with unexplained changes in neurological status or TAND symptoms, require more frequent clinical monitoring and reimaging or surgical intervention. For acutely symptomatic individuals, surgical resection is the recommended intervention, and cerebrospinal fluid diversion may also be necessary. For growing but otherwise asymptomatic SEGA, either surgical resection or medical therapy with mTOR inhibitors can be effective. Shared decision-making with the patients or their parents in selecting the best treatment option should take the following considerations into account: risk of complications or adverse effects, cost of treatment, expected length of treatment, and potential impact on TSC comorbidities. Patients with unilateral, single, gross total resectable SEGA without individual risk factors or other comorbidities preferentially may benefit from surgery, whereas patients with multisystem disease or multiple or infiltrating SEGA lesions that are not amenable to gross total resection may favor mTOR inhibitor treatment.

Optimal outcome is associated with early detection and treatment, so surveillance by MRI should be performed every 1-3 years in all individuals with TSC until the age of 25 years. The frequency of scans within the recommended range of every 1-3 years should be clinically determined, with scans performed more frequently in those asymptomatic SEGA

patients who are younger, whose SEGA are larger or growing, or who are developmentally or cognitively disabled such that they cannot reliably report subtle symptoms.

Individuals without SEGA by the age of 25 years do not need continued surveillance imaging, but those with asymptomatic SEGA present in childhood should continue to be monitored by MRI for life because of the possibility of growth. There is insufficient evidence to determine the recommended frequency of MRI surveillance in this latter group, but important clinical factors that would favor shorter intervals include SEGA with proximity to foramen of Monro, large size, or recently discovered. However, once stability is clearly established, it may be possible to increase the interval of surveillance monitoring over time.

Strong evidence demonstrates superior efficacy for the treatment of infantile spasms with vigabatrin in patients with TSC; therefore, vigabatrin should be first-line treatment. However, the prescribing clinician should be aware of possible side effects, particularly possible retinal toxicity, and how to monitor for these. Adrenocorticotropin hormone (ACTH) can be used as second-line therapy if treatment with vigabatrin fails.

Routine EEG is recommended in individuals with known or suspected seizure activity, but frequency should be determined by clinical need rather than a specific defined interval. If changes in sleep, behavior, or cognitive or neurological function are not explained by routine EEG, 24-hour video EEG should be considered to assess for unrecognized or subclinical seizure activity.

Early epilepsy treatment may be of benefit in infants and children during the first 24 months of life, with or without clinical manifestations. Other than for infantile spasms in TSC, there is little evidence to guide specific anticonvulsant treatment. In general, this should follow that of other epilepsies, including refractory epilepsy. Epilepsy surgery and vagus nerve stimulation may be considered for medically refractory TSC patients, but evaluation should take place at epilepsy centers with experience and expertise in TSC.

Given that the physical features of TSC such as SEGA, epilepsy, or renal failure may present with TAND-like behaviors, sudden and rapid changes in TAND should prompt an urgent overall physical workup in such individuals. After detailed initial assessment upon diagnosis, it is imperative to continue to monitor for features of TAND and their impact on daily living through basic questioning and screening procedures at each follow-up clinic visit, with a minimum frequency of once per year. Any areas of concern identified at routine TAND assessment should be followed up with more detailed evaluations by the appropriate developmental, neuropsychological, mental health, behavioral, and educational specialists and coordinated by the TSC expert team. In addition to screening at each clinical visit,

comprehensive, formal evaluations for TAND by an expert team should be performed at key scheduled time points: during the first 3 years of life (0-3 year evaluation), preschool (3-6 year evaluation), before middle school entry (6-9 year evaluation), during adolescence (12-16 year evaluation), and in early adulthood (18-25 year evaluation). In later adulthood, evaluations should be performed as clinical challenges emerge or based on TAND screening. More frequent specialty evaluations or treatment/interventions may be needed if annual screening reveals areas of concern. Several studies are under way to investigate the use of mTOR inhibitors as treatment for aspects of TAND but to date there is insufficient evidence to support the use of mTOR inhibitors. Clinical teams should therefore use evidence-based principles to guide individualized therapeutic decisions for best treatment of TAND, such as autism spectrum disorder, attention deficit hyperactivity disorder, and anxiety in patients with TSC.

Kidney

For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is currently recommended as the most effective first-line therapy in the short term.

The demonstrated tolerability so far to date is far preferable to the renal damage caused by angiomyolipoma progression as well as surgical and embolic/ablative therapies, though studies are still needed to confirm long-term benefits and safety.

Annual clinical assessment of renal function and hypertension is required. Blood pressure control is also critical, so accurate measurement of blood pressure for patients is crucial, using age-specific criteria for children. Patients with hypertension should be treated with an inhibitor of the renin-aldosterone-angiotensin system as first line therapy, but in those treated with an mTOR inhibitor regular renal function and proteinuria monitoring is recommended at minimum every 6 months.

