Royal Cornwall Hospitals
NHS Trust

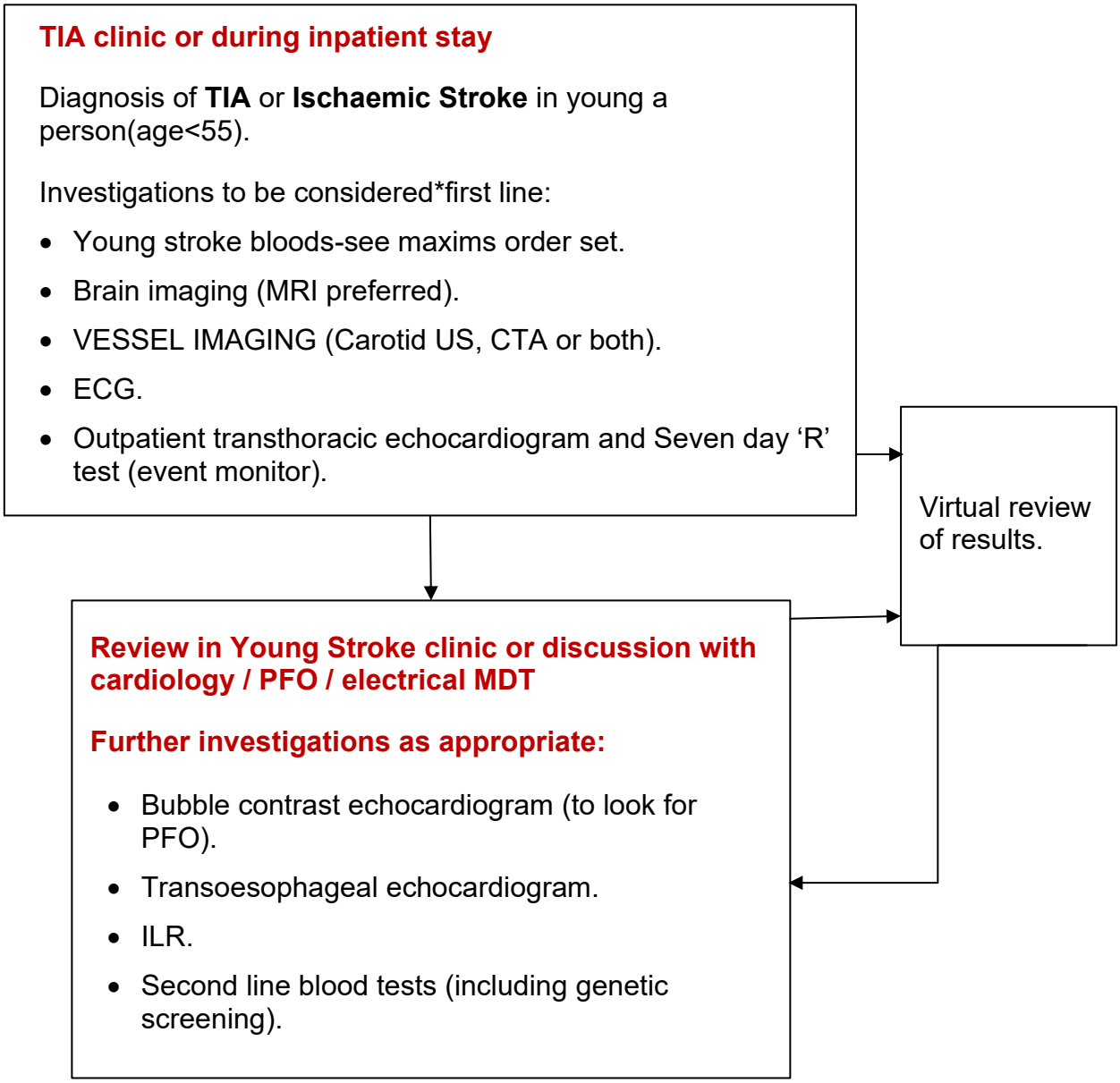
Evaluation of Stroke and Transient Ischemic Attack (TIA) in a Young Person Clinical Guideline

V1.0

November 2025

Summary

Overview of Investigation approach



*In patients with multiple pre-existing stroke risk factors (atrial fibrillation (AF), hypertension, hypercholesterolaemia, diabetes, smoking) extensive tests may not needed and investigations can be considered on an individualised basis.

