Tuberous Sclerosis Alliance

WE'LL GIVE EVERYTHING. BUT UP.

Tuberous Sclerosis Alliance and Tuberous Sclerosis Complex Clinics

Scope of Relationship Policy

ROLE OF THE TSC CLINIC

A Tuberous Sclerosis Complex (TSC) Clinic serves as the primary center for diagnosis, surveillance, and management of TSC in children and adults. The clinic model may range from a single to multi-specialty practice of board-certified healthcare providers with expertise in a specialty area related to TSC. The Clinic is expected to provide multidisciplinary care for children and adults with TSC through their clinic or referral network of specialists within their institution or partnering health systems. The TSC Clinic Guidelines describe the standards that a clinical practice should meet to be recognized by the TS Alliance as a TSC Clinic.

1. The TS Alliance strongly encourages the TSC Clinic healthcare providers to:

    a. Follow the current diagnostic criteria and recommendations for screening and follow-up[1] care of individuals with TSC.

    b. Stay abreast of the latest treatments for the various aspects of TSC.

    c. Publish research results in peer-reviewed medical journals and publications and provide the TS Alliance with a reprint.

    d. Partner with the local TS Community Alliance and/or Community Support Group to promote awareness of TSC and associated issues by participating in TS Alliance-sponsored events, such as local public relations events, medical conferences, "meet-the-expert" gatherings, and parent support group meetings.

    e. Partner with the local TS Community Alliance to provide educational materials for patients, their families, lay persons, medical and allied health care professionals.

[1] Appendix A: 2012 Diagnostic Criteria Table
Appendix B; Northrup, H., et al., Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference (2013) Pediatric Neurology
Krueger, D.A., et al., Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference (2013) Pediatric Neurology

2. Other provisions for maintaining a relationship in good-standing with TS Alliance:

    a. The TSC Clinic Director/Co-Director will maintain a professional conduct in accordance with their institutional policy

        i. If the TS Alliance becomes aware of any serious type of professional misconduct, which is under inquiry by the institution, the TSC Clinic Director or Co-Director (if applicable) will be asked to name a colleague to temporarily assume his/her role during the inquiry period.

        ii. During the inquiry period, the TSC Clinic designation will be placed on provisional status.

    b. The TSC Clinic Director/Co-Director will maintain TSC clinic designation by:
        i. Completing the TSC Clinic Update Form annually.

        ii. Notifying the TSC Clinic Liaison at jnakagawa@tsalliance.org or 240-638-4654 or 301-562-9890 if there are changes in Clinic Director/Co-Director or Coordinator during the interval period or whenever issues develop at the clinic, which are related to the TS Alliance or Community Alliance.

    c. The TSC Clinic will not solicit the Community Alliance leadership team to raise funds on behalf of their clinic.

    d. The TSC Clinic Director will serve as a resource for a new clinic starting up in another region by providing advice (if asked) about how they navigated through their institution to start their own clinic (i.e. What did or did not work).

ROLE OF THE TS ALLIANCE

The TS Alliance recognizes that the coordinated care that individual's receive at a recognized TSC Clinic plays a vital part in serving the organization's mission. As such, the TS Alliance will provide the following:

1. Marketing

   a. The TS Alliance will provide notice to area constituents about the TSC Clinic in a variety of ways. The scope of marketing is limited to three areas:
      - Targeted mailings to TS Alliance constituents;
      - Articles about the TSC Clinic in the TS Alliance quarterly magazine, *Perspective*; and
      - Information about the TSC Clinic on the TS Alliance Web site (http://www.tsalliance.org)

   b. The TS Alliance will partner with the TSC Clinic to distribute information about the clinic so that the TSC Clinic may serve as a source for consultations and referrals for individuals with TSC and their healthcare providers.

2. Business Resources

   a. Upon request, the TS Alliance will provide a sample TSC Clinic business plan, budget template, and job description for the nurse coordinator position.

   b. The TS Alliance believes that communication with other clinics and specialists who specialize in the care of individuals with TSC is important. Upon request, the TS Alliance will provide a list of other TSC Clinic Directors and their contact information.

   c. In addition, the TS Alliance will initiate contact between the clinic and the chair of the local TS Alliance volunteer branch ("Community Alliance"), if one exists in that area.

   d. Finally, TS Alliance print materials will be provided to the TSC Clinic. These materials include, but are not limited to informational brochures and the TS Alliance magazine, *Perspective.*

3. Ongoing Education, Research Opportunities & Support

   a. Education
      i. Up-to-date information on the diagnosis, care and treatment of TSC will be provided by the TS Alliance through its Web site, Perspective magazine, and other electronic and print materials.

ii. Information about continuing medical education opportunities will be posted on the TS Alliance website and by email when available.

b. Research Opportunities & Support

i. Funding opportunities are available through the TS Alliance Grants Program (http://www.tsalliance.org/researchers/grants-and-funding/))

ii. TSC Clinics in good-standing are eligible to participate in two TS Alliance supported research projects contingent on availability of funds

(a) TSC Natural History Database Project
In 2006, the TS Alliance launched the TSC Natural History Database, a web-based central research repository for detailed information about individuals with TSC. The TS Alliance conducts this project through the TS Alliance network of TSC Clinics.

(b) TSC Biosample Repository Project
In 2015, the TS Alliance established a TSC Biosample Repository to serve as a national resource providing a centralized, standardized source of high quality, well-documented human biospecimens for TSC research.

Original Scope of Relationship approved by clinic committee 1/22/2002
Modified 10/27/2003 when clinic committee approved the "fund raising policy"
Modified and approved by clinic & executive committee, March 2006
Modified 04/05/2010, approved by science & medical committee, 4/12/2010
Approved by Executive Committee, May 7, 2010
Approved by Board of Directors, June 16, 2010
ModifiedAugust 2013 and approved by science and medical committee and Board of Directors, October 4, 2013
Modified August 2015 and approved by science and medical committee and Board of Directors, October 24, 2015
Modified 05/26/2017 and approved by science and medical committee June 28, 2017 and by Executive Committee, July 7, 2017.

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Appendix A: DIAGNOSTIC CRITERIA

In 2012, the International Tuberous Sclerosis Consensus Conference reviewed prevalence and specificity of TSC-associated clinical manifestations and updated the TSC diagnostic criteria from 1998. Clinical features of TSC continue to be a principal means of diagnosis but include additional clarification and simplification. In addition, TSC may now be diagnosed via genetic testing. The new clinical and genetic diagnostic criteria of 2012 are summarized below.

Clinical Criteria

MAJOR FEATURES		MINOR FEATURES	
1	Hypomelanotic macules (≥3, at least 5mm diameter)	1	"Confetti" skin lesions
2	Angiofibromas (≥3) or fibrous cephalic plaque	2	Dental enamel pits (≥3)
3	Ungual fibromas (≥2)	3	Intraoral fibromas (≥2)
4	Shagreen patch	4	Retinal achromic patch
5	Multiple retinal hamartomas	5	Multiple renal cysts
6	Cortical dysplasias (≥3)*	6	Nonrenal hamartomas
7	Subependymal nodules (≥2)		
8	Subependymal giant cell astrocytomas		
9	Cardiac rhabdomyoma		
10	Lymphangioleiomyomatosis (LAM)**		
11	Anigiomyolipomas (≥2)**		

* Includes tubers and cerebral white matter radial migration lines.

** A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a Definite Diagnosis.

DEFINITE DIAGNOSIS: 2 major features or 1 major feature with 2 minor features
POSSIBLE DIAGNOSIS: Either 1 major feature, 1 major and 1 minor, or ≥ 2 minor features

Genetic Criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a Definite Diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out of frame insertion or deletion or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a Definite Diagnosis of TSC. Note that approximately 15% of individuals with TSC have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of Clinical Diagnostic Criteria to diagnose TSC.

