NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance

CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack

The National Institute for Health and Care Excellence (NICE) is producing guidance on using clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the external assessment report and the external assessment report erratum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

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. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Issue date: March 2024

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on clopidogrel genotype testing. The recommendations in section 1 may change after consultation.

A further committee discussion will be held if significant issues are raised during consultation. The committee will then prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England. The evaluation will then proceed to resolution.

For further details, see NICE health technology evaluations: the manual.

Key dates:

Closing date for comments: 26 April 2024

1 Recommendations

1.1 Use CYP2C19 genotype testing to assess if clopidogrel is a suitable antiplatelet for people who have just had an ischaemic stroke or transient ischaemic attack (TIA). CYP2C19 genotype testing is only recommended if:

- quality assurance processes are in place for point-of-care tests
- shared decision making for doing the test is established (see NICE guidance on shared decision making)

When interpreting test results, healthcare professionals should take into account that the prevalence of different CYP2C19 genotypes may vary between ethnic groups.

Laboratory-based testing

1.2 Use laboratory-based testing for CYP2C19 genotype testing.

Point-of-care testing

1.3 Use the Genedrive CYP2C19 ID Kit point-of-care test for CYP2C19 genotype testing when laboratory-based testing is not available.

1.4 Use the Genomadix Cube point-of-care test when laboratory-based testing and the Genedrive CYP2C19 ID Kit point-of-care test are not available.

What this means in practice

This guidance does not replace existing guidance on antiplatelet therapy when genotype testing is not available, or when results from testing have not been received. Starting antiplatelet treatment should not be delayed while waiting for test results.

This guidance is not intended to affect treatment with clopidogrel that was started in the NHS before this guidance was published. People already having clopidogrel

should continue until they and their NHS clinician consider it appropriate to stop. The guidance recommends testing only for people just after they have had a stroke or TIA. This is because the risk of another event is higher at this time and therefore so is the potential benefit of testing. But, as risk of recurrent stroke or TIA reduces over time, so does the benefit of testing. For this reason, retrospective testing for people already taking clopidogrel was outside of the scope of this assessment.

Implementing laboratory-based CYP2C19 genotype testing for everyone that has a stroke or TIA would result in a large population being tested which may require testing capacity to be scaled up over time. When implementing testing, commissioners may wish to consider:

- a phased rollout with testing initially offered to people with a higher risk of stroke recurrence who could benefit most from it, such as people who have had a non-minor stroke
- point-of-care testing as an alternative if laboratory-based testing is not feasible at this scale, or while capacity for laboratory-based testing is increased.

For more information about putting these recommendations into practice see section 4.

Why the committee made these recommendations

Clopidogrel is an antiplatelet drug used after ischaemic stroke or TIA (sometimes called a ‘mini stroke’) to reduce the risk of blood clots that can cause further strokes. Clopidogrel is metabolised into its active form by an enzyme encoded by a gene called CYP2C19. In some people CYP2C19 has variations that reduce the enzyme's function (known as ‘loss-of-function’ variants or alleles). This means clopidogrel does not work as well in these people. Testing for these alleles is known as CYP2C19 genotype testing. It aims to identify people with CYP2C19 loss-of-function alleles so they can be offered alternative antiplatelet drugs to lower their risk of blood clots.

Testing can be done in a laboratory or at the point of care (for example, on a stroke ward).

There is good clinical evidence that people with loss-of-function CYP2C19 alleles who have clopidogrel are more likely to have further strokes compared with people without loss-of-function CYP2C19 alleles. Clinical experts agreed that it would be beneficial to treat people with loss-of-function CYP2C19 alleles with alternative antiplatelet treatment, but the evidence was less clear on the size of this benefit. The economic evidence shows that CYP2C19 genotype testing is cost effective compared with not testing, regardless of which alternative antiplatelet therapy people have. So CYP2C19 genotype testing is recommended.

