NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

Final scope

August 2022

1 Introduction

The topic selection oversight panel identified clopidogrel testing after ischaemic stroke as suitable for evaluation by the NICE diagnostics assessment programme after clinical experts highlighted system interest in the topic.

The revised scope was informed by discussions at the scoping workshop on 15th July 2022, and the assessment subgroup meeting held on 29th July 2022.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and experts and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Clopidogrel is a prodrug that can be converted (metabolised) to an irreversible P2Y12 inhibitor with antiplatelet properties. Clopidogrel is given after ischaemic stroke or transient ischaemic attack to reduce the risk of further occlusive events, such as another stroke.

The *CYP2C19* gene encodes a protein that is needed to metabolise clopidogrel to its active form. Clopidogrel may be less effective in people with particular variants of this gene, who may benefit from use of an alternative antiplatelet therapy. *CYP2C19* genotyping enables identification of variants in the *CYP2C19* gene. This provides information on how effectively a person

can metabolise clopidogrel and therefore can be used to guide antiplatelet treatment.

2.2 Technology properties

Point-of-care *CYP2C19* genotype testing

Point-of-care testing is a term that describes any analytical test done by a healthcare professional outside the conventional laboratory setting (MHRA 2021). For *CYP2C19* genotyping, these could be done in locations such as acute stroke centres or acute medical wards. In practice, some point-of-care tests may be done in local hospital laboratories to account for need to store reagents at low temperatures or to ensure quality control. Clinical experts highlighted that, if point-of-care tests are used outside of laboratories, it would be important to ensure that necessary training was provided and that ongoing quality assurance was done. Experience of test operator would also be an important consideration for data on point-of-care tests, who may in practice be operated by people with much less experience of doing tests than laboratory personnel.

2.2.1 Genomadix cube CYP2C19 system (Genomadix)

The Genomadix cube CYP2C19 system is a point-of-care DNA test used to detect variants in the *CYP2C19* gene, specifically the *2, *3 and *17 alleles. The test is intended to be used in conjunction with clinical judgement and routine monitoring to determine therapeutic strategy for drugs metabolized by the CYP2C19 enzyme. The company state that clinicians should use professional judgment in the interpretation of results from this test, and that results from this type of assay should not be used in predicting a patient's response to drugs for which the drug metabolizing enzyme activity of that allele, or the drug metabolic pathway, has not been clearly established.

The technology comprises:

- Genomadix Cube platform. This contains the Genomadix analyser thermal cycling instrument for polymerase chain reaction (PCR) amplification, the software user interface, and barcode scanner
- Genomadix Cube test kit. This includes buccal swabs and a cartridge containing all the reagents needed to determine *CYP2C19* genotype. The cartridges must be stored between −15°C and −80°C and used within 15 minutes of removal from the freezer.

Samples are run on the Genomadix cube system, which combines and automates DNA extraction, PCR amplification, and fluorescence-based detection of *CYP2C19* alleles. The test uses 3 buccal swab samples, which

are inserted into the reagent cartridge in the Cube. The company states that the test takes 1 hour to run for each cartridge. The test report will either display the detected diplotype or an inconclusive result.

When the test result is inconclusive, the company state that the test should be repeated with new swabs and a new cartridge. Results are stored locally on a laptop connected to the device and can be exported as a PDF. Optional external controls are available to check proper performance of the platform as per local requirements for accreditation.

2.2.2 Genedrive CYP2C19 ID Kit (Genedrive Diagnostics)

The Genedrive System is a point-of-care gene amplification device used for qualitative in vitro molecular diagnostic tests. Although not yet available, the Genedrive CYP2C19 ID Kit is under development and is expected to be available to the NHS after Q1 2023. The company state that the test will be able to detect the *2, *3, *4, *8, *17 and *35 alleles.