1. Aim/Purpose of this Guideline

This guideline provides a framework for the evaluation of patients diagnosed with Stroke and TIA in a young person (usually aged <55). Routine investigative work-up will be detailed in this guideline, to assist in identification of an underlying cause of unexplained cerebral infarct.

Data Protection Act 2018 (UK General Data Protection Regulation – GDPR) Legislation.

The Trust has a duty under the Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 please see the Information Use Framework Policy or contact the Information Governance Team.

Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1. This document is intended for use by clinicians within the Eldercare Department, under the guidance of a consultant. It is not for general use by non-specialists.

2.2. The guideline does not include the general management of acute stroke, which can be found here Acute Stroke Management Clinical Guideline Sub paragraph.

2.3. **Definition and Exclusions**

2.3.1. Ischaemic Stroke (cerebral infarct) – occurs when a blood clot blocks an artery that carries blood to the brain.

2.3.2. Haemorrhagic stroke (primary intracerebral haemorrhage) – defined as non-traumatic spontaneous bleeding into to the brain tissue – excluded from this guideline.

2.3.3. Other forms of brain injury: Subdural, extradural, subarachnoid and trauma-related intracerebral haemorrhage, cerebral trauma and diffuse axonal injury, are also excluded from this guideline.

2.3.4. The aetiopathology of cerebral infarct can be differentiated by the TOAST classification [Adams HP et al. Stroke 1993, 24:35-41] in the following five types:

- Large vessel disease – LVD.
- Small vessel disease – SVD.
- Cardioembolic stroke – CE.
- Stroke of other determined aetiology – usually a known diagnosis of an underlying cardiac condition, lupus or other predisposing condition.
- Cryptogenic stroke – CS.

2.3.5. CS is presumed diagnosis ("**presumed cryptogenic stroke**" – PCS) pending investigational workup. PCS eventually gets split into:

- **Confirmed cryptogenic stroke (CS)** – no cause found after detailed investigation. About 2/3rds of all CS is "**Embolic Stroke of Unknown Source**" (ESUS). This subcategory can be used if evidence of cerebral infarcts in keeping with embolism e.g. multiple cerebral infarcts across vascular territories, cortical infarction, cortical syndromes (TACS/PACS).
- Reclassified into 1-4 above after appropriate investigation. In the scenario of Presumed Cryptogenic Syndrome (PCS), structured evaluation may lead to reclassification to one of the other categories (e.g. LVD, SVD, CE, or other determined aetiology), confirmation of the presumed diagnosis i.e. CCS with or without subclassification as ESUS.

Appendix 3. provides information about causes of stroke in young people, as well as further information on clinical associations and investigations.

2.4. Investigative approach

2.4.1. Brain imaging

a) MR brain - is the preferred imaging modality for patients with suspected TIA, after they've been seen in the TIA clinic. MRI has higher sensitivity for detection of acute cerebral infarction. Identification of acute cerebral infarction, which confirms diagnosis of stroke, may have a bearing on further investigations and definitive management downstream, such as closure of patent foramen ovale in patients with stroke under 60. It is therefore particularly relevant to confirm diagnosis of ischaemic stroke in younger patients.

b) CT brain - if already performed in the context of hyperacute stroke presentation, may be adequate as the sole imaging modality, especially if cerebral infarction has been demonstrated on the scan. CT brain is also appropriate as imaging modality where MRI is not feasible e.g. patient tolerability, contraindications e.g. pacemaker. Discuss with Eldercare/Stroke Consultant about need for MRI brain.

2.4.2. **Vessel imaging** – is performed to identify carotid stenosis which may be eligible for surgical revascularisation in addition to best medical treatment. Vessel imaging may also identify arterial dissection, which can present with ischaemic stroke/TIA. Imaging can take the form of:

a) CT carotid angiogram – this may already have been performed for patients who present with hyperacute stroke. If the severity of any carotid stenosis has not been stated in the report, it may be necessary to ask a Vascular Radiologist to review the scan and quantify the stenosis severity (if present).

b) Carotid doppler ultrasound – this may not be necessary if CT carotid angiogram has already been performed.

c) In some cases, both imaging modalities (carotid ultrasound and CT angiogram) may be necessary for the sake of corroboration, if one initial imaging modality were to demonstrate significant carotid stenosis and the patient is candidate for surgical revascularization.

d) MR or CT venogram – may be necessary to evaluate for venous sinus thrombus where it is clinically indicated e.g. if imaging suggests venous infarction, which be accompanied with haemorrhage and in the right clinical context (presentation with headache, focal neurological symptoms, seizures, and any predisposition to venous thrombosis such as malignancy).

