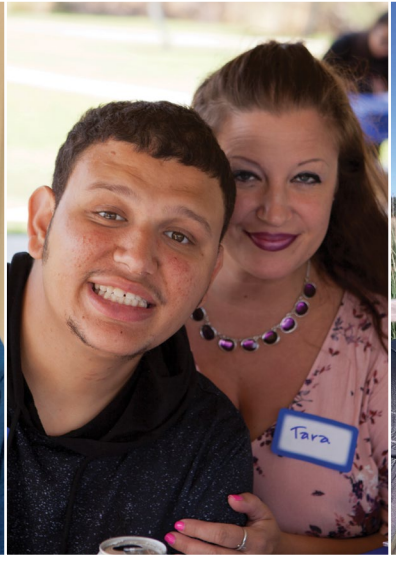
An introduction to tuberous sclerosis complex

TSC Alliance®



This booklet is intended to provide basic information about tuberous sclerosis complex (TSC). It is not intended to, nor does it, constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment or otherwise based on the information in this brochure without first consulting a physician. The TSC Alliance® does not promote or recommend any treatment, therapy, institution or healthcare plan.

Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder that can affect multiple organ systems. Care for an individual with TSC requires ongoing surveillance management. This may involve medical specialists, allied healthcare specialists and those skilled in educational and psychological care. As such, it is important for individuals with TSC, their family and/or caregivers to educate themselves about the disease and to facilitate communication between the healthcare providers and other professionals with whom they interact.

This booklet explains the clinical manifestations of TSC and its variable features; outlines some of the commonly needed medical tests and their purpose; and helps individuals cope with the diagnosis. Luckily, a strong bond exists within the vast TSC community, and the TSC Alliance® helps provide the guidance, support, services and networking to improve the lives of those affected by TSC.

Contents

What is TSC?

Tuberous sclerosis complex (TSC) is a genetic disorder that affects many organs and causes non-cancerous tumors in the skin, kidney, brain, heart, eyes, lungs, teeth or oral cavity, and other organs. Individuals with TSC may be initially diagnosed because of involvement in any or all of these organs, often depending on the age at which a person receives the diagnosis. The severity of TSC can range from mild to severe, even within the same family if more than one person has TSC.

The diagnosis of TSC and further evaluation of people at risk for TSC involve careful examination of the skin, heart, eyes, brain, lungs and kidneys, as well as genetic testing. It is important to know the disorder's manifestations and to follow the recommendations for screening and evaluating TSC.

It is estimated that TSC affects 1 in 6,000 live births. Nearly 1 million people worldwide are estimated to have TSC, with approximately 50,000 in the United States. TSC shows no gender bias and occurs in all races and ethnic groups.

Individuals of all ages may receive the diagnosis of TSC depending on the manifestations they have. The diagnosis of TSC may occur after the development of facial angiofibromas in an adolescent, because of the presence of heart tumors (cardiac rhabdomyomas) in a newborn or the onset of kidney problems in an adult. However, in the majority of cases, the diagnosis of TSC comes after the start of seizures.

How is TSC diagnosed?

Clinical diagnosis of TSC is based on a careful physical exam in combination with imaging studies. The specific studies to be performed depend on the age of the individual who is suspected to have TSC. Computed tomography (CT) or magnetic resonance imaging (MRI) may be used to image the brain to look for tubers and other brain involvement. A high-resolution CT (HRCT) of the lungs or MRI of the liver, pancreas and kidneys may show tumors and/or cysts in those organs. Doctors should carefully examine the skin for the wide variety of skin features, such as fibromas found on the fingernails and toenails, dental pits and/or gum fibromas found on examination of the mouth. A Wood's lamp or ultraviolet light may be useful for locating the hypomelanotic macules (areas of the skin that are lighter than the surrounding, normal skin), which can be hard to see on infants and individuals with pale or fair skin. The eyes should be examined for abnormalities of the retina. The heart should also be examined using an echocardiogram (ultrasound of the heart) and EKG (electrocardiogram, or ECG) to detect cardiac rhabdomyomas.

The International TSC Consensus Group updated the 2012 diagnostic criteria and surveillance and management recommendations in 2021. Genetic testing for TSC can be used to diagnose and/or confirm a clinical diagnosis if a disease-causing variant is found in an individual. There is no single clinical feature absolutely specific to the condition. In addition, many features of TSC, such as seizures and intellectual disability, are seen in individuals *without* TSC. Therefore, a constellation of features is necessary for the clinical diagnosis, with certain features contributing more heavily to the diagnosis, and an increasing number of features making the clinical suspicion of TSC more likely.

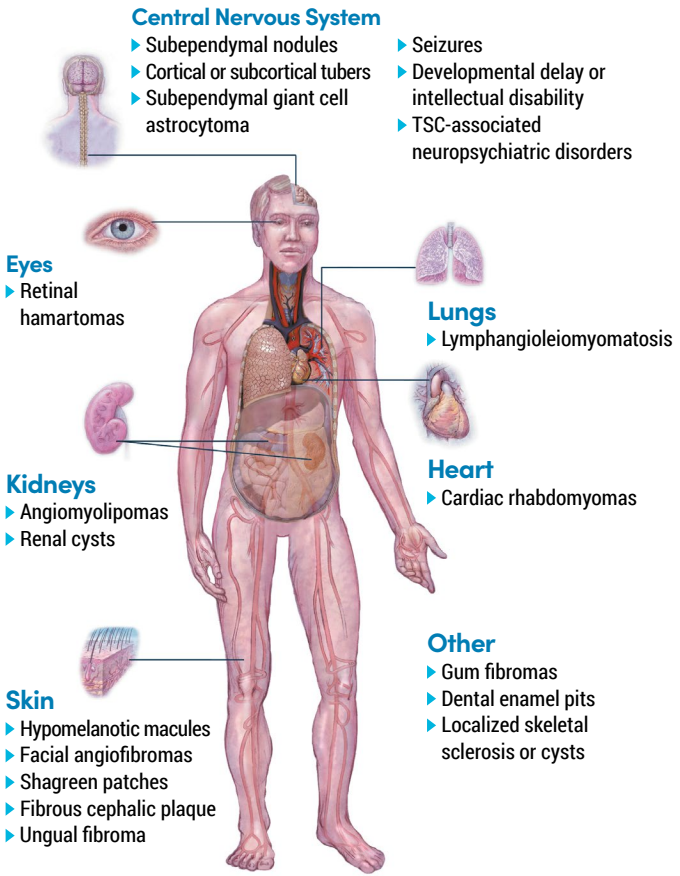
Clinical features of TSC

Brain and neurological function

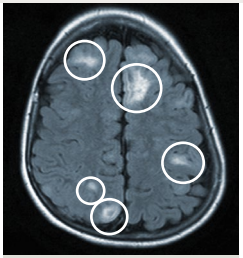
Several types of brain abnormalities may be seen in individuals with TSC, including cortical tubers, subependymal nodules and subependymal giant cell astrocytoma (SEGA). Some individuals will have all of these changes, whereas others will have none. The vast majority of people with TSC, however, will have one of these abnormalities.