The test will comprise:

- Genedrive System analyser, which is a rapid thermocycler capable of PCR and isothermal based amplification techniques
- Genedrive CYP2C19 ID Kit. This will include an assay cartridge containing reagents, a sample collection swab, a transfer capillary and a collection buffer. The cartridges will be able to be stored at room temperature.

The test will use a single buccal swab to collect the sample. The company states that each cartridge will run in less than 1 hour. The result of the test will be automated and will not require user interpretation. The diplotype and metaboliser status will be displayed on the device. Results will be able to be transferred electronically to patient records by internet or through third-party middleware, or printed with an optional label printer. External controls for all targeted alleles will be available in a separate kit to check proper performance of the platform.

Laboratory-based *CYP2C19* genotype testing

Genomic testing in the NHS is delivered through a network of 7 Genomic Laboratory Hubs (GLHs). The National Genomic Test Directory outlines the genomic tests that are commissioned for the NHS in England, specifying which tests are available and the patients who are eligible to access a test. *CYP2C19* genotype testing is not currently included in the Test Directory, which is updated annually.

Clinical experts have indicated that there are several technologies already in place in diagnostic genetic laboratories that could be used to implement this testing into routine service. These include both targeted variant detection and DNA sequencing-based approaches. The approach used would likely depend on considerations such as the number of *CYP2C19* alleles being tested for, scale of testing, and required turnaround times. The availability of specific genomic testing platforms available at a local level would also impact on what approach could be used, which can differ between GLHs. Some of the available potential testing approaches are outlined below:

2.2.3 CYP2C19 gene sequencing-based approaches

Gene sequencing approaches determine the order of DNA bases in a particular segment of DNA. In NHS laboratories, this could be done through Sanger sequencing or next-generation sequencing (NGS).

Sanger sequencing is a routine genomic testing approach used in all NHS genomic laboratory hubs. Sanger sequencing sequences a single DNA fragment at a time. This approach could be used for detecting a small number of *CYP2C19* alleles in smaller sample numbers. This would involve sequencing the 3 regions of interest in the *CYP2C19* gene. However, with greater sample numbers or if more alleles are tested for, then Sanger sequencing may become expensive and lead to longer turnaround times.

NGS technologies sequence millions of short DNA sequences in parallel (that is, they are massively parallel). This offers several advantages over Sanger sequencing, such as higher sensitivity, quicker turnaround for large sample numbers and a lower limit of detection.

2.2.4 Targeted CYP2C19 gene variant detection

Targeted genotyping assays are used to amplify and detect specific variants in target genomic DNA. The methods of detection, variants detected, equipment requirements and throughput capability vary between systems. Examples include:

- PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher)
- Other PCR-based genotyping panels that use proprietary detection methods, such as the xTAG CYP2C19 Kit v3 (Luminex)
- Variant detection using mass spectrometry, such as MassARRAY (Agena Bioscience)
- Loop-mediated isothermal amplification (LAMP), such as the LAMP human CYP2C19 mutation KIT (LaCAR MDx Technologies)

3 Target conditions

3.1 Ischaemic stroke and transient ischaemic attack

A stroke occurs when the blood supply to a part of the brain is restricted or stopped. Most strokes (about 85%) are caused by a blockage in a blood vessel (artery) that supplies blood to the brain (NHS 2019). This is known as ischaemic stroke. A transient ischaemic attack (TIA) or 'mini stroke' has the same clinical presentation as a stroke except symptoms disappear within 24 hours.

The symptoms experienced depend on the part of the brain that is affected. They usually occur suddenly and without any warning. Common symptoms include loss of movement or sensation in an arm or leg, problems speaking, a drooping of one side of the face or problems with vision.

A stroke can occur at any age. The average age for stroke varies across the UK, with a median age of 77 years (interquartile range 67 to 85). A quarter of strokes occur in people of working age (NICE guidance on stroke and TIA in over 16s).