2.5. **Cardiac work up**

2.5.1. First line tests (requested from TIA clinic or during inpatient stay).

a) ECG – All patients should have either a 12-lead ECG or rhythm strip from the Kardia device (to detect AF).

b) Cardiac rhythm monitoring.

- Initial cardiac holter monitoring – 24-hour cardiac monitoring is usually the initial test of choice for detection of paroxysmal AF. This may be done as inpatient (at the discretion of the Consultant) if high clinical suspicion for paroxysmal AF (e.g. multiple embolic events, atrial enlargement, frequent atrial ectopics).

- Prolonged cardiac monitor – is performed on an outpatient basis by way of a ‘R test’ or similar for a period of seven days in order to increase the likelihood of detecting paroxysmal AF.

a) Transthoracic echocardiogram (TTE) – can be requested as inpatient (at discretion of consultant) if admitted with confirmed cerebral infarction / ischaemic stroke and concerned about endocarditis or mural thrombus (recent transmural MI). For patients seen in TIA clinic, TTE can be requested as outpatient.

2.5.2. Second line tests (usually requested after review in Young Stroke clinic or following discussion with Cardiology / PFO MDT).

a) Bubble contrast echocardiogram (BCE) – requested for patients with confirmed cerebral infarction (on brain imaging) aged under 60, to look for the presence of patent foramen ovale (PFO). Bubble echocardiogram is not usually requested for patients with TIA where there is no evidence of cerebral infarction (as any identified PFO would not be eligible for NHS funded PFO closure).

b) Transoesophageal echocardiogram (TOE) – requested occasionally after discussion with Cardiology or at PFO MDT to evaluate for intracardiac thrombus, fibroelastoma or prosthetic valves.

c) Implantable Loop Recorder (ILR) – requested occasionally after discussion with Cardiology or the PFO/Cardiology Electrical MDTs, if it is felt a longer period of monitoring is required to detect paroxysmal AF.

2.6. **Bloods**

First line tests	**Second line tests**
All patients <55. To be done in TIA clinic or when inpatient after diagnosis of Stroke or TIA by Eldercare/Stroke Consultant.	For some patients - if fits clinical criteria. After review in Young Stroke clinic.
FBC, ESR, U+E, CRP, LFT, Bone, Chol, TSH, and glucose.	Lactate (if this is raised or suggestive clinical features then consider MELAS).
Fabrys: dried blood spot test.	CADASIL if MRI or clinical features suggestive. See Appendix 3.
Coagulation screen	
If anaemic or high MCV check B12 and folate.	If B12/folate low – replace and discuss further testing with Simon Fleming (homocysteine, etc.).
Antiphospholipid screen (lupus anticoagulant, anticardiolipin antibodies and anti B2 glycoprotein).	Hb electrophoresis – if sickle cell suspected.
ANA Autoantibody screen and ANCA.	Extended Autoantibody panel [ENA, dsDNA] if persistently elevated ANA.
HIV, syphilis.	
Lipoprotein A.	

2.7. **Other investigations**

- Investigation for Secondary causes – if hypertension in young stroke e.g. 24-hour urine collection for metanephrines and cortisol, renal ultrasound, urine dipstix, and renin:aldersterone levels.
- Urine - If suspicion of iv drug use, send urinalysis and request 'Illicit Drugs screen'.
- CXR – if clinical suspicion of sarcoidosis.

