# Journalist's Guide:
# **Tuberous Sclerosis Complex (TSC)**

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# Contents

## Reporting on Tuberous Sclerosis Complex

Healthcare reporters play a key role in disseminating information to improve awareness and education of challenging medical conditions. In the case of lesser known diseases, where information may be scarce, the responsibility to provide accessible and accurate reporting can be significant. One such example is tuberous sclerosis complex (TSC), an uncommon and complicated genetic disorder that may affect many organs and systems throughout the body. Because TSC can have different manifestations and associated diseases, including seizures, developmental delays, autism, kidney complications and skin lesions, which may be treated by various physician specialties, knowledge on the disease can be limited, dispersed and sometimes vague[1,2]. Thus, it is important to have a collective resource for reporters to facilitate a comprehensive understanding of the disease.

To help increase your knowledge of this multisystem disease that affects up to one million people worldwide, the TSC media handbook has been developed by Novartis Pharmaceuticals Corporation (NPC) to provide journalists with background about TSC. The following provides essential information needed to better understand the complex clinical manifestations of the disease and the challenges of living with TSC.

This handbook provides information that may assist in your reporting of TSC, as it provides helpful tools that can assist in the development of stories surrounding TSC. Since TSC is a multisystem disorder, information in this handbook will be helpful to reporters covering the condition from a range of medical perspectives, including but not limited to neurology, nephrology, urology, dermatology, genetics, cardiology, pulmonology and ophthalmology[1].

We hope you find the handbook useful as you consider reporting on TSC in the future.

# Tuberous Sclerosis Complex Overview

## Introduction

Tuberous sclerosis complex, also known as tuberous sclerosis (TS), is a genetic disorder that may cause non-cancerous tumors to form in vital organs and can affect many different parts of the body, including the brain and kidney as well as the heart, lungs and skin[1].

Although non-cancerous, these tumors may lead to severe and potentially life-threatening complications[1]. As a result, this disease can impact the quality of life for both those living with it and their caregivers[3].

## Disease Background

Tuberous sclerosis is named after one of the characteristics of the disease, called *tubers*, which are potato-like nodules that form in the brain. With age, tubers calcify and become hard, or *sclerotic*. Tubers were first described by French physician Désiré-Magloire Bourneville more than 100 years ago, and the disease was once known as Bourneville's disease[1].

### Genetic Nature

Tuberous sclerosis complex is caused by defects in the *TSC1* and/or *TSC2* genes. Scientists believe that when these genes are defective, activity in a signaling pathway called mTOR (mammalian target of rapamycin), which acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism, is increased[1,4]. This can cause uncontrolled tumor cell growth and proliferation, blood vessel growth and altered cellular metabolism[1,4].

While about one-third of all patients inherit TSC from a parent with the disease, the remaining cases occur as sporadic cases due to spontaneous mutations in the *TSC1* and/or *TSC2* genes[5].

In familial cases, TSC is an autosomal dominant disorder, meaning the disorder can be transmitted directly from parent to child. Children who inherit TSC may not have the same symptoms as their parent and they may have either a milder or more severe form of TSC[1].

## Signs, Symptoms and Resulting Disorders

Signs and symptoms of TSC vary depending on which system and which organs are involved. The natural course of the disease varies from individual to individual, with symptoms ranging from very mild to quite severe[1].

Skin lesions and seizures are the two most common resulting disorders of TSC[6]. Seizures from infancy into childhood tend to be of increasing frequency and severity[7]. Non-cancerous tumors in the brain can lead to life-threatening brain swelling (hydrocephalus), and larger renal (kidney) tumors may cause severe and life-threatening bleeding, require invasive intervention or result in kidney failure[1,4].

| Signs, symptoms and resulting disorders of TSC include, but are not limited to: |
|---|
| • Non-cancerous tumor growth in organs such as the brain, kidney, heart, lungs and skin[1] |
| • Skin abnormalities[1] |
| • Seizures[1] |
| • Mental disabilities[1] |
| • Autism[1] |
| • Behavioral problems[1] |
| • Shortness of breath[1] |
| • Brain swelling (hydrocephalus)[4] |

For further details on TSC manifestations and diseases associated with TSC, please refer to pages 10-15.

## Diagnosis

Many patients with TSC show evidence of the disease in the first year of life. However, because manifestations vary from patient to patient and can take years to develop, many children are not diagnosed until later in life[1].

In addition to careful clinical examination, diagnostic tools such as computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, which may show tubers in the brain, and an ultrasound of the heart, liver and kidneys, which may show tumors in those organs, are used to diagnose TSC[1].

Neurologist Manuel Rodriguez Gomez published diagnostic criteria for individuals with TSC, which were last updated in 1999. The Gomez criteria are based on clinical and pathologic experiences, echocardiographic images performed in the last two decades, CT and MRI scans and ultrasounds[8].

### Prognosis

The prognosis for individuals with TSC varies extensively and depends on the severity of symptoms. Those with mild symptoms have a normal life expectancy, while those who are significantly affected can suffer from severe mental retardation and persistent epilepsy[1].

Individuals with TSC may be at risk for life-threatening conditions related to their brain tumors, kidney lesions or a rare lung disease associated with TSC. For example, brain tumors associated with TSC can cause life-threatening brain swelling (hydrocephalus) and kidney tumors may cause fatal hemorrhage[1,4].

## Management

As noted earlier, TSC is a lifelong condition, and individuals need to be monitored by a doctor to ensure they are receiving the best possible treatments. Due to the varied symptoms and manifestations of TSC, care by a clinician experienced with the disorder is optimal. Many patients with TSC may also see several doctors to address the multisystem nature of the disease such as a neurologist, nephrologist, urologist, dermatologist, geneticist and pulmonologist[1,2].