Cortical tubers

Cortical tubers are best visualized using MRI of the brain. The cortical tuber, for which TSC was originally named, is a disorganized area of the brain that contains abnormal cells. Some individuals with TSC will have numerous tubers, whereas others will not have any. The tubers are more difficult to see in an infant's brain than in a more mature brain, but it is still possible to image the tubers in a newborn. Tubers and/or the brain area surrounding a tuber play a role in the development of



seizures in individuals with TSC. However, recent studies have shown that there may also be numerous scattered abnormal cells throughout the brain of an individual with TSC, and the role of these cells in seizure development is not clear.



Multiple cortical tubers shown on MRI.

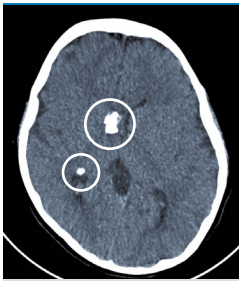
Subependymal nodules

Subependymal nodules (SENs) are small accumulations of cells that are located on the walls of the cerebral ventricles (the spaces in the brain that contain cerebrospinal fluid [CSF]). The nodules often accumulate calcium and are then easily identified on MRI imaging of the brain.

Subependymal giant cell astrocytoma (SEGA)

This type of non-cancerous brain tumor develops in 5% to 15% of individuals with TSC and may be detected during pregnancy or at birth. SEGA growth is most common during childhood, teenage and young adult ages, and the chance for its growth greatly decreases after the mid-20s. An MRI study should be performed at the time of diagnosis of TSC to get a baseline image, and then every 1 to 3 years until the age of 25 years. Follow-up scan frequency should be determined by the physician based on various clinical factors such as the previously described symptoms. Similarly, a follow-up scan should be performed more frequently than annually if SEGA has increased in size between consecutive imaging studies.

If a SEGA grows large enough, it can block the flow of CSF inside the ventricles of the brain causing hydrocephalus. With this condition, pressure will build up within the brain resulting in symptoms that may include vomiting, nausea, headache and changes in appetite, behavior and mood. Should this occur, the tumor may have to be removed surgically. Since the SEGA is a benign (non-cancerous) tumor, radiation should never be used to treat this type of brain tumor. Everolimus or Afinitor® is an mTOR inhibitor drug taken by mouth to shrink the tumor. In the United States, the Food and Drug Administration (FDA) approved this drug in 2010 to treat SEGA. Common side effects associated with these drugs include stomatitis (mouth sores) and upper respiratory infections. Recurrence of tumor growth has been reported when mTOR inhibitor therapy is stopped. It



Tumors shown by CT scan with contrast.

is important to discuss the risks and benefits of surgery compared to mTOR inhibitor therapy with the doctor.

Neurological involvement

Epilepsy, intellectual disabilities (mild to severe), and psychiatric and behavioral problems are the most common neurological manifestations in TSC. Individuals with milder forms of TSC commonly have little or no neurological impairment, although they may still have minor learning disabilities and/or mental health issues.

Epilepsy/seizure disorders

Seizures remain one of the most common neurological features of TSC, occurring in 85% of individuals with TSC. Some infants will be diagnosed with TSC after they begin having a type of seizure called infantile spasms. Older children and adults may develop multiple types of seizures including generalized and focal onset seizures. More than 50% of individuals with TSC who have epilepsy will not respond to standard antiseizure medications and have intractable epilepsy.

Techniques can be used to identify the specific area where the seizures begin (called the seizure focus) and improved neurosurgical techniques used to remove that specific area of the brain. Although not all individuals with TSC who undergo brain surgery for epilepsy are seizure-free, many cases result in a significant improvement in seizure frequency and/or severity. In the United States, vigabatrin (Sabril®/Vigadrone®) and adrenocorticotropic hormone (ACTH, Acthar Gel®) are approved for treatment of infantile spasms. Additionally, everolimus and cannabidiol (Epidiolex®) are approved to treat seizures associated with TSC. If you live in another country, ask your/your child's doctor if these drugs are available.

Intellectual disability

Approximately 45% to 60% of individuals with TSC have intellectual disabilities, although the degree of intellectual dysfunction ranges from very mild to severe. Some children appear to develop normally until the onset of seizures, when their progress slows, or they actually lose developmental milestones. Individuals whose seizures continue unchecked even after treatment (intractable seizures) have a higher likelihood of intellectual impairment.

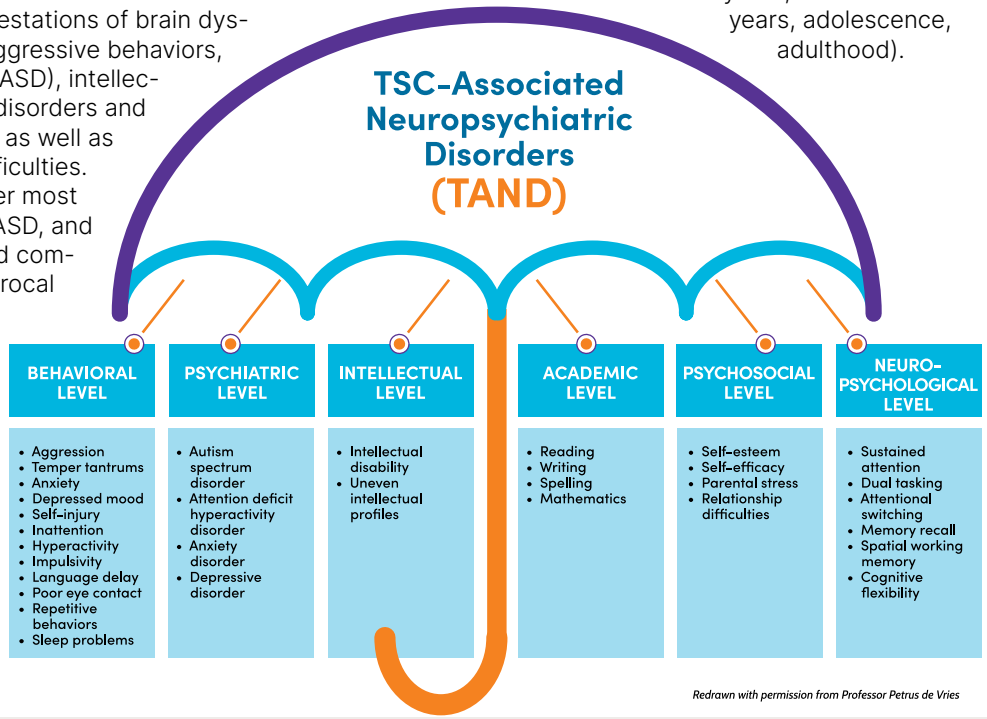
While most individuals with TSC who have intellectual disabilities also have epilepsy, many individuals with TSC that have seizures do not have significant intellectual disabilities. Some individuals with TSC may have mild learning disabilities that are essential to consider when early interventions, school programs, or career choices are being made.