There are around 100,000 strokes every year in the UK, of which around 57,000 are first strokes (NICE CKS 2022). The incidence of first-ever TIA is around 50 per 100,000 people per year. The number of hospital admissions per year for stroke in England is approximately 126,000. Figures for 2020/2021 from the Sentinel Stroke National Audit Programme (SSNAP) show that 14% of people with stroke admitted to hospital with stroke in England, Wales and Northern Ireland died whilst on the stroke care pathway. There are approximately 1.3 million stroke survivors in the UK (NICE CKS 2022). People who have had a stroke are also at increased risk of other occlusive vascular events such as myocardial infarction (Gunnoo et al. 2016).

Stroke is the single biggest cause of disability in adults. The Stroke Association has estimated an annual cost to the NHS in England of £2.98 billion per year. In addition, annual social care costs have been estimated at £13.7 billion, with the annual cost of lost productivity at £1.3 billion. About 1 in 20 stroke survivors have to move into a care home because of the effects of their stroke (SSNAP 2020/21).

3.2 *CYP2C19* genetic variants

The *CYP2C19* gene has numerous alternative versions or variant forms (alleles) which give rise to CYP2C19 enzymes with different levels of activity. Each *CYP2C19* allele is given a star (*) number for identification. Star alleles for *CYP2C19* are catalogued by the Pharmaco-gene variation (PharmVar)

consortium. The *CYP2C19*1* allele refers to the allele with normal enzyme function (that is, the absence of any sequence variants known to affect CYP2C19 enzyme function). The US association of molecular pathology pharmacogenomics working group has made recommendations for *CYP2C19* allele selection and considers the *2, *3 and *17 alleles as tier 1 alleles that are essential for testing (Pratt et al. 2018). The clinical function of each allele is classified by the Clinical Pharmacogenetics Implementation Consortium (CPIC) as either normal function, no function, decreased function, increased function or uncertain (PharmVar, Lee et al. 2022).

People with 2 loss of function alleles (for example, a *2/*2 genotype) have no CYP2C19 enzyme activity, cannot activate clopidogrel to its active form and are classed as poor metabolisers. People with a single loss of function allele (for example, a *1/*2 genotype) are classed as intermediate metabolisers with significantly reduced enzyme activity. The *17 allele is a variant associated with increased enzyme function. People with this allele are classed as rapid metabolisers if they have a single *17 allele (for example, *1/*17 genotype), and ultrarapid metabolisers if they have a *17/*17 genotype. Carriers may have increased inhibition of platelet reactivity and higher risk of bleeding compared to non-carriers.

The frequencies of the *CYP2C19* star alleles differ significantly between different ethnic populations. The *2 allele is the most common loss of function allele, with frequencies of around 15% in people from a European family background, 18% in people from an African American or Caribbean family background and 27% to 28% in people from an Asian family background (PharmGKB). The *3 allele is present at relatively low frequencies in most populations (less than 1%), however it is more frequent in people from an Asian family background where the allele frequency is around 2% to 7% (PharmGKB). The *17 allele frequency is around 22% in people from a European family background, 21% in people from an African American or Caribbean family background and 2% to 17% in people from an Asian family background (PharmGKB).

3.3 Diagnostic and care pathway

Current practice

NICE guidance on stroke and transient ischaemic attack in over 16s recommends that all people with a suspected stroke should be admitted to a specialist acute stroke unit after initial assessment by first responders. For those identified as having ischaemic stroke (rather than haemorrhagic stroke), daily aspirin 300 mg should be offered to all within 24 hours, unless there is a severe allergy or intolerance. Aspirin should be continued until 2 weeks after

the onset of stroke symptoms or until discharge, at which time definitive long-term antithrombotic treatment is started. For TIA, secondary prevention in addition to aspirin should be offered as soon as diagnosis is confirmed.