Appendix B: DIAGNOSTIC CRITERIA PUBLICATIONS

Additional peer-reviewed, published consensus papers are available free of charge with open access to anyone at www.tsalliance.org/consensus

Pediatric Neurology 49 (2013) 243–254

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

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

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex is highly variable in clinical presentation and findings. Disease manifestations continue to develop over the lifetime of an affected individual. Accurate diagnosis is fundamental to implementation of appropriate medical surveillance and treatment. Although significant advances have been made in the past 15 years in the understanding and treatment of tuberous sclerosis complex, current clinical diagnostic criteria have not been critically evaluated or updated since the last clinical consensus conference in 1998. **METHODS:** The 2012 International Tuberous Sclerosis Complex Consensus Group, comprising 79 specialists from 14 countries, was organized into 12 subcommittees, each led by a clinician with advanced expertise in tuberous sclerosis complex and the relevant medical subspecialty. Each subcommittee focused on a specific disease area with important diagnostic implications and was charged with reviewing prevalence and specificity of disease-associated clinical findings and their impact on suspecting and confirming the diagnosis of tuberous sclerosis complex. **RESULTS:** Clinical features of tuberous sclerosis complex continue to be a principal means of diagnosis. Key changes compared with 1998 criteria are the new inclusion of genetic testing results and reducing diagnostic classes from three (possible, probable, and definite) to two (possible, definite). Additional minor changes to specific criterion were made for additional clarification and simplification. **CONCLUSIONS:** The 2012 International Tuberous Sclerosis Complex Diagnostic Criteria provide current, updated means using best available evidence to establish diagnosis of tuberous sclerosis complex in affected individuals.

Keywords: diagnostic criteria, clinical features, tuberous sclerosis

Pediatr Neurol 2013; 49: 243-254

See related articles on pages 223 *and* 255.

Introduction

Tuberous sclerosis complex (TSC) was initially described approximately 150 years ago by von Recklinghausen in 1862.[1] TSC is an extremely variable disease that can affect virtually any organ in the body. The most common findings are benign tumors in the skin, brain, kidneys, lung, and heart that lead to organ dysfunction as the normal parenchyma is replaced by a variety of cell types.[2] Disease manifestations in different organ systems can vary widely between even closely related individuals and the protean nature of the condition can make clinical diagnosis challenging. TSC was underdiagnosed until the 1980s when individuals with less severe manifestations of the disease began to be recognized. Before the 1980s, incidence rates for TSC were quoted at between 1/100,000 and 1/200,000.[3,4] Recent studies estimate a frequency of 1/6000 to 1/10,000 live births and a population prevalence of around 1 in 20,000.[5,6] Although TSC was recognized to be a genetic disease more than 100 years ago,[7] the underlying molecular etiology was not unraveled until the discovery of the two causative genes, *TSC1* and *TSC2*.[8,9]

The second International Tuberous Sclerosis Complex Consensus Conference was held June 13-14, 2012, in Washington, DC. Seventy-nine experts (Appendix) from 14

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TABLE.
Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)†
11. Angiomyolipomas (≥2)†

Minor features

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

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

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

* Includes tubers and cerebral white matter radial migration lines.

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

countries convened to finalize diagnostic, surveillance, and management recommendations for patients with TSC. A summary report of the current, updated surveillance and management recommendations for the standardized, optimal clinical management of patients with TSC is provided separately.[10] One of the major goals of the conference was to revisit the clinical diagnostic criteria published subsequent to the first International TSC Consensus Conference in 1998.[11] Since 1998, one additional manuscript regarding the diagnostic criteria has been published that was designed to provide more guidance to practitioners by including pictures of the major and minor findings.[12] At the 2012 meeting, the most significant change recommended to the diagnostic criteria was the incorporation of genetic testing. Although the *TSC1* and *TSC2* genes were discovered before the 1998 conference, molecular testing was not widely available at that time. Molecular testing of the *TSC1* and *TSC2* genes yields a positive mutation result for 75-90% of TSC-affected individuals categorized as "definite" by the 1998 Consensus Conference Clinical Diagnostic Criteria.[2] The use of molecular testing in medicine has expanded greatly since the 1990s, becoming widely accepted as invaluable in the diagnosis of diseases with a genetic basis. Utilization of genetic testing for TSC was addressed along with refinement of clinical criteria.

Genetic diagnostic criteria

Comprehensive and reliable screens for *TSC1* and *TSC2* mutations are well-established, and many pathogenic mutations have been identified (www.lovd.nl/TSC1, www.lovd/TSC2). The recommendation of the Genetics Panel was to make identification of a pathogenic mutation in *TSC1* or *TSC2* an independent diagnostic criterion, sufficient for the diagnosis or prediction of TSC regardless of the clinical findings (Table part A). This will facilitate the diagnosis of TSC in some, particularly young individuals, allowing earlier implementation of surveillance and treatment with potential for better clinical outcomes. A "pathogenic" mutation was defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the TSC1 or TSC2 proteins (e.g., nonsense mutation or frameshift mutations, large genomic deletions) or is a missense mutation whose effect on protein function has been established by functional assessment.[13,14] *TSC1* and *TSC2* genetic variants whose functional effect is less certain are not definitely pathogenic and would not be considered a major diagnostic criterion. A significant fraction (10-25%) of TSC patients have no mutation identified by conventional genetic testing. Therefore, a normal result does not exclude TSC. Nonetheless, if the mutation in an affected relative is known, testing for that mutation has very high predictive value for family members. Assembled experts at the Consensus Conference agreed with the recommendation that identification of a pathogenic mutation in *TSC1* or *TSC2* is an independent diagnostic criterion.

Clinical diagnostic criteria

In addition to diagnosis by genetic analysis, the clinical diagnostic criteria used to establish the diagnosis of TSC were also reviewed at the conference. Special attention was

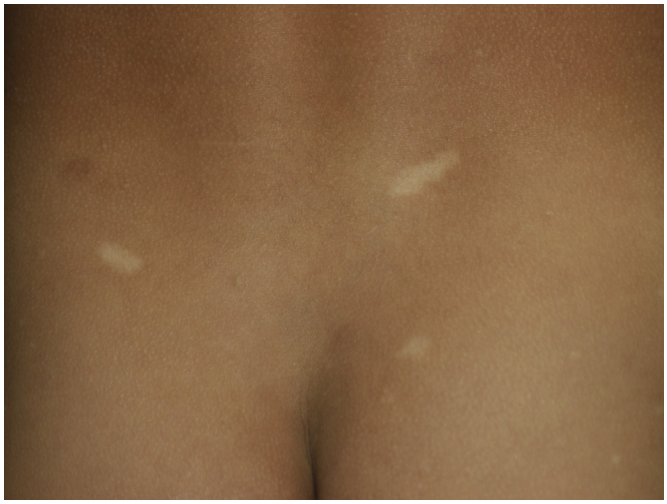

FIGURE 1.
Three hypopigmented macules the lower back/upper buttocks.

given to evaluate the sensitivity and specificity of clinical findings with respect to TSC diagnosis. Panels were assigned to the following focus areas for this process, and specific attempts were made to refine and simplify the clinical diagnostic criteria that included 11 major features and nine minor features according to the 1998 Conference. The individual panels were organized as follows: (1) dermatology and dentistry; (2) ophthalmology; (3) brain structure, tubers, and tumors; (4) epilepsy; (5) TSC-associated neuropsychiatric disorders; (6) cardiology; (7) pulmonology; (8) nephrology; (9) endocrinology; (10) gastroenterology; and (11) care integration. The recommendations of each panel were presented to the entire congress for discussion, modification if necessary, and final approval. The new, updated diagnostic clinical criteria now include 11 major features and six minor features (Table part B).

Dermatologic and dental features

The dermatology and dental panel recommended retaining the existing mucocutaneous criteria and suggested minor changes regarding their number, size, or nomenclature. The major features (with changes italicized) include: (1) hypomelanotic macules (≥3, *at least 5-mm diameter*), (2) angiofibromas (≥3) or *fibrous cephalic* plaque, (3) ungual fibromas (≥*2*), and (4) shagreen patch. The revised minor features include: (1) "confetti" skin lesions,

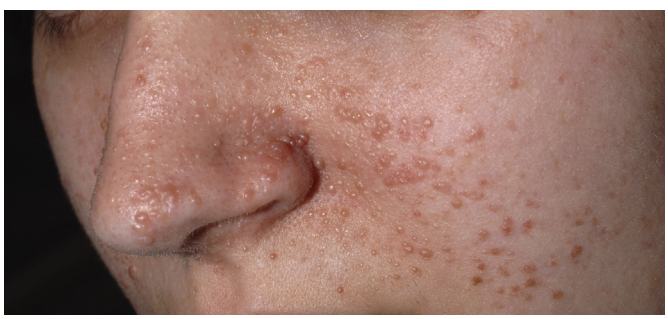

FIGURE 2.
Facial angiofibromas.

(2) dental enamel pits (≥*3*), and (3) *intraoral* fibromas (≥2). Nearly 100% of individuals affected with TSC have skin or dental findings of the disease that are easily detectable on physical examination. It is therefore important that these features be highlighted to aid in bringing TSC patients to medical attention.

