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Citation for final published version:

Amin, S., Kingswood, J. C., Bolton, P. F., Elmslie, F., Gale, D. P., Harland, C., Johnson, S. R., Parker, A., Sampson, Julian R. , Smeaton, M., Wright, I. and O'Callaghan, F. J. 2019. The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. QJM: An International Journal of Medicine 112 (3) , pp. 171-182. 10.1093/qjmed/hcy215

Publishers page: http://dx.doi.org/10.1093/qjmed/hcy215

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The UK guidelines for management and surveillance of Tuberous Sclerosis Complex.

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Keywords: Tuberous Sclerosis Complex, Guidelines
Word count: 5926
References: 75

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Abstract

Background:

The severity of Tuberous Sclerosis Complex (TSC) can vary among affected individuals. Complications of TSC can be life threatening, with significant impact on patients' quality of life. Management may vary dependent on treating physician, local and national policies, and funding. There are no current UK guidelines. We conducted a Delphi consensus process to reach agreed guidance for the management of patients with TSC in the UK.

Methods:

We performed a literature search and reviewed the 2012/13 international guideline for TSC management. Based on these, a Delphi questionnaire was formed. We invited 86 clinicians and medical researchers to complete an online survey in two rounds. All the people surveyed were based in the UK. Clinicians were identified through the regional TSC clinics, and researchers were identified through publications. In round one, 55 questions were asked. In round two, 18 questions were asked in order to obtain consensus on the outstanding points that had been contentious in round one. The data was analysed by a core committee and subcommittees, which consisted of UK experts in different aspects of TSC. The Tuberous Sclerosis Association was consulted.

Results:

51 TSC experts took part in this survey. Two rounds were required to achieve consensus. The responders were neurologists, nephrologists, psychiatrist, psychologists, oncologists, general paediatricians, dermatologist, urologists, radiologists, clinical geneticists, neurosurgeons, respiratory and neurodisability clinicians.

Conclusions:

These new UK guidelines for the management and surveillance of TSC patients provide consensus guidance for delivery of best clinical care to individuals with TSC in the UK.

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Introduction

Tuberous Sclerosis Complex (TSC) is a genetic disease caused by mutations in the tumour suppressor genes *TSC1* and *TSC2*, located on chromosomes 9 and 16.(1, 2) Approximately two-thirds of cases occur sporadically. The incidence has been estimated to be 1 per 5,800 live births.(3) The protein products of *TSC1* and *TSC2* (hamartin and tuberin) function together within the cell and have an inhibitory effect on the mammalian target of rapamycin (mTOR), a protein kinase that influences cell growth and division and the synthesis of proteins and other cell components.(4) Mutations in either *TSC1* or *TSC2* lead to over-activation of the mTOR pathway and relatively uncontrolled cell growth that causes growth of benign tumours (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones.(5)

The management of TSC has varied dependent on treating physician, local and national policies and funding. There are no current UK guidelines. We conducted a Delphi consensus process to reach agreement amongst UK experts on the management of patients with TSC. The Delphi process is a well established, commonly used and widely accepted approach to achieve consensus. It was first established by Dalkey et al.(6) The process has been used in other walks of life for example to gain consensus in programme planning, resource utilisation and policy making. In a Delphi process answers from expert respondents to a series of questions are collected in an iterative fashion until, where possible, consensus is achieved.

The Delphi process provides consensus guidance for the delivery of best clinical care. It is important that the subjects are selected carefully. A danger is that when questions address issues without an evidence base, some respondents may provide answers despite a lack of specific knowledge. It is crucial, therefore, that the respondents are experts in the field. It is generally believed that 15-20 subjects could be sufficient to take part in a Delphi process but the higher the number of the subjects and homogeneity of response, the better the outcome. There does not seem to be a universally agreed proportion for Delphi consensus. It has been suggested that this might depend on the sample numbers, aims of the research and resources available. Some papers have suggested that consensus should be equated with 51% agreement amongst respondents; others recommend 60 or 70%.(7)

Methods:

We performed a literature search and considered mortality, morbidities, diagnosis, treatment and surveillance of TSC. We used MEDLINE, the Cochrane library and google scholar to perform the search. We also reviewed the most recent international guidelines for TSC management.(8) Based on these, we drew up 55 questions in round one of our Delphi survey. We created a core committee to oversee the questions and analyse the data. A priori consensus was defined as 70% agreement among participants. We invited 86 clinicians and researchers to complete the online survey. All the people surveyed were based in the UK. Clinicians were identified through the regional TSC clinics in the UK, Tuberous Sclerosis Association

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and British Paediatric Neurology Association while the researchers were identified through publications. We invited all the first and last authors of papers on TSC published since January 2000 until January 2017 in the UK. Respondents were advised to complete only sections of the survey, which were relevant to their expertise. As TSC is a multi-system disease, a cardiologist, for example, may not want to comment on the neurological management of TSC. Conversely a paediatrician who provides holistic care for his/her TSC patients may have relevant views on several aspects of the disease. In round two, 18 questions were asked to obtain consensus on the outstanding points that had been contentious in round one, or that needed clarification. The surveys were conducted over 6 months from June 2017-November 2017. A weekly electronic reminder was sent to the responders. The data were analysed by a core committee and subcommittee that consisted of UK experts in different fields within TSC.

51 experts (60%) responded to the survey. Two rounds were required to achieve consensus. The responders were neurologists, nephrologists, psychiatrists, psychologists, oncologists, general paediatricians, dermatologists, urologists, radiologists, clinical geneticists, neurosurgeons, respiratory physicians and neurodisability clinicians. A priori consensus was defined as 70% agreement among participants.

We are reporting the recommendations for the management of TSC based on the Delphi consensus results and expert opinions. For each aspect of TSC there is a committee to give expert opinion. Their opinion is based on their practice and latest evidence. The recommendations have been presented under two sections: Delphi consensus and expert opinion.

Patient and Public Involvement

This work has been completed with collaboration with the Tuberous Sclerosis Association (TSA). TSA is professional organisation providing support to families affected by TSC across the UK. Patients were not directly involved.

Genetics

Tuberous sclerosis complex is an autosomal dominant condition. TSC displays genetic heterogeneity with two known loci: *TSC1* gene on chromosome 9q34.3 and *TSC2* gene on chromosome 16p13.3.(9, 10) *TSC2* mutations are more commonly identified in sporadic cases of TSC and more likely to be associated with severe disease.(11) Contiguous deletions of *TSC2* and the adjacent *PKD1* gene, found in a few per cent of patients, are associated with a high risk of severe polycystic kidney disease.(12)

Almost three thousand different TSC-causing mutations in the *TSC1* and *TSC2* genes have been identified.(13) A significant fraction (approximately 15%) of TSC patients have no mutation identified by conventional genetic testing. Therefore, a normal result does not exclude a diagnosis of TSC.

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Genetics – recommendations and results of consensus

Delphi consensus

There was consensus to offer a genetic test at baseline in those with definite or probable TSC. Testing may clarify the diagnosis of TSC in cases that do not fulfil clinical criteria for a definite clinical diagnosis and is a prerequisite for the application of genetic technologies in family planning.(14, 15)

Expert opinion

All patients should have a three-generation family history obtained to determine if additional family members are affected or at risk of TSC. Genetic testing and counselling should be offered to individuals with TSC when they reach reproductive age. First-degree relatives of affected individuals should be offered clinical assessment and where possible genetic testing, in families in which a mutation has been identified in the index case.