In most patients with TSC, the first element of managing the disease is making the appropriate diagnosis by identifying major and minor diagnostic features. The second feature of managing TSC is long-term follow-up care, including monitoring of lesion growth, particularly of brain and kidney tumors associated with TSC. Surgery can also address complications related to brain tumors associated with TSC or to address hemorrhage from kidney tumors[9].

While there is no cure for TSC, treatments are available for a number of the symptoms. For example, antiepileptic drugs may be used to help control seizures. Intervention programs including special schooling and occupational therapy may benefit individuals with special needs and developmental issues[1].

## Research

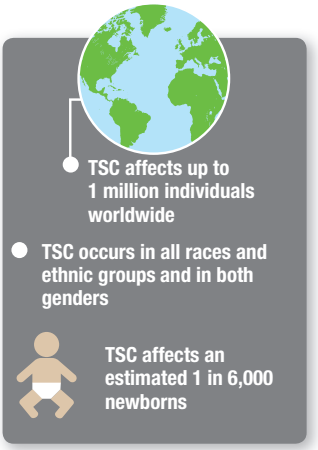
Research studies conducted on TSC range from basic scientific investigations to clinical research[1].

Scientists studying TSC seek to increase basic understanding of the disease by examining the *TSC1* and *TSC2* genes that cause the disorder as well as the proteins *tuberin* and *hamartin* produced by these genes[1].

Investigators conducting clinical research are studying the signaling pathway in which the *TSC1* and *TSC2* protein products and the mTOR protein are involved, as well as focusing on understanding in detail how the disease develops to better define new ways of controlling or preventing the development of the disease[1].

Pharmaceutical corporations such as Novartis are also supporting and conducting TSC research.

# Tuberous Sclerosis Complex Key Statistics




## Occurrence

Up to one million people worldwide are affected by TSC[10]. Tuberous sclerosis complex occurs in all races, ethnic groups and in both genders[1].

The disease affects an estimated one in 6,000 newborns, though many cases are undiagnosed in infants due to mild forms of initial symptoms[1]. About one-third of all patients with TSC genetically inherit the disease, while in the remaining patients, the disease is acquired as a result of spontaneous genetic mutation[5].

## Prevalence/Frequency of Common Manifestations of TSC

**Skin lesions** affect more than 90% of patients with TSC[9]

- **Angiofibromas, or reddish raised lesions,** are present in approximately 75% of TSC patients[2]
- **Hypomelanotic Macules, or light, oval or ash-shaped patches of skin,** are present in more than 90% of individuals with TSC[11]
- **Shagreen Patches, or yellowish-brown or pink colored patches of raised skin,** are present in up to 30% of patients
- **Fingernail or toenail tumors, or non-taumatic ungual or periungual fibroma (Koenen tumors)** affect 20% of patients with TSC[11,12]

**Neurological manifestations**

- **Seizures/ Epilepsy** affect up to 90% of patients with TSC[9]
- **Autistic characteristics** are exhibited by up to 60% of TSC patients[3]
- **Mental disabilities, or developmental disorders,** occur in one-half to two-thirds of individuals with TSC[1]

**Brain lesions**

- **Subependymal nodules (SEN),** affect up to 90% of patients with TSC[13]
- **Cortical tubers** may appear in more than 80% of patients in cerebral lobes[9]
- **Subependymal giant cell astrocytomas (SEGA)** occur in up to 20% of individuals with TSC[4]

**Kidney tumors, or renal angiomyolipomas,** occur in up to 80% of patients with TSC[1]

**Eye tumors, or multiple retinal nodular harmatomas,** affect 40-50% of patients[2]

**Heart tumors, or cardiac rhabdomyomas,** occur in two-thirds of newborns with TSC[11]

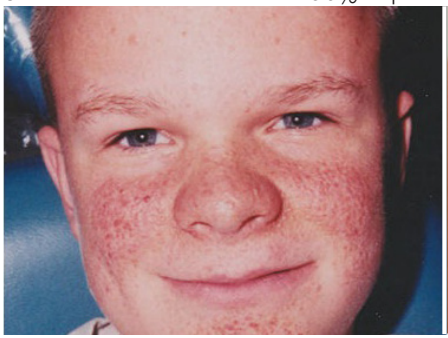
**Lung disease, or lymphangioleiomyomatosis (LAM),** is present in up to 34% of women and a low percentage of men with TSC[14]

*Note: TSC manifestations listed in decreasing order of prevalence/frequency*

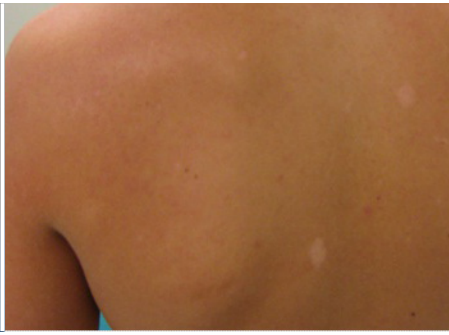
# Manifestations of Tuberous Sclerosis Complex*

## Skin Lesions

Skin lesions affect more than 90% of patients with TSC[9].



*Angiofibroma*



*Hypomelanotic Macules*

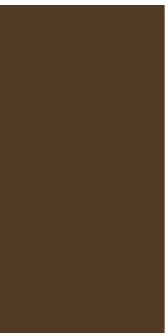
Facial angiofibromas are reddish raised lesions usually seen on the face that sometimes resemble acne. They may appear in early childhood, but typically become prominent in late childhood/early adolescence. Facial plaques may be present in infancy, but usually present at a later age than facial angiofibromas[2].