TSC-associated neuropsychiatric disorders (TAND)

TSC is associated with a wide range of cognitive, behavioral and psychiatric manifestations. TAND is a new terminology proposed to describe the interrelated functional and clinical manifestations of brain dysfunction in TSC, including aggressive behaviors, autism spectrum disorders (ASD), intellectual disabilities, psychiatric disorders and neuropsychological deficits, as well as school and occupational difficulties.

TSC is the genetic disorder most commonly associated with ASD, and suggestions of language and communication difficulties, reciprocal social interaction difficulties, and unusual patterns of behavior and play should trigger a careful developmental evaluation as soon as they are noted.

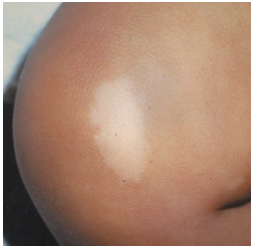
The 2021 TSC Consensus Guidelines recommend all individuals be screened for TAND upon diagnosis and at least annually. More detailed evaluations should follow from screening. Every individual with TSC should also have a comprehensive formal evaluation at key developmental timepoints (i.e., infancy, toddler, pre-school, early school years, middle school years, adolescence, adulthood).



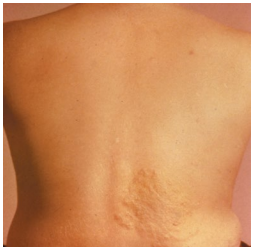
Redrawn with permission from Professor Petrus de Vries

Skin

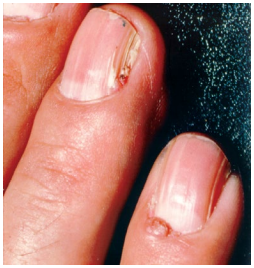
Skin lesions resulting from TSC include the following:



Hypomelanotic macules are flat areas of skin that appear lighter than the surrounding skin. They can be any size or shape or may be the classic "ash-leaf" shape (as called in older literature). The skin cells in this area of the skin contain less pigment, so the area appears lighter than the surrounding skin.

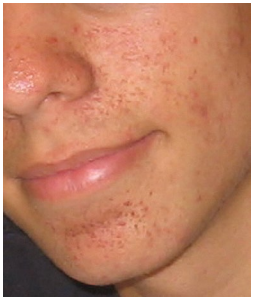


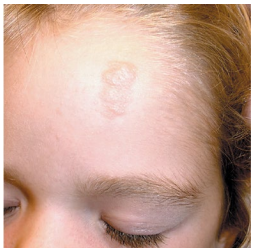
The **shagreen patch** is a patch of skin similar in color to surrounding skin but may be tough and dimpled like an orange peel. The shagreen patch is usually found on the lower back and nape of the neck, but they may also be seen on other parts of the body.



Ungual fibromas are small fibrous growths that appear around the fingernails or toenails and are usually not seen until adult life. Surgical excision or laser ablation may be used to remove these lesions.

Facial angiofibromas are benign tumors of the face that often appear across the checks and nose and on the chin. They are initially small reddish spots or bumps that may increase in size with age. Facial angiofibromas are rarely present at birth, but often appear as the child reaches 4 or 5 years of age or older. Some individuals with TSC will never develop this manifestation of the disease. There are several surgical approaches used to treat angiofibromas, including the use of lasers. Evidence shows medical treatments may also be effective. Many studies have shown topical rapamycin treatment can be promising for the treatment for angiofibroma.





A **fibrous cephalic plaque** is similar to the angiofibroma but is found on the forehead and scalp. These flesh-colored plaques are soft or compressible or doughy to hard lesions. At the initial examination, a physician will use a Wood's lamp (an ultraviolet light) to better visualize the hypomelanotic macules, especially on infants and people with very pale skin. The skin should be carefully examined for other manifestations of TSC as well.

Kidney

Renal (kidney) angiomyolipomas are non-cancerous tumors and are the most common type of kidney lesion in TSC. Angiomyolipomas occur in 70% to 80% of adults and older children with TSC. These tumors begin to grow in childhood in many individuals with TSC but usually grow very slowly and may not be problematic until young adulthood. Individuals with TSC should have their kidneys imaged at the time of diagnosis and then every one to three years throughout his/her lifetime. MRI is the best imaging technique for renal involvement. Angiomyolipomas larger than 4 cm are more likely to cause symptoms such as hematuria (blood in the urine) because they often have abnormal blood vessels in them.

mTOR inhibitors are now the standard of care for preventative treatment of enlarging angiomyolipomas to prevent future bleeding and other problems. This is because of the high recurrence and re-bleeding rate following embolization and the success of mTOR inhibitor trials. Selective embolization remains a feasible second-line alternative and is still the first-line treatment for angiomyolipomas that are actively bleeding. When feasible, selective embolization is preferred to surgical intervention. Although surgery is sometimes necessary to remove the angiomyolipoma, nephrectomy (removal of a kidney) should be avoided.

Blood pressure should be monitored at each visit to the physician because it can be the first sign of increasing kidney involvement. Other signs to watch for are blood in the urine and complaints of abdominal or flank (the side of the body between the pelvis or hip and the last rib) pain. The use of urine and blood tests to monitor kidney function is not sufficient for individuals with TSC because they may have extensive involvement due to angiomyolipomas and still have normal test results.

Another common finding in individuals with TSC is renal cysts. Many individuals with TSC will have single cysts in one or both kidneys. Unless they grow to

occupy a large portion of the kidney, cysts usually do not require treatment.