Central Nervous System

Epilepsy

The central nervous system is commonly involved in TSC. Epileptic seizures are a common presenting problem and are thought to arise from cortical / subcortical tubers or the surrounding tissue. Most patients with TSC present with seizures during infancy, typically between three and eight months old, and up to one third of them develop epileptic spasms. However, in some studies epileptic spasms has been reported to be the presenting symptoms in up to 69% of patients with TSC.(16) Many go on to develop refractory epilepsy throughout life.(17, 18)

Epileptic spasms when combined with a hypsarrhythmic pattern on the EEG and with evidence of developmental arrest constitute the epilepsy syndrome known as West Syndrome. TSC is the cause of 10–20% of those diagnosed with West syndrome. Epileptic spasms can lead to severe cognitive and developmental impairment.(19) They are commonly misdiagnosed initially in infants, often leading to long lead-times between onset and initiation of effective treatment. Longer lead-times to treatment are associated with worse developmental outcomes.(20)

Animal studies have shown that mTOR inhibitors prevent the development of epilepsy and underlying brain abnormalities associated with epileptogenesis in TSC animal models.(21) Krueger et al have recently reported that everolimus was associated with a clinically relevant reduction in the overall frequency of clinical and subclinical seizures in individuals with TSC.(22) There are other reports that demonstrate that mTOR inhibitors everolimus / rapamycin, are effective in the treatment of epilepsy associated TSC in adults and children.(23, 24) A recently published Phase III trial has shown that everolimus, when used as an adjunctive

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therapy, significantly reduced treatment-resistant focal seizures in individuals with TSC compared with placebo.(25)

Epilepsy– recommendations and results of consensus

Delphi consensus

There is debate as to whether a baseline standard EEG (electroencephalogram) should be performed in all individuals with TSC regardless of seizure activity. There was no consensus on this in this survey. 68% of the responders suggested no baseline standard EEG when there is no suspicion of seizure activity.

There was no consensus on the need for treatment of interictal epileptiform abnormalities on EEG in infants, children and adults with TSC without clinical seizure activity. There are some suggestions that treating multiple spikes on EEG before onset of clinical seizures may reduce the risk of later clinical seizures, modify later phases of epileptogenesis, and reduce the risk of both drug-resistance and neurodevelopmental delay associated with epilepsy.(26) However, currently this has not yet been corroborated with prospective randomised trials.

Expert opinion

A standard EEG in individuals with suspected seizure activity should be performed. Perform 24-hr video EEG if changes in sleep, behaviour, or cognitive or neurological function are not explained by a standard EEG.

Parents should be taught to recognise epileptic spasms and focal seizures in infants, and EEG should be repeated urgently if there is suspicion of seizures. Paediatric neurologists should be involved in their care. Families and patients should be counselled about Sudden Unexpected Death in Epilepsy (SUDEP).(27)

Vigabatrin is the recommended first-line therapy for epileptic spasms in infancy. Hormonal therapies (oral prednisolone or ACTH) should be used if treatment with vigabatrin is unsuccessful.(28) Anticonvulsant therapy of other seizure types in TSC should generally follow the principles used in other epilepsies. Everolimus should be offered, if possible, to individuals with treatment resistant focal seizures. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression. Epilepsy surgery must be performed at designated epilepsy surgery centres in the UK.

Sub-Ependymal Giant Cell Astrocytoma (SEGA)

Sub-ependymal giant cell astrocytomas (SEGAs) are seen in approximately 5-20% of patients with TSC. They are slow growing “benign” tumours. As they often grow adjacent to the Foramen of Monro, they can cause hydrocephalus.(29)

The management of asymptomatic SEGA lesions has been controversial because

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the natural history of these lesions is unclear. Some clinicians have advocated the removal of all lesions that have shown evidence of interval growth, whilst others have argued for the removal only of lesions that become symptomatic. In the literature, some patients had SEGA resection because they had developed symptomatic hydrocephalus, whereas some patients had surgery because of an increase in tumour size, or had early surgery to prevent complications. The outcome from surgery appears to be less favourable if the operation is done after the patients present acutely with hydrocephalus.(30, 31)

It has been shown that rapamycin is effective in reducing the size of TSC related solid tumours such as SEGA. Franz et al treated 4 TSC patients who had SEGA with rapamycin at standard immunosuppressive doses (serum levels 5–15ng/ml) from 2.5 to 20 months. It was reported that the treatment was well tolerated and all SEGAs showed regression. Cessation of therapy resulted in tumour regrowth in one patient.(22)

Krueger et al investigated the efficacy and safety of everolimus in an open trial in 28 patients with TSC who had SEGA. Everolimus was given orally, at a dose of 3.0 mg/m^2 per day, in order to attain a trough concentration of 5 to 15 ng/ml. The treatment was given for the median duration of 21.5 months. It was noted that everolimus was associated with a reduction of at least 30% of the volume of SEGA in 21 patients (75%) and at least 50% in 9 patients (32%). Single cases of grade 3 treatment-related sinusitis, pneumonia, viral bronchitis, tooth infection, stomatitis, and leukopenia were reported.(22) It was also noted that the clinical and electrographic seizures were significantly reduced at 6 months.(32)

In a phase III international, multicentre, double-blind, randomized, placebo-controlled trial, Franz et al evaluated the efficacy and safety of everolimus in 117 patients, aged between 0.8-26.6 years with SEGA. Everolimus was associated with a significantly greater overall SEGA response rate (>/= 50% shrinkage), compared with placebo (35% vs. 0%). In addition, 78% of patients receiving everolimus showed a shrinkage of >/= 30% compared to 15% on placebo, and none of the patients taking everolimus progressed compared to 14% on placebo. This response was shown to be durable over 47 months.(33) The frequency of seizures was not different between the treatment and placebo groups. It was demonstrated that everolimus was associated with greater partial skin lesion (facial angiofibromas) response (42% vs. 11%). In addition, angiomyolipoma (AML) response rates were 53% vs. 0%, compared with the placebo group.(32)

SEGA- recommendations and results of consensus

Delphi consensus

There was consensus that patients with newly diagnosed or suspected TSC, should have magnetic resonance imaging (MRI) of the brain to assess for the presence of SEGA.

There was consensus to perform MRI of the brain every 1-3 years in asymptomatic TSC patients without SEGA younger than 25 years of age, to monitor for growth or new occurrence. It is believed that the majority of these lesions stop growing in third decade of life.(29) However, there are some case reports of SEGA growth after the

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age of 25.(29) There was consensus to stop performing routine brain MRI scan at the age of 25 if there is no evidence of SEGA lesions.

There was consensus that MRI scan should be repeated in asymptomatic patients with SEGA. 56% of the responders suggested that the scan should be repeated 1-3 yearly. There was no consensus as to when to stop routine brain MRI scans in individuals with SEGA lesions. However, most responders suggested that this should be judged case by case, depending on their learning disabilities, communication abilities, and the SEGA interval growth.