2.8. List of investigations for Presumed Cryptogenic Stroke to identify 'other defined aetiologies'.

Arterial dissection	**Autoimmune disease**	**Thrombophilic disease**	**Genetic conditions**
Appropriate angiographic imaging in discussion with Radiologist – usually CT or MR angiogram.	Basic autoantibody testing. Vasculitis screen (ANA, ANCA) Myeloma screen Syphilis and HIV serology.	Basic arterial thrombophilia screen. • Lupus anticoagulant, anti-cardiolipin and beta2glcoprotein. • +/-Homocysteine level (ideally fasting if feasible). (if elevated, repeat in fasting state, with B12/folate).	If there is FH of young stroke, or other genetic conditions, consider referral to the Exeter Clinical Genetics service. (See Appendix).
Consider referral to Genetics if considering underlying causes such as Marfan's.	If ANA is positive • Consider false + and drug induced ANA +. • Repeat in six weeks to confirm. • If persistently +, undertake. Extended autoantibody testing (ENA panel, dsDNA, beta2glycoprotein). **Note: overlap with thrombophilia screen.**	Extended venous thrombophilia screen Indications: • Suspected right to left heart shunt (e.g. PFO). • H/o recurrent VTE or presence of right-to-left shunt. • Multiple unprovoked VTE. **Note: check if tests have already been performed.**	Screening for Fabry's disease for all under 55.

Arterial dissection	Autoimmune disease	Thrombophilic disease	Genetic conditions
		What tests to do: Prothrombin Factors • Activated protein C, activated Xa, P20210A mutation. Deficiency of anticlotting factors. • Protein Culture and Sensitivity, ATIII, FV leiden.	

2.9. References

- National Clinical Guidelines for Stroke 2023 Update National Clinical Guideline for Stroke.
- Kernan et al 2014 Stroke – AHA/ASA Guidelines for prevention of Stroke in patient with ischaemic stroke or TIA Guidelines for the Prevention of Stroke in patients with stroke and Transient Ischemic Attack | Stroke.
- ASA Cryptogenic Stroke initiative Cryptogenic Stroke Initiative | American Stroke Association.
- Yaghi S, Elkind MS. Cryptogenic stroke: a diagnostic challenge. Neuro Clin Pract. 2014; 4: 386-393.
- Royal Cornwall Hospitals NHS Trust. Acute Stroke Management Clinical Guideline version 9.1 (December 2023).

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Routine investigative work up for young stroke patients.
Lead	Dr Lisa Manning, Stroke Specialty Lead.
Tool	Monitor usage of routine investigations against patient outcomes.
Frequency	Monitored annually and shared at the Stroke governance meeting.
Reporting arrangements	Report will be presented to stroke governance meeting and documented in the meeting minutes.
Acting on recommendations and Lead(s)	Stroke specialty governance.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned within 2 months. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Evaluation of Stroke and TIA in a Young Person Clinical Guideline V1.0
This document replaces (exact title of previous version):	New Document
Date Issued/Approved:	October 2025
Date Valid From:	November 2025
Date Valid To:	November 2028
Directorate/Department responsible (author/owner):	Dr Lisa Manning, Stroke Specialty Lead
Contact details:	01872 252447
Brief summary of contents:	Guideline for routine investigations for Young Stroke patients.
Suggested Keywords:	Stroke, TIA, guideline.
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** No
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Specialty Governance, Care Group Governance
Manager confirming approval processes:	Andrew Stenton
Name of Governance Lead confirming consultation and ratification:	Paul Evangelista
Links to key external standards:	None required
Related Documents:	Acute Stroke Management Clinical Guideline
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet

Information Category	Detailed Information
Document Library Folder/Sub Folder:	Clinical/Stroke

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
September 2025	V1.0	Initial issue	Dr Lisa Manning, Eldercare consultant

All or part of this document can be released under the Freedom of Information Act 2000.

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document.

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity, and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy/policy/proposal/service function to be assessed:	Evaluation of Stroke and TIA in a young person V1.0
Directorate and service area:	Stroke, Acute Emergency Medicine.
Is this a new or existing Policy?	New.
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Clare Pitt, Service Manager for Stroke.
Contact details:	01872 252447

Information Category	Detailed Information
1. **Policy Aim - Who is the Policy aimed at?** (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	Clinicians undertaking assessments and care for young stroke patients.
2. **Policy Objectives**	To ensure consistency of routine investigations
3. **Policy Intended Outcomes**	Quality consistency of appropriate investigations for all young stroke patients
4. **How will you measure each outcome?**	Annual monitoring of the use of routine investigations and patient outcomes
5. **Who is intended to benefit from the policy?**	Patients

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/visitors: No • Local groups/system partners: No • External organisations: No • Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/groups:** Eldercare Governance, Care group Governance, Stroke Governance.
6c. What was the outcome of the consultation?	Agreed.
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff, or patient surveys:** No.