Hypomelanotic macules

Hypomelanotic macules are a significant feature because they are observed in about 90% of individuals with TSC, they typically appear at birth or infancy, and they may be a presenting sign of TSC (Fig 1).[15-21] At the 1998 Consensus, it was stipulated that an individual must have three or more hypopigmented macules, because one or two lesions are relatively common in the general population.[22,23] In the updated criteria, it was recommended that hypomelanotic macules meet a size requirement of at least 5-mm diameter to distinguish hypomelanotic macules from smaller and more numerous "confetti" lesions. In addition, it was suggested that poliosis, circumscribed areas of hypomelanosis of hair, be included in the count of hypomelanotic macules.

Angiofibromas or fibrous cephalic plaque

Facial angiofibromas occur in about 75% of TSC patients (Fig 2),[15,16,18,21] with onset typically between ages 2 and 5 years.[24] Although most TSC patients have several facial angiofibromas, milder cases of TSC with limited facial angiofibromas have been described. However, because one or two isolated sporadic lesions may be observed in the general population,[25] the presence of at least three facial angiofibroma lesions is now recommended to meet this major criteria for TSC. Multiple facial angiofibromas have also been observed in Birt-Hogg-Dubé (BHD) syndrome, and multiple endocrine neoplasia type 1 (MEN1).[26,27] In these conditions, the age of onset of angiofibromas is later than in TSC. Therefore, multiple facial angiofibromas remains a major feature for diagnosis when their onset occurs in childhood. In the unusual circumstance when angiofibromas have their onset in adulthood, they should be considered as a minor feature and the differential diagnosis expanded to include BHD and MEN1. When angiofibromas are few or later in onset, a skin biopsy may be required to confirm the clinical diagnosis.

The forehead plaque is observed in about 25% of TSC patients and this feature was paired with angiofibromas for the diagnostic criteria in 1998 (Fig 3A). The panel recommended changing the terminology from forehead plaque to fibrous cephalic plaque. This term was created to increase awareness that these fibrous plaques, although often located unilaterally on the forehead, may occur on other parts of the face or scalp (Fig 3B). Fibrous cephalic plaques, which are histologically similar to angiofibromas, may be the most specific skin finding for TSC.

Ungual fibromas

Ungual fibromas were retained as a major feature (Fig 4). The previous designation as "nontraumatic" was eliminated because recall of trauma may be unreliable and trauma may play a role in the formation of TSC ungual fibromas.[28] This designation was replaced with the requirement that they be

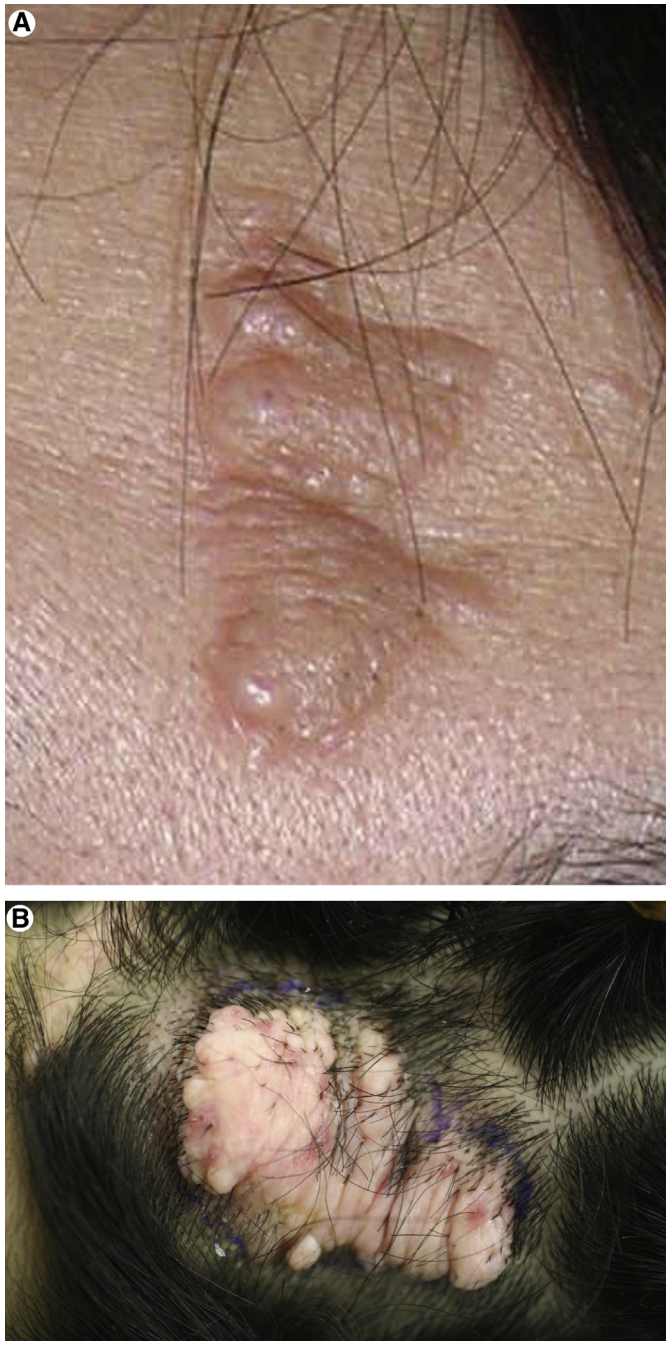

FIGURE 3.
(A) Fibrous plaque on face. (B) Fibrous plaque on scalp.

multiple (≥2) because ungual fibromas that occur in the general population in response to trauma are usually solitary.[29] The redundant phrase "ungual and periungual fibromas" was replaced with "ungual fibromas" used to encompass both periungual and subungual fibromas. Ungual fibromas are less common than some of the other TSC skin findings, with a frequency of about 20% overall but as high as 80% in older adults.[15,16,28] The greater frequency in adults is due to later onset, typically in the second decade or later.[18,21] Therefore, their utility in diagnosis is usually limited to adolescents and adults.[24]

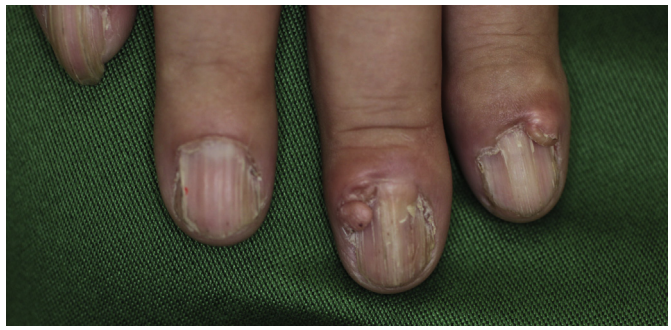

FIGURE 4.
Ungual fibromas.

Shagreen patch

The presence of a shagreen patch was retained as a major feature, but the criterion was updated by deletion of "connective tissue nevus" because this term encompasses a variety of skin lesions with excessive dermal connective tissue that are not necessarily associated with TSC. Shagreen patches commonly take the form of large plaques on the lower back that have a bumpy or orange-peel surface, and this clinical appearance is nearly always specific for TSC (Fig 5). Smaller collagenomas on the trunk exhibit the same histologic changes as shagreen patches but are less specific for TSC because they may also occur as an isolated finding or in other genetic syndromes including MEN1,[26] BHD,[30] and Cowden syndrome.[31] Shagreen patches are observed in about 50% of individuals with TSC and typically have their onset in the first decade of life.[15,16,18,21]

"Confetti" skin lesions

Confetti skin lesions are numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs.[31] Their frequency varies widely in different studies, from 3% in children to about 58% overall.[15,24] Despite their relatively low frequency, confetti lesions may still be useful for diagnosis and they were retained as a minor feature. Their utility in adults is limited by the fact that many adults in the general population develop similar-appearing lesions as a consequence of chronic sun exposure. In such cases, the diagnosis of confetti lesions may be supported by a history of onset in

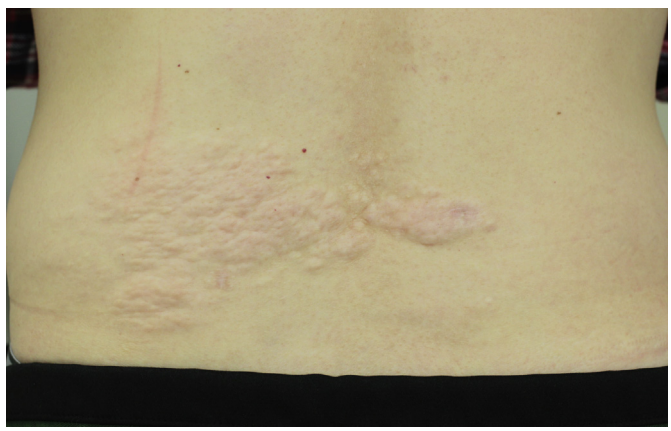

FIGURE 5.
Shagreen patch on dorsolumbar area of back.