There was consensus that symptomatic and asymptomatic SEGA lesions, which are actively growing and likely to enlarge beyond 1cm, should be treated.

There was consensus that the first line treatment for growing SEGA lesions should be surgery. There was consensus that growing SEGA lesions should be discussed at an MDT meeting that should include neurosurgeons, neurologists (paediatric or adult as appropriate), neuroradiologists and clinicians expert in the management of TSC (if not already covered by clinicians already listed).

Expert opinion

Patients with large or growing SEGA, or with SEGA causing ventricular enlargement who remain asymptomatic, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential for new symptoms.

Surgical resection should be performed in a specialised centre with expertise in resecting intraventricular lesions.(29) In determining the best treatment option, discussion of the complication risks, adverse effects, costs, length of treatment, and potential impact on TSC-associated comorbidities should be included in the decision-making process. Patients, carers and parents should be part of this decision making process.

The NHS England commissioning policy states that the inclusion criteria for treatment with everolimus are as follows:

“Patient presents with SEGA lesion(s) and has at least one lesion of baseline longest diameter 1cm as assessed by multiphase MRI and is considered not amenable to surgery as assessed by a properly constituted MDT (as defined in the Governance Arrangements).

Specifically, MDT decides that:

- SEGA is too difficult to remove surgically; OR
- SEGA needs reduction in size prior to surgery; OR
- SEGA lesion(s) are multiple or infiltrative; OR
- Surgery has been performed and there is residual SEGA (i.e. it was not possible to completely excise) that needs treating.

AND
The patient presents with:

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- significant growth in target SEGA lesion(s) (as decided by properly constituted MDT since patient's last annual MRI); OR
- unequivocal worsening of non-target lesions of SEGA; OR
- the appearance of new lesion(s) of baseline longest diameter 1cm; OR
- symptoms of new or worsening hydrocephalus (but where urgent surgery is not required); OR
- patient presents for the first time with lesion(s) of baseline longest diameter 1cm (accounting for patients not cared for in a surveillance programme); OR
- partially excised SEGA lesion(s) known to be growing before surgery.

Exclusion criteria:
Any patient presenting with raised intracranial pressure (a surgical solution would be necessary as it would not be possible to wait for mTOR inhibition to take effect)."

Neurodevelopmental and Neuropsychiatric disorders

Approximately 25-60% of individuals with TSC have autistic spectrum disorders (ASD).(34) There are multiple factors contributing to the development of ASD in TSC including epilepsy during the critical period of brain development (35) and the existence of tubers in the temporal lobe.(36) Approximately 30–60% of patients with TSC have symptoms related to attention-deficit–hyperactivity disorder (ADHD).(37) The exact cause of attentional problems is not known but it is believed to be multifactorial. There is an elevated prevalence of neuropsychiatric/neurodevelopmental disorders in TSC such as depression, bipolar disorder, anxiety, schizophrenia, psychosis, auditory hallucinations and anorexia nervosa.(38, 39)

Neurodevelopmental and Neuropsychiatric disorders
Recommendations and results of consensus

Delphi Consensus
There was consensus that a baseline assessment for neuropsychiatric/neurodevelopmental conditions including autism spectrum disorder and attention deficit hyperactivity disorder, or marked behavioural disturbances should be performed.

There was consensus to use the TSC Associated Neuropsychiatric Disorders (TAND) check list annually to check if there is any evidence of neuropsychiatric/neurodevelopmental disorders. In depth assessment should be undertaken when indicated. Treatment should follow the NICE guidelines.

There was consensus that developmental status should be formally evaluated at key developmental time points and periods of transition, which are infancy (0-3 years), preschool (3-6 years), middle school (6-11 years), adolescence (12-18 years), and as clinically indicated. This is to identify specific educational/cognitive disorders and intellectual disabilities. It informs treatment and care planning and choice of educational provision. Consideration should be given to the need for support for

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special educational needs and an assessment for an Education and Health Care Plan (EHCP).

Expert opinion
Marked changes in behaviour/cognitive status (either sudden or insidious), should prompt investigation for possible medical complications of TSC (e.g. SEGA; seizures; non-convulsive status; metabolic disturbances; adverse side effects of medications, etc.).

TSC clinics should have established links and care pathways with developmental paediatric, educational and CAMHS specialist services to help ensure an integrated, responsive and timely multidisciplinary approach, which includes consultation and liaison.

Kidney

Angiomyolipoma (AML)

Renal involvement is potentially serious and common in TSC. AMLs and cysts are the two characteristic renal lesions.(40) AML was first described by Grawitz in 1900 who used the term 'renal angiomyolipoma' to describe a large renal tumour comprised of fat, muscle, and blood vessels.(41)

Renal AMLs can be associated with TSC, and with sporadic lymphangioleiomyomatosis (LAM) in individuals that do not have systemic features of TSC. Growth of AMLs in individuals with TSC is often first detected during childhood and they tend to increase in number and size with age.(42) Approximately 80% of patients with TSC have AMLs and 30% have cysts.(40) AML is the leading cause of death in individuals with TSC.(27) The presenting features of AMLs are haematuria, pain, high blood pressure and premature loss of glomerular filtration rate (GFR). Haematuria can sometimes be life threatening. (27, 43) AMLs frequently develop aneurysms that can rupture and can cause retroperitoneal haemorrhage or haematuria. Up to 20% of patients with such haemorrhage present in hypovolemic shock.(44) Patients with AMLs are likely to require lifelong health-care follow-up.

Bissler et al. investigated rapamycin in TSC patients and patients with sporadic LAM with renal AMLs. This study was a non-randomized, open-label trial to study whether rapamycin reduces the AML size in these patients. Rapamycin was given for 12 months. 18 patients completed a 24-month assessment. Kidney AML volumes were reduced to approximately 53% of the baseline value after 12 months of starting the drug. Tumour regrowth to 86% of the baseline value was noted at 24 months. Five patients had six serious adverse events while receiving rapamycin, including diarrhoea, pyelonephritis, stomatitis, and respiratory infections.(45)

In a multicentre, phase 2 trial, Davies et al investigated the efficacy and safety of rapamycin for AML in adults with TSC, or sporadic LAM. 16 patients, who had AMLs of more than 2 cm diameter, were treated with rapamycin for up to 2 years. Patients received daily oral doses of rapamycin to achieve initial trough blood levels of 3 to 6 ng/ml, with an increase to 6 to 10 ng/ml at 2 months. They reported shrinkage of

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AMLs in all patients, and that 8 (50%) had a formal partial response by RECIST* criteria (*Response Evaluation Criteria In Solid Tumours) of a 30% or more reduction in the sum of the longest diameters of their AMLs. They reported that all patients suffered from grade 1 or 2 adverse events such as mouth ulcers, hyperlipidemia, and peripheral oedema. The treatment had to be terminated in one patient due to side effects. In addition, the tumour size increased upon treatment cessation.(46, 47)

Similar results were obtained in another placebo-controlled trial of sirolimus by Dabora and colleagues.(48)