The Royal College of Physicians (RCP) national clinical guideline for stroke (2016) suggests that clopidogrel could be considered as the initial antiplatelet agent for people who are allergic to or intolerant of aspirin. Clinical experts noted that if a person with stroke is already taking aspirin, they may start clopidogrel earlier. Experts also said that some people will not be able to tolerate any form of antiplatelet therapy. In these cases, treatment would focus on other methods of reducing risk of further stroke, such as ACE inhibitors, statins, or lifestyle modification.

For people who have had an ischaemic stroke that is not associated with atrial fibrillation, NICE TA210 recommends clopidogrel as an option to prevent further occlusive vascular events. If clopidogrel is contraindicated or not tolerated, modified-release dipyridamole in combination with aspirin, or aspirin alone, are alternative options. People receiving clopidogrel, dipyridamole and aspirin or aspirin alone after an ischaemic stroke continue treatment until they or their clinician consider it appropriate to stop.

NICE TA210 recommends modified-release dipyridamole in combination with aspirin for people who have had a TIA. At the time of guidance, clopidogrel was not licenced to treat people with TIA so no recommendation on use for this indication could be made. In 2021, some formulations of clopidogrel received an updated indication to include adult patients with moderate to high-risk TIA (ABCD2 score 4 or more) or minor ischaemic stroke (NIHSS 3 or less) within 24 hours of the event, alongside aspirin (EMA 2021). Clinical experts commented that clopidogrel is typically used after TIA in the NHS, and treatment is usually started earlier than 2 weeks after stroke.

The European Stroke Organisation (ESO) recommends the long-term use of antiplatelet therapy after ischaemic stroke or TIA to reduce the risk of recurrent stroke (Dawson et al. 2022).

The RCP national clinical guideline for stroke recommends that, for long-term vascular prevention in people with ischaemic stroke or TIA without paroxysmal or permanent atrial fibrillation:

- clopidogrel 75 mg daily should be the standard antithrombotic treatment;
- aspirin 75 mg daily with modified-release dipyridamole 200 mg twice daily should be used for those who are unable to tolerate clopidogrel;

- aspirin 75 mg daily should be used if both clopidogrel and modified-release dipyridamole are contraindicated or not tolerated;
- modified-release dipyridamole 200 mg twice daily should be used if both clopidogrel and aspirin are contraindicated or not tolerated.

RCP guidance also recommends that people with non-disabling stroke or TIA should receive treatment for secondary prevention as soon as the diagnosis is confirmed, including clopidogrel 300 mg loading dose followed by 75 mg daily.

Dual antiplatelet therapy

Clinical experts advised that dual antiplatelet therapy with clopidogrel and aspirin is often used for people with minor ischaemic stroke or high-risk TIA, although guidance varies.

The NICE clinical knowledge summary on secondary prevention following stroke and TIA states that aspirin may be used alongside clopidogrel in some circumstances (for example high risk of TIA). The ESO and British Medical Journal recommend up to 21 days of clopidogrel and aspirin dual therapy for people who have had a minor ischaemic stroke or high-risk TIA in the last 24 hours (Dawson et al. 2021, Prasad et al. 2018). The American Heart Association/American Stroke Association guideline for the secondary prevention of ischaemic stroke recommends initiating dual antiplatelet therapy (typically aspirin and clopidogrel) within the first 7 days after stroke onset for people with recent minor stroke or high-risk TIA (Kleindorfer et al. 2021). All recommendations advise to switch to antiplatelet monotherapy in the long term, as dual antiplatelet therapy is associated with an increased risk of bleeding and no benefit in long-term reduction of recurrent stroke risk (Kleindorfer et al. 2021, Prasad et al. 2018).

The NICE guidance on stroke and transient ischaemic attack in over 16s includes a research recommendation on whether modified-release dipyridamole or clopidogrel with aspirin improves outcomes compared with aspirin alone when administered early after acute ischaemic stroke. The RCP do not currently recommend the combination of aspirin and clopidogrel unless there is another indication, for example acute coronary syndrome or a recent coronary stent (RCP national clinical guideline for stroke 2016).