A relatively small number of individuals with TSC also have polycystic kidney disease (PKD). The TSC2 gene is located next to one of the genes for PKD on chromosome 16, so large deletions of this chromosome sometimes result in part of both the TSC2 and PKD genes being deleted. An individual with both genes affected will have both diseases. PKD is characterized by polycystic kidneys, or kidneys that have multiple cysts. These cysts grow and multiply over time, also causing the mass of the kidney to increase. Ultimately, the diseased kidney shuts down causing end-stage renal disease for which dialysis and transplantation are the only forms of treatment.

Eye

Nearly 50% of individuals with TSC have involvement of one or both eyes, but visual loss is uncommon. This may be higher as many individuals with TSC do not receive a good eye exam that would reveal either hamartomas or depigmented areas of the retina.

Retinal hamartomas are benign and usually do not change over time. Rare instances have documented tumors that change over time. It is possible that some of the hamartomas do change over time but go unrecognized since some individuals with TSC do not receive repeated eye exams where the change would be noted.

Depigmented areas on the retina are seen in about 25% of the individuals with eye involvement in TSC. The significance of these findings is not known, but they may be important in the diagnosis of TSC in individuals with no other symptoms. These depigmented areas of the retina may have the same origin as those on the skin (hypopigmented macules), but this is not known at present.

Lung

Lung involvement is far more common in women with TSC than men. The average age of onset is during the childbearing years, although lung involvement can occasionally occur in teenagers with TSC, as well as in postmenopausal women. This suggests that lung involvement in TSC could be estrogen-related. However, a very small number of men with lung disease have been reported. Many women who have lung involvement due to TSC have lymphangioleiomyomatosis (LAM), a degenerative cystic disease of the lungs. The first symptoms of lung involvement in an individual with

TSC may be shortness of breath after mild exercise, cough, or spontaneous pneumothorax (a collection of air or gas in the chest causing the lung to collapse). Progression of such lung involvement to pulmonary failure can sometimes occur, and some individuals may require lung transplantation.

Recent studies have shown that, by age 40, around 80% of women with TSC have cysts in the lung, but not all of them will have LAM symptoms. It is recommended that women with TSC have a high-resolution chest computed tomography (HRCT) (not a regular x-ray) sometime around 18 years of age or at the time of diagnosis of TSC for adult women. HRCT of the lung is superior to a regular x-ray because the early signs of lung involvement may easily be missed on an x-ray. Cigarette smoking and estrogen-containing medications should be avoided, and HRCT, pulmonary function test and a 6-minute walk test should be repeated at regular intervals. The individual should be followed closely by a pulmonologist familiar with TSC and LAM.

Teeth and oral cavity

Oral involvement in TSC can include gum fibromas and dental pits. The fibromas appear as overgrowth of the gums and can be quite extensive, although this finding is not common in individuals with TSC. Dental pits occur in about 7% of the general population and in about 90% of those with TSC. The pits are seen on both the front and back surfaces of the teeth, which are areas that do not normally develop cavities. The dental pits can be revealed using a dental plaque-disclosing stain. Examination of the teeth is noninvasive and can usually be performed by a dental hygienist or other healthcare provider. Meticulous dental hygiene, including regular brushing and flossing, is an important aspect in preventative care for individuals with TSC.

Other organ systems

Cysts and angiomyolipomas similar to those found in the kidneys have been observed in other organs such as the adrenal gland, liver, lung, ovary and pancreas. These lesions are usually asymptomatic and do not require treatment. Biopsy of a suspicious lesion is recommended only when the lesion is unusually large, growing, causing symptoms, or exhibiting other suspicious characteristics. If they are symptomatic, they should be treated by the appropriate specialist and be removed if medically necessary.

Genetics of TSC

Genes are the biochemical instructions found inside the cell, not unlike the programs found inside computers. Human beings have 22 pairs of chromosomes, as well as a pair of sex chromosomes. Females have two X chromosomes, and males have an X and a Y chromosome. Our genes come in pairs, with one copy inherited from the mother and the other from the father. All people have variations in their genes – some of which cause diseases and others increase risk for developing some diseases, and some variations cause no problems at all. Some of these variations have been passed down from one parent, and some variations are unique to individual human beings.

TSC is caused by a change or variation (called a mutation when it causes disease) in either the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16. TSC is an autosomal dominant genetic disorder. This means an individual with TSC has a mutation in one copy of either of the TSC genes that then causes the disease. Many genetic disorders such as TSC can be sporadic, meaning the disorder has not previously occurred in that family. Such sporadic occurrences are the result of a new genetic mutation and account for approximately two-thirds of all cases of TSC. The remaining one-third of cases are the result of a TSC gene containing a mutation being passed along (inherited) from either the mother or the father to their child.

Individuals with TSC have a 50% chance of passing their condition on to each of their children. If parents are unaffected, the chance of a sibling of someone diagnosed with TSC also having TSC is approximately 1% to 2%. The ability to differentiate between an inherited and sporadic occurrence of TSC sometimes relies on a thorough evaluation of the family members of the individual with TSC. This may involve evaluation of the parents, as well as some or all of the siblings.

There are no known cases of an individual having a disease-causing variant in both genes, and TSC does not skip a generation. It is possible for a member of the family to have such a mild case of TSC as to seem unaffected. At this point, the severity or risk of specific TSC features cannot be predicted by knowing an individual's genetic mutation.

Significant progress in understanding the function(s) of the TSC genes has translated into clinical trials to test medications for their ability to stop tumor growth and to impact the neurologic features of TSC, including seizures and cognition. The TSC genes work together as a complex in a specific signaling pathway in cells that regulate cell growth. Ongoing basic and clinical research are moving rapidly forward, hopefully to the

day when the symptoms of TSC can be prevented.

Genetic testing

Genetic testing allows individuals with TSC, family members and healthcare providers to know exactly what mutation in either the TSC1 or TSC2 gene caused TSC. This information may be helpful for a number of reasons. In some cases, the identification of a TSC1 or TSC2 mutation will facilitate a definite genetic diagnosis of TSC in an individual who has not yet developed enough symptoms for a clinical diagnosis. In approximately 15% of individuals with TSC, no mutation is identified in either TSC1 or TSC2. While a negative DNA test result cannot rule out a diagnosis of TSC, a positive result confirms the diagnosis. In other cases, an individual may have a definite diagnosis of TSC, and family members may wish to know their own genetic status without undergoing extensive clinical evaluations. Upon identifying the TSC mutation in the individual with a definite diagnosis of TSC, any other family member can be easily tested to determine

whether he or she is also affected. In addition, the availability of DNA mutation results makes reproductive decision-making possible.