Exist-2 was a placebo controlled phase 3 RCT investigating the efficacy and safety of everolimus in treating renal AMLs > 3cm in adults. 118 patients (median age 31·0 years; IQR 18·0–61·0) were randomly assigned to receive everolimus (n=79) or placebo (n=39). At the data cut-off in the first report,(49) double-blind treatment was on-going for 98 patients; the two main reasons for discontinuation were disease progression (nine placebo patients) followed by adverse events (two everolimus patients; four placebo patients). The AML response rate (Defined as >/= 50% shrinkage) was 42% (33 of 79 [95% CI 31–53%]) for everolimus and 0% (0 of 39 [0–9%]) for placebo one-sided Cochran-Mantel-Haenszel test p<0·0001). The most common adverse events in the everolimus and placebo groups were stomatitis (48% [38 of 79], 8% [3 of 39], respectively), nasopharyngitis (24% [19 of 79] and 31% [12 of 39]), and acne-like skin lesions (22% [17 of 79] and 5% [2 of 39]). In addition, 80% of everolimus patients had a >/= 30% reduction in AML volume compared to 3% on placebo. By 12 months 8% of the everolimus patients and 75%
of the placebo patients had shown progression – but none of the everolimus patients who showed a response progressed. This response was durable up to 46.9 months.(50)

AML – recommendations and results of consensus

Delphi consensus

Consensus was reached on the management of kidney AMLs. For newly diagnosed or suspected patients with TSC, an MRI of the abdomen should be performed to assess for the presence of AML and renal cysts, regardless of age. MRI is the optimal imaging modality as some lesions, such as fat poor AMLs, can be over looked on ultrasound scans. CT is an alternative to MRI but the cumulative dose of ionising radiation needs to be considered. Both the brain and kidney MRI scans should ideally be combined and be done at the same time. MRI of the abdomen may also reveal aortic aneurysms or extrarenal hamartomas of the liver, pancreas, and other abdominal organs that can also occur in individuals with TSC.(27)

Patients should be screened for secondary hypertension by measuring blood pressure. At the time of diagnosis renal function (i.e. glomerular filtration rate) should be evaluated.(51, 52)

There was consensus that all patients with TSC should have regular kidney imaging. 68% of the responders suggested that kidney imaging should be repeated annually and 28% suggested that the kidney imaging should be repeated every 2 years.

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There was consensus that blood pressure measurement and kidney function tests should be repeated annually.

There was consensus that growing AMLs measuring ≥3cm in diameter should be treated with mTOR inhibitors.

Expert opinion
For existing patients, if general anaesthetic (GA) is not required, they should have annual MRI of the abdomen to assess for the progression of AML and renal cystic disease throughout their lifetime. If GA is required, and on MRI the anatomy and pathology are judged to be easy to interpret by ultrasound scan, then the next surveillance scan or two could be ultrasound. Patients with Vagal Nerve Stimulator may not be able to have MRI scan. CT scan can be performed for those patients.

Everolimus is licensed for the treatment of growing AMLs that are > 3cm and not acutely bleeding in adults. It is funded for use in the NHS for adults and children (for whom it is off license) because the results from Exist-1 show it is highly effective in children.(53, 54) Selective embolization or kidney-sparing resection are possible second-line therapies for asymptomatic AMLs.

Embolization followed by corticosteroids is first-line therapy for AML presenting with acute haemorrhage. Nephrectomy should be avoided, if possible.

Lung

Lymphangioleiomyomatosis (LAM)

Pulmonary LAM occurs almost exclusively in female patients. However, there are some case reports of male individuals with LAM and TSC. The true prevalence of LAM lesions is not well known as not all TSC patients are screened for LAM. They can present with progressive shortness of breath, recurrent pneumothoraces, and deterioration in lung function.(55)

LAM is characterized by abnormal proliferation or infiltration of smooth muscle cells, lymphatic vessels and cystic destruction of the lung. These cells are thought to express a melanogenisis-associated antigen recognized by HMB45 and they may express estrogen and progesterone receptor proteins.(56)

Mutations in *TSC2* gene occur in both TSC-associated and sporadic LAM smooth muscle cells and lead to overactivation of the mTOR pathway. mTOR inhibitors, such as rapamycin, have been shown to improve lung function in patients with LAM and reduce the size of the lesions. However, it has been found that lung function declines and the lesions re-grow once the drug is discontinued.(57)

LAM – recommendations and results of consensus

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Delphi consensus

There was consensus in this Delphi process to perform a baseline high-resolution chest computed tomography (HRCT) in females of child-bearing age. There was consensus to repeat HRCT in patients with LAM. The frequency of the scans should depend on patient's disease progression. There was consensus that individuals with LAM detected on HRCT should have annual pulmonary function testing and 6-minute walk test where practicable, and these should be repeated more frequently in those have progressive disease.

There was consensus to offer HRCT every 5-10 years to women without LAM on their baseline scan, or if symptoms of LAM develop. This should be performed until the menopause. There was no consensus on performing routine baseline pulmonary function testing or 6-minute walk test in patients who are newly diagnosed, or have suspected TSC.

There was consensus that mTOR inhibitors should be used to treat individuals with LAM if there is evidence of progressive LAM lesions.

Expert opinion

Assessment of those with LAM who are unable to perform pulmonary function testing, including those with learning difficulties, may be more difficult. Carers should be aware of the significance of increasing dyspnoea and the symptoms of pneumothorax. Clinical assessment should include a discussion of LAM symptoms, including exertional dyspnoea and pneumothorax with the individual and their carers. Six-minute walk testing or informal assessment of hypoxaemia during exertion may still be possible and may identify progressive lung disease. HRCT can be performed as described above and if there are otherwise unexplained worsening of respiratory symptoms.

Adult males should also undergo testing if they are symptomatic. Adolescent and adult females should be offered counselling on oestrogen use. All patients should be offered counselling regarding smoking risk. There is some evidence that oestrogen-containing contraceptives can exacerbate pulmonary LAM.(58, 59)

mTOR inhibitors should be used to treat individuals with LAM if there is evidence of progressive LAM lesions or loss of lung function ie if lung function falls more quickly than expected for age.(60) Patients with progressive disease or specific complications for which no other therapy is available should be considered for treatment with an mTOR inhibitor. Those likely to benefit from an mTOR inhibitor according to current evidence are those with progressive deterioration in lung function and those with chylous complications.

Skin

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Skin involvement is common in TSC. Lesions such as facial angiofibromatosis, hypomelanotic macules, shagreen patches, forehead fibrous plaques, skin tags and periungual fibromas are observed in individuals with TSC.(3)

Facial angiofibromas can affect approximately 86% of patients with TSC. They are benign tumours on the face that generally become noticeable at around the age of five years. They can have a huge impact on a patient's self-esteem. In addition, they are known to cause recurrent bleeding, irritation, infection, facial scarring and disfigurement.(61)

Systemic mTOR inhibitors such as everolimus and rapamycin have been used to treat TSC related complications and it has been shown that they improve facial angiofibromas.(22, 32) However, their use is constrained by concerns about systemic side effects. There have been several case reports of the use of topical sirolimus ointment for the treatment of facial angiofibromas. Different sirolimus ointment strength, preparation and regimes have been used. Amin et al used sirolimus ointment 0.1% for facial angiofibromas in children and adults with TSC, using a standardised and validated facial angiofibroma severity index to measure outcome. They also assessed the effect of this treatment on quality of life. It was noted that objective assessment shows that sirolimus ointment 0.1% administered once a day in a clinic setting is effective in treating facial angiofibromas. It is safe and well tolerated. It has a positive impact on patients' quality of life and it is likely to be most beneficial when started in childhood.(48, 62-65)

Skin – recommendations and results of consensus

Delphi consensus
There was consensus to perform a detailed clinical dermatological inspection/exam using Wood's light in newly diagnosed or patients with suspected TSC. Then, an annual clinical dermatological inspection/examination should be performed. There was consensus that facial angiofibromas can be treated with topical mTOR inhibitors.