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	

Protected Characteristic	(Yes or No)	Rationale
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment: Clare Pitt, Service Manager for Stroke.

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis

Appendix 3. Causes of stroke in young person and further information

1. Cardio embolism

This may present as cortical stroke syndrome; alternatively imaging may demonstrate cortical infarction, or multiple infarcts in multiple vascular territories

Causes include:

- Atrial fibrillation/flutter – older age, ischaemic/valvular heart disease, hypertension, alcohol excess, smoking.
- Mural thrombus - especially if transmural MI within last 3 months.
- Endocarditis – clinical suspicion, or high risk based on presence of prosthetic valves.
- Other valvular heart disease, such as mitral stenosis.
- Aortic arch atherosclerosis – consider CT angiogram of arch, or TOE.
- Patent foramen ovale – can be present in 1:4 to 1:5 of the 'normal' population; however a large PFO with a right-to-left shunt may be potentially relevant in a young person with cryptogenic stroke (or TIA, with confirmed cerebral infarction on brain imaging e,g, MRI evidence of stroke).

2. Arterial dissection

- Young stroke with paucity of risk factors.
- History of neck trauma or extreme movement temporarily associated with onset.
- Head/neck pain (some may even report thunderclap headache).
- Horner's syndrome.
- Dissection of internal carotid or vertebral arteries may or may not be associated with cerebral infarction / clinical features of stroke.
- Imaging with CT or MR angiogram can be used to identify arterial dissection.
- Management may be with either antiplatelet or anticoagulation therapy, as per responsible Consultant.
- Consider genetic testing if clinical features of Marfan's syndrome.

3. Autoimmune disease

Known history of autoimmune disease.

Clinical stigmata of vasculitis.

- Neurological features (may be difficult to isolate from stroke related neurology):

- Mononeuritis multiplex (damage to 2 or more named nerves, typically “foot drop”).
- Polyneuropathy (distal, symmetric).
- Radiculopathy and/or plexopathy (nerve root or plexus distribution).

- Non-neurological features:
  - Constitutional: fever, malaise, weight loss.
  - Skin: palpable non-blanching purpura or skin ulcers.
  - ENT: allergic rhinitis / nasal polyps.
  - GI: intestinal angina (polyarteritis nodosa).
  - Large vessel: absent/asymmetric pulses, bruits on large vessel auscultation.

Often have headaches, personality changes, fluctuating consciousness, meningism,urine dip test (proteinuria, haematuria, casts).Positive antibodies on autoimmune testing (ANA, ANCA, myeloma, syphilis, HIV).

Imaging: consider FDG PET scan, CSF examination, angiography or biopsy (from suspected organ).

Management: it is important to differentiate between primary systemic vasculitis from secondary causes (e.g. inflammatory conditions like SLE; a variety of infections; neoplasia and drug-related) to direct management. Patients with vasculitis should ideally be managed by a multi-disciplinary team including Neurology and Rheumatology. Steroids are the mainstay of treatment, with ongoing management in liaison with Rheumatology and Neurology depending on concomitant disease.

4. Thrombophilic disease

- Antiphospholipid syndrome.

  Antiphospholipid syndrome (APLS) is an acquired thrombophilia with known increased risk of arterial and venous thrombosis. There may be a history of recurrent miscarriage.

  Initial screen for young stroke patients should include testing of lupus anticoagulant, IgM and IgG anticardiolipin antibodies and IgM and IgG anti B2 glycoprotein antibodies. These five tests are combined as a Maxims orderset labelled ‘Antiphospholipid screen’. Be aware that positive results can be transient, a single positive result does not qualify as an APLS diagnosis. Any positive results should be followed by repeat testing after 12 weeks.

  Antithrombotic strategy (anticoagulation type e.g. DOAC or warfarin) can be discussed with Haematology. Patients who are ‘triple’ positive, defined as positive lupus anticoagulant plus positive anticardiolipin antibody (either IgM or IgG) plus positive anti B2 glycoprotein (either IgM or IgG) have a high risk of recurrent thrombosis and usually need to be treated with warfarin. In single or double positive cases, warfarin is still recommended but a DOAC can be a reasonable alternative.

- Inherited thrombophilias.

