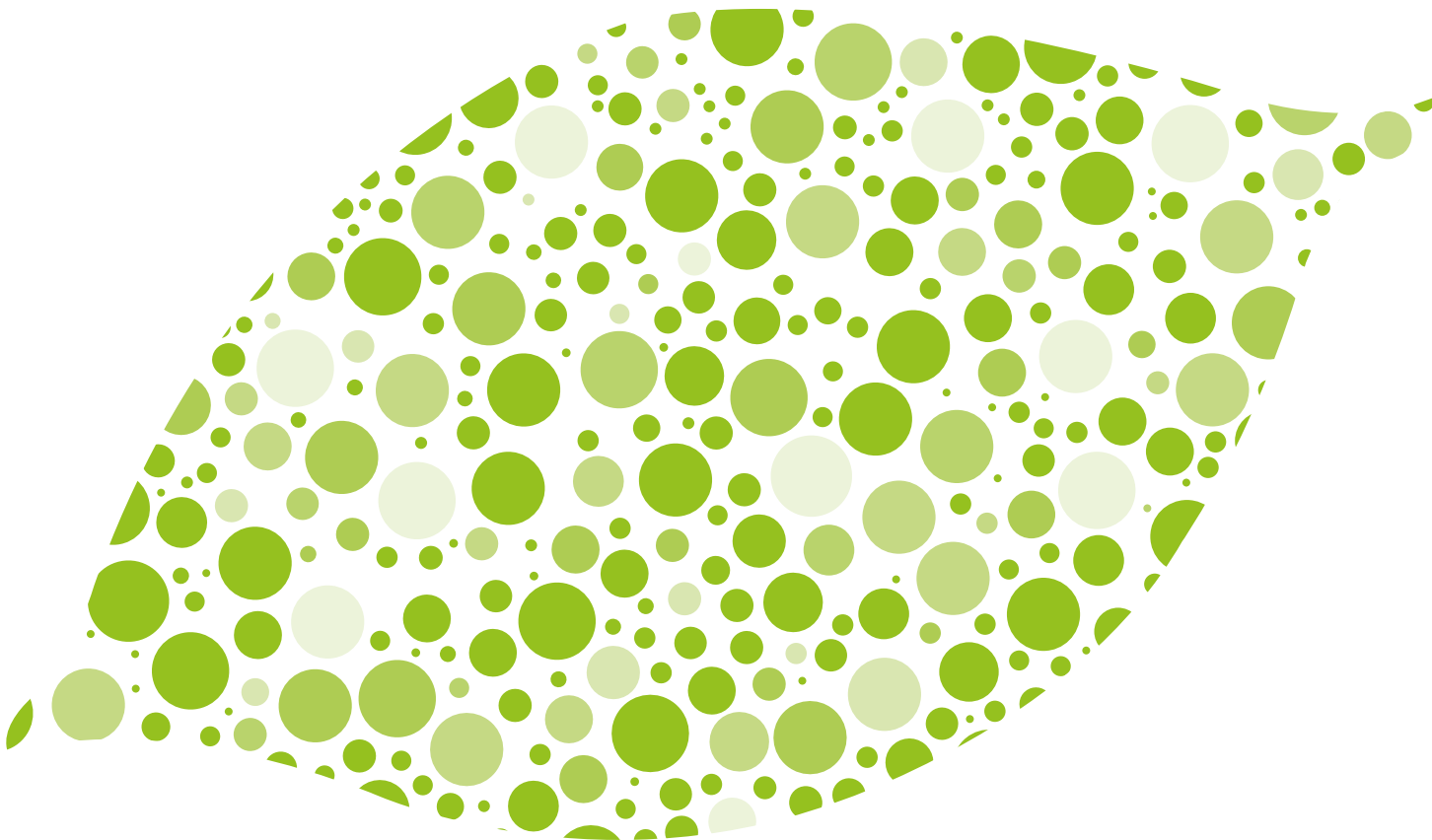


# UK guidelines for managing tuberous sclerosis complex

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A summary for clinicians  
in the NHS