Angiofibromas are present in approximately 75% of TSC patients and are one of the common types of skin lesions[2].

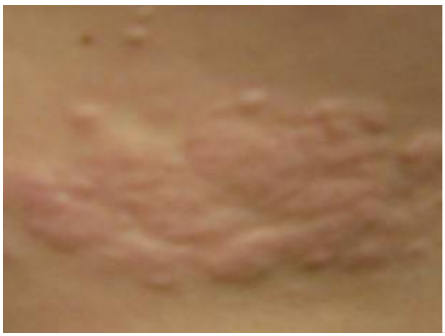
Hypomelanotic macules generally appear as white or light patches of skin and most often are oval or ash-leafed in shape. They can range in number from two to more than 100 and typically appear on the trunk and buttocks, but can appear anywhere on the body, although rarely on the face[12,15].

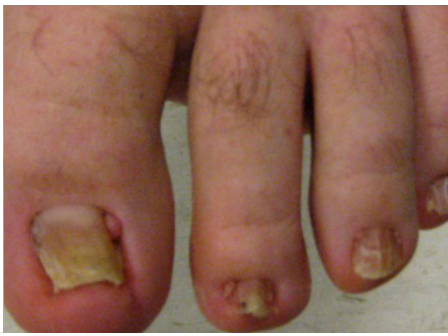
Hypomelanotic macules may be visible at birth or early infancy, but presentation can be delayed for years. Due to their possible presentation at birth, they are often the first visually detectable sign of TSC. More than 90% of individuals with TSC have hypomelanotic macules[11].

**Note: Not all people with TSC are affected by every TSC manifestation, and severity of symptoms and resulting disorders varies from patient to patient.*



*Shagreen Patch*





*Non-traumatic Ungual or Periungual Fibroma (fingernail or toenail tumors)*

Shagreen patches appear as a yellowish-brown or pink colored patch of raised, firm or rubbery skin, ranging in size from one to 10cm. They typically appear on the back[11,16].

Shagreen patches can be found in infants and generally develop around 10 years of age or older. They are present in up to 30% of patients[11,13,17].

Non-traumatic ungual or periungual fibromas (also known as Koenen tumors) are fingernail or toenail tumors which can be smooth, red or flesh-colored bumps under or around the skin of nail beds. They range in size from 5-10mm and are most commonly found on the toes[2,18].

They typically appear during or around the beginning of puberty and affect 20% of patients[2,9].

## Neurological Manifestations

Neurological manifestations are the most frequent cause of disease-related disability in patients with TSC[3].

### Seizures/Epilepsy

Seizures occur because of sudden, abnormal electrical activity in the brain and are present in up to 90% of patients with TSC[9,19]. From infancy into childhood, seizures tend to be of increasing frequency and severity[7].

The most common types of seizures that affect TSC patients are infantile spasms, partial motor seizures and generalized tonic clonic seizures[5].

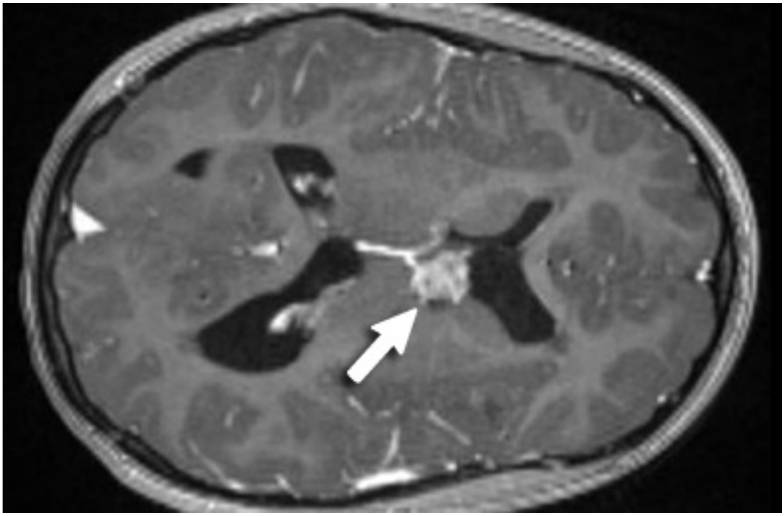
### Mental Disabilities

Approximately one-half to two-thirds of individuals with TSC have mental disabilities, which can range from mild learning disabilities to severe mental retardation[1].

### Autism

Autism is a common developmental disorder found in patients with TSC and is characterized by difficulties with social interaction, struggles with verbal and nonverbal communication and repetitive behavior[20]. Up to 60% of TSC patients exhibit autistic characteristics[3].

## Brain Lesions

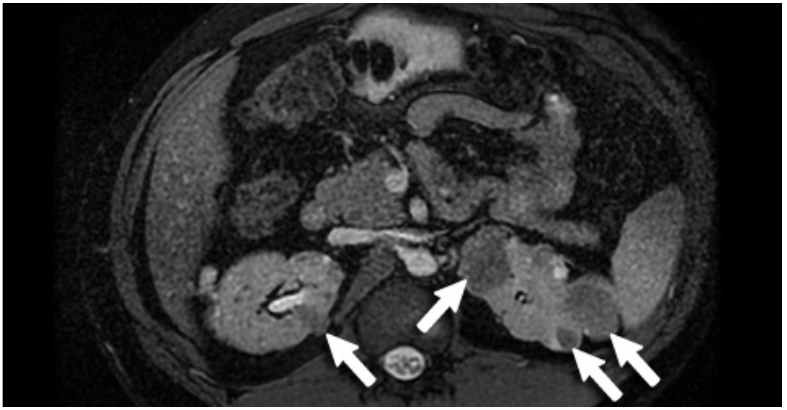


Subependymal giant cell astrocytoma (SEGA) is a type of non-cancerous brain tumor associated with TSC. Subependymal giant cell astrocytomas are one of three types of brain lesions associated with TSC; other brain lesions include *cortical tubers*, which may be detected prenatally, and *subependymal nodules* (SENs), which may be detected during early childhood and may turn into SEGAs[1,4,9].

