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Tuberous sclerosis complex (TSC) is a dominantly inherited, genetic disorder affecting cellular differentiation, proliferation and migration early in development, resulting in the development of tumors in multiple organ systems, often referred to as hamartias and hamartomas. The diagnosis of TSC and evaluation of at-risk persons involves careful examination of the skin, heart, lungs, eyes, brain and kidneys. Presenting features may be in any or all of these organs and the prognosis can be difficult to predict, with variability ranging from a mild disorder manifesting only as skin findings and asymptomatic brain lesions to a more severe course involving epilepsy, intellectual disability, autism spectrum disorder and extensive kidney disease.

Accurate diagnosis allows for timely referrals of affected individuals to appropriate specialists to determine if other problems exist. However, many individuals with TSC report that their diagnosis came after much delay or uncertainty. Despite being one of the more common genetic disorders seen in children and adults, with an estimated incidence of one per 5,800 live births, the diagnosis of TSC is often difficult or delayed due to the variable expression of the disease and the variable age of onset of the symptoms. Genetic testing may now aid in the diagnosis of TSC because DNA testing identifies the mutation in either the TSC1 or TSC2 gene in more than 90 percent of the cases. The following review discusses the diagnosis and features of TSC, the importance of coordinating further evaluations for individuals with TSC and their family members and the role that genetic testing will play in TSC diagnosis and management.

Note: Terms highlighted with bold type throughout the text are defined in the Glossary.
There are no known pathognomonic signs for TSC as no single clinical feature is unique to the disease. In addition, many features known to be present in some individuals with TSC, such as epilepsy and intellectual disability, are too common in the general population to help establish the diagnosis. A constellation of features is therefore necessary for a diagnosis of TSC, with more specific features contributing more heavily to the diagnosis and an increasing number of features making the clinical suspicion of TSC more likely.

In July 1998, the Tuberous Sclerosis Alliance (TS Alliance) and the National Institutes of Health (NIH) convened a consensus conference to evaluate and review the clinical diagnostic criteria that had been previously established in 1992. Recommendations made by the assembled experts were published in the Journal of Child Neurology and provide the most specific clinical criteria for diagnosing TSC.

A diagnosis is considered definite when an individual has either two “Major Features” of TSC or one “Major Feature” and two “Minor Features” (see Table 1). The health care professional should consider TSC probable when the individual has one “Major Feature” and one “Minor Feature,” while a possible diagnosis results from the presence of either one “Major Feature” or two or more “Minor Features.”

An individual is considered to have a definite diagnosis of TSC only if he or she has two major features of the disorder or one major and two minor features. Epilepsy and intellectual disability are not considered diagnostic features although

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**Table 1. Diagnostic Criteria for Tuberous Sclerosis Complex**

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<tr>
<th>MAJOR FEATURES</th>
<th>MINOR FEATURES</th>
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<tr>
<td>1. Facial angiofibromas or forehead plaque</td>
<td>1. Multiple, randomly distributed pits in dental enamel</td>
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<tr>
<td>2. Non-traumatic ungula or periungual fibroma</td>
<td>2. Hamartomatous rectal polyps</td>
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<tr>
<td>3. Hypomelanotic macules (three or more)</td>
<td>3. Bone cysts</td>
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<td>4. Shagreen patch (connective tissue nevus)</td>
<td>4. Cerebral white matter radial migration lines</td>
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<tr>
<td>5. Multiple retinal nodular hamartomas</td>
<td>5. Gingival fibromas</td>
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<tr>
<td>7. Subependymal nodule</td>
<td>7. Retinal achromic patch</td>
</tr>
<tr>
<td>8. Subependymal giant cell astrocytoma</td>
<td>8. Confetti skin lesions</td>
</tr>
<tr>
<td>9. Cardiac rhabdomyoma, single or multiple</td>
<td>9. Multiple renal cysts</td>
</tr>
<tr>
<td>10. Lymphangioleiomyomatosis</td>
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<tr>
<td>11. Renal angiomyolipomas</td>
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1. The co-occurrence of cerebral cortical dysplasia and cerebral white matter radial migration lines should be considered as one major feature of TSC.
2. In individuals with both lymphangioleiomyomatosis and renal angiomyolipoma, another feature of TSC must be identified before a definite diagnosis is assigned.
3. Histologic confirmation of these features is suggested.
4. Radiographic confirmation of these features is sufficient.
they may be the presenting symptom that then leads to a diagnosis of TSC.

Despite the availability of diagnostic criteria, making a diagnosis of TSC can be difficult given the age-dependent presentation of many of the symptoms. For example, newborns with a cardiac rhabdomyoma have a greater than 50 percent risk of having TSC. However, an absolute diagnosis of TSC may be difficult because other signs, such as hypomelanotic macules or retinal hamartomas, may not appear until later. Another factor limiting accurate diagnosis of TSC is the frequent occurrence of many of these clinical signs as isolated findings in the general population. The presence of a single hypomelanotic macule, for example, has been reported in about 5 percent of the general population. This report and others led the 1998 consensus conference participants to agree that three or more hypomelanotic macules be present before they are called a symptom of TSC. The decision renders the macules a more specific finding, but can, in some cases, limit the ability to confirm a diagnosis of TSC in a newborn until three or more hypomelanotic macules have developed.

In an individual whose diagnosis is uncertain, the health care professional needs to consider further testing and determine whether imaging studies are warranted. While TSC is occasionally confirmed during the first week of life with cranial computed tomography (CT) or magnetic resonance imaging (MRI), most infants undergoing such evaluations first present with seizures as an indication for imaging. In the case of a newborn or infant without seizures and a questionable diagnosis, some parents and physicians may feel uncomfortable subjecting the child to imaging studies. A consultation with a health care professional familiar with the diagnosis of TSC to discuss the benefits, risks and limitations of imaging procedures could help the family make an informed decision regarding further testing.

When the clinical criteria for TSC diagnosis were developed, genetic testing was still limited in its scope. Today, genetic testing for TSC mutations is readily available. Direct sequencing of the TSC1 and TSC2 genes detects approximately 90 percent of the causative mutations in persons with a definite diagnosis of TSC. While the sensitivity of the genetic testing for TSC mutations is not yet determined in persons with probable or possible diagnoses, preliminary experience indicates that it may, in a proportion of cases, enable rapid diagnosis in the newborn period. Given the highly penetrant nature of TSC mutations and the specificity of genetic testing for single gene disorders, a positive genetic test should be considered diagnostic of TSC. The available molecular diagnostic test will make future TSC diagnosis more rapid and precise.
CLINICAL FEATURES OF TSC

Clinical features of TSC are most commonly seen in the skin, eyes, brain, kidneys, heart and lungs. Additional features have been reported in the gums, teeth and bones, as well as in most other major organs. The physical findings can vary greatly since TSC can affect different organ systems in different ways at different times in the individual’s life. Neurological and dermatological abnormalities are the most common physical findings, each occurring in as many as 90 to 95 percent of individuals with TSC.

NEUROLOGICAL MANIFESTATIONS

Abnormal neurological findings are based on the location and size of tubers and the presence and growth of subependymal nodules (SENs) and subependymal giant cell astrocytoma (SEGA) (also referred to as subependymal giant cell tumor (SGCT)).

Tubers are noted most commonly in the cerebral cortex, without clear predilection for any particular lobe or area of the brain. They may also occur in the cerebellum. Rarely, they have been noted in the brain stem and spinal cord.

Cortical tubers are characterized by architectural disarray of the layers of the cerebral cortex, particularly lack or disruption of cortical lamination. Overall cellularity varies, being either low because of reduced numbers of neurons or significantly increased primarily as a result of an increase in the number of astrocytes. A conspicuous feature of tubers is the presence of very large, abnormal cells, often called balloon cells. The number, size and location of tubers vary widely from one individual to another. Depending on the location of tubers, neurological findings can include seizures, abnormalities in cognition (either global delays or specific location-related deficits like language delays), cranial nerves and focal motor/sensory/reflex abnormalities, cerebellar dysfunction or gait abnormalities.

Subependymal Nodules or SENs are typically found lining the wall of the lateral ventricles and may be either discrete or roughly confluent areas of firm, rounded hypertrophic tissue. SENs may occur anywhere along the ventricular surface, but most commonly occur at the caudothalamic groove in the vicinity of the foramen of Monroe. SENs become SEGAs in 5 to 10 percent of cases. Growth can occur in an indolent fashion, resulting in ventricular obstruction and hydrocephalus. Since this process can occur very gradually, individuals with TSC may have marked hydrocephalus when they finally become symptomatic. In this situation, blindness or other permanent neurological deficit may ensue despite prompt
CLINICAL FEATURES OF TSC CONTENTS

intervention. Initially the manifestations of a SEGA may be quite subtle, such as a change in the individual's personality or behavior, a change in seizure frequency or severity, or nausea, weight loss and headaches. SEGAs usually exhibit significant growth before puberty, but they may continue to enlarge into young adulthood and requiring treatment. With careful and consistent clinical follow-up, SEGAs can be treated before clinical symptoms occur.