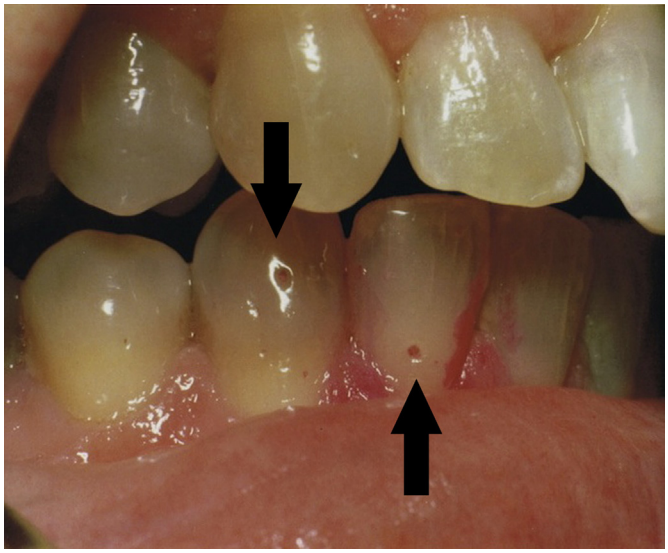

FIGURE 6.
Dental pits indicated by arrows.

the first decade of life or by asymmetric involvement of one body region over another.

Dental enamel pits

Dental enamel pits, previously included as a minor feature listed as "multiple, randomly distributed pits in dental enamel" were again included as a minor feature (Fig 6). The designation was simplified to dental enamel pits ($\geq$3) for the entire dentition. Dental pits are much more common in TSC patients than the general population, with Mlynarczyk reporting 100% of adult TSC patients (n = 50) as having pitting compared with 7% of 250 adult control subjects.[32] Because they are relatively common in the population, they are listed as a minor feature.

Intraoral fibromas

Gingival fibromas have long been associated with TSC and were listed as a minor feature in the 1998 consensus document (Fig 7). They occur in about 20-50% of individuals with TSC, with greater frequency in adults than children.[15,21,33,34]

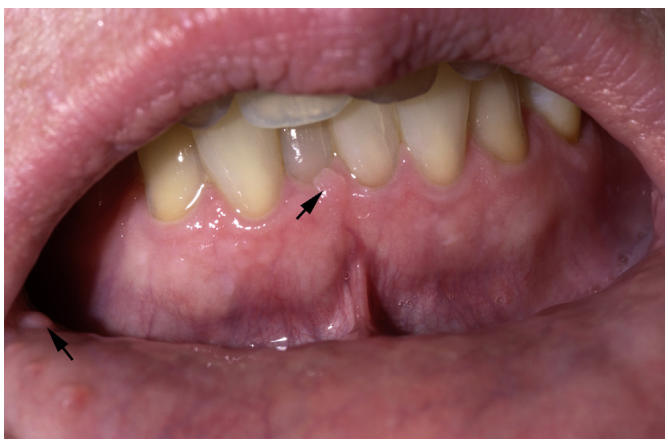

FIGURE 7.
Intraoral fibromas (gingival and labial indicated by arrows).

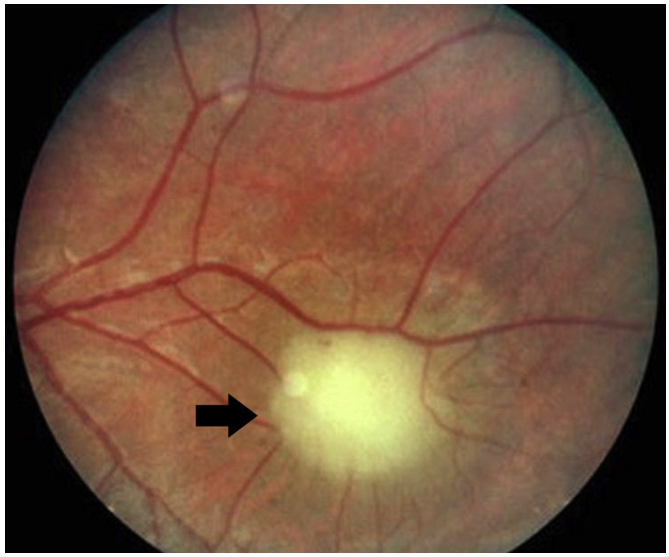

FIGURE 8.
Retinal hamartoma indicated by arrow.

Fibromas in TSC may also be observed on the buccal or labial mucosa and even the tongue,[34] so this criterion was modified to include fibromas at other intraoral sites. A stipulation was added for the presence of two or more intraoral fibromas because solitary oral fibromas may occur in the general population, particularly on the tongue or buccal mucosa along the bite line from repeated trauma.[35,36]

Bone cysts

Bone cysts were included in the 1998 criteria as a minor feature of TSC. Because of the lack of specificity for TSC and because the feature is rarely identified in the absence of additional TSC clinical features, a decision was made to delete "bone cysts" from the clinical diagnostic criteria.

Ophthalmologic features

Multiple retinal hamartomas

The finding of more than one retinal hamartoma was determined to be significant and specific enough to retain as a major feature (Fig 8). These lesions have similar histologic features to the tubers located in the brains of TSC patients. They are observed in 30-50% of TSC patients and it is not unusual to have multiple lesions in the same patient.[37,38] The prevalence of retinal hamartomas in non-TSC populations is not known, but rare case reports have been made and a recent series of 3573 healthy term newborns identified only two cases of astrocytic hamartomas in that population.[39] Fortunately, these lesions in TSC usually do not cause problems with vision and are a good marker for the disease, particularly in young children who might not yet have many other features.

Retinal achromic patch

The presence of a retinal achromic patch was determined at the 1998 conference to constitute a minor feature (Fig 9). The assembled experts at the 2012 conference concurred with the previous recommendation. Retinal achromic patches are basically areas of hypopigmentation on the retina. These patches have been noted to occur in 39% of TSC

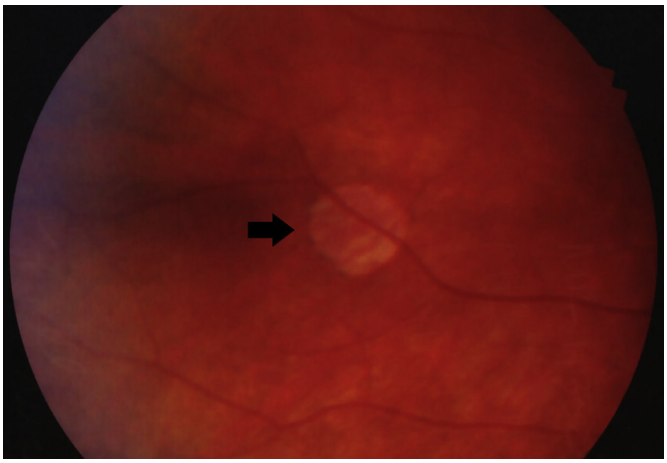

FIGURE 9.
Retinal achromic patch indicated by arrow.

patients.[38,40] Incidence in the general population is estimated at 1 in 20,000.[41]

Central nervous system features

Because medical problems relating to the brain result in the greatest morbidity and mortality in TSC, three panels at the 2012 Consensus Conference devoted their efforts to central nervous system–related findings of TSC. The panels were: (3) brain structure, tubers, and tumors; (4) epilepsy; and (5) TSC-associated neuropsychiatric disorders. The three panels were in agreement that there should be three neurological findings categorized as major features and that the minor feature of cerebral white matter radial migration lines should be subsumed into one of the major features as reviewed in the following sections. Thus, findings relating to the central nervous were streamlined.

Cortical dysplasias

Cortical dysplasias are congenital abnormalities caused, at least in part, when a group of neurons fail to migrate to the proper area of the brain during development. The cortical tubers observed in ~90% of TSC patients and the pathologic finding for which the disorder is named, are a type of focal cortical dysplasia. Cerebral white matter radial migration lines arise from a similar pathologic process as cortical tubers and other forms of cortical dysplasia and in TSC it is not unusual to find tubers and white matter migrational abnormalities together (Fig 10A). Both types of cortical dysplasia in TSC are commonly associated with intractable epilepsy and learning difficulties in TSC. The pathologic and clinical overlap between "cortical tuber" as a major feature and "cerebral white matter radial migration lines" as a minor feature in the 1998 diagnostic criteria were felt to no longer represent separate processes and are replaced with a single major feature in the new classification "cortical dysplasia." However, it is appreciated that a single area of focal cortical dysplasia or even two can be observed in an individual who does not have TSC; thus, in the new diagnostic criteria, multiple areas of focal cortical dysplasia count only as one major feature and additional clinical features are necessary to establish a definite diagnosis of TSC.