Expert opinion
Currently, funding is not available for topical mTOR inhibitors for all patients in the UK. Some patients are obtaining this treatment via Individual Funding Request (IFR) through TSC clinics.

Laser treatment can also be used for treating facial angiofibromas.(63, 66) Surgical excision can be considered for larger solitary lesions. Surgical excision can be considered for ungual fibromas which are causing problems.

Teeth

Dental enamel pitting is observed in most patients with TSC. Dental pitting can also be observed in the general population, but at lower frequency and with fewer lesions than in TSC. Oral fibromas are also common in adults with TSC. They are mostly gingival but they can occur on the tongue.(67)

Teeth – recommendations and results of consensus

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Expert opinion
Periodic oral evaluation should occur every 6-12 months, consistent with surveillance recommendations for all individuals in the general population. Periodic preventive measures as well as oral hygiene education, especially in patients with learning disabilities, is important.

Dental pits can be treated with restorative treatments if the patient is at high cavity risk, although they rarely cause symptoms or an increased incidence of dental decay.(68)

Oral fibromas can be excised surgically if symptomatic or if interfering with oral hygiene. Oral fibromas may recur once excised; therefore, periodic oral evaluation is encouraged.(69)

Heart

Cardiac rhabdomyomas are the most common heart tumours in children and are closely associated with TSC. The prevalence of TSC associated with fetal cardiac rhabdomyoma is at least 50–80%. The presence of multiple rhabdomyomas correlates very highly with a diagnosis of TSC, and is likely to approach 100%.(70) Most cardiac rhabdomyomas either partially or completely regress during the first 2–4 years.(71) However, they can cause life-threatening complications such as intra-cavity obstruction, diminished myocardial function, and rhythm disturbances.(72)

Heart – recommendations and consensus

Delphi consensus
There was consensus that a baseline electrocardiogram (ECG) should be performed in all patients to check for arrhythmia and conduction abnormalities such as Wolff–Parkinson–White syndrome (WPW).(73) There was consensus that all children and symptomatic adults at baseline should be offered an echocardiogram to evaluate for rhabdomyomas.

There was consensus to repeat echocardiogram in asymptomatic patients with rhabdomyomas. 53% of the responders suggested that an echocardiogram should be repeated every 1-3 years in asymptomatic patients, until either there is complete regression of cardiac rhabdomyomas or the first signs of regression.

In addition, there was consensus to perform a 12- lead ECG at a minimum of every 3-5 years.

Expert opinion
The natural history of these lesions is spontaneous regression. It may not be necessary to continue scanning these patients until complete regression. Continuous scanning is not beneficial in the absence of cardiac symptoms.

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In patients with clinical symptoms, additional risk factors, or significant abnormalities on routine echocardiogram or ECG, more frequent interval assessment may be needed and may include ambulatory event monitoring. Patients with hemodynamic instability and or life threatening arrhythmia should be treated with antiarrhythmic medications, surgery or mTOR inhibitors depending on the situation.(74)

Eye

Approximately half of patients with TSC have retinal or optic nerve hamartomas; in half of these patients the hamartomas occur bilaterally.

Three morphological types of retinal hamartomas have been reported in literature:(75-77)

1. flat, smooth, non-calcified, grey, translucent lesions;
2. elevated, multinodular, calcified, opaque lesions, resembling mulberries;
3. transitional lesions which have morphological features of both the first and second types.

Other retinal findings which have been reported include retinal pigmentary disturbances, ranging from hyperpigmented areas to hypopigmented areas at the posterior pole or midperiphery.(78) Non-retinal findings in TSC include angiofibromas of the eyelids, coloboma of the iris, lens and choroid, strabismus, poliosis of eyelashes, papilloedema, and sector iris depigmentation.(79)

Eye – recommendations and results of consensus

Delphi consensus

There was consensus to perform a baseline ophthalmologic evaluation, including fundoscopic evaluation for all individuals diagnosed with TSC to evaluate for hamartomas and hypo-pigmented lesions of the retina.

There was no agreement on whether routine ophthalmic assessment should just be fundoscopy by direct ophthalmoscopy or a detailed ophthalmological review by an ophthalmologist.

Expert opinion

It may be unachievable to aim to offer a detailed ophthalmology review regularly. It is very rare for retinal hamartomas to cause problems. It is necessary that these patients receive a regular fundoscopy examination during their clinic visits to check for papilloedema. Symptomatic changes due to retinal hamartomas are very rare. Macular oedema and vitreous haemorrhage have been thought to associated with retinal hamartomas. More frequent assessment, including in those treated with vigabatrin, is of no proven benefit and not recommended unless new clinical concerns arise.(80)

Table 1 and 2 show surveillance and management recommendations for newly diagnosed or suspected TSC, and for patients already diagnosed with TSC.

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Conclusion

An agreed guideline for managing patients with TSC should improve the complex and multi-specialty issues faced by patients with this rare disorder. The clinical presentation of TSC is variable and the progression and severity of organ involvement can vary according to the individual's age, genotype and treatment. Consequently it is challenging to manage TSC patients optimally without the guidance of an evidence based approach agreed by a range of specialists with appropriate expertise. Most patients in the UK should have access to regional TSC specialist clinics where multisystem management can be coordinated. However, there is a wide variation in the type and the quality of care they receive, due to limited awareness and variable funding. The aim of this consensus guideline is to agree surveillance and management expectations for TSC patients in UK. In addition, this information should be available to those professionals who are managing TSC patients locally. It will also help policy makers and planners to plan and allocate budgets for TSC services. The financial and technological limitations of the NHS in the UK currently prevent implementation of some of the 2013 International Consensus Guidelines for TSC surveillance and management. In addition, they do not reflect the UK opinion. The guidance suggested here was determined by conducting a Delphi process undertaken by TSC experts working in the NHS across the UK and attempts to set out a realistic standard that should be achievable in this setting.