Clinical experts stated that dual antiplatelet therapy is not used for moderate or severe ischaemic stroke as the increased risk of bleeding and conversion to haemorrhagic stroke is considered too high.

Existing guidance on clopidogrel genotyping

In 2022, CPIC issued guidance on *CYP2C19* genotyping when considering clopidogrel for neurovascular indications, which includes acute ischaemic stroke and TIA. An alternative P2Y12 inhibitor should be considered if clinically indicated and no contraindication for people who are identified as intermediate or poor metabolisers of clopidogrel, based on genotype. Regarding dose escalation, CPIC considers that current evidence does not support a dose escalation strategy for clopidogrel based on *CYP2C19* genotype. However, if clopidogrel cannot be avoided, increasing the dose of clopidogrel from 75 mg a day to 225 mg a day could be considered for intermediate metabolisers only (this is off-label use).

No change in clopidogrel therapy is recommended for rapid or ultrarapid metabolisers, although guidance on *CYP2C19* genotyping for use of other drugs does contain recommendations for rapid or ultrarapid metabolisers (see sections 3.4 and 6.3).

The French National Network of Pharmacogenetics (RNPGx) guideline for *CYP2C19* and clopidogrel has similar recommendations to CPIC, and also recommends testing for the main *CYP2C19* deficiency alleles before clopidogrel treatment (Abdullah-Koolmees et al. 2021).

The Royal Dutch Pharmacists Association Pharmacogenetics Working Group (DPWG) recommends people with stroke avoid clopidogrel if they are *CYP2C19* poor metabolisers (DPWG guidelines 2018). It also recommends considering an alternative drug or doubling the clopidogrel dose to 150 mg a day (600 mg loading dose) for *CYP2C19* intermediate metabolisers (this is off label use). No action is required for patients who are *CYP2C19* ultra-rapid metabolisers. The Dutch Pharmacogenetics Working Group considers that genotyping before starting clopidogrel in people who have had a stroke is essential for drug efficacy.

Clinical experts suggested that aspirin with modified-release dipyridamole would be the most likely alternative treatment to clopidogrel in the NHS, although some said that ticagrelor may be used (this is off label use; see section 6.5).

3.4 Patient issues and preferences

The CYP2C19 enzyme catalyses the metabolism of many drugs, including proton-pump inhibitors, benzodiazepines, selective serotonin reuptake inhibitors and tricyclic antidepressants (Tornio & Backman 2018). Testing for *CYP2C19* variants could help inform clinical management of other conditions that may be treated with these classes of drug. So, the implications of knowing *CYP2C19* genotype may affect treatment of non-stroke conditions.

This may include treatments that a person is already taking, potentially requiring reassessment of therapy (see also section 6.3).

Errors in genetic testing could result in people being assigned an incorrect genotype. This could have long-term adverse health effects, such as side effects of alternative antiplatelet therapies.

4 Comparator

Under current practice, genetic testing for *CYP2C19* is not done before clopidogrel use after ischaemic stroke or transient ischaemic attack.

5 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack represent a cost-effective use of NHS resources?
Populations	People who have had non-cardioembolic ischaemic stroke or transient ischaemic attack for whom clopidogrel treatment is being considered. Where data permits, the following subgroups may be considered: • People of different ethnicities • People with different severity of stroke (TIA, moderate or severe ischaemic stroke) • People who would receive clopidogrel earlier than 2 weeks after onset of symptoms • Children and young people

Intervention	Genetic testing of the *CYP2C19* gene.
	This can be using:
	• A point-of-care test:
	  ○ Genomadix cube CYP2C19 system
	  ○ Genedrive system CYP2C19 test
	• Laboratory-based testing

Comparator	No genetic testing before using clopidogrel
Healthcare setting	• Specialist acute stroke units • Secondary care • Clinical laboratories