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## Abbreviations

<b>AML</b>	Angiomyolipoma	<b>LAM</b>	Lymphangi leiomyomatosis
<b>HRCT</b>	High-resolution chest computed tomography	<b>MRI</b>	Magnetic resonance imaging
<b>CAMHS</b>	Child and adolescent mental health services	<b>SEGA</b>	Sub-ependymal giant cell astrocytoma
<b>CT</b>	Computed tomography	<b>SUDEP</b>	Sudden unexpected death in epilepsy
<b>ECG</b>	Electrocardiogram	<b>TAND checklist</b>	TSC Associated Neuropsychiatric Disorders checklist
<b>EEG</b>	Electroencephalogram	<b>TSC</b>	Tuberous sclerosis complex
<b>GFR</b>	Glomerular filtration rate		

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## About this summary

This summary provides a quick guide to recommendations from the guidelines on the diagnosis, assessment, surveillance and treatment of patients with tuberous sclerosis complex (TSC) in the UK.

This guide has two main sections. The first is on assessments and other activities at

baseline for patients with newly diagnosed or suspected TSC. The second section presents recommendations for the care of patients who have already been diagnosed with definite or possible TSC. Within each section, there are recommendations relevant to clinicians with different areas of expertise.

## Using the guidelines

The guidelines were developed by TSC experts from many different specialties to give guidance on how to provide the best NHS clinical care for everyone with TSC. There is more information about how the recommendations were developed on page 10.

While taking account of the recommendations in the guidelines, healthcare professionals should tailor them to meet a patient's individual needs and circumstances.

## TSA viewpoint: Involving patients and their families and carers



The Tuberos Sclerosis Association believes that actively involving people living with TSC in making decisions about their own care, treatment and support can help people to stay well and manage their own condition better.

This guideline sets out recommendations developed by UK-based experts on TSC. Their aim was to reach consensus on what represents best practice in clinical care within the NHS and make it available to all patients with TSC who are diagnosed, assessed, monitored and treated in the NHS.

Every person living with TSC is unique and every individual is differently affected by the condition. Healthcare professionals should discuss these recommendations with people living with TSC and their families and carers, and take the recommendations into account alongside the patient's individual needs, preferences and values.

# Baseline assessments for patients with newly diagnosed or suspected TSC

These recommendations are for the care of patients in whom TSC is suspected or who have been newly diagnosed with TSC. They cover the assessments and some other actions that should be carried out at baseline. There are many different presentations that may indicate TSC and people may present at any stage of life. Therefore, the sequence of assessments will not be the same for all patients.

## Baseline assessments



**Genetic testing**



**Kidneys**



**Skin**



**Heart**



**Central nervous system**



**Lungs**



**Dental and oral**



**Eyes**



## Genetic screening

Offer genetic testing to all patients, **or**:

- If genetic testing cannot be offered to all patients, offer it for reproductive counselling or when a TSC diagnosis is likely but cannot be clinically confirmed.

Obtain a three-generation family history.

For patients at or reaching reproductive age:

- Ensure that the availability of preimplantation, prenatal and non-invasive prenatal diagnosis options is discussed where appropriate.

For first-degree relatives of people with TSC:

- Offer clinical assessment and, where possible, genetic testing (first degree relatives are parents, offspring and siblings).



## Central nervous system

Perform MRI of the brain to assess for the presence of sub-ependymal giant cell astrocytoma (SEGA) or other lesions.

Assess for neuropsychiatric and neurodevelopmental disorders.

For people with suspected epileptic seizure activity:

- Perform a standard electroencephalogram (EEG).
- If a standard EEG does not explain changes in sleep, behaviour, or cognitive or neurological function, perform 24-hour video EEG.

For children:

- Teach parents how to recognise infantile spasms and focal seizures.
- Repeat EEG urgently if there is a suspicion of seizures.
- Involve paediatric neurologists in the diagnosis and care of children with (or with suspected) epileptic seizures.

## Kidneys

Perform MRI of the abdomen to check for the presence of angiomyolipoma (AML), renal cysts or other renal lesions, **or**:

- If MRI is contra-indicated, perform a CT or, in special circumstances, an ultrasound scan (see section below).

Take blood pressure.

Assess glomerular filtration rate (GFR) to check kidney function.

Combine brain and abdominal MRI scans when possible. When scanning the abdomen to assess the kidneys, also check for lesions in the liver, pancreas and other abdominal organs.

## Lungs

Provide advice about the risks associated with smoking.

For adolescent and adult females:

- Provide advice to avoid the use of oestrogen (for example, oestrogen-containing contraceptives) if possible.