Brain imaging for TSC should be performed at the time of diagnosis to obtain baseline images and then repeated every one to three years (as determined by the individual with TSC and his or her family and health care professional). If a SEGA is identified, a CT or MRI should be performed every three to six months to monitor interval growth and the development of early hydrocephalus. Imaging studies also document the extent and number of cortical tubers present. On occasion they may reveal rare vascular lesions such as aneurysms.

Multiple factors then need to be considered when planning serial neuroimaging examinations. In addition to T1- and T2-weighted MRI sequences, fluid-attenuated inversion recovery (FLAIR) sequences are often useful. FLAIR is superior for the identification of tubers and subcortical abnormalities. Enhancement of SENs by gadolinium contrast is not in itself a reliable indication that a SEN is going to grow or that treatment is necessary.

Some neurosurgeons have performed resections on SEGAs that exhibit an interval increase in size on serial imaging. Others obtain more frequent imaging studies when a lesion increases in size, provided no signs/symptoms of ventricular obstruction, new focal neurological deficit or increased intracranial pressure are noted. Occasionally, SEGAs may stabilize or stop growing spontaneously after increasing in size, so careful monitoring is necessary.

Surgical removal of SEGAs was the treatment of choice when interval increase in size on serial imaging was detected, and may be the treatment of choice for some individuals with TSC. However, a new treatment was approved in 2010 that provides an option for the treatment of SEGAs. Everolimus (Afinitor®) was approved by the Food and Drug Administration (FDA) for the treatment of SEGA in individuals with TSC. This drug is an inhibitor of the protein called mammalian target of rapamycin (mTOR) and acts to reduce the size of SEGAs. Clinical trials indicate that everolimus reduced the size of the SEGAs by 50% or more in 35% of the individuals in the study, with continued usage of the drug necessary to maintain the reduced tumor size. Since mTOR inhibitors also act to suppress the immune system, careful discussion and consideration should be
taken in deciding on the optimal treatment of SEGA for each individual with TSC.

**EPILEPSY**

Early studies showed nearly 90 percent of individuals with TSC also have epilepsy. However, due to the increased diagnosis of more mildly affected individuals, more recent studies indicate epilepsy affects approximately 60 percent of individuals with TSC over their lifetime. Seizures can begin at any age, though the majority of individuals with TSC begin to have seizures during the first year of life. While many different types of seizures are seen in individuals with TSC, infantile spasms are especially common and need to be emphasized as an excellent specific therapy has been identified. Infantile spasms often begin around four to six months of life and usually involve brief flexion movement of the arms and head with abduction of the arms. They generally occur in clusters with children having many seizures per day. Other manifestations of epilepsy in individuals with TSC include simple partial, complex partial, atypical absence, myoclonic and generalized tonic-clonic seizures. They are generally treated with conventional medical therapies though other treatment modalities often are employed as well.

**COGNITIVE DEVELOPMENT, BEHAVIORAL DISORDERS AND PSYCHIATRIC MANIFESTATIONS**

TSC is associated with a wide range of cognitive, behavioral and psychiatric manifestations. These manifestations are often of greater concern to individuals with TSC and their families and caregivers than other symptoms of TSC such as epilepsy, skin lesions or kidney problems. Care should be taken to perform appropriate assessments at regular intervals as detailed in the Consensus clinical guidelines for the assessment of cognitive and behavioral problems in individuals with TSC. Appropriate screening will identify these issues and lead to implementation of relevant intervention strategies to facilitate the development of appropriate skills, to prevent the emergence of further problems, and to manage existing disorders, syndromes or psychological issues.

**COGNITIVE DEVELOPMENT**

About half of individuals with TSC have normal intelligence, while the other half have intellectual disabilities, ranging from mild learning disabilities to severe intellectual disability. The majority of individuals with TSC falls into either a severely disabled group or has normal intelligence. This “bimodal distribution” is important, because the behavioral and psychiatric problems associated with the “able” and the “severely disabled” groups may be different.

![Global Intellectual Ability ('IQ') in TSC](image)

**Figure 4.** Most individuals with TSC fall within a group having a lower average IQ but with a wide distribution of intellectual ability similar to that of the general population. A smaller subset of individuals with TSC have profound deficits in intellectual ability relative to the general population as measured by an IQ test.

Individuals with normal overall intellectual abilities are at increased risk of specific cognitive
deficits. These include attention deficits (e.g., difficulties sustaining attention, switching of tasks), executive control problems (e.g., planning, sequencing), language (e.g., expressive or receptive language delay), learning and memory problems, and visual-spatial difficulties. Children with TSC who have such neuropsychological deficits often present with specific scholastic difficulties in reading, writing, spelling and arithmetic. Because of these difficulties, a number of children with TSC are often diagnosed with dyspraxia or dyslexia.

Children with intellectual disabilities may require special education programs in appropriate school settings. Adults with intellectual disabilities may require ongoing support in adult life. For children with specific learning difficulties, appropriate educational provisions should be made in collaboration with the school systems.

BEHAVIORAL DISORDER AND PSYCHIATRIC MANIFESTATIONS

A very significant proportion of children and adults with TSC will present with a range of behavioral and psychiatric difficulties. It is of utmost importance to identify these problems and to implement appropriate management strategies.

In children with TSC who have severe, global intellectual disabilities, autism spectrum disorders may present in up to 50 percent of cases. TSC is the genetic disorder most commonly associated with autism spectrum disorder, and suggestions of language and communication difficulties, reciprocal social interaction difficulties and unusual patterns of behavior and play should trigger a careful developmental evaluation. Behaviors often associated with autism spectrum disorder include poor eye contact, repetitive play with objects, self-stimulation, lack of interest in toys, idiosyncratic responses to noise and obsessive or compulsive behaviors. Individuals with normal overall abilities are still at increased risk for autism spectrum disorders, but the manifestations may be more subtle requiring assessment by appropriate specialists.

Attention Deficit Hyperactivity Disorder (ADHD) and related behaviors (such as impulsivity, over-activity and attention problems in daily life) are also seen in about half of children with TSC. ADHD-related behaviors are more likely to be seen in those with severe disabilities, but are also highly over-represented in individuals with TSC with normal abilities. Appropriate diagnosis and intervention is required. It is important to keep in mind that a number of children who present with specific cognitive difficulties do not present with severe impulsivity or hyperactivity, but will still require appropriate intervention.

Self-injurious behaviors, aggressive outbursts, difficult temper tantrums and chronic sleep problems may be seen in children with TSC and should be explored with careful behavioral analysis and appropriate treatments and/or therapies implemented.

In older children, adolescents and adults, anxiety and mood-related disorders become increasingly prevalent. Anxiety and mood symptoms are seen in individuals with and without global cognitive impairment, and can be very debilitating to higher-functioning adolescents and adults. Evaluation and diagnosis of anxiety and mood disorders should lead to comprehensive treatment plans including pharmacological and cognitive-behavioral interventions.

There is no clear systematic evidence of an increased prevalence of psychiatric disorders in TSC, but any hallucinatory or delusional phenomena should raise suspicion of epilepsy-related abnormalities, particularly involving the temporal lobes, and/or psychiatric issues that should be treated by the appropriate health care professionals.

In conclusion, when working with individuals with TSC, health care professionals should:

• Keep in mind that the spectrum and range of cognitive, behavioral and psychiatric issues in TSC are varied and therefore require thorough assessment and careful individual treatment planning.

• Maintain a broad approach where physical, pharmacological and behavioral factors are considered for management and outcome assessment.
• Carefully examine patients, especially children, for learning difficulties, autism spectrum disorders, disruptive behaviors and language disorders.
• Consider mood and emotional disorders in children, adolescents and adults with TSC.
• Remember that individuals with normal intelligence are still at a high risk of specific cognitive, neuropsychological and psychiatric disorders.

**WARNING SIGN:** Regression in development, intellectual abilities or physical skills at any age should be investigated thoroughly with psychological, neurological and/or neuroimaging assessments as appropriate. Cases of regression have been documented to be caused by unrecognized non-convulsive status epilepticus, which should be aggressively investigated using electroencephalogram (EEG) monitoring that includes a prolonged sleep segment.

**DERMATOLOGICAL MANIFESTATIONS**

The best-known skin manifestations of TSC are facial **angiofibromas**, which may not appear until late childhood or early adolescence. Facial angiofibromas are cutaneous hamartomas and are not related to excessive sebum or acne. (They were incorrectly named adenoma sebaceum in the past). They begin as flat, reddish macular lesions that can be mistaken for freckles early on. Over time, facial angiofibromas become increasingly erythematous and nodular and occasionally present with a sensitive surface that may easily bleed. Facial angiofibromas typically are noted first in childhood when they begin to appear between the ages of 2-5 years and may exhibit progression during puberty and adolescence. They may become large and disfiguring if left untreated. Seventy five to ninety percent of individuals with TSC will develop facial angiofibromas during their lifetime.

Other skin lesions consist of hypomelanotic macules (i.e., ash leaf), ungula or gingival fibromas.
and thickened, firm areas of subcutaneous tissue often at the lower back or on the buttocks or torso (shagreen patch) or forehead and face (fibrous plaques).