Outcomes: intermediate measures	Intermediate measures for consideration may include: • Test failure rate • Test accuracy • Number of people with variant forms of *CYP2C19* detected (and incidence of particular alleles) • Prognosis and/or risk of adverse drug events for people with *CYP2C19* gene variants (for example, occlusive vascular events or bleeding) • Time to results • Time to starting antiplatelet treatment, or to change of antiplatelet treatment • Impact of test result on decisions about care • Ease of use of test • Use of healthcare resources (such as length of stay in hospital)
Outcomes: clinical	Clinical outcomes for consideration may include: • Adverse events from drug therapy (such as bleeding or headache) • Morbidity (such as incidence of recurrent stroke or other occlusive vascular events) • Mortality
Outcomes: patient-reported	Patient-reported outcomes for consideration may include: • Heath-related quality of life
Outcomes: costs	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of stroke and other occlusive vascular events (including acute treatment and rehabilitation) • Cost of drug treatment (including adverse events such as bleeding) • Cost of genetic testing (including device costs or service costs as appropriate, quality assurance costs, costs related to informatics and data storage, and time for staff to do testing and interpret results, and discuss with people about implications of testing)
Measuring cost-effectiveness	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

6.1 Cost of laboratory testing

There are many methods for determining *CYP2C19* genotype that could be used in NHS laboratories (see sections 2.2.3 and 2.2.4). Which tests are used may depend on local practice and availability, and so the cost of testing may vary. The assessment should investigate the impact of laboratory-based test cost on cost effectiveness, for example by doing threshold analysis to determine the maximum price for a laboratory-based genetic test that could still be cost-effective.

6.2 Time to starting antiplatelet therapy

People with stroke are often transferred between services (for example specialist stroke centres, local hospitals, or primary care) depending on their specific requirements and preferences. RCP guidance recommends that hospital inpatients with stroke who have mild-to-moderate disability should be offered early supported discharge. Clopidogrel therapy may be started earlier than 2 weeks after symptom onset if people are discharged to primary or community care earlier.

Recurrent stroke within 6 months of the initial stroke onset happens in 2 to 3% of people (SSNAP 2020/21), and the risk of stroke after TIA is highest in the first 7 days (Giles & Rothwell 2007). Dual antiplatelet therapy may be most effective at reducing the risk of recurrent stroke when given soon (less than a week) after the onset of symptoms (Kleindorfer et al. 2021, Prasad et al. 2018). In this scenario, clopidogrel is normally started within 2 weeks after symptom onset (see section 3.3). The time it takes to access genetic test results may therefore affect clinical outcomes.

A clinical expert advised that antiplatelet therapy should be given immediately after stenting to avoid clots forming around the stent. However, they have to give antiplatelet drugs other than clopidogrel as they currently have no way of knowing whether clopidogrel will work. In this context, rapid access to *CYP2C19* genotyping using a point-of-care test may allow some people without loss-of-function variants to be given clopidogrel and reduce the risk of bleeding. Other clinical experts commented that stenting is not often done for ischaemic stroke or TIA alone, and that the population receiving stents after ischaemic stroke or TIA is small and heterogeneous.

Clinical experts commented that time to results from laboratory-based tests is variable, and if needed could potentially be delivered at reduced turnaround times.

If genetic test results are not immediately available, people may start clopidogrel treatment before their *CYP2C19* genotype is known. Clinical experts commented that clopidogrel would not be delayed in this situation, but changes to treatment would be considered if genotyping results subsequently indicated a person had loss-of-function alleles. The assessment may wish to consider scenario analyses on the effect of changing the time to test result on clinical outcomes and costs.