For females of child-bearing age:

- Perform baseline high-resolution chest computed tomography (HRCT).

For adult males who are symptomatic:

- Perform baseline high-resolution chest computed tomography (HRCT).

## Skin

Perform a detailed clinical dermatological examination, including an investigation using Wood's light.

## Dental and oral

Perform a detailed clinical dental examination, looking for abnormal tooth eruption, dental pits and oral fibromas.

## Heart

Perform an electrocardiogram (ECG) to check for arrhythmia and conduction abnormalities.

For all children:

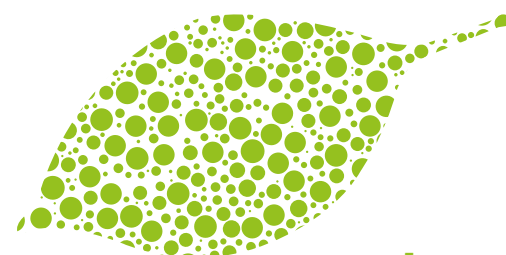
- Perform an echocardiogram to check for rhabdomyomas.

For adults with symptoms that suggest heart problems (for example, shortness of breath, fainting, palpitations):

- Perform an echocardiogram to check for rhabdomyomas.

## Eyes

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



# Monitoring and treating patients already diagnosed with TSC

These recommendations are for the care of patients who have already been diagnosed with definite or possible TSC. They include recommendations for surveillance and treatment, and some particular issues for discussion with patients and their families or carers.

There is a wide range of different clinical presentations of TSC. The organs affected and the progression and severity of TSC can vary depending on the patient's age, genotype and treatment. Therefore, treatment and care must be tailored to individual circumstances.

## Surveillance and treatment



**Genetics**



**Sub-ependymal giant cell astrocytomas (SEGAs)**



**Neurodevelopmental and neuropsychiatric disorders**



**Epilepsy**



**Kidneys**



**Lung**



**Skin**



**Dental and oral**



**Heart**



**Eyes**



**Liver and pancreas**



## Genetics

Offer first-degree relatives a clinical assessment and, where possible, genetic testing (unless this has already been done at diagnosis). First-degree relatives are parents, children and siblings.

For patients at or reaching reproductive age:

- Ensure that the availability of preimplantation, prenatal and non-invasive prenatal diagnosis options is discussed where appropriate.



## Sub-ependymal giant cell astrocytomas (SEGAs)

### Surveillance

For patients who **do not** have a sub-ependymal giant cell astrocytoma (SEGA) and are younger than age 25 and without symptoms that suggest raised intracranial pressure:

- Perform MRI of the brain every 1–3 years.

For all patients who **do have** a SEGA and are without symptoms that suggest raised intracranial pressure:

- Perform MRI of the brain every 1–3 years.

Perform MRI scans more frequently for patients with a large or growing SEGA, or for patients with a SEGA causing ventricular enlargement who remain asymptomatic.

Use clinical judgement about when to stop routine MRI scans of the brain in an adult patient with SEGA lesions, taking account of any learning disability, their communication abilities, and the SEGA growth interval.

It is believed that the majority of SEGA lesions stop growing in the third decade of life. However, there have been case reports of SEGA growth in patients older than 25.

## Managing large or growing SEGAs

Ensure patients and their families are informed about potential new symptoms associated with a large or growing SEGA or with a SEGA causing ventricular enlargement in patients who are currently asymptomatic.

Potential new symptoms could include those that may indicate raised intracranial pressure, new or progressing neurological problems, or TSC-associated neuropsychiatric disorders (TAND) and other significant deterioration in epilepsy or TAND problems.

Discuss the management of a growing SEGA in a meeting of a multidisciplinary team that includes oncologists, neurologists, neuro-radiologists, neurosurgeons and TSC experts.

Involve the patient and (as appropriate) their family or carer in discussion about the management for a growing SEGA.

Offer surgery as first-line treatment for a growing SEGA, but in choosing surgery or an mTOR inhibitor, take into account TSC co-morbidities and the wishes of the patient and (as appropriate) their family or carer. Surgical resection should only be performed in a specialised centre with expertise in resecting intraventricular lesions.

Offer everolimus to patients who have at least one SEGA lesion of baseline longest diameter 1cm as assessed by multiphase MRI that is not amenable to surgery as assessed by a properly constituted multidisciplinary team. For full details see the NHS England commissioning criteria.