Subependymal giant cell astrocytomas arise in the brain and can affect children and adults and may occur in up to 20% of patients with TSC[4].

If SEGAs grow, they may pose a significant medical risk, including the potential for swelling in the brain (hydrocephalus) and blindness or other neurologic symptoms if the tumors block circulation of cerebrospinal fluid. The treatment of SEGA depends on a number of factors, including the location, size and growth of the tumor[4,21].

## Kidney Tumors

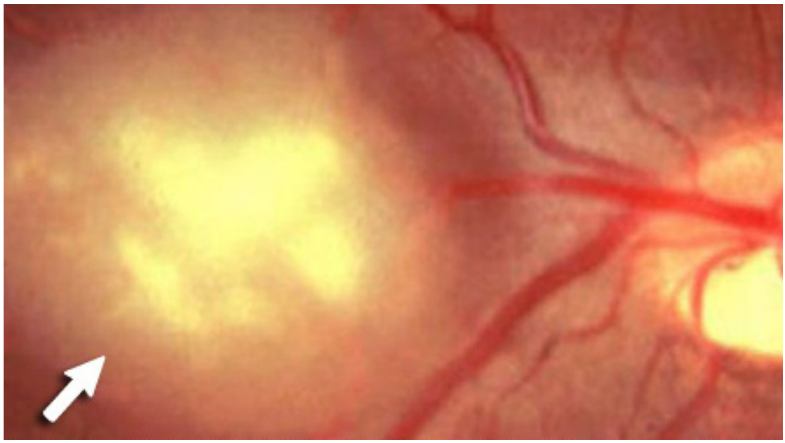


Renal angiomyolipomas are non-cancerous kidney tumors associated with TSC that are composed of abnormal blood vessels, smooth muscle and fat. Renal angiomyolipomas can be difficult to manage as multiple lesions may form and they can occur bilaterally. These growing tumors may lead to life-threatening complications[1].

They occur in up to 80% of patients, with typical onset occurring between the ages of 15 and 30 and prevalence increases with age[1,11].

Renal angiomyolipomas are the most common cause of morbidity and mortality in adult TSC patients. Tumor symptoms among patients with symptomatic lesions may include nausea, pain and bleeding[1,22].

## Eye Tumors

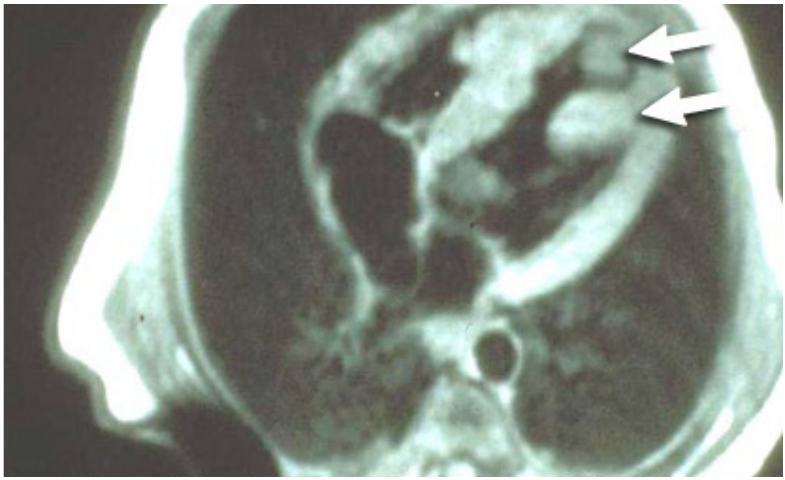


Multiple retinal nodular harmatomas are benign tumors sometimes found in the eyes of individuals with TSC and are frequently located near retinal vessels. Some can appear as white patches on the retina, called phakomas[1].

Multiple retinal nodular harmatomas affect up to 50% of patients. They are rare in children[2,14].

Generally, multiple retinal nodular harmatomas do not cause vision loss or other vision problems, but they can be used to help diagnose the disease[1].

## Heart Tumors

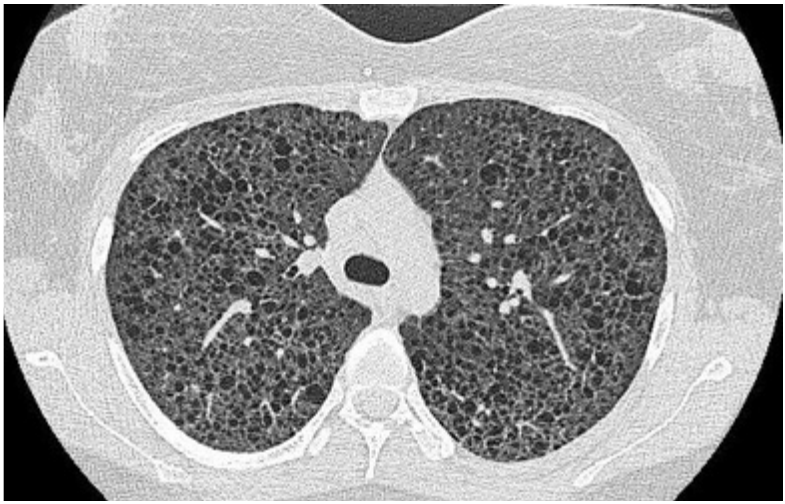


Cardiac rhabdomyomas are tumors that form in the heart. They are white-yellow/tan lesions that can range in size from 1mm to 9cm[1,23].