6.3 Effect of *CYP2C19* genotyping on use of drugs for conditions other than stroke or TIA

As described in section 3.4, drugs other than clopidogrel are also metabolised by the CYP2C19 enzyme. CPIC has published guidelines for the use of voriconazole, selective serotonin reuptake inhibitors, tricyclic antidepressants and proton pump inhibitors, as well as clopidogrel for cardiovascular indications, based on *CYP2C19* genotype (CYP2C19 CPIC guidelines). Knowledge of *CYP2C19* genotype may therefore impact management of conditions other than ischaemic stroke or TIA. If possible, the assessment should consider the impact of *CYP2C19* genotyping beyond the use of clopidogrel after ischaemic stroke or TIA.

6.4 Children and young people

Children (up to 12 years old) and young people (between 12 and 17 years old) are less likely than adults to have a stroke, but strokes do occur in around 400 children a year (Stroke Association). Clinical experts have stated that clopidogrel is not commonly used in children or young people, and there is little data reporting its use. The Royal College of Paediatrics and Child Health guideline for diagnosis, management and rehabilitation of stroke in childhood 2017 recommends aspirin to prevent recurrence of ischaemic stroke in children. Other antiplatelet agents such as clopidogrel should only be considered when there are other risk factors for cerebrovascular disease that justify their use, due to lack of comparative data. Clinical experts stated that the causes of stroke in children and young people are very different to those in older adults and are highly variable.

6.5 Ticagrelor

Ticagrelor is an antiplatelet therapy that is manufactured by AstraZeneca (brand name Brilique). Ticagrelor inhibits the same receptor as clopidogrel but does not require metabolism by CYP2C19. In combination with aspirin, ticagrelor is recommended to prevent atherothrombotic events in adults with acute coronary syndromes for up to a year (NICE TA236), or in adults who have had a myocardial infarction and who are high risk of a further event, for

up to 3 years (NICE TA420). A NICE appraisal of ticagrelor to prevent stroke after previous ischaemic stroke or high-risk TIA was started in 2020, but was suspended in 2021 after the company advised that they were no longer pursuing a Marketing Authorisation Application from the Medicines and Healthcare products Regulatory Agency (MHRA) for this indication at this time (NICE GID-TA10663). NICE Clinical Knowledge Summaries state that ticagrelor with aspirin may be initiated in secondary care for some people (for example people at high risk of TIA, or with intracranial stenosis) for 30 days, followed by antiplatelet monotherapy. Clinical experts considered that ticagrelor could be an option for antiplatelet therapy for people with ischaemic stroke or TIA only if other options were unsuitable and if the risk of bleeding was manageable.

6.6 Prevalence of *CYP2C19* loss-of-function alleles varies by family background

Prevalence of *CYP2C19* loss-of-function alleles is higher in some ethnic groups (see section 7). These groups may particularly benefit from genetic testing, as under current practice, more people would be at higher risk of further occlusive vascular events because of clopidogrel resistance. The scope (Table 1) specifies that people of different ethnicities should be a subgroup, if data permits. However, even if no data is found, exploratory analysis should be done to assess the impact of higher prevalence of *CYP2C19* loss-of-function alleles on clinical and cost effectiveness.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Race is a protected characteristic under the Equality Act (2010). Prevalence of *CYP2C19* loss-of-function alleles vary by family background. People with an Asian family background have a prevalence of these alleles of around 60%, compared to around 30% for people with a European family background (Narasimhalu et al. 2020; Pilling et al. 2020; Pan et al. 2017). Therefore, lack of efficacy from clopidogrel in people with loss-of-function alleles could disproportionately affect ethnic groups with a higher prevalence.

Additionally, some alleles are more common in some ethnic groups than others. For example, *CYP2C19**5 is about 50 times as prevalent in people with East Asian family background compared with a European family background (PharmGKB). Tests that do not detect all relevant alleles could miss people with specific loss-of-function variants, which could

disproportionately affect different ethnic groups based on the prevalence of these alleles.

Strokes happen more often in people who are from Black African, Black Caribbean, or South Asian family backgrounds (Stroke Association, King's Fund 2021). Improving antiplatelet therapy would be particularly beneficial in these groups.