**Hypomelanotic macules** are usually round or oval in shape and vary in size from a few millimeters to as much as five centimeters in length. Sometimes they have an irregular, reticulated appearance, as if white confetti paper had been strewn over the skin (confetti lesions), especially on the arms and legs. When the scalp is involved, an area of poliosis (patch of white hair) can result. Hypomelanotic macules may be present at birth or not show up until later in life. They vary widely in location and number from person to person. Once the criterion of “three or more hypomelanotic macules” has been met, the number or size is not essential. Finding three or more in a person who does not have the disease is uncommon. A common technique for enhancing their visualization involves examination of the skin under ultraviolet light using a Woods lamp.

Fibromas of the skin occur in multiple locations. When present in the lumbar region, they are called a “shagreen patch.” As the overlying skin may be dimpled like the skin of an orange, they are often easier to detect by palpation than direct visualization. They occasionally itch or are associated with dysesthesia. Shagreen patches are rarely found in infants, become more common after the first decade of life and persist through life.

Fibromas can also occur in the periungual regions, gingivae or potentially anywhere in cutaneous or mucosal tissues. The underlying tissue may be hypertrophic or hamartomatous. Symptoms can result from local irritation, such as that created by shoes, dentures, shaving and disruption of the nail bed.
RENAL MANIFESTATIONS

Renal manifestations of TSC are the third most common clinical feature. Four types of lesions can occur: angiomyolipomas (AMLS), isolated renal cyst(s), autosomal dominant polycystic kidney disease (PKD) and renal cell carcinoma.

Angiomyolipomas (AMLS) are noted in as many as 80 percent of individuals with TSC, typically detected after age three. AMLs typically grow very slowly over several years. Growth spurts may be seen in preadolescent boys and post-menarche in girls. They also can occur as isolated lesions in persons without TSC. Individuals with TSC may have multiple small AMLs studding the surface of the kidney, multiple small AMLs throughout the kidney, or one or more larger AML. The larger AMLs are more apt to be symptomatic, particularly when greater than 4-6 cm in their largest diameter. They often produce nonspecific complaints such as flank pain. Of concern are potentially life-threatening retroperitoneal hemorrhages from rupture of dysplastic, aneurysmal blood vessels in the AMLs. These hemorrhages also can destroy adjacent normal renal parenchyma or produce abdominal distention and obstruction due to mass effects. Some studies suggest that as many as 75 percent of AMLs will increase in size over time. Exactly when intervention is warranted varies from one individual to another. Very large AMLs (> 6-8 cm in diameter) are likely to progress and often result in hemorrhage, particularly if prominent abnormal vasculature is present. AMLs with fewer dysplastic vessels may have a smaller risk of catastrophic hemorrhage but can present problems from their sheer size. If there are too many AMLs to count, they are not surgically resectable, which can lead to hypertension and renal failure if too much normal kidney tissue is destroyed between the AMLs.

Renal imaging is performed to assess changes in the size of AMLs. They may not grow significantly until after puberty, but excessive growth has been seen in young children. It is recommended that renal imaging, after an initial study, be repeated every two to three years if no lesions are seen. After lesions are observed, renal imaging should be performed every year. When there are many lesions, renal ultrasound is less useful as a screening tool especially to detect either fat-poor AMLs or the development of renal cell carcinoma. For this reason, CT or MRI of the kidneys can provide better visualization of involved areas.

MRI and MR angiography are often helpful in planning therapy. Because of their substantial blood supply, standard surgical resection can result in excessive bleeding, with nephrectomy being the end result. When feasible, selective embolization is the preferred intervention. This procedure typically is able to spare functional renal tissue, directly addresses the chief risk of retroperitoneal hemorrhage, and has a substantially lower rate of morbidity than standard surgery. Some individuals with TSC experience “post embolization syndrome” consisting of fever, flank pain and malaise as the embolized lesion...
becomes necrotic. This usually can be prevented by a tapering treatment with steroids.

Individual renal cysts (as opposed to polycystic kidney disease) are found in some individuals with TSC. They are rarely if ever symptomatic. Simple renal cysts often occur with AMLs and this combination should suggest the diagnosis of TSC. Sometimes multiple renal cysts can be confused with true polycystic kidney disease.

Polycystic Kidney Disease (PKD) occurs in 2 to 3 percent of persons with TSC and usually presents early in life with hypertension, hematuria or renal failure. This occurs as the result of a genetic abnormality (usually a single large deletion) affecting both the TSC2 gene and the PKD1 gene immediately adjacent to it on chromosome 16. Individuals with TSC who have PKD will eventually have relatively little normal-appearing renal tissue and often will eventually require renal transplantation. They are highly susceptible to complications of urinary tract infection (UTI) or nephrolithiasis, which can produce acute renal failure. This should be kept in mind when using therapies that predispose the individual to UTI or kidney stones, such as steroids, topiramate, zonisamide or the ketogenic diet.

Renal cell carcinoma appears to occur more frequently in individuals with TSC than the general population, and at an earlier age, although further research is required to confirm the relationship. In one series, five of 403 patients with TSC had histologic evidence of a renal cell carcinoma. Nonetheless, a large AML that has little or no fat (adipose tissue) is more common in this population. A rapidly expanding renal mass in the absence of hemorrhage with no fat evident in imaging studies is suggestive of the diagnosis of renal cell carcinoma. MRI of the abdomen can be useful in differentiating a large AML from a true malignancy.

CARDIAC MANIFESTATIONS

Cardiac involvement in TSC is usually maximal at birth or early in life and it may be the presenting sign of TSC, particularly in early infancy. Fifty to 60 percent of individuals with TSC have evidence of cardiac involvement, usually in the form of rhabdomyomas. Conversely, anywhere from 50 to 85 percent of infants with isolated cardiac rhabdomyomas have a definite diagnosis of TSC. Echocardiography is, therefore, performed as part of the baseline evaluation in an individual with newly diagnosed TSC.

Rhabdomyomas are benign tumors that may be focal or diffuse and infiltrating in character. They produce symptoms primarily through outflow tract obstruction or by interfering with valvular function. They can also disrupt electrical conductivity and cause arrhythmias. Diffuse
rhabdomyomas also may result in decreased contractility and cardiomyopathy. In such cases surgical treatment, inotropic support and related measures may be necessary.

Rhabdomyomas develop during intrauterine life (usually between 22 and 26 weeks of gestation). As a result, many more cases are now being identified by obstetricians and/or gynecologists during routine Level II ultrasounds at 20 to 28 weeks gestation. Rhabdomyomas that lead to obstruction of normal cardiac blood flow, however, are a recognized medical emergency. The most severe cases can result in non-immune hydrops fetalis with fetal/neonatal death. In such cases, surgical intervention is necessary and should be performed in coordination with a prepared high-risk obstetric service and a Level III neonatal intensive care unit. The majority of rhabdomyomas do not interfere with cardiac hemodynamics and are clinically asymptomatic.

Cardiac rhabdomyomas typically undergo spontaneous regression in the first few years of life, although residual areas of histologically abnormal myocardium may persist. These lesions can involve the cardiac conducting system and thereby may predispose an affected individual to ventricular pre-excitation or other arrhythmias not only in infancy, but also later in life. Such residual areas may not be apparent on echocardiography, yet still produce arrhythmia. In cases where an abnormal electrocardiogram (EKG) is noted, consultation with a cardiologist and annual monitoring by Holter monitor (for change in quality of arrhythmia) and echocardiography (change in contractility) may be indicated. This may have an under-appreciated significance, as individuals with TSC often require anti-epileptic or psychotropic drugs that possibly affect cardiac conduction.

OPHTHALMIC MANIFESTATIONS

At least 50 percent of individuals with TSC have ophthalmologic abnormalities; some studies have reported the prevalence as high as 80 percent. These lesions are characterized as hamartomas, specifically retinal astrocytomas, which tend to become calcified over time. Initially appearing as rounded, nodular or lobulated areas on fundoscopic examination, they become whitish in color as they calcify. The hamartomas tend to be indolent and rarely produce symptoms or require intervention. In the rare occasion that visual acuity is affected, a retinal hamartoma may be found impinging upon and compromising the retinal fovea and/or optic nerve. Hypopigmented areas of the retina, iris and even eyelashes have also been reported. These are analogous to hypomelanotic macules of the skin and poliosis of the hair.

![Figure 11. A retinal astrocytoma near the left disc in an individual with TSC. Photograph used with permission from the Canadian Neuroophthalmology Group at www.neuroophthalmology.ca.](image-url)
Three forms of symptomatic pulmonary involvement in TSC have been described: multifocal micronodular pneumocyte hyperplasia (MMPH), pulmonary cysts and lymphangioleiomyomatosis (LAM). Involvement occurs primarily in adult women with TSC. It was long thought to be distinctly uncommon, affecting 1 percent or less of women with TSC. However, recent prospective and retrospective studies have found cystic pulmonary abnormalities in as many as 40 percent of women with TSC, although many of these women remain asymptomatic.

Symptomatic pulmonary disease in men and even children has been reported anecdotally. The true incidence of pulmonary abnormalities in these populations is not known, although it is certainly lower than in adult women with TSC.

Sporadic LAM results from mutations in one of the TSC genes. These individuals have lung involvement and often have AMLs in the kidney and lymph nodes, but do not have other manifestations of TSC. It is critical that individuals diagnosed with sporadic LAM receive a clinical evaluation for other TSC involvement.