  The association between inherited thrombotic disorders and stroke is not well characterised, and testing has not been shown to change clinical management. Testing for inherited thrombophilia in the context of young stroke is not recommended. On a case by case basis if there is an opinion that thrombophilia testing will significantly change a management decision then please discuss with haematology as these tests should not be performed without appropriate consent.

5. Genetic conditions

If a rare mongenic cause of Stroke is suspected, consider seeking advice from the Clinical Genetics service based at Exeter. Referrals can be made to rduh.pcgreferrals@nhs.net.

The National genomic test director (NHS England » National genomic test directory) specifies which genetic tests are commissioned by NHS England, as well as the eligibility criteria for testing. These will be described below for some of the rare genetic conditions associated with Stroke.

The standard request form for all genetic tests can be accessed here: SWGLH Genomic Test Request Form which can be given to the patient to take to phlebotomy or GP, and can accompany the blood sample to the local lab.

Occasionally, additional testing may be required, requiring Whole Genome Sequencing – this will require additional paperwork. In such circumstances, discuss individual cases with the South West Genomic Laboratory Hub here: https://www.nbt.nhs.uk/south-west-genomic-laboratory-hub.

- Fabrys disease (α-galactosidase deficiency) affected patients may present with painful burning sensation in hands and feet or angiokeratomas in 'bathing trunk' distribution. As it is a multi-system disorder there may be visual problems, cardiomyopathy, myocardial ischaemia and stroke, other symptoms include decreased sweating, fever, and gastrointestinal difficulties, particularly after eating. A detailed family history, systemic enquiry and physical examination should be undertaken before testing. Due to the large number of mutations on the gene, a pattern is hard to find.

- The 'Dried blood spot' test is the first line investigation for Fabrys disease, where the activity of the enzyme alpha-galactosidase is measured against a small blood sample spotted onto a filter paper card.

- In heterozygous females alpha-galactosidase enzyme activity may be in the normal range. Therefore women may require the DNA test.

- For genetic testing, this is the eligibility criteria as set by the National genomic test director.

R335 Fabry disease

Testing criteria

- In males: clinical and Laboratory features and characteristic of Fabry disease following alph-galactosidase A enzyme testing.
- In females: clinical features characteristic of Fabry disease.

Referrals for testing will be triaged by the Genomic Laboratory: testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in pathway

Following alpha-galactosidase A enzyme testing.

Requesting Specialties

- Cardiology.
- Clinical genetics.
- Dermatology.
- Metabolic medicine.
- Nephrology.
- Ophthalmology.

Specialist service group

- Metabolic.

Associated tests

Please note all the tests below will be undertaken for R335 clinical indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal family structure	Scope	Target type	Target name	Method
R335.1	GLA single gene sequencing	Singleton	Small variants	Single gene(s)	GLA (1323)	Single gene sequencing<10 amplicons.
R335.2	GLA MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GLA (1323)	MLPA or equivalent.

- **CADASIL** – often causes severe migraine with aura in 20s, associated with psychiatric features, recurrent lacunar strokes in 40s, progressive subcortical dementia in 50s. MRI shows severe white matter disease and lacunar infarcts – characteristically also affects anterior temporal lobes. Usually exhibits autosomal dominant inheritance but may be sporadic. A detailed family history and systemic enquiry should be undertaken before testing. Only check if a patient exhibits some of these features or MRI is suggestive.

  For genetic testing, this is the eligibility criteria as set by the National genomic test director.

R337 CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy).

Testing criteria

A confident clinical diagnosis of CADASIL including:

Cerebral ischaemic event below age of 50 or >50 if with a family history of dementia/migraine, and one or more of:

- Cognitive impairment with recurrent ischaemic attacks, Or,
- Subcortcal lacunar lesions on MRI scan in white matter.

Overlapping indications

E58 Adult onset neurodegenerative disorder test should be used on atypical cases where a broader differential diagnosis is under consideration.

Refferals for testing will be triaged by the Genomic laboratory:testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in the pathway

At presentation.

Requesting specialties

- Clinical Genetics.
- Neurology.

Specialist service group

- Neurology.