They occur in two-thirds of newborns with TSC and are found more frequently in male patients. Cardiac rhabdomyomas frequently emerge during infancy, shrink as patients age and may disappear spontaneously, meaning the individual is not affected later in life[1,2].

Cardiac rhabdomyomas are typically asymptomatic but in rare cases can result in complications such as heart valve dysfunction or arrhythmias[1].

## Lung Disease



Lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by an abnormal accumulation of muscle-like cells in the lungs, lymph nodes and kidneys[17]. There are two forms of LAM; one that occurs mostly in women with TSC and sporadic LAM that occur for unknown reasons[24].

Lymphangioleiomyomatosis is present in up to 34% of women and in low percentage of men with TSC[14].

Lymphangioleiomyomatosis can cause “collapsed lung” with symptoms of pain and persistent shortness of breath[24].

# Living with Tuberous Sclerosis Complex

## Patient and Caregivers' Journeys

Tuberous sclerosis complex can have a significant impact on the quality of life for both those living with it and their caregivers, as symptoms can range from mild to quite severe[1,3].

### A Lifelong Disease

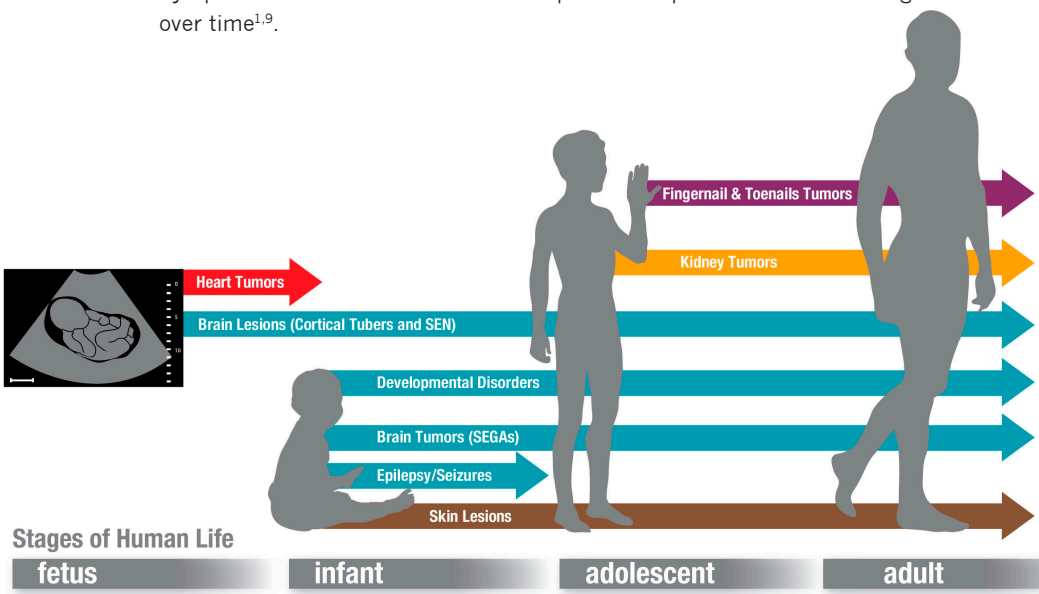
Tuberous sclerosis complex is a lifelong genetic disorder. Many patients with TSC show evidence of the disease in the first year of life and it affects one in 6,000 newborns. Genetic testing is also available and offers the potential for prenatal diagnosis. However, because manifestations vary from patient to patient and can take years to develop, many children are not diagnosed until later in life[1,9].

Since symptoms and manifestations of TSC vary from individual to individual and change over time, people with TSC should ideally be monitored by a specialist experienced with the disorder to ensure they are receiving the best possible care[1].

Those with mild symptoms have a normal life expectancy, while those who are severely affected can suffer from debilitating and potentially life-threatening symptoms[1].

### A Patient's Journey

Symptoms of TSC manifest at distinct points in a patient's life and change over time[1,9].



### Fetal Development

Manifestations of TSC such as heart tumors, certain kinds of brain lesions and developmental disorders form while an individual with TSC is in fetal development[9]. Heart tumors are typically asymptomatic and usually do not affect patients later in life but in rare cases can result in complications[1]. Brain lesions known as SENs, which can also develop in the fetus, can lead TSC patients to develop SEGAs, or brain tumors, later in life[13].

Developmental disorders which develop in the fetus will affect a patient throughout his or her life and can range from mild learning disabilities to severe mental retardation[1,25]. Depending on the severity, some individuals with TSC need to enroll in special education[1].

### Infancy/Childhood

A number of TSC manifestations including brain tumors, epilepsy/seizures, eye tumors and skin lesions present in infancy or childhood[9]. If not diagnosed earlier, many people affected by TSC become aware of the condition in early childhood through seizures and/or dermatologic manifestations[1].

Brain tumors, or SEGAs, often develop in childhood and need to be monitored carefully via MRI and CT scans. If they grow too big, they can pose a significant medical risk, including the potential for swelling in the brain[1,4].

Seizures have been reported in the majority of TSC patients[9]. Seizures associated with TSC can be difficult to manage and can span a patient's lifetime, with two-thirds of patients not achieving epileptic remission[1].

Eye tumors associated with TSC are rare in children and do not cause vision problems but can be used to help diagnose the disease[1].

Skin abnormalities develop in infancy and become more prevalent as patients age. In infants, these abnormalities are often difficult to see without the assistance of an ultraviolet light. While most cause no health-related problems, in some cases these skin abnormalities may be quite noticeable and differentiate people with TSC from their peers[1,2].