MMPH consists of hyperplasia of type II pneumocytes, seen as nodular densities on chest CT scans. This condition occurs with equal frequency in men and women with TSC and has not been reported to produce clinical symptoms.

Pulmonary cysts may be single or multiple as seen in imaging studies. Solitary lesions may remain clinically silent or rupture, with resultant pneumothorax producing acute dyspnea and hemoptysis. Multiple cystic lesions may result in respiratory insufficiency or even pulmonary hypertension (usually in the case of LAM).

Lymphangioleiomyomatosis (LAM) is more insidious and is a result of the invasion of the potential space between lung alveolar cells and capillary endothelium by a smooth-muscle-like cell. Interstitial fibrosing alveolitis develops with progressive restrictive lung disease. It also occurs, although less frequently, in women who do not have TSC (incidence of sporadic LAM is approximately one per 100,000). About 60 percent of women with sporadic LAM also have renal AMLs but do not have other characteristics of TSC. Smooth muscle cells undergo abnormal proliferation with secondary compromise of bronchioles, venules and lymphatic structures.

Slowly, normal pulmonary elasticity is lost, with resultant decrease in vital capacity and increase in residual volume. Pulmonary hypertension and worsening hypoxia and hypercapnia eventually supervene. When LAM is suspected clinically, high-resolution CT of the chest is the most sensitive diagnostic modality. A recent study showed that measuring blood levels of a growth factor (VEGF-D) may correlate with the diagnosis of LAM in women with sporadic LAM. The correlation between VEGF-D levels and a diagnosis of LAM in individuals with TSC has only been done in a small number of individuals and requires further study.
Due to the overwhelming predominance of LAM in women, it is possible that estrogen accelerates the progression of the condition. Some individuals have been treated with hormonal therapy (i.e., progesterone) to counteract the estrogen effect, although this has not been proven conclusively to be of benefit. Bronchodilators are helpful in selected cases. A clinical trial to test the efficacy and safety of mTOR inhibitors to treat LAM was recently completed and indicates that mTOR inhibitors may be beneficial in some women with LAM, especially those with chylous effusions.

LAM may be progressive in a small percentage of individuals with TSC, especially women. Recent studies have shown that approximately 40 percent of women with TSC have subtle signs of LAM. It is recommended that individuals with TSC should receive a baseline of CT of the lungs at diagnosis for adults or before the age of 18.

In cases where LAM is progressive, a lung transplant may be necessary. Treatment of LAM with mTOR inhibitors may prevent progression of the disease in some women, and should be considered by women with TSC who have LAM, and for those with sporadic LAM. Interestingly, LAM occasionally has recurred in transplanted lungs. Researchers have identified cells in the lungs and kidneys with the same genetic composition, suggesting that the cells migrated from renal AMLs to the lungs of women with LAM, regardless of whether they have TSC. These cells frequently have abnormalities of either TSC1 or TSC2, which produce the characteristic smooth muscle hypertrophy and subsequent destruction of normal lung tissue.

**ORAL MANIFESTIONS**

There are three oral manifestations of TSC that may be present. These include pitting of the dental enamel in the teeth, gingival hypertrophy and gingival fibromas. These generally appear in children with TSC, but may continue to be problematic in adults.

Pitting of the dental enamel is invariably present in the permanent teeth of individuals with TSC, particularly larger numbers of pits (>14). They are seen in the primary (deciduous) teeth of 30 percent of affected children. This sign has led to interest in counting dental pits as an inexpensive bedside screening procedure. Small numbers (<6) of dental pits may occur in about 10 percent of healthy controls. However, accurate assessment of dental pits may be possible only after staining the teeth and by a dentist or person trained to look for them. These factors have limited the utility of this feature of TSC for diagnosis.

The first dental exam should occur at around 18 months when possible with follow-up dental visits every four months. Crowned teeth should be sealed once eruption is complete and chewy sweets (e.g., jelly beans, caramel, taffy, dried fruit) should be avoided as much as possible. There is no evidence of an increased incidence of cavities.
in individuals with TSC, but good oral hygiene should be stressed to prevent tooth decay.

Gingival fibromas occur in 70 percent of adults with TSC, in 50 percent of children with mixed dentition (both primary and permanent teeth) and in only 3 percent of children with only primary teeth. Gingival fibromas may produce local irritation or interfere with dental alignment and may require surgical resection in selected cases. Isolated gingival fibromas can occur in individuals who do not have TSC. However, gingival fibroma(s) in association with large numbers (>10) of dental pits is highly suggestive of TSC and should prompt further diagnostic evaluation.

OTHER ORGAN SYSTEMS

GASTROINTESTINAL TRACT

Hamartomas and polyposis of the stomach, intestine and colon may occur. These almost never cause significant symptoms, although gastrointestinal hamartomas occasionally may bleed, leading to positive test for fecal occult blood. Blood loss is almost always minimal and rarely if ever results in anemia or clinical symptoms.

LIVER

Hepatic cysts and hepatic AMLs, typically asymptomatic and nonprogressive, have been reported in as many as 24 percent of individuals with TSC, with a marked female predominance (female-to-male ratio 5:1). Rare cases reporting growth of hepatic AMLs that required resection have been noted.

BONE

Sclerotic and hypertrophic lesions of bone may be found incidentally on radiography performed for other indications. Occasionally they may be palpable or associated with non-specific, vague, aching pains. Osseous lesions rarely if ever produce serious difficulty and they require only symptomatic treatment, if any at all.

ANEURYSMS

A small number of individuals with TSC may develop arterial aneurysms. Aneurysms have been reported intracranially, as well as in the abdominal aorta and axillary arteries. It is thought that the aneurysmic vessels actually have small defects in the walls of the vessels reminiscent of hypopigmented macules of the skin that weaken the wall in that specific location.

Like lung disease, gastrointestinal and osseous abnormalities are seen primarily in adults, in whom these abnormalities may be the presenting manifestations of TSC. Recognition of the true nature of these lesions is important, as adult-oriented practitioners are generally unaware of the broad spectrum of TSC. Pulmonary, renal, gastrointestinal and bone findings may be mistaken for emphysema, neoplasia or other disorders and inappropriate measures may be undertaken.
### Table 2. TSC Manifestations and Symptoms

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESCRIPTION</th>
<th>AGE OF ONSET</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomelanotic Macules</td>
<td>Areas of skin containing less pigment than surrounding skin. Most easily seen by UV light examination (especially in fair-skinned individuals); possible anywhere on skin’s surface, most commonly on trunk and buttocks, rarely on face; can be any shape.</td>
<td>May be present at birth or may develop during infancy</td>
<td>87-100%</td>
</tr>
<tr>
<td>Facial angiofibromas</td>
<td>Solid red or pink papules, bilaterally symmetrical over nose, cheeks and chin</td>
<td>Generally begin to appear between two and five years of age; become more prominent at puberty.</td>
<td>75-90%</td>
</tr>
<tr>
<td>Shagreen Patches</td>
<td>Connective tissue hamartoma; a patch of elevated skin, with texture of orange peel, seen on dorsal body surfaces (usually lumbosacral region).</td>
<td>Rarely seen in infants, more common during later childhood (10+ years).</td>
<td>50%</td>
</tr>
<tr>
<td>Fibrous facial plaques</td>
<td>Large, flesh-colored, fibrous plaques on forehead and scalp.</td>
<td>May be seen in newborns, but typically present along with facial angiofibromas.</td>
<td>20-40%</td>
</tr>
<tr>
<td>Ungual or periungual fibromas</td>
<td>Papules arising from the finger or toenail bed.</td>
<td>Usually appear at or after puberty.</td>
<td>Up to 88% of adults with TSC</td>
</tr>
<tr>
<td><strong>EYES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal hamartomas</td>
<td>Rounded, nodular or lobulated areas on the retina</td>
<td>May be present in infancy.</td>
<td>44-87%</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subependymal nodules (SEN)</td>
<td>Hamartomas located along outer walls of lateral ventricles.</td>
<td>Can be seen in newborns</td>
<td>70-80%</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma (SEGA) or tumor (SGCT)</td>
<td>Hamartomas (tumors) that grow in the lateral ventricles; developing from an enlarging SEN.</td>
<td>Most frequently seen in childhood and adolescence (ages 5-18 years).</td>
<td>5-20%</td>
</tr>
</tbody>
</table>
### Table 2. TSC Manifestations and Symptoms (continued)