Associated tests

Code	Name	Optimal family structure	Scope	Target type	Target name	Method
R337.1	NOTCH3 single gene sequencing	Singleton	Small variants	Single gene(s)	NOTCH3 (1311)	Single gene sequencing>= 10 amplicons

- MELAS – usually presents in children and young adults. Often stroke like episodes associated with seizures affecting occipital lobes initially. Other features may include short stature, short stature, Sensorineural deafness, Some learning disability, Episodic vomiting due to ileus, Migraine like episodes, Diabetes, exercise intolerance, proximal muscle weakness. Late features may be dementia and cortical blindness. A detailed family history, systemic enquiry and physical examination should be undertaken - only check if a patient exhibits some of these features. First line investigation should be serum lactate, which may be raised.

  For genetic testing, this is the eligibility criteria as set by the National genomic test director.

Mitochondrial

R64 MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) **or MIDD**

Testing criteria

Adult onset sensorineural hearing loss and diabetes or family history suggestive of a diagnosis of maternally inherited diabetes and deafness **Or,**

A Clinical presentation compatible with MELAS.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the Proband or family.

Where in pathway

At presentation.

Requesting Specialties

- Clinical genetics.
- Endocrinology.
- Neurology.

Specialist service group

- Mitochondrial.

Code	Name	Optimal family structure	Scope	Target type	Target name	Method
R64.1	MTTL1 3243A>G Targeted variant testing	Singleton	Small variants	Single interval	MTTL1 3243A>G	Targeted variant testing.

- Homocystinuria – is a rare autosomal recessive disorder where the amino acid methionine is not metabolised. It usually presents in childhood with seizures, visual problems, learning disability, the patient may have marfanoid features. Mildly raised homocysteine is associated with some stroke patients, but it is not clear whether it is causal, and treatment studies have not shown benefit. So it should not be routinely checked but considered if patients exhibit above features. Whether low B12 and folate causing high homocysteine levels actually cause stroke is open to debate. If young stroke patients are anaemic or have high MCV they should have B12 and folate checked – if levels are low, they should be replaced.

- If homocystinuria is being considered as a diagnosis, please obtain advice from rduh.pcgreferrals@nhs.net.

- Information on testing can be obtained from the Exeter Genomics Laboratory NHS Royal Devon | Exeter Genomics Laboratory.

- COL4A1 Mutation - genetic disorder of collagen function. Often causes minor strokes in childhood and can be associated with severe migraine. Can cause small vessel infarcts, microbleeds, larger haemorrhages, white matter disease, aneurysms. Stroke after minor head trauma or exercise can occur. MRI with gradient echo sequence will show the various manifestations. A detailed family history should be obtained and a neurology opinion should be sought before contemplating testing.

Appendix 4. Crib sheet for detailed history and examination in the setting of Presumed Cryptogenic Stroke.

Complete prior to confirming diagnosis of CCS

History	Record any findings
Symptom screen: Alopecia, scalp necrosis. Lens dislocation. Mouth ulcers. Jaw or tongue claudication. Visual loss (suggestive of ischaemic optic neuropathy). Rashes. Joint swelling. Acroparaesthesia (+/- neuropathic pain). Claudication. Heat intolerance/ hypohidrosis. Constitutional symptoms: anorexia, weight loss, malaise.	
PMH: Rheumatic heart disease. Malignancy. Seizure disorder. Spinal problems. HIV. Syphilis (or migration from high risk region e.g. SE Asia, sub-Saharan Africa, Latin America or Caribbean). PMR. Premature bilateral cataract. High burden of migraine with aura. Pregnancy morbidity (miscarriage, foetal death, eclampsia or pre-eclampsia).	
Examination	
Fundoscopy. Malar rash. Livedo reticularis. Angiokeratomas. Detailed peripheral pulse examination (absent pulses, claudication).	

Appendix 5. Grid for Cryptogenic stroke testing

Test	Results
TTE	
Cardiac Rhythm monitor: 24 hour ECG. Prolonged Cardiac Monitor (e.g. 7 day R test).	
Other Cardiac Ix • BCE. • TOE.	
Vessel imaging • Carotid US. • CT / MR angiogram.	
Bloods Routine Stroke bloods: • TC / LDLc/ nonHDLc. • Gluc / HbA1c. • CRP. • LFT. • TSH. • FBC. 1st line Young Stroke bloods: • ANA. • ANCA. • HIV/ Syphilis. • Fabry's (if under 55). • Lipoprotein A. • APLS screen. 2nd line / extended Stroke bloods: • Genetic testing. • Extended Autoantibody panel. • Extended thrombophilia panel.	