Subependymal nodules and subependymal giant cell astrocytomas

Subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA) will continue to represent two separate major features (Fig 10B). Both of these lesions were also included in the 1998 Consensus Conference Criteria as major features. Histologically, the two lesions are similar and both are relatively specific to TSC although not exclusive to the disorder. Subependymal nodules are benign growths that develop along the wall of the ependymal lining of the lateral and third ventricles. They are observed in 80% of TSC patients and often prenatally detected or at birth.[42] SEGAs

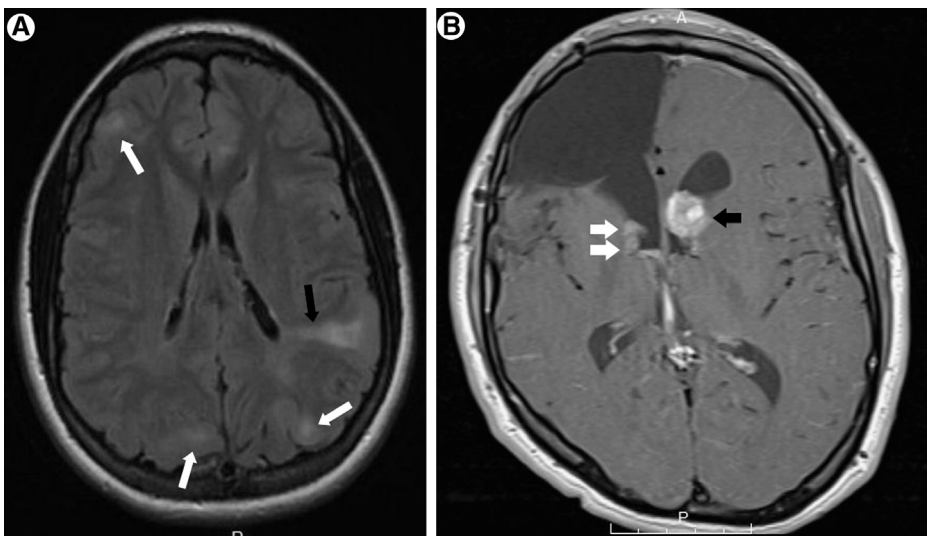

FIGURE 10.
(A) Axial magnetic resonance imaging (MRI) (T2 fluid-attenuated inversion recovery) of the brain, demonstrating cortical dysplasia (tubers and radial migration lines indicated by white and black arrows, respectively). (B) Axial MRI (T1 + contrast) of the brain, demonstrating subependymal nodules (left, two white arrows) and subependymal giant cell astrocytoma (right, black arrow). This patient also has undergone previous partial frontal lobectomy for epilepsy.

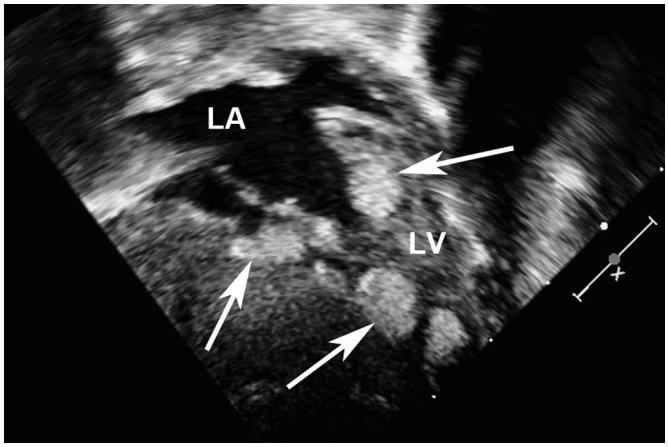

FIGURE 11.
Echocardiogram indicating cardiac rhabdomyomas (arrows).

have an incidence of 5-15% in TSC and may also be detected prenatally or at birth, although they are much more likely to arise during childhood or adolescence and it would be unusual for one to occur after the age of 20 years if not already previously present.[42] It is widely accepted that SEGAs typically arise from SEN, especially near the foramen of Monro. Although benign and typically slow-growing, they can cause serious neurologic compromise including obstructive hydrocephalus. Both SENs and SEGAs may progressively calcify over time.[42]

Cardiovascular features

The cardiology panel recommended retaining "cardiac rhabdomyoma" as a major feature and determined that there is no need to specify one versus more than one.

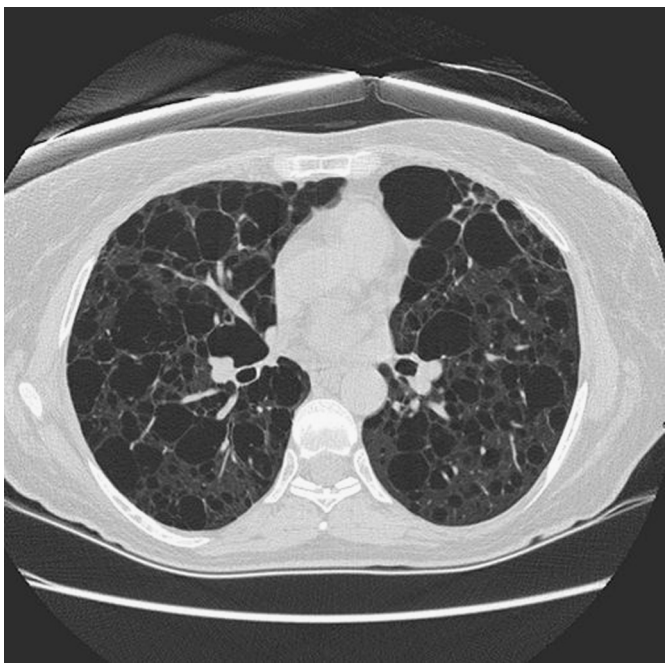

FIGURE 12.
Axial high-resolution chest computed tomography, demonstrating lymphangioleiomyomatosis.

Cardiac rhabdomyoma

Cardiac rhabdomyomas are benign tumors of the heart that are rarely observed in non-TSC–affected individuals (Fig 11). These lesions usually do not cause serious medical problems, but they are highly specific to TSC and often the first noted manifestation of disease, and therefore remain a major feature. Tumors are most frequently located in the ventricles, where they can compromise ventricular function and on occasion interfere with valve function or result in outflow obstruction.[43] These tumors are frequently observed in TSC-affected individuals during fetal life but after birth, they often regress and in some individuals may no longer be detectable by echocardiographic examination.[44,45] They are associated with cardiac arrhythmias including atrial and ventricular arrhythmia and the Wolff-Parkinson-White syndrome.

The prenatal presence of a cardiac rhabdomyoma is associated with a 75-80% risk of TSC, with multiple rhabdomyomas conveying an even higher risk.[46-48] Further, in the era preceding genetic testing, there was a $<$0.1% occurrence of cardiac rhabdomyoma in individuals not affected with TSC. Because they are frequently observed in fetal life, unlike other findings in TSC, they are important in bringing the patient to medical attention early in life. At that point, new interventions may be more likely to improve prognosis.

Pulmonary features

The pulmonology panel recommended retaining the finding of lymphangioleiomyomatosis (LAM) as a major feature of the clinical criteria to diagnose TSC. The other experts agreed with this recommendation.