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Table 1: Surveillance and management recommendations for newly diagnosed or suspected tuberous sclerosis complex (TSC)

Genetic screening at baseline	
Genetic testing should be offered at baseline to all patients	consensus
If it is impossible to offer genetic testing to all patients, then genetic testing should be offered for reproductive counselling or when a TSC diagnosis is likely but cannot be clinically confirmed	expert opinion
Obtain three-generation family history	expert opinion
First-degree relatives of individuals with TSC should be offered clinical assessment and where possible genetic testing	expert opinion
Ensure that the availability of preimplantation, prenatal and non-invasive prenatal diagnosis options is discussed where appropriate	expert opinion

Central nervous system screening at baseline	
Perform MRI of the brain for all patients	consensus
Perform a baseline assessment for neuropsychiatric / neurodevelopmental disorders	consensus
Obtain a standard EEG in individuals with suspected epileptic seizure activity	consensus
Perform 24-hr video EEG, if changes in sleep, behaviour, or cognitive or neurological function are not explained by a standard EEG	expert opinion
Teach parents to recognise infantile spasms and focal seizures and repeat EEG urgently if there is a suspicion of seizures. Paediatric neurologists should be involved in their management	expert opinion

Kidney screening at baseline	
Perform MRI of the abdomen.	consensus
If MRI is contraindicated, perform CT or ultrasound scan	expert opinion
Check blood pressure and glomerular filtration rate (GFR)	consensus

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Lung screening at baseline	
Perform baseline high-resolution chest computed tomography (HRCT) in females of child-bearing age	consensus
Adult males, if symptomatic, should also undergo HRCT	expert opinion
Provide counselling on oestrogen use in adolescent and adult females	expert opinion
Provide counselling on smoking risks in all patients	expert opinion

Skin screening at baseline	
Perform a detailed clinical dermatological inspection/exam using Wood's light	consensus

Dental screening at baseline	
Perform a detailed clinical dental inspection/exam looking for abnormal tooth eruption, dental pits and oral fibromas	expert opinion

Heart screening at baseline	
Perform a baseline ECG	consensus
Perform a baseline echocardiogram in all children and symptomatic adults.	consensus

Eye screening at baseline	
Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal lesions and visual field deficits.	consensus

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Table 2: Surveillance and management recommendations for patients already diagnosed with definite or possible tuberous sclerosis complex (TSC)

Genetic surveillance	
First-degree relatives of individuals with TSC should be offered clinical assessment and where possible genetic testing.	expert opinion
Ensure that the availability of preimplantation, prenatal and non-invasive prenatal diagnosis options is discussed where appropriate.	expert opinion

SEGA surveillance	
Perform MRI of the brain every 1-3 years in asymptomatic TSC patients, without SEGA, younger than age 25.	consensus
Perform MRI of the brain every 1-3 years in asymptomatic TSC patients, with SEGA	consensus
There was no consensus as to when to stop routine brain MRI scans in individuals with SEGA lesions. However, most responders suggested that this should be judged case by case, depending on their learning disabilities, communication abilities, and the SEGA interval growth.	consensus
Patients with large or growing SEGA, or with SEGA causing ventricular enlargement who remain asymptomatic, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms	expert opinion
Growing SEGAs should be discussed at MDT with oncologists, neurologists, neuro-radiologists, neurosurgeons and TSC experts	consensus
The patient or family should be involved in this discussion.	expert opinion
The first line of treatment for growing SEGAs is surgery	consensus
Surgical resection should only be performed in a specialised centre with expertise in resecting intraventricular lesions if possible	expert opinion
Everolimus can be offered as per NHS England commissioning criteria	expert opinion

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Surveillance for neurodevelopmental and Neuropsychiatric disorders	
At each annual clinical review, the TAND check list should be used	consensus
In-depth neuropsychology and neuropsychiatric assessments should be undertaken when indicated	consensus
Treatment should follow the NICE guidelines	expert opinion
Developmental status should be formally evaluated at key developmental time points and periods of transition, which are infancy (0-3 years), preschool (3-6 years), middle school (6-11 years), adolescence (12-18 years), and as clinically indicated	consensus
TSC clinics should have established links and care pathways with developmental paediatric, educational and CAMHS specialist services to help ensure a seamless, integrated, responsive and timely multidisciplinary approach, which includes consultation and liaison	expert opinion

Epilepsy surveillance	
Obtain a standard EEG in individuals with suspected epileptic seizure activity	consensus
Perform 24-hour video EEG, if changes in sleep, behaviour, or cognitive or neurological function are not explained by a standard EEG	expert opinion
Vigabatrin is the recommended first-line therapy for infantile spasms. Hormonal treatments should be used if treatment with vigabatrin is unsuccessful	expert opinion
Everolimus should be offered, if possible, to individuals with treatment resistant focal seizures	expert opinion
Epilepsy surgery should be considered for TSC patients with refractory epilepsy.	expert opinion
Families and patients should be counselled about the risk of SUDEP	expert opinion

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Kidney surveillance	
Kidney imaging should be repeated regularly	consensus
If a GA is not required, patients with renal lesions, should have annual MRI of the abdomen to assess for the progression of AML, renal cystic disease and occurrence of the rare renal cancer throughout the lifetime of the patient. If MRI scan is impossible to perform annually and if on MRI the anatomy and pathology are judged to be easy to interpret by ultrasound scan, then the next surveillance scan or two could be an US, or fast low dose CT scan could be used	expert opinion
In the absence of renal lesions, the scans should be repeated every 1-3 years through childhood and early adult life	expert opinion
If GA is required and on MRI the anatomy and pathology are judged to be easy to interpret by US scan, then the next surveillance scan or two could be an US, or the new fast low dose CT scan could be used if this avoids an anaesthetic	expert opinion
Assess renal function (including determination of glomerular filtration rate [GFR]) and blood pressure annually in adults and children with renal lesions	consensus
Embolization covered by corticosteroids is first-line therapy for AMLs presenting with acute haemorrhage	expert opinion
Every attempt should be made to avoid nephrectomy	expert opinion
For asymptomatic, growing AML measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy	consensus
Selective embolization or kidney-sparing resections are possible second-line therapies for asymptomatic AMLs	expert opinion

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Lung surveillance	
Provide counselling on oestrogen use in adolescent and adult females	expert opinion
Provide counselling on smoking risks in all patients	expert opinion
Obtain HRCT every 5-10 years in asymptomatic females of childbearing age, if there is no evidence of LAM on their baseline HRCT. This should be performed until menopause	consensus
Individuals with LAM detected on HRCT should have annual pulmonary function testing (pulmonary function testing and 6-minute walk test) and more often if they have progressive disease	consensus
mTOR inhibitors should be used to treat individuals with LAM if there is evidence of progressive loss of lung function	consensus

Skin surveillance	
Perform a detailed clinical dermatologic inspection/exam annually	consensus
Patients and families should be counselled to use sunblock (SPF 30+) routinely	expert opinion
Facial angiofibromas should be treated with topical mTOR inhibitors	consensus
Laser treatment can be used to treat these lesions	expert opinion
Surgical excision can be considered for larger solitary lesions	expert opinion
Surgical excision can be considered for ungual fibromas that are causing problems	expert opinion

Teeth surveillance	
Periodic oral evaluation should occur every 6-12 months, consistent with surveillance recommendations for all individuals in the general population. Periodic preventive measures as well as oral hygiene education especially in patients with learning disabilities are important	expert opinion
Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions can be treated with surgical excision or curettage when present	expert opinion

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Heart surveillance	
Echocardiogram should be repeated every 1-3 years in asymptomatic patients until either complete regression of cardiac rhabdomyomas or until first sign of cardiac rhabdomyomas regression	consensus
12- lead ECG is recommended at minimum every 3-5 years	consensus
In patients with clinical symptoms, additional risk factors, or significant abnormalities on routine echocardiogram or ECG, more frequent interval assessment may be needed and may include ambulatory event monitoring	expert opinion
Patients with hemodynamic instability and or life threatening arrhythmia should be treated	expert opinion

Eye surveillance	
Regular fundoscopy by direct ophthalmoscopy examination during each clinic visit should be performed	consensus
More frequent assessment, including those treated with vigabatrin, is of no proven benefit and not recommended unless new clinical concerns arise	expert opinion

Liver and pancreatic surveillance	
Liver and pancreas should be assessed for lesions during annual abdominal MRI scan	consensus

Author's contribution
All individuals listed as authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted from the list.