People who have had a stroke may have impaired cognitive function and physical disability that limits activity. Disability is a protected characteristic under the Equality Act (2010).

Acceptability and consent for genetic testing may differ according to religious or philosophical beliefs. These are protected characteristics under the Equality Act 2010.

8 Potential implementation issues

As described in section 3, the ischaemic stroke population is very large. If clopidogrel genotyping using the NHS Genomic Medicine Service was recommended, additional testing capacity may be needed to meet the demand.

Currently, genetic testing is not part of the stroke care pathway. Implementation of genetic testing would require training of all people involved in acute stroke care, and education about the clinical need and benefits of testing.

The nature and extent of information provided to people prior to the testing being done, and level of consent required prior to testing, would also need to be clarified if testing was widely adopted. As noted in the equalities section, the acceptability and consent for genetic testing may differ according to religious or philosophical beliefs.

Knowledge of *CYP2C19* genotype may affect prescribing decisions for many drugs other than clopidogrel (see section 3.4). Integration of genetic test results into people's medical records is needed to ensure that the information remains accessible throughout their lifetime. Clinical experts commented that approaches to clearly coding this information into health records need further development. This may be used to justify why clopidogrel is not being used and also to inform use of other treatments that *CYP2C19* genotype could affect. It is important that people are informed of the result of genetic testing and whether this has affected their prescription. Clinical experts commented that pathways to allow pharmacogenetic information obtained for one

condition to be used to inform treatment of another are not yet in place, and that this is a wider issue for pharmacogenomic testing.

9 Authors

Jacob Grant
Topic Lead

Simon Webster
Technical Analyst

Thomas Walker
Technical Adviser

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Appendix A Glossary of terms

The **ABCD2 score** is a tool to estimate the risk of stroke after a suspected TIA.

ACE (angiotensin-converting enzyme) inhibitors are medications that help relax blood vessels to lower blood pressure.

An **allele** is a variant of a DNA sequence found at a particular place in the genome. People have 2 allele versions of each gene, one from each parent.

Atherothrombotic events are sudden, unpredictable disruptions of atherosclerotic plaques.

Atherosclerosis is the build-up of plaques formed of cholesterol, fat, blood cells and other substances in the arteries.

Buccal refers to the cheek, so a buccal swab is used to take a sample of cells from the inside of the cheek.

CYP2C19 is a liver enzyme that is involved in the metabolism of a variety of drugs. CYP2C19 is encoded by the ***CYP2C19* gene**. The versions of the *CYP2C19* gene that a person has determines the function of the enzyme that is expressed.

The **National Institute of Health Stroke Scale/Score (NIHSS)** is used to measure how severe a stroke is, and incorporates 11 components.

Occlusive vascular events refer to conditions involving the narrowing or blocking of an artery. These include ischaemic stroke, TIA and myocardial infarction.

P2Y12 is a receptor involved in the aggregation of platelets (clotting).

Statins are medications that can help lower the level of low-density lipoprotein cholesterol in the blood.

Appendix B Abbreviations

ABCD2	Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis
BMJ	British Medical Journal
CKS	Clinical knowledge summaries
CPIC	Clinical Pharmacogenetics Implementation Consortium
EMA	European Medicines Agency
ESO	European Stroke Organisation
GLH	Genomic Laboratory Hub
LAMP	Loop-mediated isothermal amplification
MHRA	Medicines and Healthcare products Regulatory Agency
NGS	Next generation sequencing
NIHSS	National Institute of Health Stroke Scale/Score
PCR	Polymerase chain reaction
RCP	Royal College of Physicians
RNPGX	French National Network of Pharmacogenetics
SNP	Single nucleotide polymorphism
SSNAP	Sentinel Stroke National Audit Programme
TIA	Transient ischaemic attack

Appendix C References

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