## Neurodevelopmental and neuropsychiatric disorders

### Surveillance

Use the TAND checklist at each annual review.

Carry out in-depth neuropsychology and neuropsychiatric assessments when indicated.

### Treatment and management

Offer treatment and care in line with relevant NICE guidelines. See NICE Pathways for up-to-date information, particularly information on common

mental health problems, depression, anxiety, autism spectrum disorder and learning disability.

Formally evaluate developmental status at key developmental time points and periods of transition:

- Infancy (0–3 years)
- Preschool (>3–6 years)
- Middle school (>6–11 years)
- Adolescence (12–18 years)

**and** as clinically indicated.

Ensure that TSC clinics have established links and care pathways with developmental paediatric, educational and Child and Adolescent Mental Health Service (CAMHS) specialist services to enable a seamless, integrated, responsive and timely multidisciplinary approach that includes consultation and liaison.

## Epilepsy

### Investigations

For people with suspected epileptic seizure activity:

- Perform a standard electroencephalogram (EEG).
- If a standard EEG does not explain changes in sleep, behaviour, or cognitive or neurological function, perform 24-hour video EEG.

### Treatment

#### *Infantile spasms*

- The recommended first-line therapy is vigabatrin. If treatment with vigabatrin is unsuccessful, offer hormonal (adrenocorticotrophic hormone or prednisolone) treatments.

#### *Refractory focal seizures*

Seizures are considered to be refractory (also known as uncontrolled or intractable) when 2 different antiepileptic drugs given at therapeutic doses have failed to control a person's seizures.

- After considering epilepsy surgery or a vagal nerve stimulator, offer everolimus for refractory focal onset seizures associated with tuberous sclerosis complex in patients aged 2 years or older in line with the NHS England commissioning policy.

## Advice and information for patients, families and carers

Ensure the risk of sudden unexpected death in epilepsy (SUDEP) is discussed with patients and families (see the recommendations in the NICE guideline).

For children:

- Teach parents how to recognise infantile spasms and focal seizures.
- Repeat EEG urgently if there is a suspicion of seizures when they had not been previously diagnosed.
- Involve paediatric neurologists in the diagnosis and care of children with (or with suspected) epileptic seizures.

## Kidneys

### Kidney imaging

Kidney imaging should be repeated regularly as follows.

For patients who have renal lesions:

- Regardless of need for a general anaesthetic, carry out annual MRI of the abdomen to assess for the progression of AML, renal cystic disease, and occurrence of renal cancer (which is rare).
- If MRI scanning cannot be performed (for example, patients with a vagal nerve stimulator may not be able to have an MRI scan), use fast low-dose CT scanning.
- If the MRI (or CT) scan shows anatomy and pathology that are judged to be easy to interpret by ultrasound scan, then the next 1 or 2 scans could be done by ultrasound.
- Continue imaging throughout the life of the patient.

For patients who do not have renal lesions:

- Carry out imaging as above every 1–3 years through childhood and early adult life.

### Renal function

In adults and children with renal lesions, assess renal function (including glomerular filtration rate [GFR]) and blood pressure annually.

## Treatment of renal angiomyolipomas (AMLs)

For renal angiomyolipomas (AMLs) presenting with acute haemorrhage, use embolization with a short course of corticosteroids as first-line therapy.

Make every attempt to avoid nephrectomy.

For asymptomatic, growing AMLs larger than 3cm in diameter, use an mTOR inhibitor as first-line therapy. See the NHS England criteria for commissioning the use of everolimus to treat AMLs associated with TSC in children from 3 years of age and adults. (Note that treatment with everolimus is unlicensed for the paediatric age range, but it is recommended by experts and funded by the NHS.)

For asymptomatic AMLs, selective embolisation or kidney-sparing resections are possible second-line therapies.

## Lung

### Ongoing advice and information

Provide advice about the risks associated with smoking.

For adolescent and adult females:

- Provide advice to avoid the use of oestrogen (for example, oestrogen-containing contraceptives) if possible.

### Surveillance for lymphangiomyomatosis (LAM)

For asymptomatic females of childbearing age:

- Carry out high-resolution chest computed tomography (HRCT) every 5–10 years if there is no evidence of lymphangioleiomyomatosis (LAM) on the baseline HRCT.
- Continue this surveillance regimen until menopause.