SA, JCK and FJO designed the questionnaire, analysed the results and drafted the article.
SA collected data
PFB, FE, DPG, CH, SRJ, AP, JRS, MS and IW analysed the results and drafted the article.

The authors and contributors have approved the acknowledgement of their contributions. All the authors had complete access to the study data that support the publication.

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All the authors have read the manuscript and agreed to its being submitted for publication. We certify that the submission (aside from the abstract) is not under review at any other publication and the data in the manuscript is original.

Conflict of interest
No conflict of interest to report

Data sharing
No additional data available

Ethical approval
Ethical approval is not required

Funding statement
This project has not been funded.

References

1. van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science. 1997;277(5327):805-8.
2. Consortium ECTS. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell. 1993;75(7):1305-15.
3. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125-7.
4. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC, Blenis J. Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc Natl Acad Sci U S A. 2002;99(21):13571-6.
5. Kwiatkowski DJ. Tuberous sclerosis: from tubers to mTOR. Ann Hum Genet. 2003;67(Pt 1):87-96.
6. Dalkey NC, & Helmer, O. An experimental application of the Delphi method to the use of experts. . *Management Science* 1963
7. Mullen PM. Delphi: myths and reality. J Health Organ Manag. 2003;17(1):37-52.
8. Northrup H, Krueger DA, Group ITSCC. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243-54.
9. Fryer AE, Chalmers A, Connor JM, Fraser I, Povey S, Yates AD, et al. Evidence that the gene for tuberous sclerosis is on chromosome 9. Lancet. 1987;1(8534):659-61.
10. Kandt RS, Haines JL, Smith M, Northrup H, Gardner RJ, Short MP, et al. Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. Nat Genet. 1992;2(1):37-41.

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11. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001;68(1):64-80.
12. Sampson JR, Maheshwar MM, Aspinwall R, Thompson P, Cheadle JP, Ravine D, et al. Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. Am J Hum Genet. 1997;61(4):843-51.
13. http://chromium.lovd.nl/LOVD2/TSC/home.php?select_db=TSC1.
14. Au KS, Williams AT, Gambello MJ, Northrup H. Molecular genetic basis of tuberous sclerosis complex: from bench to bedside. J Child Neurol. 2004;19(9):699-709.
15. Northrup H. Tuberous sclerosis complex: genetic aspects. J Dermatol. 1992;19(11):914-9.
16. Pampiglione G, Pugh E. Letter: Infantile spasms and subsequent appearance of tuberous sclerosis syndrome. Lancet. 1975;2(7943):1046.
17. O'Callaghan FJ, Harris T, Joinson C, Bolton P, Noakes M, Presdee D, et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. Arch Dis Child. 2004;89(6):530-3.
18. Riikonen R. Infantile spasms: therapy and outcome. J Child Neurol. 2004;19(6):401-4.
19. Hunt A, Dennis J. Psychiatric disorder among children with tuberous sclerosis. Dev Med Child Neurol. 1987;29(2):190-8.
20. Koo B, Hwang PA, Logan WJ. Infantile spasms: outcome and prognostic factors of cryptogenic and symptomatic groups. Neurology. 1993;43(11):2322-7.
21. Wong M. Mammalian target of rapamycin (mTOR) inhibition as a potential antiepileptogenic therapy: From tuberous sclerosis to common acquired epilepsies. Epilepsia. 2010;51(1):27-36.
22. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363(19):1801-11.
23. Cardamone M, Flanagan D, Mowat D, Kennedy SE, Chopra M, Lawson JA. Mammalian target of rapamycin inhibitors for intractable epilepsy and subependymal giant cell astrocytomas in tuberous sclerosis complex. J Pediatr. 2014;164(5):1195-200.
24. Canpolat M, Per H, Gumus H, Yikilmaz A, Unal E, Patiroglu T, et al. Rapamycin has a beneficial effect on controlling epilepsy in children with tuberous sclerosis complex: results of 7 children from a cohort of 86. Childs Nerv Syst. 2014;30(2):227-40.
25. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016;388(10056):2153-63.
26. Jóźwiak S, Kotulska K, Domańska-Pakieła D, Lojszczyk B, Syczewska M, Chmielewski D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol. 2011;15(5):424-31.
27. Amin S, Lux A, Calder N, Laugharne M, Osborne J, O'callaghan F. Causes of mortality in individuals with tuberous sclerosis complex. Dev Med Child Neurol. 2017;59(6):612-7.
28. Skin (Dermatological) Manifestations in TSC. http://tsalliance.org/pages.aspx?content=601. Tuberous Sclerosis Alliance; 30th

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March 2012.
29. Amin S, Carter M, Edwards RJ, Pople I, Aquilina K, Merrifield J, et al. The outcome of surgical management of subependymal giant cell astrocytoma in tuberous sclerosis complex. Eur J Paediatr Neurol. 2013;17(1):36-44.
30. Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology. 2004;63(8):1457-61.
31. Torres OA, Roach ES, Delgado MR, Sparagana SP, Sheffield E, Swift D, et al. Early diagnosis of subependymal giant cell astrocytoma in patients with tuberous sclerosis. J Child Neurol. 1998;13(4):173-7.
32. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013;381(9861):125-32.
33. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost MD, Kuperman R, et al. Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. PLoS One. 2016;11(6):e0158476.
34. Smalley SL, Tanguay PE, Smith M, Gutierrez G. Autism and tuberous sclerosis. J Autism Dev Disord. 1992;22(3):339-55.
35. Humphrey A, Neville BG, Clarke A, Bolton PF. Autistic regression associated with seizure onset in an infant with tuberous sclerosis. Dev Med Child Neurol. 2006;48(7):609-11.
36. Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain. 2002;125(Pt 6):1247-55.
37. Huang CH, Peng SS, Weng WC, Su YN, Lee WT, Group NTUHTSCNTS. The relationship of neuroimaging findings and neuropsychiatric comorbidities in children with tuberous sclerosis complex. J Formos Med Assoc. 2015;114(9):849-54.
38. Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. Epilepsy Behav. 2007;11(4):506-13.
39. Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol. 2004;19(9):666-74.
40. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. BJU Int. 2004;94(6):853-7.
41. P G. Demonstration eines grossen Angio-Myo-Lipoms der Niere. Dtsch Med Wochenschr; 1900.
42. Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. J Urol. 1998;160(1):141-5.
43. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc. 1991;66(8):792-6.
44. Cook JA, Oliver K, Mueller RF, Sampson J. A cross sectional study of renal involvement in tuberous sclerosis. J Med Genet. 1996;33(6):480-4.
45. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008;358(2):140-51.
46. Davies DM, Johnson SR, Tattersfield AE, Kingswood JC, Cox JA, McCartney DL, et al. Sirolimus therapy in tuberous sclerosis or sporadic lymphangioleiomyomatosis. N Engl J Med. 2008;358(2):200-3.