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESCRIPTION</th>
<th>AGE OF ONSET</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical or subcortical tubers</td>
<td>Hypomyelinated hamartias involving the cerebral cortex and underlying white matter.</td>
<td>Can be seen as early as 20 weeks gestation, and in newborns.</td>
<td>70%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Seizure types most frequently seen are partial motor, complex partial and partial secondarily generalized (including infantile spasms).</td>
<td>May occur at any age, most commonly in children. Rarely the presenting symptom in adults.</td>
<td>75-90%</td>
</tr>
<tr>
<td>Developmental delay and intellectual disability</td>
<td>Mild to severe.</td>
<td>Children with TSC are at risk and should receive appropriate screening early in life.</td>
<td>50%</td>
</tr>
<tr>
<td>Autism spectrum disorder or pervasive developmental disorder</td>
<td>Lack of eye contact, delayed speech may be indicators.</td>
<td>Children with TSC are at risk and should receive appropriate screening early in life.</td>
<td>26-36%</td>
</tr>
<tr>
<td><strong>KIDNEYS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma (AML)</td>
<td>Proliferations of blood vessels, smooth muscle and fat tissue; more common in females; isolated solitary AML may occur in general population.</td>
<td>Generally very small early, may grow significantly. Usually develop after the age of three.</td>
<td>80% by age 10.5 years</td>
</tr>
<tr>
<td>Renal cysts</td>
<td>Single or multiple isolated cysts, may be bilateral.</td>
<td>May be present at birth.</td>
<td>20%</td>
</tr>
<tr>
<td>Polycystic Kidney Disease (PKD)</td>
<td>Bilateral multiple cysts.</td>
<td>May be present at birth.</td>
<td>2%</td>
</tr>
<tr>
<td>Malignant angiomyolipoma, oncocytoma &amp; renal cell carcinoma</td>
<td>Solid kidney lesions.</td>
<td>All rare, but seen more often in younger adults with TSC than in general population.</td>
<td>2%</td>
</tr>
</tbody>
</table>
### Table 2. TSC Manifestations and Symptoms (continued)

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESCRIPTION</th>
<th>AGE OF ONSET</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEART</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac rhabdomyomas</td>
<td>Most common cardiac tumor in infants and children; can be seen in any of the four chambers, more commonly in ventricles; majority have no cardiac symptoms; arrhythmias seen in some individuals; often regress with age.</td>
<td>Often diagnosed prenatally via ultrasound or in first year.</td>
<td>47-67%</td>
</tr>
<tr>
<td><strong>LUNGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis (LAM)</td>
<td>Primarily seen in women; presents with shortness of breath or pneumothorax; there exists a distinct group of women with sporadic LAM with lung and kidney involvement without other TSC symptoms and without constitutional mutations.</td>
<td>Adulthood.</td>
<td>30-40%</td>
</tr>
<tr>
<td>Pulmonary cysts</td>
<td>Isolated single or multiple cysts; may be bilateral.</td>
<td>Young Adulthood.</td>
<td>30-40%</td>
</tr>
<tr>
<td>Multifocal micronodular pneumocyte hyperplasia (MMPH)</td>
<td>Nodular densities seen on CT scans.</td>
<td>Adulthood.</td>
<td>12%</td>
</tr>
<tr>
<td><strong>ORAL, GASTROINTESTINAL TRACT AND HEPATIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral and gingival fibromas</td>
<td>Fleshy growths in the mouth and on gums.</td>
<td>Early to late childhood.</td>
<td>69%</td>
</tr>
<tr>
<td>Dental pits</td>
<td>Pit-shaped enamel defects on teeth.</td>
<td>Childhood on milk teeth, more common in permanent teeth.</td>
<td>97%</td>
</tr>
<tr>
<td>Polyps</td>
<td>Fibroadenomatous polyps in all parts of gastrointestinal tract, less common in esophagus and stomach.</td>
<td>Unknown.</td>
<td>Unknown.</td>
</tr>
<tr>
<td>Hepatic angiomyolipoma (AML)</td>
<td>Proliferations of blood vessels, smooth muscle and fat tissue similar and perhaps identical to renal AMLs.</td>
<td>Childhood and may increase in incidence in adults.</td>
<td>16-24%</td>
</tr>
</tbody>
</table>
TSC can be inherited as an autosomal dominant genetic condition. Individuals with TSC have a 50 percent chance of passing the condition on to each of their children. Many dominant genetic disorders can be sporadic and occur for the first time in an individual. Sporadic occurrences are the result of a new genetic mutation and account for approximately 67 percent of individuals with TSC. Differentiating between an inherited and a sporadic occurrence of TSC sometimes requires a thorough clinical evaluation of the family members of an affected child, as well as genetic testing.

In some cases, apparently unaffected parents of a child with TSC can go on to have another affected child, despite assurances that they themselves are not affected. The term germline mosaicism describes the phenomenon when an individual has cells in their germline (ovum or sperm cells) that carry a genetic mutation, despite the absence of detectable clinical symptoms of the condition or a mutation in the cells in the blood (therefore, no mutation is identified during genetic testing). Germline mosaicism has been documented to occur in TSC. Low-level somatic mosaicism is also thought to occur in individuals with TSC. This type of mosaicism may mean that an individual with TSC will have mutations in only some of the cells in specific organ systems and not in others. For example, an individual with low-level mosaicism may have mutations in one of the TSC genes in only a small percentage of the cells in the skin, brain and blood. Therefore, testing for the mutation in a blood sample will result in a negative finding. Given the complicated nature of TSC genetics, all families who have a relative with TSC should be referred to a genetic counselor or geneticist to discuss their unique genetic risk for either developing symptoms associated with TSC or having a child with TSC.

In order to discuss genetic testing and its role in the evaluation and treatment of individuals with TSC, we must first review TSC genetics. Mutations or deletions in either the TSC1 or TSC2 genes cause TSC. To develop TSC, it is sufficient to have a mutation in either TSC1 or TSC2. There are no known cases of an individual having a mutation in both genes. It is still uncertain whether we will be able to predict the severity of an individual’s TSC by virtue of knowing their exact mutation, but preliminary evidence suggests that mutations in TSC2 tend to produce more symptoms with increased severity than mutations in TSC1. Further studies are needed to clarify this issue.

Research into the roles these genes and their protein products play in the human body is ongoing, but the two genes are known to work together as a single protein complex. This complex likely has multiple functions, but recent evidence indicates an important inhibitory role of the PI3 Kinase-AKT-mTOR pathway that regulates cell growth. These genes may have other important functions that have not yet been identified. A clinical trial utilizing an mTOR inhibitor led to the approval of Everolimus (Afinitor®) for treatment of SEGAs in individuals with TSC. Other clinical trials are ongoing to test the efficacy and safety of mTOR inhibitors for other manifestations of TSC.

Genetic testing allows the person with TSC, his or her family and the health care professional to know exactly what mutation or deletion caused the disorder. This information may be desired for a number of reasons. In some cases, the identification of a TSC1 or TSC2 mutation will enable the health care professional to make
a definite diagnosis of TSC in a person who may not yet have developed enough symptoms for a clinical diagnosis. While a negative DNA test result cannot rule out a diagnosis of TSC, a positive one does confirm a diagnosis. However, it is important to remember that the TSC genes have a high number of polymorphisms (changes in the sequence of the genes that are not disease-causing). This requires that all genetic alterations found in an individual be compared to a database of known mutations and benign polymorphisms.

Upon identifying the TSC mutation in the affected individual, any other at-risk family members can be easily tested to determine whether they are also affected. In addition, the availability of DNA mutation testing results makes reproductive planning options and prenatal diagnosis available, if desired by the family. A molecular genetic diagnostic test is commercially available through Athena Diagnostics. For more information visit their website at www.athenadiagnostics.com or call 1-800-394-4493, extension 2.
Many of the features of TSC are nonspecific and can be seen as isolated findings or as features of another disorder.

SKIN

Hypopigmented macules have been observed in 0.8 percent of newborns in some studies and in most cases have no medical significance. Other conditions with hypopigmented macules as part of the phenotype include vitiligo, nevus depigmentosus, nevus anemicus, piebaldism and Vogt-Koyang-Harada syndrome. Associated findings can usually distinguish these conditions from TSC. One study determined that individuals with TSC typically have three or more hypopigmented macules.

A single facial angiofibroma, likewise, is not diagnostic of TSC. On physical examination, acne vulgaris, acne rosacea or multiple trichoepithelioma can be mistaken for angiofibromas, but biopsy easily distinguishes among them. The shagreen patch of TSC does not differ from other connective tissue nevi, which are rare but are seen sporadically or in families.

Ungual fibromas can result from trauma, but generally these are single lesions and their presence can be explained (e.g., a particular manner of holding a golf club). Ungual fibromas must be distinguished from epithelial inclusion cysts, verruca vulgaris and infantile digital fibromatosis.

CENTRAL NERVOUS SYSTEM (CNS)

The brain lesions seen in individuals with TSC can be distinguished with CNS imaging studies; cortical tubers, subependymal giant cell astrocytomas or tumors, and subependymal nodules are easily distinguishable from one another. White matter migration lines and focal cortical dysplasia probably arise by a similar mechanism and are often seen in individuals with TSC. However, these lesions can be seen independently and are relatively nonspecific; they are considered a minor diagnostic criteria for TSC.

Seizures and epilepsy are no longer included in the diagnostic criteria for TSC because the differential diagnosis for epilepsy is so large and varied. Even infantile spasms are not specific enough to be included because they are seen in children who do not have TSC.

KIDNEYS

Renal cysts are seen commonly in the general population (1 to 2 percent), but are uncommon in persons under 30 years of age. AMLs are rare tumors sometimes observed in individuals with no other medical problems. Studies have shown that these sporadic AMLs can have loss of heterozygosity for the TSC2 gene and surrounding markers, leading to the conclusion that these sporadic AMLs occur as a result of loss of function of the TSC2 gene in individuals not otherwise affected with TSC.