Lymphangioleiomyomatosis

Histologically, LAM is associated with interstitial expansion of the lung with benign-appearing smooth muscle cells that infiltrate all lung structures.[49,50] Patients typically present with progressive dyspnea on exertion and recurrent pneumothoraces in the third to fourth decade of life. Cystic pulmonary parenchymal changes consistent with LAM are observed in 30-40% of female TSC patients (Fig 12), but recent studies suggest that lung involvement may increase with age such that up to 80% of TSC females are affected by age 40.[51] Cystic changes consistent with LAM are also observed in about 10-12% of males with TSC, but symptomatic LAM in males is very rare.[52,53] It is important to note that lung is rarely biopsied in TSC patients with pulmonary parenchymal changes, so it is possible that processes other than LAM may result in cystic lung disease in TSC patients. LAM is also diagnosed in individuals who do not have TSC, and is referred to as sporadic LAM (S-LAM).[49] In these patients, LAM is thought to occur through two somatic mutations in the *TSC2* gene, rather than through a germ line mutation and a "second-hit" somatic mutation that is typical for TSC.[54] That about one third of S-LAM patients have renal angiomyolipomas, another major feature in the diagnostic criteria for TSC, led to the conclusion by the 1998 consensus group that when both angiomyolipoma and LAM were present, other TSC features must be present for the diagnosis of TSC (status per current Consensus Conference discussed in next section). The

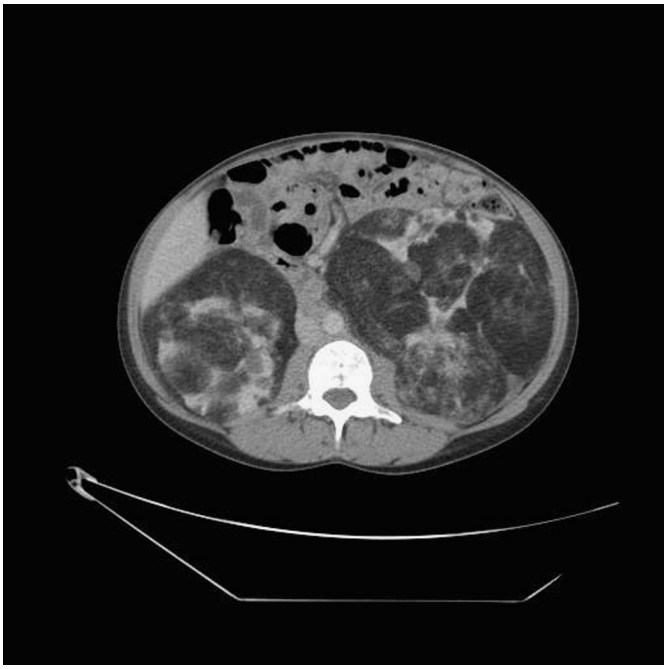

FIGURE 13.
Axial abdominal computed tomography, illustrating multiple bilateral renal angiomyolipomata. The darker areas are fat containing angiomyolipomatous tissue.

members of the pulmonology panel agreed with the principle that TSC diagnostic criteria must clearly differentiate S-LAM from TSC-LAM, and suggested the following modified language: "When angiomyolipomas and LAM are both present in a patient with suspected TSC, together they constitute only one major criterion."

The diagnosis of LAM as defined by the pulmonology panel is: (1) pathologic examination consistent with LAM, (2) characteristic as defined by the European Respiratory Society (ERS) criteria high-resolution chest computed tomography (HRCT) with profusion of cysts (>4) and no confounding comorbid conditions or exposures in a patient with at least one other major criteria for TSC (other than angiomyolipoma), or two other minor criteria, *OR* (3) characteristic or compatible (ERS criteria) HRCT in the setting of no confounding comorbid conditions or exposures, plus one of the following: abdominal or thoracic lymphangioleiomyomas, chylous pleural effusion, or chylous ascites.[49]

Other manifestations of tuberous sclerosis in the lung include multifocal micronodular pneumocyte hyperplasia (MMPH) and clear cell tumor of the lung. In MMPH, multiple pulmonary nodules composed of benign alveolar type II cells are found scattered throughout the lung. These lesions stain with cytokeratin and surfactant proteins A and B, but not with HMB-45, alpha smooth muscle actin, or hormonal receptors.[55] MMPH does not have known prognostic or physiologic consequences, although there have been at least two reports of respiratory failure associated with MMPH.[55,56] The precise prevalence of MMPH in patients with TSC is not known, but may be as high as 40-58%.[57,58] There is no gender restriction and MMPH may occur in the presence or absence of LAM in patients with TSC.[58] MMPH can be confused with atypical adenomatous hyperplasia, which is premalignant lesion that is not clearly associated with TSC. Clear cell tumor of the lung (CCSTL) is a rare and typically benign mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells. Together LAM, angiomyolipoma, and CCSTL constitute the major members of the PEComa family of lung tumors.[59] The members of the pulmonary subcommittee did not feel that the specificity of MMPH and CCSTL for TSC have been established with sufficient clarity to suggest their inclusion as diagnostic criteria.

Renal features

The nephrology panel attending the Consensus Conference agreed with deleting the designation of "renal" in the major feature "renal angiomyolipomas" to now use "angiomyolipomas ≥2" in the clinical diagnostic criteria. Angiomyolipomas have been identified in TSC patients in organs other than the kidney including the liver.[60] As a result, "angiomyolipomas (≥2)" was added to the major features. The nephrology panel recommended not using the abbreviation "AMLs" for angiomyolipomas. Although this abbreviation has been commonly used among individuals familiar with TSC, in most medical contexts it is more familiarly associated with acute myelocytic leukemia and thus introduces confusion across specialties. The nephrology panel also recommended retaining "multiple renal cysts" as a minor feature. This recommendation was accepted by the other panelists. Additionally, it was agreed that an individual who has LAM and renal angiomyolipomas but no other features of TSC does not meet criteria for a definite diagnosis because of the previously reviewed information regarding S-LAM.

Renal manifestations in TSC are an important source of morbidity and mortality. In the only publication assessing mortality associated with TSC,[61] renal problems in TSC were the second leading cause of premature death after severe intellectual disability. With advances in medical care, death in TSC from renal disease is much less likely; however, it continues to represent a significant medical burden to TSC patients.

Angiomyolipomas

Angiomyolipomas are benign tumors composed of vascular, smooth muscle, and adipose tissue (Fig 13).[62] These benign tumors are observed most commonly in TSC patients in the kidney but can occur in other organs. To be inclusive of angiomyolipomas in other organs, it was decided to delete "renal" and simply use the term "angiomyolipomas (N ≥ 2)" as a major recognized feature. Angiomyolipomas are a feature relatively specific to TSC. Fat-containing angiomyolipomas were observed in 80% of TSC patients, and fat-poor lesions are also common in patients with TSC, but occur in less than 0.1% of the general population.[63] Angiomyolipomas in the kidney can cause serious issues with bleeding because of its vascular nature and can lead to need for dialysis and even renal transplantation.[64]

Multiple renal cysts

Multiple renal cysts are not commonly observed in the general population,[65] but can be seen in TSC patients who

have a *TSC1* or *TSC2* mutation or as part of a contiguous gene deletion syndrome involving the *TSC2* and *PKD1* genes.[62] The *TSC2* and *PKD1* genes are immediately adjacent and transcribed in opposite directions on chromosome 16p13.3. Deletions involving both genes have been described in a small subset of TSC patients who have the TSC phenotype as well as an aggressive PKD phenotype.[66] Presence of multiple simple renal cysts in older individuals in the general population is well-described, thus the decision was made to specify multiple renal cysts and relegate this feature to the minor status. In cross-sectional studies the number of cysts in healthy people vary with age and standards have been derived to help diagnose specific cystic disease states.

Endocrine features

Limited findings of TSC have been reported in the endocrine system. Various kinds of hamartoma do occur in the endocrine system.[67] According to early reports, adrenal angiomyolipoma can be present in a quarter of TSC patients, but rarely, if ever, causes hemorrhage.[68-70] Thyroid papillary adenoma have been reported in TSC patients,[71,72] but did not cause thyroid dysfunction. There are rare case reports of other angiomyolipoma or fibroadenoma in the pituitary gland, pancreas, or gonads.[67] These tumors are considered as representing minor features under the designation "nonrenal hamartomas." The recommendation was made by the endocrinology panel to retain nonrenal hamartomas as a minor feature to include these findings in the endocrine system of TSC-affected individuals. It was speculated that neuroendocrine tumors might be slightly more prevalent in TSC patients.[67,73] However, neuroendocrine tumors are not hamartomas and are not considered part of the diagnostic criteria.

Gastrointestinal features

Similarly, gastrointestinal manifestations in TSC patients are fairly rare. Liver angiomyolipomas are reported in 10-25% of TSC patients,[74] and these lesions are included in the major features group under the heading "Angiomyolipomas" (discussed previously). Hamartomatous rectal polyps were included as a minor feature in the 1998 Diagnostic Criteria. It was decided because of the lack of specificity for TSC and because they are another type of "nonrenal hamartoma" that the specific designation of "hamartomatous rectal polyps" would be deleted from the minor criteria.