Severity of seizures and extent of developmental delays and behavioral problems associated with TSC can have an impact on the educational options for children with TSC. Day care centers must be carefully selected for young children with TSC, particularly if the children have hard-to-manage seizures.

Severely developmentally delayed children with TSC receive early intervention therapeutic services, and by elementary school and onward these children may require specialized schools, which can be difficult to locate and may require families to move locations to ensure their child has access to the right school for them. Children without significant developmental delays associated with TSC may attend elementary school classes with typically-developing children and are often treated with acceptance among their peers. However, as school work becomes more challenging, they may need to shift to special education classrooms which could signal a shift toward social isolation. People with TSC, especially girls, may face greater isolation in middle school and high school, due to changing social settings as children enter adolescence.

Behavioral problems associated with TSC can also play a determining factor in a TSC patient's educational path. Children living with TSC may have a variety of behavioral difficulties, including trouble controlling emotions, which can result in acting out, screaming and potential aggression, and obsessive-compulsive tendencies or perseveration (uncontrollable repetition of a particular response). For children with TSC, establishing consistent daily routines and recognizing triggers are instrumental to helping manage behavior.

### Adolescence

Kidney tumors and fingernail and toenail tumors associated with TSC typically develop in adolescence[9]. Adolescents can face challenges balancing the many doctors' visits required of an individual with TSC and the other interests typical of teenagers such as afterschool activities and time with friends.

Fingernail or toenail tumors usually appear during or around the beginning of puberty[9].

In addition to regular medical appointments, it is also important that teenagers with TSC have proper emotional and psychological support systems. For example, research has shown that 45% of individuals with TSC develop anxiety and 29% report symptoms of depression[26]. While anxiety and depression can present in teenagers for a number of reasons, many with TSC may develop mood disorders due to the psychological impact of having a genetic disorder.

### Transitioning to Adulthood

As people with TSC age out of pediatric management and enter adulthood, they may experience a gap in care. Patients who were treated by pediatric TSC specialists may switch to adult physicians specializing in their manifestations – such as adult neurologists and nephrologists – who may not be equipped to offer the comprehensive care provided by pediatric specialists. Those with TSC who experience cognitive impairment still function at a child's level but are treated as adults by the medical system and may require assistance that is no longer easily available to them or their families. Non-cognitively impaired adults who take responsibility for their own care after high school may experience discontinuities in care since they may no longer have parental assistance and may be more focused on college and finding a job than on managing their TSC. They may also experience challenges learning to navigate the insurance system on their own and are sometimes at a loss to find adult care that is attentive to the complexity of their potential needs.

### Adulthood

Adolescents and adults can be affected by non-cancerous kidney tumors associated with TSC, as most kidney tumors occur between the ages of 15 and 30[1,11]. With larger tumors, kidney function can be compromised and cause kidney failure[22]. Individuals with these tumors need to have their kidneys closely monitored to ensure proper kidney function.

Lung tumors associated with TSC can present in adulthood[9]. They can cause pain and persistent shortness of breath[24].

While patients with TSC must overcome multiple challenges – including the large amount of time involved for multiple doctors' visits, emotional affect of living with a serious disease and physical or mental restraints it may pose – many are able to live a normal and fulfilled life[1]. Having meaningful conversations about the disease with friends and loved ones often helps to relieve some of the emotional burden of TSC and help patients feel supported within a community.

In the past few decades, the level of TSC knowledge within the medical community has grown exponentially, aided by increased research efforts. Physicians now have more resources to better manage the disease and help patients. The media can play a role in education and awareness about TSC in society at large, which could make strides in improving the lives of people with TSC by helping the people around them better relate with what it is like to live with TSC.

## Parenting a Child with TSC

Raising a child with TSC can have an impact on the whole family. Activities associated with managing TSC become part of a family's routine, such as medical appointments, developmental and physical therapies, blood work and coping with symptoms such as seizures, and these can take an emotional toll on caregivers. Every family reacts differently to a TSC diagnosis. In some cases, taking care of a child with TSC can strengthen family relationships as they work as a team to act as collective caregivers. In others, they can become a source of conflict that puts stress on marriages and families.

### Responsibilities of a TSC Family

Care coordination, monitoring progress and providing care are the core responsibilities for TSC families. Because TSC involves so many separate specialties, which often operate independently, caregivers must become knowledgeable to operate within them. For example, the healthcare, developmental and therapeutic communities, as well as educational institutions, all have their own languages, experts, definitions and designations of ailments, service structures and provisions and evaluative frameworks that caregivers need to learn how to navigate. Caring for a child with TSC involves monitoring the child's progress in every aspect, including medical issues such as type, movement and frequency of seizures and development of other tumors, as well as developmental and educational progress. Providing direct care is often complicated by the fact that care alters over time as symptoms and associated diseases emerge and change.

### Emotional Toll

Parents and caregivers of children with TSC are faced with managing the range of emotions associated with taking care of a child who requires consistent care, vigilant medical monitoring and sometimes special education. Parents may not have time to attend to their own needs and may not have outlets to relieve their stress, which is why forming connections within the TSC community can be a source of support and comfort.

## Novartis and Tuberous Sclerosis Complex

Novartis has a heritage of commitment to rare diseases, such as TSC, focused on addressing patient needs.

Novartis is committed to understanding and improving the lives of people with TSC through clinical research, education and collaboration with the TSC community. Novartis' research in TSC has focused on leveraging the known fundamental mechanisms underlying the disease as well as the unique needs of people living with the disease to build a relevant clinical development program.