LUNGS

Some individuals who have sporadic LAM also have renal or lymph node AMLs, but do not have other findings of TSC. Children born to these individuals do inherit TSC or LAM from their affected parent. It was agreed at the TSC Consensus Conference that individuals affected with LAM and AMLs who have no other feature of TSC do not meet diagnostic criteria for TSC. With the introduction of molecular diagnostic testing for TSC, individuals diagnosed with LAM should consider obtaining testing since very mild cases of TSC may go undiagnosed.

HEART

Primary cardiac tumors are diagnosed in 0.2 percent of children presenting to pediatric cardiac referral centers, and in 0.27 percent of pediatric autopsies. It is currently thought that the majority (perhaps as many as 100%) of children with cardiac rhabdomyomas have TSC. Conversely, the prevalence of cardiac rhabdomyomas in children with TSC is dependent on the age of examination, but is estimated to be 47 to 67 percent.
Because TSC affects multiple organs, diagnostic studies are recommended for all individuals with a new diagnosis of TSC regardless of their outward manifestations of the disease. For example, published recommendations for diagnostic and follow-up evaluations suggest baseline imaging using either CT or cranial MRI modalities regardless of the presence of neurological symptoms. This suggestion is largely due to the risk of identifying a subependymal giant cell astrocytoma (SEGA), which has an increased growth potential over subependymal nodules (SEN) and therefore needs more extensive follow-up.

In order to ensure comprehensive care, referrals to a variety of specialists familiar with TSC should be coordinated. If possible, a referral to a multidisciplinary clinic specializing in TSC is ideal, as the center will likely house all necessary specialists, including a dermatologist, neurologist, geneticist, nephrologist and/or urologist, ophthalmologist and cardiologist. Further recommended examinations are listed in Table 3 below, and include referrals for neurodevelopmental assessment, given the high risk of intellectual disability, developmental delay, and behavioral problems in individuals with TSC. Continued evaluation (Tables 3 and 4 on the following pages) is suggested throughout the life of the individual with TSC, as many features may not be present until later in the individual’s life or may grow in size with age.

The clinician making the diagnosis of TSC may recommend that other, at-risk family members also be evaluated for this condition. TSC is an autosomal dominant genetic disorder, and while all persons with TSC are thought to have symptoms, the presentation of their symptoms can be highly variable even within the same family. A determination of whether or not the parents and siblings of a diagnosed child are affected is important to the provision of later genetic counseling (see Genetics of TSC and the Role of Genetic Testing), thereby making an accurate diagnosis necessary. While an estimated sixty percent of individuals diagnosed with TSC are born into families with no prior history of the disease (i.e., sporadic mutation), it is becoming more and more common for adults to learn of their own diagnosis following the diagnosis of their child or because of other medical concerns.

There is some debate as to which evaluations are necessary when testing the parents of a newly diagnosed child. The consensus is that a thorough physical examination conducted by a physician familiar with TSC will detect the majority of affected individuals. The evaluation should include a skin examination with a Woods lamp (ultraviolet light) and a retinal examination through dilated pupils. Further examination via diagnostic imaging techniques of the brain and kidneys should be ordered for the parents of children with TSC and/or for adults with medical issues that suggest a diagnosis of TSC. Diagnostic molecular testing should also be discussed with the parents of a newly diagnosed child and/or adults suspected or diagnosed with TSC.
### Table 3. Diagnostic and Surveillance Screen in TSC

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>INITIAL TESTING</th>
<th>REPEAT TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodevelopmental testing</td>
<td>At diagnosis, at school entry, at transitions and as needed if changes in behavior and/or educational performance.</td>
<td>As indicated (see Table 4)</td>
</tr>
<tr>
<td>Ophthalmologic exam</td>
<td>At diagnosis.</td>
<td>As indicated.</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>If seizures occur.</td>
<td>As indicated.</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>At diagnosis.</td>
<td>As indicated.</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>At diagnosis if a child or if cardiac symptoms occur.</td>
<td>If cardiac dysfunction occurs.</td>
</tr>
<tr>
<td>Renal magnetic resonance imaging</td>
<td>At diagnosis.</td>
<td>Every 1 to 3 years depending on renal involvement. Every year once renal involvement is identified, and more frequently if needed due to symptoms.</td>
</tr>
<tr>
<td>Chest computed tomography</td>
<td>At adolescence or young adult.</td>
<td>Every 1 to 3 years, and/or if pulmonary dysfunction occurs.</td>
</tr>
<tr>
<td>Cranial computed tomography*</td>
<td>At diagnosis.</td>
<td>Children/adolescents: every 1 to 3 years until the age of ~21 years unless symptomatic.</td>
</tr>
<tr>
<td>Cranial magnetic resonance imaging*</td>
<td>At diagnosis.</td>
<td>Children/adolescents: every 1 to 3 years until the age of ~21 years unless symptomatic.</td>
</tr>
</tbody>
</table>

*Either cranial CT or MRI, but usually not both.

Source: Adapted from Roach et al., 1999.
Table 4. The consensus clinical guidelines for the assessment of behavioral, psychiatric, intellectual, academic, and neuropsychological skills in TSC.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>AGE RANGE</th>
<th>GENERAL PURPOSE OF ASSESSMENT</th>
<th>GENERAL AREAS TO ASSESS</th>
<th>AREAS OF PARTICULAR CONCERN IN TSC</th>
<th>BEHAVIORAL, PSYCHIATRIC, AND ACADEMIC DISORDERS OF PARTICULAR CONCERN IN TSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td></td>
<td>Initial assessment of cognitive and behavioral profile</td>
<td>As listed for chronological age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infancy</td>
<td>Birth – 12 mos</td>
<td>To perform a baseline assessment for regular monitoring of development</td>
<td>Global standardized assessment of infant development</td>
<td>Impact of seizure onset and treatment on development</td>
<td></td>
</tr>
<tr>
<td>Toddler</td>
<td>1y – 2y11m</td>
<td>To identify early developmental disorders</td>
<td>Global intellectual ability and adaptive behaviors</td>
<td>Quality of eye contact, joint attention, reciprocity</td>
<td>Autism and autism spectrum disorders, Severe aggressive outbursts, Severe sleep problems</td>
</tr>
<tr>
<td>Pre-school</td>
<td>3 y to school entry</td>
<td>Evaluation of cognitive and behavioral profile to ensure the provision of appropriate educational programs</td>
<td>Global intellectual ability Specific neuropsychological skills: • Receptive and expressive language • Social-communication skills • Attentional and executive skills • Visuospatial skills • Motor skills</td>
<td>Uneven profile of abilities Poor expressive language Poor reciprocity, peer interaction Poor regulation of affect and impulse Poor bilateral coordination</td>
<td>Autism and ASD ADHD and related disorders Self-injurious behavior</td>
</tr>
<tr>
<td>Early school years</td>
<td>6y-8y</td>
<td>Monitoring the child’s ability to make appropriate educational progress</td>
<td>Global intellectual abilities Specific neuropsychological skills: • Receptive and expressive language • Social-communication skills • Memory • Attentional and executive skills • Visuospatial skills • Motor skills</td>
<td>Best time to establish baseline to assess whether specific cognitive skills and academic performance are discrepant from global intellectual abilities Poor expressive language and word retrieval Rote learning difficulties Selective attention, sustained attention difficulties</td>
<td>Academic difficulties (reading, writing, spelling, mathematics) ADHD and related disorders Peer problems Aggressive behaviors</td>
</tr>
</tbody>
</table>
### Table 4. The consensus clinical guidelines for the assessment of behavioral, psychiatric, intellectual, academic, and neuropsychological skills in TSC. (continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age Range</th>
<th>General Purpose of Assessment</th>
<th>General Areas to Assess</th>
<th>Areas of Particular Concern in TSC</th>
<th>Behavioral, Psychiatric, and Academic Disorders of Particular Concern in TSC</th>
</tr>
</thead>
</table>
| Middle school    | 9y-12y    | Comprehensive review of child's abilities, specific learning difficulties, and behavioral problems in preparation for transition to secondary education | Global intellectual abilities, Specific neuropsychological skills:  
  - Receptive and expressive language  
  - Social-communication skills  
  - Memory skills  
  - Attentional and executive skills | Subtle deficits of social communication, unusual interests, Poor working memory, episodic memory, Planning, organizational abilities, multi-tasking difficulties | Asperger's syndrome, Peer problems, Academic difficulties (reading, writing, spelling, mathematics) |
| Adolescence      | 13y-16y   | Determining individual needs and the support required for transition into adulthood                                | Global intellectual abilities, Specific neuropsychological skills:  
  - Attentional and executive skills  
  - Vocational assessment with knowledge of cognitive strengths and weaknesses  
  - Adaptive behavior and daily living skills | Poor judgement, decision-making, Depressive disorders, Anxiety disorders, Peer problems, Epilepsy-related psychotic disorders |                                                                                                    |
| Adults           | 18y+      | Newly diagnosed adults: Assessment of cognitive, behavioral and vocational profile, determining bio-psycho-social needs | Global intellectual abilities, Specific neuropsychological skills:  
  - Attentional and executive skills  
  - Memory skills | Difficulty with integrational skills, Working memory, episodic memory problems | Depressive disorders, Anxiety disorders, Epilepsy-related psychotic disorders |
| Adults (follow-up) | 18y+     | Monitoring for emergence of psychiatric problems or changes in existing cognitive and behavioral profile              | Dependent adults:  
  - Annual review of social care needs and support  
  Independent adults:  
  - Vocational advice  
  - Genetic counseling as appropriate  
  - Review if problems arise | Pay particular attention to change in cognitive abilities or behavior, Pay particular attention to change in cognitive abilities, vocational performance and behavior | Depressive disorders, Anxiety disorders, Epilepsy-related psychotic disorders |

The table shows the time points recommended for evaluation and the goals of evaluation and lists specific areas of concern for each age group. Table reproduced with permission from de Vries et al. (2005).