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Appendix. Members of the 2012 International TSC Consensus Group

Conference co-chairs:	Hope Northrup MD (Houston, Texas)
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TS Alliance representatives:	Steven Roberds PhD (Silver Spring, Maryland)
	Katie Smith (Silver Spring, Maryland)
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Original Article

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference☆

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex is a genetic disorder affecting every organ system, but disease manifestations vary significantly among affected individuals. The diverse and varied presentations and progression can be life-threatening with significant impact on cost and quality of life. Current surveillance and management practices are highly variable among region and country, reflective of the fact that last consensus recommendations occurred in 1998 and an updated, comprehensive standard is lacking that incorporates the latest scientific evidence and current best clinical practices. **METHODS:** The 2012 International Tuberous Sclerosis Complex Consensus Group, comprising 79 specialists from 14 countries, was organized into 12 separate subcommittees, each led by a clinician with advanced expertise in tuberous sclerosis complex and the relevant medical subspecialty. Each subcommittee focused on a specific disease area with important clinical management implications and was charged with formulating key clinical questions to address within its focus area, reviewing relevant literature, evaluating the strength of data, and providing a recommendation accordingly. **RESULTS:** The updated consensus recommendations for clinical surveillance and management in tuberous sclerosis complex are summarized here. The recommendations are relevant to the entire lifespan of the patient, from infancy to adulthood, including both individuals where the diagnosis is newly made as well as individuals where the diagnosis already is established. **CONCLUSIONS:** The 2012 International Tuberous Sclerosis Complex Consensus Recommendations provide an evidence-based, standardized approach for optimal clinical care provided for individuals with tuberous sclerosis complex.

Keywords: tuberous sclerosis, surveillance, treatment, management, guideline

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Introduction

The clinical manifestations of tuberous sclerosis complex (TSC) are highly diverse in both organ system involvement and severity. Any organ system can be involved, with some more prevalent during infancy and childhood and others more likely to affect individuals as adults.[1] Birth incidence is estimated to be 1:5800.[2] 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 and from childhood to adulthood on a regular basis and especially during the critical transition from pediatric to adult health care services.

In 1998, the National Institutes of Health sponsored the first Tuberous Sclerosis Complex Consensus Conference to develop recommendations for diagnosis and clinical management of patients affected by TSC.[3,4] At

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that time, the two known genes responsible for TSC cases had been identified but their function and molecular role were not yet known.[5,6] We now know that the *TSC1* and *TSC2* genes encode for hamartin (TSC1) and tuberin (TSC2), which form a regulatory complex responsible for limiting the activity of an important intracellular regulator of cell growth and metabolism known as mammalian target of rapamycin complex 1 (mTORC1) via inhibition of the small GTPase ras homolog enriched in brain (Rheb).[7] The functional relationship between TSC1/TSC2 and mTORC1 has led to important clinical advances in the use of mTORC1 inhibitors for the treatment of several clinical manifestations of TSC, including cerebral subependymal giant cell astrocytoma,[8-11] renal angiomyolipomas,[8,12,13] and pulmonary lymphangioleiomyomatosis (LAM).[8,13-15] Significant advances in imaging, surgery, interventional radiology, medical, and behavioral therapies have transformed TSC management since 1998.

The extent of medical advances in TSC and the need to standardize and optimize clinical care for individuals with TSC necessitated updating the diagnostic criteria and clinical management guidelines from 1998. In 2011, the International Tuberous Sclerosis Complex Consensus Conference was organized and sponsored by the Tuberous Sclerosis Alliance, a nonprofit patient advocacy group and member of Tuberous Sclerosis Complex International (TSCi). Identification of disease focus areas, participating clinical expert contributors, clinical questions to address, literature review process, and draft recommendations followed. On June 14-15, 2012, 79 experts from 14 countries convened in Washington, DC, to finalize diagnostic, surveillance, and management recommendations for patients with TSC. Finishing work and editing continued into early 2013. A summary report of revised diagnostic criteria for TSC is provided separately.[16] Here we summarize the updated surveillance and management recommendations for the standardized, optimal clinical management of patients with TSC.

Methods

Twelve subcommittees, each led by a clinician with advanced expertise in TSC and the relevant medical subspecialty, were organized to focus on specific disease focus topics that have important clinical management implications in TSC: (1) dermatology and dentistry; (2) nephrology; (3) pulmonology; (4) cardiology; (5) ophthalmology; (6) gastroenterology; (7) endocrinology; (8) genetics; (9) epilepsy; (10) TSC-associated neuropsychiatric disorders; (11) brain structure, tubers, and tumors; and (12) coordination of clinical care. Each subcommittee was charged with formulating key clinical questions to address within its focus area, reviewing relevant literature, evaluating the strength of data, and providing a recommendation based on evaluated literature or, if data were lacking, an expert opinion based on experience or case studies or other appropriate method. If no recommendation could be provided because there was no consensus or conflicting evidence was found of equal value or weight, the subcommittee was to provide recommendations for future research that would help resolve the conflict.

A centralized literature search was performed on March 12, 2012, for all consensus group subcommittees to use. This search used PUBMED and SCOPUS databases of all articles published between 1997 (year before last consensus conference) and 2012 (current), regardless of language. Search terms for PUBMED consisted of "tuberous sclerosis" and "humans" and "diagnosis OR therapy." Search terms for SCOPUS consisted of "tuberous sclerosis" and "diagnosis OR treatment." A total of 2692 articles were identified with this approach. Each consensus group subcommittee was then able to determine additional terms pertinent to its organ system or disease focus area to further refine articles to be reviewed and evaluated. Additional literature searches, if deemed necessary by individual subcommittees to address key clinical questions not captured by the central literature search, could be performed as needed (e.g., epilepsy surgery or organ transplantation guidelines relevant but not specific to TSC).

The evidence-based framework based on the approach of the National Comprehensive Cancer Network (NCCN) Clinical Guidelines[17] was used to grade strength of evidence and resulting recommendations. The NCCN framework allows recommendations based on all classes of evidence by categorizing recommendations with regard to the type and strength of evidence used to support the recommendation and is well-suited for application across many organ systems and specialties for a rare disease such as TSC with multisystem involvement. NCCN Clinical Guidelines category 1 recommendations are based on high-level evidence and uniform consensus, whereas category 2 recommendations are based on lower-level evidence and either uniform consensus or consensus. Category 3 recommendations are those for which a consensus cannot be reached, regardless of evidence. Additional details regarding this framework, including definitions for high- and low-level evidence, are provided in Table 1.

For the purposes of this summary document, the 2012 International Tuberous Sclerosis Complex Consensus Group surveillance and management recommendations are organized into two sections: (1) recommendations applicable at the time of initial diagnosis and (2) recommendations applicable to follow-up health care. There is some overlap with this approach because some features discovered upon initial diagnosis may require immediate intervention, additional workup, or specialist referral. By necessity, discussion in this summary is limited to the most relevant and salient points. More detailed discussion of specific recommendations for the different TSC disease focus areas, supporting evidence thereof, and other special considerations will be published separately by each International Tuberous Sclerosis Consensus Complex Group subcommittee.

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 2). 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.

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 (Category 1).

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, subependymal nodules (SEN), other types of neuronal migration defects, and subependymal giant cell astrocytomas (SEGA). If MRI is not

TABLE 1.
Recommendation categories and descriptions

Category	Description	Supporting Evidence
1	Based upon high-level evidence, there is uniform consensus that the intervention is appropriate	At least one convincing class I study OR at least two convincing and consistent class II studies OR at least three convincing and consistent class III studies
2A	Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate	At least one convincing class II study OR at least two convincing and consistent class III studies
2B	Based upon lower-level evidence, there is consensus that the intervention is appropriate	At least one convincing class III study OR at least two convincing and consistent class IV studies
3	Based upon any level of evidence, a consensus on appropriate intervention cannot be reached	Class I-IV studies that are conflicting or inadequate to form a consensus

Class Definitions for Supporting Evidence

Class I: evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.
Class II: evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment.
Class III: evidence provided by all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
Class IV: evidence provided by uncontrolled studies, case series, case reports, or expert opinion.

available or cannot be performed, computed tomography (CT) or head ultrasound (US) (in neonates or infants when fontanels are open) may be used, although results are considered suboptimal and will not always be able to detect abnormalities revealed by MRI.[18,19] (Category 1)

During infancy, focal seizures and infantile spasms (IS) are likely to be encountered,[20,21] and parents should be educated to recognize these even if none have occurred at time of first diagnosis. All pediatric patients should undergo a baseline electroencephalograph (EEG), even in the absence of recognized or reported clinical seizures. (Category 2A)

If the baseline EEG is abnormal, especially when features of TSC-associated neuropsychiatric disorders (TAND) are also present, this should be followed up with a 24-hour video EEG to assess for electrographic or subtle clinical seizure activity. (Category 3)