Despite advancing knowledge about TSC mutations, it is not possible to predict the severity of symptoms in a person with a new diagnosis of TSC. A person can have TSC and have very few or mild symptoms, while a family member with TSC can have more severe or extensive symptoms. It is thought, however, that most people who have a TSC mutation will have some signs or symptoms if examined carefully by a physician familiar with the diagnosis of TSC. The distinction between sporadic TSC and familial (or inherited) TSC is important, as it affects the risk that other persons in the family are affected. Therefore, immediate family members of a person newly diagnosed with TSC should be thoroughly examined.

Another factor that complicates the genetics of TSC is germline mosaicism. Germline mosaicism occurs when an individual has cells in his or her germline (egg or sperm cells) that carry a genetic mutation, but not in cells in other parts of the body. While quite rare, individuals with germline mosaicism may have one or more children with TSC but not have any clinical symptoms of TSC.

Given the complicated nature of TSC genetics, all families who have an affected relative with TSC should receive a referral to a genetic counselor or geneticist to discuss their unique genetic risk to either have TSC or to have a child with TSC.

Commercial laboratories in the United States offer clinical genetic testing for TSC when ordered by a doctor. Test panels and pricing vary, so it is important for your doctor to select the lab that offers the appropriate

test that will be covered by your insurance or will offer the lowest out-of-pocket cost to you. You can find a list of these laboratories at tscalliance.org/labs.

Genetic counseling

Genetic counselors are individuals trained in both genetics and counseling and work as part of the healthcare team. Genetic counselors offer individuals with TSC and their families information about the genetic nature of the condition and the risk that other family members may also have TSC. They also assist couples with making decisions about having children. The goal of genetic counseling is to ensure that the family understands the genetic implications of the diagnosis and to help individuals with TSC and their families make informed medical and personal decisions.

To locate a genetic counselor near you, contact:

- A TSC Center of Excellence or TSC Clinic at tscalliance.org/tsc-clinics
- The National Society of Genetic Counselors at nsgc.org
- Your state department of public health and ask for genetic services

Information and support

When you or a member of your family receives the diagnosis of TSC, it is likely the first time you will have heard the name of this rare genetic disorder. If you are a parent, you may ask yourself, "Did I do something to cause this?" or "Did I pass this disorder on to my child?" You may have fears for the future. These are feelings commonly felt by anyone learning to cope with this diagnosis.

If you are diagnosed with TSC as an adult, you may wonder how this will impact your life and the lives of your family, how it will affect your health and where you can find information and support.

Individuals with TSC and their families learn about the disease and how it will affect their lives in many different ways. Some individuals want to have all of the information they can get their hands on so they know all the possible issues they will have to face in the future. Others prefer to take it one step at a time and only access the information they need for their immediate issues. There is no one right approach, and everyone does this at his or her own speed and in his or her own way.

Because TSC is so variable, it is not possible to predict how an individual will be affected by TSC. The uncertainty is sometimes difficult to deal with and can cause a great deal of stress for individuals and their families. Support from your family and friends, along with open and honest communication, will provide strength for the whole family so the individual with TSC will have the support he or she needs. Participating in TSC peer support opportunities may also be helpful for everyone involved.

About the TSC Alliance

The TSC Alliance is an internationally recognized nonprofit that does everything it takes to improve the lives of people with tuberous sclerosis complex. We are a source of hope and connection for all affected by TSC. We drive research, increase care quality and access and advocate with and for people affected by the disease. Through our collaboration and partnerships, we've advanced FDA-approved treatments and created support systems around the world so no one has to navigate TSC alone.

The TSC community is our strongest ally

With the power of families and the support of donors, volunteers, researchers, educators, industry partners and more, we can create **a future where everyone with**

TSC can realize their full potential – no matter how complex their journeys are to get there.

We use a comprehensive approach to improve quality of life for people with TSC – fueling promising research while making sure that, day-to-day, individuals are diagnosed early and receive the highest quality care available. We also have a voice in policy around healthcare access and federal funding for TSC research.

Research

We ensure TSC researchers have the data and funds they need to discover breakthroughs.

- We fund investigators working on **TSC-related studies**. Often, we support focused research projects that allow researchers to develop preliminary data that will lead to additional funding from larger organizations. We also invest in early-career researchers to encourage their interest in TSC. This approach sustains their work long term and maintains momentum by fostering a diverse group of researchers dedicated to our shared mission.
- We ensure TSC researchers have the data and connections they need to make progress. Our **Natural History Database** helps us accomplish this objective. It collects clinical information from people with TSC and connects to our **Biosample Repository**. Researchers use this vast collection of data to answer questions and find patterns in the course of the disease over a lifespan and its variability person to person.

- The TSC Alliance fuels collaborative research through our **Preclinical Consortium**, bringing together industry and academia. We make preclinical testing resources available to de-risk drug development in TSC and move new treatments to clinical trials faster.

Care quality and access

We improve access to high-quality care for people with TSC.

- The TSC Alliance recognizes a network of **TSC Clinics** around the country and the world where individuals and families can find comprehensive care. Some clinics qualify as **TSC Centers of Excellence** for their outstanding clinical care for both children and adults, educational resources, community partnerships and research initiatives.

- Working with and supporting **teams of TSC experts** around the world, we play a vital role in defining what constitutes quality care. We identify and share best practices for diagnosis, surveillance and treatment with TSC Clinics and other healthcare providers so they can use them within their communities and ensure people with TSC get the best care possible.
- **No one is alone on their TSC journey with the TSC Alliance.** We're a central hub for information about TSC care and treatment, offering resources and support for individuals, families, healthcare professionals and educators to ensure quality care from diagnosis onward.
- We work to ensure school systems understand and adapt to the learning needs of students with TSC. Our **Educator Mentor Program** provides one-on-one support to any professional working in education—from pre-K to college—so they can recognize how TSC affects learning and create great educational experiences for their students. We also provide expert guidance on developing Individualized Education Programs (IEPs) and many other resources to help families navigate special education programs.
- Our easy-to-use online **TSC Navigator** tool helps guide individuals and families through the

complexities of TSC across the lifespan, proactively manage their care and live their fullest lives. Regardless of age, TSC Navigator also helps people with TSC and their caregivers face complex situations, overcome access issues and address insurance hurdles. Visit tscalliance.org/TSCnavigator.
- We help **adults living with TSC** in a variety of ways, from offering support to them and their families as they transition from pediatric to adult care to sharing resources to help further their post-high school education. We also offer educational programs, resources and open forums for independent adults with TSC as well as for caregivers of dependent or semi-dependent adults.

Community empowerment and advocacy

The TSC Alliance advocates with and on behalf of our community to ensure everyone living with TSC has what they need to live their fullest lives.