Note: Many features listed in these columns can present at any age, but are listed here at stages most commonly associated with the emergence of such difficulties in TSC.
ADDITIONAL IMAGING AND TESTING

In addition to the three main imaging procedures usually undertaken for an individual with TSC (CT or MRI scans of the brain, renal CT and/or ultrasounds and echocardiograms), additional imaging procedures or testing may be conducted. Some centers perform these evaluations annually, at least until adulthood. This is a topic of some controversy, and the natural history of TSC is currently being studied through the TS Alliance Natural History Database Project. Additional imaging should be performed as necessary to follow growing lesions or to monitor organ involvement.

POSITION EMISSION TOMOGRAPHY (PET)

There is not current indication for routine PET scanning in individuals with TSC. However, PET scans may be useful when individuals are undergoing evaluation as candidates for epilepsy surgery. PET scanning with the tracer alpha-methyltryptophan may have particular utility in identifying epileptogenic tubers as part of the evaluation for epilepsy surgery.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

There is no current indication for routine SPECT scanning in individuals with TSC. However, SPECT scans may be useful when individuals are being evaluated as candidates for epilepsy surgery.

MAGNETOENCEPHALOGRAPHY

There is no current indication for routine MEG scanning in individuals with TSC. However, MEG scans may be useful when individuals are being evaluated as candidates for epilepsy surgery.

ELECTROENCEPHALOGRAM

Electroencephalogram (EEG) should be performed on individuals with TSC when seizures are suspected. Follow-up EEGs are performed as clinically indicated. Some individuals with TSC have coexisting recognizable epilepsy syndromes such as West syndrome (i.e., infantile spasms) or Lennox-Gastaut syndrome. If so, prolonged video/EEG telemetry may be useful to help:

- Detect syndrome-specific EEG findings
- Capture and classify each of the multiple seizure types
- Educate parents on which of the events are seizures and which are non-epileptic behavioral events

ELECTROCARDIOGRAM AND ECHOCARDIOGRAPHY

A baseline electrocardiogram (ECG) is recommended for all individuals newly diagnosed with TSC since cardiac arrhythmias, although rare, may have sudden death as their presenting symptom. Follow-up ECGs should be performed every two to three years thereafter until puberty or as needed. A baseline echocardiogram should be performed on all children diagnosed with TSC and later as clinically indicated. Adults with a new diagnosis of TSC should undergo echocardiography only if symptomatic.

TREATMENT

The goals of treatment for individuals with TSC are the same as for all individuals with a multi-system chronic condition: providing the best possible quality of life with the fewest complications from the underlying disease process, fewest adverse treatment effects and fewest medications. TSC often has been under-treated, particularly from a neurological standpoint, often based on
the unfounded view that these individuals will have a poor outcome regardless of any therapy undertaken. This is clearly not the case. Even in individuals with TSC and infantile spasms, long-term outcome is not universally poor, as has been classically thought. At least 9 percent of individuals with TSC and infantile spasms have normal intelligence as adults or at long-term follow-up.

A recent study indicates that infants diagnosed with TSC prior to the onset of seizures who are treated with Vigabatrin in response to the development of an abnormal EEG have fewer seizures, a lower incidence of drug-resistant epilepsy, and fewer children require polytherapy to treat their epilepsy. In addition, fewer treated children had significant developmental delay and intellectual disabilities at 24 months of age compared to children with TSC who were treated only after the onset of clinical seizures.

Appropriate and effective therapy is not only aggressive but also relies upon recognition of the natural history of the various lesions of TSC. For example, large AMLs may be mistaken as renal cell carcinomas, solely on the basis of their size. Embolization or kidney-sparing surgery should always be done so as to avoid the unnecessary removal of the affected kidney.

ANTIEPILEPTIC DRUG THERAPIES

The main complication of TSC requiring long-term medical therapy is epilepsy. Antiepileptic medications (AEDs) are the mainstay of therapy for individuals with TSC. Unfortunately, no one medical treatment usually results in satisfactory relief for all or even most individuals with TSC. A combination of medical treatment modalities is then frequently required.

The choice of specific AEDs for treating seizures in individuals with TSC is based on the seizure type(s), epilepsy syndrome(s), other involved organ systems, age of the individual, and AED side effect profiles and formulations available.

The consensus developed at the NIH Tuberous Sclerosis Complex Consensus Conference in 1998 was that Vigabatrin was the drug of choice to treat infantile spasms in children with TSC. Vigabatrin (Sabril®) was approved by the FDA in the United States in 2009. The FDA requires that physicians who wish to prescribe Vigabatrin register prior to prescribing the medication. For more information, go to www.sabril.com

ACTH may also prove useful for the treatment of infantile spasms and is utilized in some cases of TSC, and if Vigabatrin is not effective. H.P. Acthar Gel® was approved by the FDA for the treatment of infantile spasms in 2010. The advantage of Vigabatrin use is the ability to rapidly escalate the dosage at the initiation of treatment, rapid efficacy, suitability for outpatient treatment and particularly good tolerability with generally only minor adverse effects with the exception of visual field loss (see below). There is only preliminary evidence that other broad spectrum AEDs may prove useful to treat infantile spasm.

The safety of Vigabatrin has caused concern since a specific visual field loss has been documented in treated adults and some children. There have been only isolated reports of visual field loss in children on short-term treatment with Vigabatrin having infantile spasms, but the parents must weigh the benefits and risks of Vigabatrin treatment with their child’s health care providers. The current problem is determining the risk-benefit ratio of Vigabatrin in children with infantile spasms, and specifying the groups where its use could be optimal. Visual field loss is usually asymptomatic and can be detected only by perimetric visual field studies. In children, especially in very young children or those with intellectual disabilities, it is difficult if not impossible to detect the visual field loss, and it is not yet known if children are at higher or lower risk of this adverse effect. Until a clear answer about the occurrence of this adverse effect in children has been established through randomized study, Vigabatrin may still be considered first-line therapy in infantile spasms. Children who do not achieve a good
response to Vigabatrin should be switched to ACTH or to a corticosteroid such as prednisone.

Long-term use of agents with prominent sedating properties, such as benzodiazepines or barbiturates, generally should be avoided. These drugs often aggravate underlying behavioral or cognitive problems, and there are less toxic and often more effective alternatives.

**WARNING:** Carbamazepine, oxcarbazepine and phenytoin may cause exacerbation of seizures, particularly in younger children and infants with TSC, and some clinicians believe that these AEDs can precipitate or aggravate infantile spasms. While often valuable in older children and adults in whom partial seizures predominate, caution is warranted in their use in infants and young children. It is recommended that these drugs not be used in children with TSC who are experiencing infantile spasms.

**KETGENIC DIET**

An additional therapy for intractable epilepsy is the ketogenic diet. The ketogenic diet, and variations of the diet, has been increasingly used in recent years due to their efficacy and a perception by families that it is more “natural” treatment. While it is often effective for some children, the ketogenic diet should be considered like any other medical intervention to have significant side effects and possible complications. These include kidney stones, hypoglycemia, metabolic disturbances and suppression of growth. In addition, the diet requires a very motivated and compliant family to adhere to the diet to ensure a state of ketosis in the individual. Despite these caveats and concerns, the ketogenic diet is clearly efficacious in some individuals who have medically refractory seizures and should be considered for children with intractable epilepsy.

**EPILEPSY SURGERY**

Neurosurgical care for seizures in an individual with TSC may involve focal cortical resection, corpus callosotomy and/or vagus nerve stimulation.

**FOCAL CORTICAL RESECTION:** In selected individuals with TSC, the resection of one or more seizure foci can be beneficial. Neurosurgeons with experience performing epilepsy surgery will do a complete evaluation to determine if an individual with TSC is likely to benefit from surgery. Even if seizure freedom is not achieved, surgery may reduce the severity and frequency of seizures for individuals with TSC. Epilepsy surgery should be considered for any individual with TSC who has seizures that are not controlled by AEDs.

**CORPUS CALLOSOTOMY:** Corpus callosotomy can be effective in reducing atonic and tonic seizures (i.e., drop attacks), but usually is not helpful for other seizure types and is considered palliative rather than curative. Seizure freedom following corpus callosotomy is rare, but can occur.

**VAGUS NERVE STIMULATION:** In the overall epilepsy population, 30 percent of individuals treated with vagus nerve stimulation (VNS) experienced at least a 50 percent reduction in seizure frequency, while 30 percent had a 90 percent or greater reduction and 40 percent had no improvement at all. In a small study of 20 individuals with TSC, nine individuals experienced (without adverse effects) at least a 50 percent reduction in seizure frequency, while 30 percent had no improvement at all. In a small study of 10 individuals with TSC, nine of these individuals experienced (without adverse effects) at least a 50 percent reduction in seizure frequency; half had a 90 percent or greater reduction in seizure frequency following treatment with VNS.