Imaging to diagnose polycystic disease, renal cell carcinoma or other tumors, and changes in angiomyolipoma should also be performed. MRI, often performed at the same time as brain surveillance imaging, is the preferred imaging modality, but if MRI is not available, CT or ultrasound can still provide useful information. Selective embolization followed by corticosteroids, kidney-sparing resection, or ablative therapy are acceptable second-line therapy for asymptomatic angiomyolipomas. For acute hemorrhage, embolization followed by corticosteroids is more appropriate. Nephrectomy is to be avoided because of the high incidence of complications and increased risk of chronic kidney disease stage 3-4, renal

failure, and the poor prognosis that results from chronic kidney disease. Fat-poor angiomyolipomas are not uncommon in patients with TSC, but if there is doubt and lesions are growing faster than 0.5 cm per year, a needle biopsy using a sheath technique or an open biopsy may be considered.

Lung

In individuals at risk for LAM, typically females 18 years of age and older, history at each clinical examination should inquire for symptoms of exertional dyspnea and shortness of breath. In patients with no clinical symptoms and no evidence of lung cysts on their baseline HRCT, repeat HRCT imaging should be performed every 5-10 years, using low radiation imaging protocols when available. Once cysts are detected, pace of TSC-LAM progression should be determined via HRCT testing every 2-3 years accompanied by annual pulmonary function testing and 6-minute walk test. If many cysts or other evidence of advanced TSC-LAM are present, pulmonary function testing and HRCT may be needed as frequently as every 3-6 months to assist with treatment decision-making.

In select LAM patients with moderate-to-severe lung disease or rapid progression, treatment with an mTOR inhibitor may be used to stabilize or improve pulmonary function, quality of life, and functional performance. TSC-LAM patients are candidates for lung transplantation, but it is important to note that antirejection medications may lower seizure threshold and seizure medications may interfere with antirejection medications. TSC comorbidities could also impact transplant suitability.

Skin and teeth

A skin survey should be performed annually, with focus on rapidly changing or symptomatic (problematic or functionally impacting) lesions and using pathological evaluation when required for diagnosis. Early intervention is imperative for bleeding, symptomatic, or potentially disfiguring TSC skin lesions. There is insufficient evidence to guide choice of treatment and case reports and case series document successful use of surgical excision, lasers, and topical mTOR inhibitors.

For TSC-associated dental lesions and oral fibromas, periodic oral evaluation should be performed every 3-6 months, consistent with surveillance recommendations for all individuals in the general population. Periodic preventive measures as well as oral hygiene education are an important part of patient management. Bony jaw lesions (asymmetry, asymptomatic swelling, or abnormal tooth eruption), when present, should be evaluated with a

panoramic radiograph and treated with surgical excision or curettage if symptomatic. Enamel defects (dental pits) can be treated with restorative treatments if the patient is at high cavity risk, although they rarely cause symptoms or an increased incidence of dental decay. Oral fibromas should be excised surgically if symptomatic or if interfering with oral hygiene. Oral fibromas may recur once excised; therefore, periodic oral evaluation is encouraged.

Heart

Until regression of cardiac rhabdomyomas is documented, follow-up echocardiogram should be performed every 1-3 years in asymptomatic patients. In addition, 12-lead ECG is recommended at minimum every 3-5 years to monitor for conduction defects. In patients with clinical symptoms, additional risk factors, or significant abnormalities on routine echocardiogram or ECG, more frequent interval assessment may be needed.

Eye

In individuals with no identified ophthalmologic lesions or vision symptoms at baseline, reevaluation is necessary only if new clinical concerns arise. Otherwise, annual evaluation is recommended. For patients on vigabatrin, ophthalmologic evaluation every 3 months is recommended by the United States Food and Drug Administration, although utility of such frequent assessment is questioned, especially in the young and those with developmental disabilities that limit the extent of ophthalmologic evaluation that can be performed. Thus, even in these populations, annual ophthalmologic evaluation is considered sufficient.

Other

There is limited, low-level evidence to guide recommendations for gastrointestinal, endocrine, and other hamartomatous lesions associated with TSC. Follow-up imaging to ensure stability of these lesions, when present, is recommended. Biopsy of suspicious lesions is recommended only when lesions are unusually large, growing, functional, symptomatic, multiple, or exhibit other suspicious characteristics.

3. Coordination of care and other clinical considerations in patients with TSC

TSC is a heterogeneous genetic disorder with variable expression and thus its clinical presentations are protean. The primary pathology of concern is also different depending on the age of the affected individual. The involvement of multiple organ systems, at different

stages in life, presents major difficulties in locating and identifying the expertise to comprehensively manage the medical care of individuals with TSC.

As clinical knowledge of the disease improves, the current recommendations will have to be updated periodically.