- We **advocate for state and federal funding** of TSC research and clinical care – and give the TSC community the tools to do the same. Our voices are a powerful force for accelerating discoveries.
- We **amplify the voices of the TSC community** to make sure their lived experiences play an important role in prioritizing research and ensuring new treatments.
- The more people know about TSC, the faster it can be diagnosed and treated. Through campaigns, advocacy and our powerful community of individuals and families, we **raise awareness** of the disease among healthcare professionals, nonprofits, government partners and the public at large.
- Our nationwide network of **Community Alliances** supports individuals and families affected by TSC at the local level. Every branch is run by caring and welcoming volunteers—parents, grandparents, adults and friends—who host educational meetings, raise awareness and fundraise, foster local connections and serve as a resource in their communities.
- Our network of **Global Alliances** support TSC communities around the world. Dedicated volunteers work at every Global Alliance, and we partner with them to create and implement plans to help better meet the needs of people navigating TSC outside of the United States.

Information, support and connections

- Visit tscalliance.org
- Call (800) 225-6872
- Email info@tscalliance.org

Commonly asked questions

What is the life expectancy of an individual with TSC?

With ever-improving medical care and recognition of the potential severe consequences of many of the manifestations of TSC, most people with TSC will live a normal life span. However, complications in some organs such as the kidneys, lungs and brain can lead to severe difficulties and even death if left untreated or if mistreated. Sudden unexpected death due to epilepsy (SUDEP) has also been reported in TSC, as has death due to untreated cardiac rhabdomyomas in infants with TSC. To reduce these dangers, it is important for individuals with TSC to follow the recommended screening guidelines to identify potential complications and be followed closely throughout their lives.

Is my child with TSC at risk for a developmental disability?

Children with TSC have a higher-than-average risk of developmental delay, autism spectrum disorder or pervasive developmental disorder and should be evaluated as early as possible by trained health-care professionals. Early intervention can be the key to optimal development for children with TSC. Approximately 40% of individuals with TSC will require support throughout their lives, but many will go on to lead independent lives.

If an individual with TSC who is mildly affected has a child, will the child also be mildly affected?

People with mild cases of TSC can have a child who is more severely affected. In fact, some people are so mildly affected they may go undiagnosed until their more severely affected child receives a diagnosis of TSC or until additional medical issues lead to a diagnosis.

Are the tumors cancerous?

The tumors resulting from TSC are benign or non-cancerous but may still cause problems. Tumors that grow in the brain can block the flow of cerebrospinal fluid (CSF) in the ventricles in the brain. This can lead to behavioral changes, nausea, headaches or a number of other symptoms. In the heart, the tumors are usually at their largest at birth, and then decrease in size as the individual gets older. These

heart tumors (cardiac rhabdomyomas) can cause problems at birth if they block the flow of blood or cause arrhythmias. Tumors in the eyes are not common, but they can present problems if they block too much of the retina. In some women with TSC, cysts or tumor cells in the lung can cause damage to the lung leading to shortness of breath and sometimes lung collapse. Renal angiomyolipomas occur in approximately 80% of individuals with TSC and can become so large they impair kidney function or rupture and cause significant bleeding.

Since there is no cure, what can be done?

Early diagnosis and intervention can help diminish developmental delays in individuals with TSC. Aggressive treatment of all symptoms of TSC – including tumor growth, seizures and cognitive challenges – will provide the highest quality of life possible for individuals with TSC. Surgery can help preserve the function of affected organs. Improved technology is helping to pinpoint and remove the exact portions of the brain stimulating seizures. Significant advancements in the understanding of the functions of the TSC genes are bringing new and improved therapeutic options. Each day brings us closer to improved treatments and a cure for TSC.

TSC diagnostic criteria

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

* Includes tubers and cerebral white matter radial migration lines.

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

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

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

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

TSC surveillance and management recommendations[1]

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
GENETICS	Obtain three-generation family history to assess for additional family members at risk of TSC.	Offer genetic testing and family counseling if not performed previously.
	Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed.	
BRAIN	Obtain 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).	Obtain magnetic resonance imaging (MRI) of the brain every 1 to 3 years in asymptomatic TSC patients younger than age 25 years 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 patients and 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.

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
BRAIN	During infancy, educate parents to recognize infantile spasms and focal seizures, even if none have occurred at the time of first diagnosis.	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 target of rapamycin inhibitors (mTORi) may be used for growing but otherwise asymptomatic SEGA. For large tumors, if clinical condition enables, neoadjuvant treatment with mTORi may facilitate surgery. Minimally invasive surgical techniques may increase surgical safety in selected patients. 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.
	Obtain baseline routine electroencephalogram (EEG) while awake and asleep. If abnormal, especially if features of TSC-associated neuropsychiatric disorders (TAND) are also present, follow up with 8- to 24-hour video EEG to assess for seizure activity.	Obtain routine electroencephalograph (EEG) in asymptomatic infants with TSC every 6 weeks up to age 12 months and every 3 months up to age 24 months, as abnormal EEG frequently precedes onset of clinical seizures.
		Obtain routine EEG in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 hours 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.

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
BRAIN		Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropic hormone (ACTH), synthetic ACTH or prednisolone can be used if treatment with full-dose vigabatrin for 2 weeks has not correlated with clinical improvement.
		Antiseizure medications (ASMs) for other seizure types in TSC should generally follow that of other epilepsies. Everolimus and a specific cannabidiol formulation are approved by regulatory authorities for treatment of seizures associated with TSC. No comparative effectiveness data exist to recommend ASMs, everolimus, cannabidiol, or dietary therapies over one another in specific subsets of patients.
		Epilepsy surgery should be considered for medically refractory TSC patients at epilepsy surgery centers with expertise in TSC. Special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy surgery centers with experience and expertise in TSC.
TAND	Perform comprehensive assessment for TAND across all levels of potential TAND manifestations.	Perform annual screening for TAND, using validated screening tools such as the TAND Checklist. Screening may be done more frequently depending on clinical needs. When any concerns are identified on screening, proceed to further evaluations by appropriate professionals to diagnose and treat the relevant TAND manifestation(s).