Although the results of this one study are promising, the small number of study participants with TSC makes it difficult to generalize to the entire TSC population.

As discussed, the pathologic manifestations of TSC can cause variable symptoms based on the size and location of the hamartomas. Therefore, a variety of management considerations are necessary. Table 5 describes the various treatment considerations for each of the features.
### Table 5. Treatment Considerations

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>PATHOLOGIC MANIFESTATIONS</th>
<th>MAJOR CLINICAL SYMPTOMS</th>
<th>RECOMMENDATIONS FOR MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td>Hypomelanotic macules</td>
<td>Hypomelanotic macules are frequent in the general population, but &gt;3 macules found in most individuals with TSC.</td>
<td>Utilize cosmetics to cover hypomelanotic macules on face or in other conspicuous locations, and use good sun protection.</td>
</tr>
<tr>
<td></td>
<td>Facial angiofibromas</td>
<td>Facial angiofibromas occur in a malar distribution.</td>
<td>Facial angiofibromas may require repeated laser treatment. Other methods such as dermal abrasion and surgical removal may be useful in some cases.</td>
</tr>
<tr>
<td></td>
<td>Ungual fibromas</td>
<td>Bleeding from ungula fibroma.</td>
<td>Surgical or laser removal may be required.</td>
</tr>
<tr>
<td></td>
<td>Shagreen patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-psychological and Cognitive</strong></td>
<td>Mild to severe learning disabilities, mood and affective disorders, autism spectrum disorder</td>
<td>Learning disabilities and behavioral disturbances (highly variable).</td>
<td>Early childhood programs and ongoing evaluations and treatment for specific issues.</td>
</tr>
<tr>
<td><strong>Ophthalmologic</strong></td>
<td>Mulberry lesions at margin of optic disc, plaque-like hamartomas</td>
<td>Vast majority of retinal lesions are clinically insignificant.</td>
<td>Lesions require careful evaluation for detection.</td>
</tr>
<tr>
<td></td>
<td>achromic patches</td>
<td>Reports of visual compromise have been documented.</td>
<td>When present, these lesions should be followed serially to rule out retinoblastomas.</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Lymphangio-leiomyomatosis (LAM)</td>
<td>Commonly adult women, ages 20-40. Clinical dyspnea and/or hemoptysis. Diffuse reticular pattern radiographically. Respiratory failure.</td>
<td>Serial pulmonary function testing, chest CT. Pulmonary decortication when clinically indicated. mTOR inhibitor may be clinically indicated if progression of disease is noted. Lung transplantation for end-stage disease.</td>
</tr>
</tbody>
</table>
### Table 5. Treatment Considerations (continued)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Pathologic Manifestations</th>
<th>Major Clinical Symptoms</th>
<th>Recommendations for Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Angiomyolipomas</td>
<td>AMLs may be locally invasive and involve lymph nodes.</td>
<td>Annual CT for those with renal manifestations. Semiannual CT in individuals with AMLs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic AMLs ≥3.5-4.0 cm should be studied angiographically and considered for treatment.</td>
<td>Aggressive approach to AMLs ≥3.5 cm with either arterial embolization or surgical resection.</td>
</tr>
<tr>
<td></td>
<td>Renal Cysts</td>
<td>Most single renal cysts are first discovered in childhood.</td>
<td>None.</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma</td>
<td>Carcinomas typically discovered at younger ages than expected for the general population.</td>
<td>Exploration with renal conserving surgery in those individuals with suspected renal cell carcinoma.</td>
</tr>
<tr>
<td></td>
<td>Polycystic kidney disease</td>
<td>Multiple, bilateral cysts present at birth or at a very early age.</td>
<td>Frequent monitoring and treatment of hypertension with medication may be necessary. Renal failure may eventually necessitate renal transplant.</td>
</tr>
<tr>
<td>CNS</td>
<td>Cortical hamartomas (tuber)</td>
<td>Seizures.</td>
<td>Complete resolution of seizures in select individuals unresponsive to anticonvulsants has been realized with epilepsy surgery.</td>
</tr>
<tr>
<td></td>
<td>Subependymal nodules</td>
<td>None.</td>
<td>None.</td>
</tr>
<tr>
<td></td>
<td>Subependymal giant cell astrocytoma (SEGA)</td>
<td>Headache, increased seizure frequency and/or severity, nausea, behavioral changes, weight loss, changes in vision.</td>
<td>Obstructing SEGAs have been successfully managed with either surgical removal with or without ventriculoperitoneal shunt or treatment with an mTOR inhibitor. Findings support notion of early tumor diagnosis by periodic neuroimaging and prompt treatment.</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Rhabdomyoma</td>
<td>Very common and often multiple in neonates, but generally shrink in size with age.</td>
<td>If symptomatic, medical management is usually recommended with antiarrhythmic agents and diuretics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac rhabdomyomas that block blood flow in heart.</td>
<td>Surgical intervention may be needed, but may be confounded by pre-existing unstable cardiac function.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most who develop cardiac dysfunction present in the prenatal or immediate postnatal period.</td>
<td>Overall, prognosis is poor in symptomatic individuals with extensive intramural involvement.</td>
</tr>
</tbody>
</table>

Source: Adapted from Roach et al., 1998
CONCLUSION

TSC is a multi-system disorder that can be difficult to diagnose, has an unpredictable course and is an autosomal dominant genetic disease that commonly is a sporadic mutation. Given the prevalence of TSC, it is likely that many health care providers will come into contact with a number of affected individuals in the course of their practice. Many individuals with TSC, particularly those with milder cases not involving epilepsy, will remain undiagnosed unless other medical symptoms or a diagnosis in a relative leads to the diagnosis of TSC. Health care professionals, particularly those working in neurology, pediatrics, nephrology, dermatology and cardiology, need to become familiar with the more common clinical manifestations of TSC. Familiarity will enable appropriate referrals and more rapid, accurate diagnoses and treatment for affected individuals and their families.

Upon diagnosing TSC, health care professionals should remember that the manifestations of this disorder can be varied and occur in a variety of organ systems. Therefore, TSC-related care should be coordinated via a multidisciplinary clinic or with a variety of specials. Given the unpredictability of symptoms and the complicated genetic nature of TSC all affected individuals and their relatives should be referred for genetic counseling with a geneticist or genetic counselor. Genetic testing can play a major role in clarifying diagnoses, accurately diagnosing family members of affected individuals and providing the option of reproductive testing.

Aggressive treatment of symptoms should be carried out for all individuals with TSC and those who will need ongoing support and care should receive appropriate services and medical interventions throughout their lives. With complete imaging and clinical studies at the time of diagnosis, followed by a careful program of screening and follow-up care, many individuals with TSC can lead long, independent lives.
Angiofibroma — papules with a smooth surface and a color that varies from skin color to red to reddish brown that predominate on the central face, especially involving the nasolabial folds and extending symmetrically onto the cheeks, nose and chin.

Angiomyolipoma (AML) — AMLs consist of abnormal blood vessels (angio-), smooth muscle cells (myo-) and fat (lipoma) with each present in varying degrees within the tumor.

Cardiac rhabdomyoma — most frequent cardiac tumor in children composed of aberrant glycogen-filed myocytes.

Dysplastic — abnormally shaped or dysmorphic neurons that likely make aberrant synaptic connections.

Hamartias — well-circumscribed group of dysplastic cells, appropriate for the organ or tissue involved. The cells do not multiply or grow more rapidly than normal cells in the organ.

Hamartomas — well-circumscribed group of dysplastic cells that tend to multiply excessively, thereby growing as a benign tumor that may or may not cause symptoms.

Hypomelanotic macules — also called Fitzpatrick patches, ash leaf spots, or white spots. Typically oval at one end and pointed at the other, but can be all sizes and shapes. Composed of normal number of melanocytes, but these cells produce less melanin (skin pigment).

Intellectual disability — refers to a condition of arrested or incomplete development of the mind that can occur with or without any other physical or mental disorders and is characterized by impairment of skills and overall intelligence in areas such as cognition, language, and motor and social abilities. This includes children, adolescents, adults and the elderly population.

Lymphangioleiomyomatosis (LAM) — pulmonary manifestation of TSC, also seen in sporadic cases, that involves the lymphatic system (lymph-), blood vessels (angio-), and smooth muscle (leiomyoma).

Shagreen patch — connective tissue hamartomas consisting of various amounts of vascular structures, fat, collagen, elastic tissue, smooth muscle and skin.

Subependymal giant cell astrocytoma (SEGA) (or tumor, SGCT) — tumors that generally appear in the first 20 years of life, and are thought to develop from subependymal nodules. SEGAs extend into the lateral ventricles and often obstruct the flow of cerebral spinal fluid and cause hydrocephalus, focal neurological deficits and even death if not treated. Contain a large number of astrocytes and giant cells that have markers of both neurons and glia.

Subependymal nodule — nodular lesions (typically less than 1 cm in size) located on the surfaces of the lateral and third ventricles in the brain. Develop in fetal life and often degenerate or calcify during later life. May grow to from a SEGA (see above).
REFERENCES


REFERENCES


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THANK YOU

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