For patients with LAM detected on HRCT:

- Carry out annual pulmonary function testing (pulmonary function testing and 6-minute walk test). Do this more often for patients who have progressive disease.

### Treatment for LAM

For patients with LAM who have evidence of progressive loss of lung function, treat with mTOR inhibitors.



## Skin

### Surveillance

Perform a detailed clinical dermatological examination, including an inspection using Wood's light.

### Treatment and management

Advise patients and families to use sunblock (SPF 30+) routinely.

### Facial angiofibromas

- Treat facial angiofibromas with topical mTOR inhibitors or laser.
- Consider surgical excision for larger solitary lesions.

Consider surgical excision for unguis fibromas that are causing problems.

## Dental and oral

### Surveillance

Patients should have an oral evaluation every 6–12 months, in line with surveillance recommendations for the general population.

### Prevention and treatment of lesions

Oral hygiene education should be available, especially for patients with learning disabilities.

Patients should be offered treatment to prevent oral lesions (that is, sealing of dental pits that penetrate through the enamel). (Note that this is particularly important for patients with learning disabilities).

Use surgical excision or curettage to treat symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions.

## Heart

### Surveillance

For asymptomatic patients with cardiac rhabdomyomas:

- Take an echocardiogram once every 1–3 years until complete regression of cardiac rhabdomyomas or until the first sign of progression of cardiac rhabdomyomas.

For all patients:

- Carry out a 12-lead ECG at least every 3–5 years.

For patients with clinical symptoms (for example, signs or symptoms suggesting heart problems such as palpitation, fainting, shortness of breath) or significant abnormalities on routine echocardiogram or ECG:

- More frequent assessments may be needed. These may include ambulatory event monitoring.

### Treatment

Patients with hemodynamic instability and/or life-threatening arrhythmia should be treated with antiarrhythmic medications, surgery or mTOR inhibitors, as appropriate for the situation.

## Eyes

### Surveillance

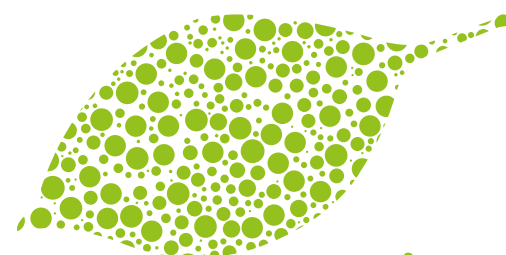
For all patients:

- Carry out regular funduscopy by direct ophthalmoscopy examination during each clinic visit.

## Liver and pancreas

### Surveillance

When carrying out MRI or CT scans to monitor kidneys, assess the liver, pancreas and the rest of the abdomen for lesions as well.



# How the UK guidelines were developed

A group of UK experts led the development of UK guidelines on management and surveillance of TSC. Their aim was to reach consensus on what represents best practice in clinical care within the NHS and make it available to all patients with TSC who are diagnosed, assessed, monitored and treated in the NHS.

The work began with a literature review, which included consideration of the 2013 international guidelines for TSC management.<sup>1</sup> The findings from the review were used to prepare 55 questions for a 'Delphi survey', which is a structured method for reaching consensus among a group of experts.

86 UK-based experts in TSC were invited to join the survey and 51 (60%) responded. The participants came from a wide range of specialties, including: neurology, nephrology, psychiatry, psychology, oncology, general paediatrics, dermatology, urology, radiology, clinical genetics, neurosurgery, respiratory medicine and neurodisability. The participants were asked to answer only those questions that were relevant to their areas of expertise.

Before the survey began, consensus was defined as 70% agreement among participants. There was consensus on many points in round 1 of the survey. A second round, using 18 questions, was conducted to try to reach consensus on the remaining contentious points.

The expert group leading the study used the results of the Delphi consensus survey and expert opinion to develop the recommendations on the management of TSC.

The full details of the study are in the published paper:

Amin S *et al.* The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. *QJM* 2019 Mar; 112(3): 171–182

## Reference

1. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: *Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol.* 2013 Oct; 49(4): 243–254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24053982>. Last accessed: March 2019.