Novartis collaborates with patient and healthcare professional organizations as well as world-class researchers to help advance disease awareness, knowledge sharing and additional research in the TSC space. Novartis is committed to partnering with TSC treaters by creating an environment that fosters connections and networking across specialties.

# Additional Resources

Following is an overview on where to obtain credible information regarding TSC.

## Sources for Medical Reporting

**Note: Novartis does not endorse and is not responsible for the content of any of the listed resources This is not an exhaustive list of resources.*

### Medical Journals

Articles published in peer-reviewed medical journals provide the primary source for credible medical news. In peer-reviewed journals, independent experts screen submitted scientific papers to ensure that they meet the accepted standards of their discipline.

Medical journals such as *The Lancet*, the *British Medical Journal*, *The New England Journal of Medicine* (NEJM) and the *Journal of the American Medical Association* (JAMA) encapsulate many different aspects of medicine and appeal to a wide variety of healthcare professionals. Specialty medical journals that may focus on manifestations of TSC include *Archives of Dermatology, Journal of Child Neurology, Journal of Nephrology* and *Neurology*.

### Medical Conferences

Researchers share preliminary and updated results of their work at medical conferences[27]. Typical formats for presentation of information at medical conferences include:

- Presentation abstract: a synopsis of the study submitted for presentation at a medical conference. The sponsoring organization will publish the accepted abstracts prior to or during the conference, in an abstract book and often online, and may make them available to reporters.
- Oral presentation: research that has been selected for presentation by means of a live lecture during the conference (usually with slides).
- Poster presentation: the study is summarized on a large paper poster board, illustrating the research methods and outcomes in text and graphics. Typically, a poster presentation allows viewers to discuss the study with one or more of the researchers[28].

*Caution: Check with individual journals and conference sponsors for their embargo policies.*

*Tip: Sign up with journals and conference sponsors to receive e-mail alerts of upcoming publications and meetings.*

### Medical Literature Databases

- Thomson Reuters – http://science.thomsonreuters.com/mjl
- PubMed (US) – www.pubmed.gov

### Clinical Trial Databases

- International Clinical Trials Registry Platform (WHO) – www.who.int/ictrp
- Clinical Trials (USA) – www.clinicaltrials.gov

### Government Agencies and Resources

- European Medicines Agency (EU) – www.ema.europa.eu
- US Food and Drug Administration (USA) – www.fda.gov
- World Health Organization – www.who.int
- National Institutes of Health – www.nih.gov
- National Institute of Neurological Disorders and Stroke – http://www.ninds.nih.gov

### Professional and Patient Organizations

- Tuberous Sclerosis Alliance (US) – www.tsalliance.org
- Tuberous Sclerosis Association (UK) – www.tuberous-sclerosis.org
- Australasian Tuberous Sclerosis Society (Australia) – www.atss.org.au
- TSC Canada (Canada) – www.tscanada.ca
- American Academy of Neurology (US) – www.aan.com
- American Association of Kidney Patients (US) – www.aakp.org
- Autism Society of America (US) – www.autism-society.org
- Global Autism Collaboration – www.autism.com
- Epilepsy Foundation (US) – www.epilepsyfoundation.org
- American Urological Association (US) – www.auanet.org
- European Organisation for Rare Diseases – http://www.eurordis.org
- National Organization for Rare Disorders – http://www.rarediseases.org

## Peer-Reviewed Medical Journals

**Note: Novartis does not endorse and is not responsible for the content of any of the listed resources. This is not an exhaustive list of resources.*

Archives of Dermatology: (archderm.ama-assn.org) – Publishes material that helps in the development and testing of the effectiveness of diagnosis and treatment in medical and surgical dermatology, pediatric and geriatric dermatology, and oncologic and aesthetic dermatologic surgery.

Archives of Neurology: (http://archneur.ama-assn.org) – Publishes scientific information primarily important for those physicians caring for people with neurologic disorders but also for those interested in the structure and function of the normal and diseased nervous system.

Journal of Child Neurology: (www. jcn.sagepub.com) – Publishes articles about nervous system disorders in children. Material covers patients up to age 18 and covers topics such as: therapies, procedures, diagnosis, evaluation and management.

Journal of Nephrology: (www.jnephrol.com) – Publishes original manuscripts dealing with both clinical and laboratory investigations of relevance to the broad fields of nephrology, dialysis and transplantation.

Kidney International: (www.nature.com/ki) – Publishes articles intended to inform the renal researcher and the practicing nephrologist on all aspects of renal research.

Neurology: (www.neurology.org) – Publishes articles that are meant to advance the field of neurology. Material is intended for physicians who work with the nervous system. The publication covers new and basic clinical research.

The Journal of the American Medical Association: (www.jama.ama-assn.org) – Publishes articles on a diverse range of medical topics.

The Lancet: (http://www.thelancet.com) – Publishes medical news, original research, and reviews on all aspects of clinical medicine and public health.

The New England Journal of Medicine: (www.nejm.org) – Publishes new medical research findings, review articles and editorial opinion on a wide variety of topics of importance to biomedical science and clinical practice. Material is published with an emphasis on internal medicine and specialty areas including allergy/immunology, cardiology, endocrinology, gastroenterology, hematology, kidney disease, oncology, pulmonary disease, rheumatology, HIV and infectious diseases.

## Commonly Used Terms

The following terms frequently appear in journal articles and conference presentations:

### Statistical Terms

Confidence Interval (CI): describes how precise a particular result is and suggests how reliable it may be beyond the specific study. In a clinical trial, the CI indicates the limits within which the difference between two treatments is likely to lie. Confidence intervals are reported as a range of values above and below the study finding; the more narrow the range, the more precise the result. For example, a disease that is present in 25% of a population with a CI of plus or minus 5% means that the actual value can lie anywhere between 20% and 30%[29].

