Diagnosing TSC
by Making Clinical Connections

TSC = tuberous sclerosis complex.
### Genetic Criteria
- Does the patient have any family members with similar symptoms—especially siblings, parents, or grandparents?
- Identification of either a *TSC1* or *TSC2* pathogenic mutation
- 10% to 25% of TSC patients have no mutation identified by genetic testing
- Normal genetic testing result does not exclude TSC

### Major Criteria

#### Retinal Manifestations
- Has the patient been diagnosed with retinal hamartomas?
  - Multiple retinal hamartomas
  - Seen in 30% to 50% of TSC patients

#### Neurologic Manifestations of TSC
- Has the patient shown evidence or been diagnosed with epilepsy or neuropsychiatric disorders?
  - Cortical dysplasias\(^a\)
  - Seen in 90% of TSC patients
  - Subependymal nodules (SENs)
  - Seen in 80% of TSC patients; often detected prenatally or at birth
  - Subependymal giant cell astrocytomas (SEGAs)
  - Incidence of 5% to 15%; can cause serious neurologic compromise

#### Cardiovascular Manifestations
- According to medical history, has the patient had a cardiac rhabdomyoma?
  - Cardiac rhabdomyoma
  - Finding is highly specific to TSC

#### Pulmonary Manifestations
- Does the patient experience progressive dyspnea on exertion and recurrent pneumothoraces?
  - Lymphangioleiomyomatosis (LAM)\(^b\)
  - Seen in 30% to 40% of female TSC patients
  - Lung involvement may increase with age (up to 80% of TSC females by age 40)
  - Angiomyolipomas (≥2)\(^b\)
  - Relatively specific to TSC
  - Fat-containing angiomyolipomas are seen in 80% of TSC patients
  - Can cause serious issues with bleeding; may lead to dialysis and nephrectomy/transplantation

#### Dermatologic Manifestations
- Does the patient have any major dermatologic manifestations of TSC? (see reverse)
  - Skin lesions are seen in ≥90% of patients with TSC

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\(^a\) Includes tubers and cerebral white matter radial migration lines.
\(^b\) A combination of the 2 clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
Does the patient have evidence of any of the following minor features of TSC?

### Definite Diagnosis of Tuberous Sclerosis Complex (TSC)
- Either a TSC1 or TSC2 mutation is detected in normal tissue
- ≥2 major features or 1 major feature with ≥2 minor features

### Possible Diagnosis of TSC
- Either 1 major feature or ≥2 minor features

#### Suspect TSC?
If you see ≥1 dermatologic lesion associated with this disease, also consider asking the following targeted questions:

#### Relevant diagnostic testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>• 3-generation family history; genetic testing recommended when diagnosis suspected but cannot be clinically confirmed</td>
</tr>
<tr>
<td>Brain</td>
<td>• Magnetic resonance imaging (MRI) for tubers, SEN, SEGA</td>
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<td>• Computed tomography (CT) or head ultrasound (in neonates/infants with open fontanels)</td>
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<tr>
<td></td>
<td>• Electroencephalography (EEG) for all pediatric patients (even in absence of apparent seizures); 24-h EEG recommended if abnormal or if TSC-associated neurologic changes are evident</td>
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<tr>
<td>Kidney</td>
<td>• Assess for angiomyolipomas and renal cysts by MRI</td>
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<tr>
<td></td>
<td>• Screen for hypertension, determine glomerular filtration rate</td>
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<tr>
<td>Lung</td>
<td>• Baseline pulmonary function testing</td>
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<tr>
<td>Skin</td>
<td>• Detailed dermatologic inspection</td>
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<tr>
<td>Teeth</td>
<td>• Detailed clinical dental inspection</td>
</tr>
<tr>
<td>Heart</td>
<td>• Echocardiograms in pediatric patients and electrocardiograms for all ages</td>
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<tr>
<td>Eye</td>
<td>• Complete ophthalmologic exam</td>
</tr>
</tbody>
</table>
Skin lesions are present in $\geq 90\%$ of patients with TSC. Knowing how to differentiate TSC-associated lesions from other skin disorders may help you diagnose TSC. The following table summarizes dermatologic symptoms that are considered **major** clinical diagnostic criteria for TSC.$^2$

## Test 1: Physical exam: Look for skin abnormalities and differential diagnoses

<table>
<thead>
<tr>
<th>Image</th>
<th>Skin Lesion</th>
<th>Age at Onset</th>
<th>Consideration</th>
</tr>
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</table>
| ![Hypomelanotic macules](image) | Hypomelanotic macules | • At birth or infancy | • Observed in about 90% of individuals with TSC  
• $\geq 3$ lesions at least 5 mm in diameter must be present  
(1 or 2 lesions is relatively common in general population) |

### Differential Image

- Hypomelanotic macules
- Nevus anemicus
- Nevus depigmentosus
- Piebaldism
- Early vitiligo

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| ![Angiofibromas](image) | Angiofibromas | • Ages 2 to 5 | • Occur in 75% of TSC patients  
• $\geq 3$ lesions must be present  
(1 or 2 isolated sporadic lesions often present in general population) |

### Differential Image

- Angiofibromas
- Acne vulgaris
- Rosacea
- Multiple trichoepithelioma

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| ![Fibrous cephalic plaque](image) | Fibrous cephalic plaque | • Ages 2 to 5 | • Occurs in 25% of TSC patients  
• Most specific skin finding for TSC  
• Most common on forehead, but may occur on other parts of face or scalp |
## Test 1: Physical exam

Look for skin abnormalities and differential diagnoses

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| ![Ungual fibromas](image1.png) | Ungual fibromas | Second decade or later | • Occur in 20% of TSC patients overall, but in up to 80% of older adults  
• ≥2 must be present |

### Differential Image

- ![Epithelial inclusion cysts](image2.png)
- ![Verruca vulgaris](image3.png)
- ![Infantile digital fibromatosis](image4.png)

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<tr>
<td><img src="image5.png" alt="Shagreen patch" /></td>
<td>Shagreen patch</td>
<td>First decade</td>
<td>• Occurs in 50% of TSC patients</td>
</tr>
</tbody>
</table>

### Differential Image

- ![Connective tissue nevi](image6.png)

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**Worth noting**... minor dermatologic/dental features of TSC include “confetti” skin lesions, multiple (>3) dental enamel pits, and multiple (≥2) intraoral fibromas.
References