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
TAND	Refer as appropriate to suitable professionals to initiate evidence-based interventions based on the TAND profile of needs identified above	Perform comprehensive formal evaluation for TAND across all levels of TAND at key developmental time points: infancy (0 to 3 years), preschool (3 to 6 years), pre-middle school (6 to 9 years), adolescence (12 to 16 years), early adulthood (18 to 25 years), and as needed thereafter.
	Provide parent/caregiver education and training about TAND to ensure families know what to look out for in emerging TAND manifestations (e.g., autism spectrum disorder, language disorders, attention deficit hyperactivity disorder, anxiety disorders).	Refer to appropriate professionals for the management/intervention of relevant TAND manifestations. Interventions should be personalized to the TAND profile of each individual and be based on evidence-based practice guidelines/practice parameters for individual manifestations (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder).
	Provide psychological and social support to families around diagnosis, coming to terms with the diagnosis of TSC and TAND, and ensure strategies are in place to support caregiver well-being.	Aim for early identification of TAND manifestations and early intervention.
		Many people with TSC have academic/scholastic difficulties. Therefore, always consider the need for an individual educational program (IEP/IEDP).

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
TAND		Sudden and unexpected change in behavior should prompt physical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease, medications).
		Provide psychological and social support to families and caregivers and ensure strategies are in place to support caregiver wellbeing. Continue to provide parent/caregiver education and training about TAND to ensure families know what to look out for in emerging TAND manifestations across the lifespan.
KIDNEY (RENAL)	Obtain MRI of the abdomen to assess for the presence of angiomyolipomas and renal cysts.	Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1 to 3 years throughout the patient's lifetime.
	Screen for hypertension by obtaining an accurate blood pressure.	Assess renal function including determination of glomerular filtration rate and blood pressure at least annually.
	Evaluate renal function by determination of glomerular filtration rate (GFR).	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.

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
LUNG (PULMONARY)	Inquire about tobacco exposure, connective tissue disease manifestations, signs of chyle leak, and pulmonary manifestations of dyspnea, cough, and spontaneous pneumothorax in all adult patients with TSC.	Inquire about smoking, occupational exposures, connective tissue disease (CTD) symptoms, chyle leak, and pulmonary manifestations such as dyspnea, cough, and spontaneous pneumothorax in all adults at each clinic visit.
	Perform baseline chest CT in all females, and symptomatic males, starting at the age of 18 years or older.	For adult females with a negative screening CT who remain asymptomatic, obtain high resolution CT (HRCT) to screen for the presence of LAM every 5 years through menopause. Low-dose CT protocols preferred.
	Perform baseline PFTs and 6MWT in patients with evidence of cystic lung disease consistent with LAM on the screening chest CT.	For patients with evidence of cystic lung disease consistent with LAM on screening CT, obtain follow-up HRCT after 1 to 3 years, and on a case-by-case basis thereafter at least every 5 years depending upon the individual circumstances. Low-dose CT protocols preferred.
		Perform routine serial PFT monitoring at least annually in patients with evidence of LAM on HRCT and more frequently in patients who are progressing rapidly or who are being monitored for response to therapy.
		Use mTOR inhibitors for treatment of LAM in patients with abnormal lung function (FEV1 < 70% predicted), physiological evidence of substantial disease burden (abnormal DLCO (<80% or less than lower limit of normal [when available]), air trapping (RV > 120%), resting or exercise-induced oxygen desaturation), rapid decline (rate of decline in FEV1 > 90ml/year), and problematic chylous effusions.

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
LUNG (PULMONARY)		Counsel patients regarding the risk of pregnancy and exogenous estrogen use. Avoid routine use of hormonal therapy or doxycycline for the treatment of LAM. Advise patients against tobacco smoke exposure.
		Trial inhaled bronchodilators in patients with symptoms of wheezing, dyspnea, chest tightness, or obstructive defect on spirometry, with continued use in patients who derive symptomatic benefit.
		Consider measurement of annual VEGF-D levels in patients who are unable to perform reliable PFTs to monitor adequacy of pharmacodynamic suppression of the mTOR pathway.
SKIN	Perform a detailed clinical dermatologic inspection/exam.	Perform annual skin examinations for children with TSC. Adult dermatologic evaluation frequency depends on the cutaneous manifestation. Close surveillance and intervention are generally recommended for TSC-related skin lesions that rapidly change in size and/or number, cause functional interference, pain, or bleeding, or inhibit social interactions.
		Provide ongoing education on sun protection.
		For flat or minimally elevated lesions, topical mTOR inhibitor treatment is recommended. Watch for improvement in skin lesions over several months; if lesions do not improve, or if earlier intervention is indicated, then consider use of surgical approaches. For protuberant lesions, consider surgical approaches (e.g., excision, lasers).

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
TEETH	Perform a detailed clinical dental inspection/exam.	Perform a detailed clinical dental inspection/exam at minimum every 6 months. Take a panoramic radiograph to evaluate dental development or if asymmetry, asymptomatic swelling, or delayed/ abnormal tooth eruption occurs.
		Enamel pits may be managed by preventive measures as first-line treatment (sealants, fluoride). They may be managed by restorations if preventive measures fail, or if symptomatic, carious, or there is an aesthetic concern.
		Symptomatic or deforming oral fibromas and bony jaw lesions should be treated with surgical excision or curettage when present.
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 every 1 to 3 years in asymptomatic pediatric patients until regression of cardiac rhabdomyomas is documented. More frequent or advanced diagnostic assessment may be required for symptomatic patients.
	Obtain an echocardiogram in pediatric patients, especially if younger than three years of age	Obtain electrocardiogram every 3 to 5 years 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.
	Obtain an electrocardiogram in all ages to assess for underlying conduction defects.	

	For the newly diagnosed or suspected TSC	For individuals already diagnosed with TSC
EYE	Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal findings (astrocytic hamartoma and achromic patch) and visual field deficits.	Perform annual ophthalmic evaluation for those with or without visual symptoms at baseline. Rare cases of aggressive lesions or those causing vision loss due to their location affecting the fovea or optic nerve may require intervention. mTOR inhibitors have been used with some success to treat problematic retinal astrocytic hamartomas.
		For patients receiving vigabatrin, there are specific concerns related to visual field loss which appears to correlate with total cumulative dose. Physicians responsible for monitoring children on vigabatrin can offer serial fundus examinations to detect retinal changes.
OTHER		Identification of unexpected functional and nonfunctional pancreatic neuroendrocrine tumors (PNETS) have been found during abdominal MRI surveillance in individuals with TSC. Further monitoring and evaluation should be referred to endocrinology.

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Glossary

Attention-deficit hyperactivity disorder (ADHD)
ADHD is generally considered to be a developmental disorder, largely neurological in nature. The disorder is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity. Science recognizes three subtypes of ADHD (inattentive, hyperactive-impulsive, and combined).

Autism spectrum disorder (ASD)
Autism is a complex brain disorder that inhibits a person's ability to communicate and develop social relationships and is often accompanied by extreme behavioral challenges.

Benign tumors
Non-cancerous growths. Most forms of benign tumors do not metastasize (spread to and grow in a distant focus in normal tissues elsewhere in the body).