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47. Davies DM, de Vries PJ, Johnson SR, McCartney DL, Cox JA, Serra AL, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res. 2011;17(12):4071-81.
48. Dabora SL, Franz DN, Ashwal S, Sagalowsky A, DiMario FJ, Miles D, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF- D levels decrease. PLoS One. 2011;6(9):e23379.
49. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013;381(9869):817-24.
50. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Belousova E, Frost MD, et al. Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. PLoS One. 2017;12(8):e0180939.
51. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
52. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629-37.
53. Bissler JJ, Franz DN, Frost MD, Belousova E, Bebin EM, Sparagana S, et al. The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma. Pediatr Nephrol. 2018;33(1):101-9.
54. Kingswood JC, Jozwiak S, Belousova ED, Frost MD, Kuperman RA, Bebin EM, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. Nephrol Dial Transplant. 2014;29(6):1203-10.
55. Hancock E, Tomkins S, Sampson J, Osborne J. Lymphangioleiomyomatosis and tuberous sclerosis. Respir Med. 2002;96(1):7-13.
56. Chan JK, Tsang WY, Pau MY, Tang MC, Pang SW, Fletcher CD. Lymphangiomyomatosis and angiomyolipoma: closely related entities characterized by hamartomatous proliferation of HMB-45-positive smooth muscle. Histopathology. 1993;22(5):445-55.
57. Taillé C, Debray MP, Crestani B. Sirolimus treatment for pulmonary lymphangioleiomyomatosis. Ann Intern Med. 2007;146(9):687-8.
58. Berger U, Khaghani A, Pomerance A, Yacoub MH, Coombes RC. Pulmonary lymphangioleiomyomatosis and steroid receptors. An immunocytochemical study. Am J Clin Pathol. 1990;93(5):609-14.
59. Taveira-DaSilva AM, Moss J. Clinical features, epidemiology, and therapy of lymphangioleiomyomatosis. Clin Epidemiol. 2015;7:249-57.
60. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364(17):1595-606.
61. Koenig MK, Hebert AA, Roberson J, Samuels J, Slopis J, Woerner A, et al. Topical rapamycin therapy to alleviate the cutaneous manifestations of tuberous sclerosis complex: a double-blind, randomized, controlled trial to evaluate the safety and efficacy of topically applied rapamycin. Drugs R D. 2012;12(3):121-6.
62. S AMIN AL, A KHAN, F O'CALLAGHAN. Sirolimus ointment for facial angiofibromas in individuals with tuberous sclerosis
complex (TSC). 2017.

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63. Amin S, Lux A, Khan A, O'Callaghan F. Sirolimus Ointment for Facial Angiofibromas in Individuals with Tuberous Sclerosis Complex. Int Sch Res Notices. 2017;2017:8404378.
64. Wataya-Kaneda M, Ohno Y, Fujita Y, Yokozeki H, Niizeki H, Ogai M, et al. Sirolimus Gel Treatment vs Placebo for Facial Angiofibromas in Patients With Tuberous Sclerosis Complex: A Randomized Clinical Trial. JAMA Dermatol. 2018;154(7):781-8.
65. Koenig MK, Bell CS, Hebert AA, Roberson J, Samuels JA, Slopis JM, et al. Efficacy and Safety of Topical Rapamycin in Patients With Facial Angiofibromas Secondary to Tuberous Sclerosis Complex: The TREATMENT Randomized Clinical Trial. JAMA Dermatol. 2018;154(7):773-80.
66. Pantelis A, Bootz F, Kühnel T. [Laser skin resurfacing and fibrin sealing as successful treatment for facial angiofibromas in tuberous sclerosis]. HNO. 2007;55(13):1009-11.
67. Amin S, O'Callaghan FJ. Glossal hamartoma in tuberous sclerosis. Arch Dis Child. 2013;98(2):161.
68. Mlynarczyk G. Enamel pitting: a common symptom of tuberous sclerosis. Oral Surg Oral Med Oral Pathol. 1991;71(1):63-7.
69. Sparling JD, Hong CH, Brahim JS, Moss J, Darling TN. Oral findings in 58 adults with tuberous sclerosis complex. J Am Acad Dermatol. 2007;56(5):786-90.
70. Tworetzky W, McElhinney DB, Margossian R, Moon-Grady AJ, Sallee D, Goldmuntz E, et al. Association between cardiac tumors and tuberous sclerosis in the fetus and neonate. Am J Cardiol. 2003;92(4):487-9.
71. Karnak I, Alehan D, Ekinci S, Büyükpamukçu N. Cardiac rhabdomyoma as an unusual mediastinal mass in a newborn. Pediatr Surg Int. 2007;23(8):811-4.
72. Verhaaren HA, Vanakker O, De Wolf D, Suys B, François K, Matthys D. Left ventricular outflow obstruction in rhabdomyoma of infancy: meta-analysis of the literature. J Pediatr. 2003;143(2):258-63.
73. Krueger DA, Franz DN. Current management of tuberous sclerosis complex. Paediatr Drugs. 2008;10(5):299-313.
74. Demir HA, Ekici F, Yazal Erdem A, Emir S, Tunç B. Everolimus: a challenging drug in the treatment of multifocal inoperable cardiac rhabdomyoma. Pediatrics. 2012;130(1):e243-7.
75. Robertson DM. Ophthalmic manifestations of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:17-25.
76. Nyboer JH, Robertson DM, Gomez MR. Retinal lesions in tuberous sclerosis. Arch Ophthalmol. 1976;94(8):1277-80.
77. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85(4):420-3.
78. Lucchese NJ, Goldberg MF. Iris and fundus pigmentary changes in tuberous sclerosis. J Pediatr Ophthalmol Strabismus. 1981;18(6):45-6.
79. Shelton RW. The incidence of ocular lesions in tuberous sclerosis. Ann Ophthalmol. 1975;7(6):771-4.
80. Mennel S, Meyer CH, Peter S, Schmidt JC, Kroll P. Current treatment modalities for exudative retinal hamartomas secondary to tuberous sclerosis: review of the literature. Acta Ophthalmol Scand. 2007;85(2):127-32.

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Tuberous Sclerosis Complex (TSC)
mammalian target of rapamycin (mTOR)
Sudden Unexpected Death in Epilepsy (SUDEP)
Sub-Ependymal Giant Cell Astrocytoma (SEGA)
angiomyolipoma (AML)
magnetic resonance imaging (MRI)
autistic spectrum disorders (ASD)
attention-deficit–hyperactivity disorder (ADHD)
TSC Associated Neuropsychiatric Disorders(TAND)
Education and Health Care Plan (EHCP)
lymphangioleiomyomatosis (LAM)
glomerular filtration rate (GFR)
general anaesthetic (GA)
Vagal Nerve stimulator (VNS)
high-resolution chest computed tomography (HRCT)
Individual Funding Request (IFR)
Parkinson–White syndrome (WPW)

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