Mean: the sum of a set of numbers divided by how many numbers are in the set. In a clinical study, there will always be patients who will fall above or below the mean[30].

Median: the middle value in an even set of measurements[30].

P-value (probability value): a measure of probability that a difference between groups during an experiment happened by chance. For example, a p-value of .01 (p = 0.01) means there is a 1 in 100 (1%) chance the result occurred by chance. In a clinical trial, the lower the p-value, the more likely it is that the difference between groups was caused by the treatment being studied[29].

Statistical significance: results that are statistically significant are unlikely to be due to chance. A p-value less than 0.05 (meaning that the result would have arisen by chance on less than one occasion in 20) is generally considered statistically significant. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed[31,32].

## Clinical Trial Terms

Blinded trial: a study in which the patients (single-blinded) or the patients and their doctors (double-blinded) do not know which drug or treatment is being given; the opposite of an open-label study[33].

Clinical trial: a research study that tests the effectiveness and safety of medications, devices, and/or treatment paradigms in humans[31].

- Phase I clinical trial: initial studies conducted with a small number of volunteers with or without the disease (can be fewer than 80) to assess the safety and various dose ranges for an experimental treatment[32].
- Phase II clinical trial: mid-stage studies (which occur after a Phase I trial) typically involving a larger number of patient volunteers to further assess safety and effectiveness of an experimental treatment[32].
- Phase III clinical trial: large trials (which occur after Phase II) carried out to confirm the effectiveness of an experimental treatment, and identify adverse events. Phase III trials are conducted to compare an experimental treatment to commonly used treatments, and collect information to evaluate the overall risk/benefit ratio. Phase III trials provide the basis for applications with regulatory agencies for authorization to market a new drug[32].
- Endpoint: an overall measurable outcome that the study is designed to evaluate. The primary endpoint(s) measure outcomes related to the main objective of the study and secondary endpoints evaluate measures for other related questions in the study[31,34].

Non-inferiority trial: a study intended to show that the effect of a treatment is not worse than that of an active control, by no more than a specified range[35].

Open-label trial: a study in which both the patients and the doctors know which treatment is being given; opposite of a blinded study[35].

Post-hoc analysis: an examination of data, after a clinical trial has concluded, for analyses that were not specified previously[36].

Prospective trial: a study or clinical trial in which participants are identified and then followed forward in time[29].

Randomized trial: a study in which the participants are assigned by chance to separate groups that compare different treatments. Large, randomized, double-blind, controlled prospective clinical trials are considered to provide the highest quality of scientific evidence[29,34].

Retrospective study: a study in which a search is made for a relationship between one (usually current) phenomenon or condition and another that occurred in the past. Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the condition. A retrospective study is also called a case-control study[31].

Sub-analysis study: a study that examines data from a subset of patients from a clinical trial[31].

# Glossary

**Angiofibromas** are reddish or raised skin lesions, present in approximately 75% of TSC patients[2].

**Autosomal dominant disorder** is a disorder that can be genetically transmitted directly from parent to child. TSC is an autosomal dominant disorder[12].

**Cardiac rhabdomyomas** are tumors that form in the heart and occur in two-thirds of newborns with TSC[11].

**Cortical tubers** are a type of brain lesion which may be detected prenatally and occur in more than 80% of TSC patients[9].

**Hydrocephalus** is a buildup of fluid inside the skull which leads to brain swelling. Non-cancerous tumors associated with TSC inside the brain can lead to life-threatening hydrocephalus[4,9].

**Hypomelanotic macules** are or light, oval or ash-shaped patches of skin present in more than 90% of individuals with TSC[11].

**Koenen tumor** see periungual fibromas.

**Lymphangioleiomyomatosis (LAM)** is a rare lung disease present in up to 34% of women and a low percentage of men with TSC[24].

**mTOR (mammalian target of rapamycin)** is a signaling pathway which acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism and is increased in individuals with TSC[1]. This can cause uncontrolled tumor cell growth and proliferation, blood vessel growth and altered cellular metabolism[1].

**Multiple tetinal nodular harmatomas** are benign tumors sometimes found in the eyes of individuals with TSC and affect up to 50% of patients[2].

**Non-taumatic ungual tumors** are fingernail tumors which can be smooth, red or flesh-colored bumps under or around the skin of nail beds and affect 20% of patients with TSC[11].

**Periunual fibromas,** also known as koenen tumors, are toenail tumors which can be smooth, red or flesh-colored bumps under or around the skin of nail beds and affect up to 88% of patients[12].

**Phakomas** are a type of multiple retinal nodular harmatoma, or benign eye tumors, which can appear as white patches on the retina[1].

**Renal angiomyolipomas** are non-cancerous kidney tumors associated with TSC which occur in up to 80% of patients[1].

**Sclerotic** is a term used to describe tubers which have calcified and become hard with age[1].

**Shagreen patches** are or yellowish-brown or pink colored patches of raised skin present in up to 30% of patients[11,12].

**Subependymal giant cell astrocytoma (SEGA)** is a type of non-cancerous brain tumor associated with TSC that can affect children and adults and may occur in up to 20% of patients[4].

**Subependymal nodules (SENs)** are a type of brain lesion associated with TSC that may be detected during early childhood, can sometimes turn into SEGAs and affect up to 90% of patients[9,13].

***TSC1* / *TSC2* genes,** when defected, can cause TSC. Only one of the genes needs to be affected for TSC to be present. The *TSC1* gene produces a protein called hamartin and the *TSC2* gene produces a protein called tuberin[1].

**Tubers** are potato-like nodules that form in the brain of TSC patients[1].

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