TAND is new terminology proposed to describe the interrelated functional and clinical manifestations of brain dysfunction common in TSC, including aggressive behaviors, autism spectrum disorders, intellectual disabilities, psychiatric disorders, and neuropsychological deficits as well school and occupational difficulties.[22] All patients should receive a comprehensive assessment at diagnosis to determine a baseline for future evaluations and to identify areas requiring immediate or early intervention. Comprehensive assessment is likely to require multidisciplinary involvement and clinical teams should maintain a low threshold to initiate early interventions and other management strategies. (Category 1)

TABLE 2.
Surveillance and management recommendations for 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) • During infancy, educate parents to recognize infantile spasms, 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 funduscopy, to assess for retinal lesions and visual field deficits

Parents of school-going age should be considered for an individual education plan (IEP) based on the individual TAND profile. (Category 2A)

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 US are performed.[23] 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. In addition to imaging, 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[24,25] or children.[26] Alternatively, measurement of serum cystatin C concentration can be used to evaluate GFR.[27] (Category 1)

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.[28,29] Counseling on smoking risks and estrogen use (such as some oral contraceptive preparations), which can compound the impact of LAM, should also occur in adolescents and adults. (Category 2A)

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. (Category 2A)

Heart

In pediatric patients, especially younger than three years of age, an echocardiogram 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. (Category 1)

In the absence of cardiac symptoms or concerning medical history, echocardiogram is not necessary in adults, but as conduction defects may still be present and may influence medication choice and dosing,[30] a baseline ECG is still recommended. (Category 2A)

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. (Category 1)

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 or other concerning history that warrants specific investigation. (Category 3)

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 3).[20] 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 angiomyolipomata 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.

Genetics

Genetic testing and 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, where a mutation has been identified in the index case, genetic testing. (Category 1)

Brain

Symptomatic SEGA or SEGA associated with increasing ventricular enlargement, or with unexplained changes in neurological status or TAND symptoms, require intervention or more frequent clinical monitoring and reimaging. 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.[31,32] 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

TABLE 3.
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 or newly considering having children
Brain	• Obtain magnetic resonance imaging (MRI) of the brain every 1-3 yr in asymptomatic TSC patients younger than age 25 yr to monitor for new occurrence of subependymal giant cell astrocytoma (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. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEGA. In determining the best treatment option, discussion of the complication risks, adverse effects, cost, length of treatment, and potential impact on TSC-associated comorbidities should be included in the decision-making process. • Perform screening for TSC-associated neuropsychiatric disorders (TAND) features at least annually at each clinical visit. Perform comprehensive formal evaluation for TAND at key developmental time points: infancy (0-3 yr), preschool (3-6 yr), pre-middle school (6-9 yr), adolescence (12-16 yr), early adulthood (18-25 yr), and as needed thereafter. Management strategies should be based on the TAND profile of each patient and should be based on evidence-based good practice guidelines/practice parameters for individual disorders (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder). Always consider the need for an individual educational program (IEP). Sudden change in behavior should prompt medical/clinical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease). • Obtain routine electroencephalograph (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, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centers with experience and expertise in TSC.
Kidney	• Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yr 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. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy. 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 yr 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 when present.
Heart	• Obtain an echocardiogram every 1-3 yr 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 yr 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.

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. (Category 1)

Optimal outcome is associated with early detection and treatment,[33] 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. (Category 2A)

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. (Category 3)

Strong evidence demonstrates superior efficacy for the treatment of infantile spasms with vigabatrin in patients

with TSC[34–37]; 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. (Category 1)

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. (Category 2A)

Early epilepsy treatment may be of benefit in infants and children during the first 24 months of life if ictal discharges occur, with or without clinical manifestations.[38] 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, but it should be noted that the prevalence of medically refractory epilepsy is high in TSC even with adequate trials of currently available anticonvulsant medications.[30,39] 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, and special consideration should be given to children at younger ages experiencing neurological regression. (Category 2A)

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. (Category 1)

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. (Category 1)

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. (Category 2A)

Several studies are under way to investigate the use of mTOR inhibitors as treatment for aspects of TAND. To date there is insufficient evidence to support the use of mTOR inhibitors as treatment for any aspects of TAND. There are no other TSC-specific neuropsychiatric interventions to date. However, there is high level evidence of treatment strategies for individual disorders associated with TAND, such as autism spectrum disorder, attention deficit hyperactivity disorder, and anxiety. Clinical teams should therefore use evidence-based principles to guide therapeutic decisions for best treatment of TAND in individuals with TSC, individualized to each patient. (Category 3)

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.[8,13,14,40] The demonstrated tolerability so far to date is far preferable to the renal damage caused by angiomyolipoma progression as well as surgical and embolitic/ablative therapies, though studies are still needed to confirm long-term benefits and safety. (Category 1)

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.[41] Patients with hypertension should be treated with an inhibitor of the renin-aldosterone-angiotensin system as first line therapy, but avoiding an angiotensin-converting enzyme inhibitor in those treated with an mTOR inhibitor. (Category 1)

Imaging to diagnose polycystic disease, renal cell carcinoma or other tumors,[42,43] and changes in angiomyolipoma should also be performed. MRI, often obtainable at the same time as brain surveillance imaging, is the preferred imaging modality, but if MRI is not available, CT or US can still provide useful information.[44] Selective embolization followed by corticosteroids,[45] kidney-sparing resection, or ablative therapy for exophytic lesions are acceptable second-line therapy for asymptomatic angiomyolipomata. For acute hemorrhage, embolization followed by corticosteroids is more appropriate.[46] Nephrectomy is to be avoided because of the high incidence of complications and increased risk of future renal insufficiency, end-stage renal failure, and the poor prognosis that results from chronic kidney disease.[12,47] Fat-poor angiomyolipomata are not uncommon in patients with TSC, but if there is doubt and lesions are growing faster than 0.5 cm per year,[48] a needle biopsy using a sheath technique or an open biopsy may be considered. (Category 2A)

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. (Category 1)

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.[8,13–15] (Category 1)

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. (Category 2A)

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 indicated for bleeding, symptomatic, or potentially disfiguring TSC skin lesions. There is insufficient evidence to guide choice of treatment—case reports and case series document successful use of surgical excision, lasers, and topical mTOR inhibitors.[49-53] (Category 3)

For TSC-associated dental lesions and oral fibromas, periodic oral evaluation should occur 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 important in 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 or deforming.[54] 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.[55,56] 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.[57] (Category 3)

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 and may include ambulatory event monitoring. (Category 1)

Eye

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 disability that limit the extent of ophthalmologic evaluation that can be performed.[30,58] Thus, even in these populations, annual ophthalmologic evaluation is considered more appropriate. (Category 2B)

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. (Category 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. The purpose of the 2012 International TSC Consensus Conference was to provide recommendations that help standardize the approach to managing TSC regardless of age or severity of the disease. Currently in the United States and many other countries, specialized TSC clinics have been established. Ideally, all TSC patients would have access to these clinics to ensure the appropriateness of care and treatment, but this ultimately may not be possible. In circumstances in which individuals with TSC do not have access to the specialized TSC clinics, the recommendations from the TSC Consensus Conference will be of significant value. Another source of invaluable information would be prominent advocacy groups such as the Tuberous Sclerosis Alliance in the United States and many similar groups in countries throughout the world who are also members of Tuberous Sclerosis International.

Resources must be used efficiently, particularly when there are financial or technological limitations. Transition clinics or clinics/facilities that treat both children and adults with TSC are important, particularly for the more severely affected and those with multiorgan system effects. Doing so can avoid duplicative tests and services and ensure appropriate surveillance and symptom management is in place to prevent more costly medical complications. TSC clinics may be institution-based or community-based using a network of clinicians expert in the different aspects of TSC. These clinics must be able to address the psychosocial challenges that face the individual and their family or caregivers as well as the medical needs.

These diagnostic and surveillance recommendations were developed from an ever-increasing understanding of TSC and supported by published, scientific investigation. Continued improvement in clinical knowledge will likely come from planned and ongoing clinical trials investigating a host of potential treatments for TSC, and also from longitudinal databases (e.g., the US TSC Natural History Database, the TOSCA European TSC Registry), which will serve to capture information on the many manifestations and

treatments of TSC throughout the human life cycle. As clinical knowledge of the disease improves, the current recommendations will have to be updated periodically.

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The absence of evidence does not constitute evidence of absence.

William Safire

Appendix. Members of the 2012 International TSC Consensus Group

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