Cancer
Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

Cannabidiol
Cannabidiol, or CBD, is a naturally occurring substance in the cannabis plant. One highly purified form of cannabidiol has been approved in the US for treating seizures associated with TSC and is marketed with the brand name Epidiolex®.

Cardiac rhabdomyoma
A benign tumor composed of muscle tissue that occurs in the heart.

CT (computerized tomography)
A technique for creating images of the internal structures of the body. CT scans are formed from computerized imagery of many highly precise X-rays.

Cyst
A closed sac containing fluid or semisolid material, developing abnormally in a body cavity or structure. Cysts can impair the function of surrounding tissue.

Dermatologist
A healthcare provider specializing in disorders of the skin.

Developmental delay
Delay in the normal cognitive and/or physical development of a child.

Early intervention
A federally mandated, state administered program that provides interventions for children aged 0 to 3 years who have or who are at risk of having developmental delays. The programs usually include various therapies (physical, occupational, speech, etc.).

Echocardiogram (echo)
A noninvasive test that uses high frequency sound waves (ultrasound) to produce an image of the heart.

EKG (electrocardiogram or ECG)
This noninvasive recording of the

electric activity of the heart shows if there are abnormal cardiac electrical impulses and/or rhythms.

Epilepsy
When a person has had two or more seizures that have not been provoked by specific events such as trauma, infection, fever or chemical change, he or she is considered to have epilepsy.

Facial angiofibroma
A benign tumor of the face composed mainly of blood vessels and fibrous tissue. Angiofibromas initially appear as pink or red bumps and can form a butterfly-shaped distribution around the nose, cheeks and chin.

Genetic counselor
A trained healthcare professional educated in providing genetic risk and diagnostic information. Genetic counselors help individuals with genetic diseases and their families make medical and personal decisions based on their genetic information.

Genetic disorder
A disease or condition caused by an absent or defective gene or abnormal chromosome.

Hamartoma
A benign tumor in an organ composed of tissue elements normally found at that site but that are growing in a disorganized mass.

Hypomelanotic macule
Skin abnormality featuring less color, or pigment, than normal. In TSC, hypopigmentation appears in the form of spots, or hypomelanotic macules, on any part of the body. These spots are benign and pose no physical threat.

Infantile or epileptic spasms
A severe type of seizure that typically occurs between the ages of 2 months and 2 years, although most children who develop this type of seizure are around 6 months old. Onset uncommonly may be later when it is referred to as epileptic spasms. It is identified by sudden jerks caused by muscle contractions, flexing of the body and neck and stiffening of the limbs. Each of these seizures lasts a very short time but can occur in long or short clusters. If left untreated, infantile spasms can have a devastating effect on a child's intellectual development.

Laser ablation
This is procedure uses a high energy pulse of light, which produces heat to remove tissue.

Lymphangioleiomyomatosis (LAM)
LAM is a lung disease caused by mutations in the TSC genes that can occur in individuals with TSC, primarily women, or in sporadic cases. Cystic lung destruction leads to loss of lung function in LAM.

Malignant tumor
A cancerous tumor.

Metastasis
The spread of cancer from its primary

site to other places in the body (e.g., brain, liver).

Magnetic resonance imaging (MRI)
A noninvasive system producing images of brain tissues by using radio waves and strong magnetic fields. MRI can detect tumors, tubers and other soft tissue abnormalities.

mTOR inhibitor
A drug that inhibits the activity of a protein known as mTOR (mechanistic target of rapamycin). Examples include sirolimus, also known as rapamycin or Rapamune®, and everolimus, also known as RAD001 or Afinitor®.

Neurologist
A healthcare provider who specializes in the function and disorders of the nervous system.

Neurosurgery
Any surgery that involves the brain, the nerves or the spinal column. Neurosurgery of the brain may be performed in an attempt to control seizures, to remove a brain tumor or to alleviate the pressure from hydrocephalus.

Pathogenic
Disease-causing.

Polycystic kidney disease (PKD)
Polycystic means "multiple cysts." In effect, PKD denotes multiple cysts on each kidney. These cysts grow and multiply over time, also causing the mass of the kidney to increase. Ultimately, the diseased kidney shuts down causing end-stage renal disease for which dialysis and transplantation are the only forms of treatment.
PKD comes in two forms. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common, affecting 1-in-400 to 1-in-500 adults. Autosomal Recessive Polycystic Kidney Disease (ARPKD) is far less common, affecting 1-in-10,000 at a far younger age, including newborns, infants and children.

Seizure
In normal brain function, tiny electrical charges pass from nerve cells in the brain to the rest of the body. A seizure occurs when the normal pattern is interrupted by sudden and unusually intense bursts of electrical energy that may cause strange sensations, emotions, behaviors or convulsions, muscle spasms and loss of consciousness. These unusual bursts are called seizures.

Shagreen patch
Abnormal patches of skin resembling an orange peel, usually found on the lower back or the back of the neck. Shagreen patches may be present on other parts of the body as well.

Stereo electroencephalography (SEEG)
This is a minimally invasive procedure where wires with contacts are applied directly to the surface of the brain to record the activity to help the doctor determine if epilepsy surgery should be performed.

Subependymal giant cell astrocytoma (SEGA)
A benign tumor found in the brain of individuals with TSC. SEGAs typically grow near or in the ventricles and can cause hydrocephalus (increased pressure in the brain) if they block the flow of cerebrospinal fluid (CSF).

Subependymal nodule (SEN)
A non-cancerous nodule (collection of cells) located along the edge of the brain's ventricles. Subependymal nodules can grow into SEGAs, and some subependymal nodules become calcified (filled with a calcium deposit).

TAND
TSC-associated neuropsychiatric disorders (TAND) including aggressive behaviors, autism spectrum disorders, intellectual disabilities, psychiatric disorders, neuropsychological problems, and school and occupational difficulties often expressed by individuals with TSC.

Tuber
An area of the brain that contains a disorganized collection of abnormal cells; usually found in the outer layers of the brain called the cortex but can be found in deeper areas of the brain.

Tumor
Tumor is primarily used to denote abnormal growth of tissue. This growth can be either malignant or benign.

Ungual fibromas
Benign fibrous tumors found in the areas around the fingernails and toenails.

Video EEG monitoring
This procedure is when a video camera records what the person is doing during a seizure at the same time the EEG is recording the brain activity.

Wood's lamp
An ultraviolet light used to detect hypopigmented macules in TSC and to diagnose other skin and scalp diseases.

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*These articles are downloadable at tscalliance.org/medpubs.

Hope no matter how complex

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