# About the Tuberous Sclerosis Association

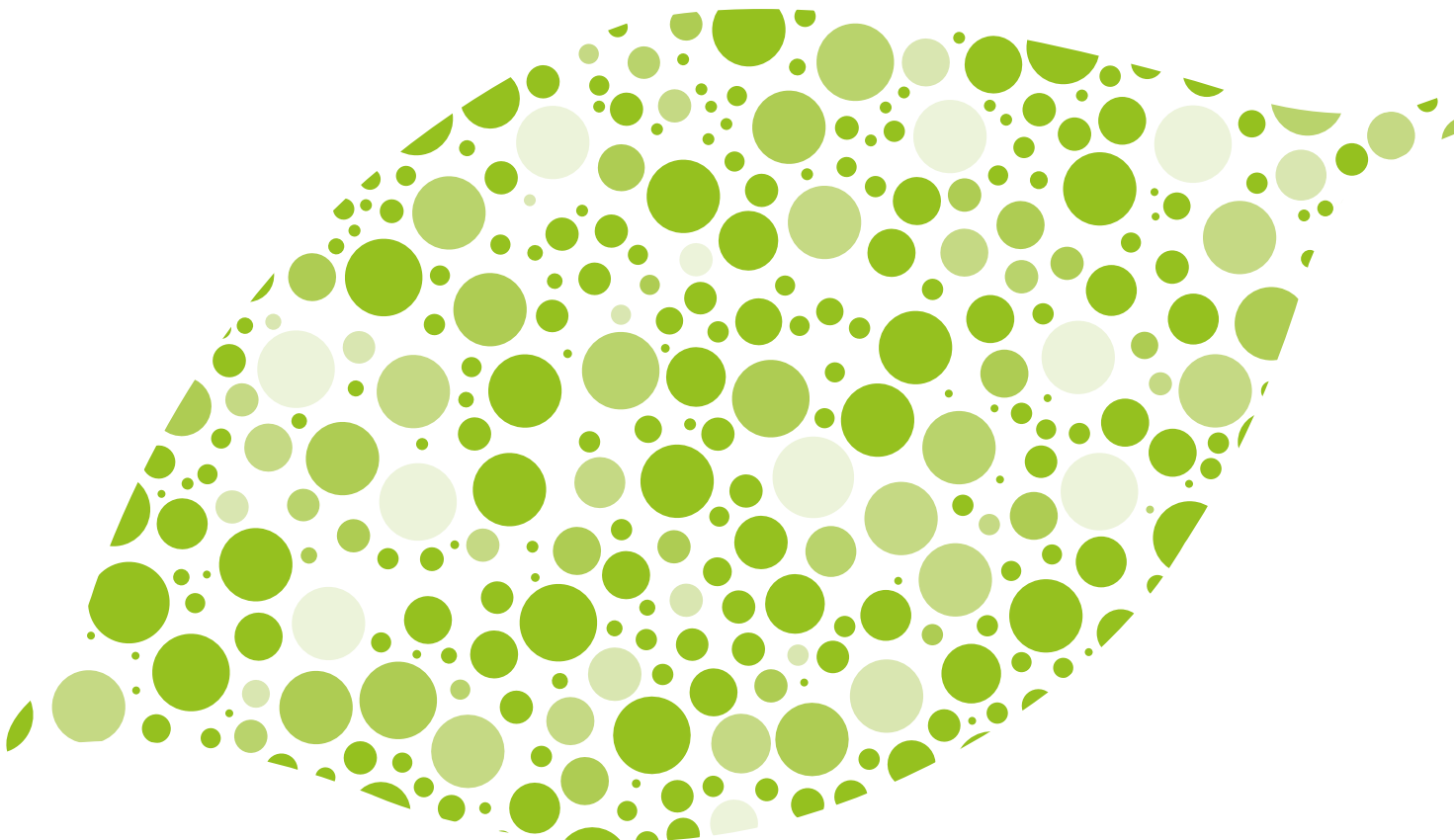


The Tuberous Sclerosis Association (TSA) is the only UK charity dedicated to supporting people living with TSC and their families. Our vision is a world where TSC and its effects are conquered. Our mission is to provide help for today and a cure for tomorrow.

## **Our aims are to:**

- Make a positive impact on the health and wellbeing of people living with TSC, their families and carers
- Lead research into the tools, technologies and treatments which eliminate the effects of TSC
- Lead innovation in the integration of medical and social care services.

You can find more information at [www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org)



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