The long-term health benefits of laboratory-based and point-of-care CYP2C19 genotype testing are very similar. But, some less-common loss-of-function CYP2C19 alleles occur at a higher rate in certain ethnic groups. This means that tests that only identify the most common alleles may disproportionately fail to identify people with loss-of-function alleles in these groups. Laboratory-based testing could identify a wider range of alleles than point-of-care tests. It can also be changed more easily to test for other pharmacogenomic markers if needed. Centralised laboratory testing would also provide more consistency across the NHS. So, laboratory tests should be used if possible.

Evidence from studies provided by the company, suggests that the Genedrive CYP2C19 ID Kit works well. It can detect more CYP2C19 alleles than the Genomadix Cube point-of-care test. It also:

- does not need a freezer to store reagents
- can connect with electronic patient records and
- is cheaper per test than laboratory tests and the Genomadix Cube.

There are likely to be considerable barriers to implementing laboratory-based testing for everyone who has had an ischaemic stroke or TIA. If laboratory-based testing is not available, or it will take a long time to develop capacity to provide it, then point-of-

care tests could be used. So, the Genedrive CYP2C19 ID Kit should be used when laboratory-based testing is not available.

There is good evidence that the Genomadix Cube point-of-care test can accurately detect 2 of the most common loss-of-function CYP2C19 alleles. But it does not detect other less-common alleles, so it should only be used when laboratory-based testing and the Genedrive CYP2C19 ID Kit are not available.

2 The diagnostic tests

Clinical need and practice

Clopidogrel and secondary prevention

2.1 People who have had a stroke are at increased risk of further occlusive vascular events, such as recurrent stroke or myocardial infarction. For those with non-cardioembolic ischaemic stroke or transient ischaemic attack (TIA), the antiplatelet drug clopidogrel can be used to reduce this risk.

2.2 People with non-minor ischaemic stroke are normally offered clopidogrel after taking aspirin for 2 weeks. People with TIA or minor stroke may start clopidogrel immediately. Detailed guidance on current practice can be found in NICE's guidance on stroke and transient ischaemic attack in over 16s, NICE's guidance on clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events, and the Royal College of Physicians national clinical guideline for stroke.

CYP2C19 genotype and clopidogrel

2.3 Clopidogrel is a prodrug. The CYP2C19 gene encodes the CYP2C19 enzyme, which is needed to metabolise clopidogrel to its active form.

2.4 The CYP2C19 gene has many alternative versions (alleles) that produce variations of the CYP2C19 enzyme with different levels of activity. Each allele is given a star (*) number for identification. The function of each

allele can be described as 'normal', 'completely absent', 'decreased' or 'increased', or the function may be uncertain.

2.5 Clopidogrel is less effective in people with alleles that produce CYP2C19 enzymes with completely absent or decreased function.

2.6 People with 2 loss-of-function alleles have no CYP2C19 enzyme activity. They cannot activate clopidogrel to its active form and are classed as 'poor metabolisers'. People with only 1 loss-of-function allele have reduced enzyme activity and are classed as 'intermediate metabolisers'.

2.7 Loss-of-function alleles are more common in certain ethnic groups, such as people with an Asian family background. The Clinical Pharmacogenetics Implementation Consortium's guideline for clopidogrel and CYP2C19 contains further information about the distribution of loss-of-function alleles by ethnic group.

CYP2C19 genotype testing

2.8 CYP2C19 genotype testing can identify which CYP2C19 alleles a person has. This provides information on how well a person can metabolise clopidogrel and so can be used to guide antiplatelet treatment.

The interventions

2.9 Genetic testing of the CYP2C19 gene, either by laboratory-based or point-of-care test.

Laboratory-based CYP2C19 genotype testing

2.10 Clinical experts indicated that there are several methods that diagnostic genetic laboratories could use to implement CYP2C19 genotype testing. These include:

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

- Targeted genotyping assays, which 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.

  Laboratory testing usually requires a blood sample.

Genedrive CYP2C19 ID Kit

2.11 The Genedrive System is a point-of-care gene amplification device used for qualitative in vitro molecular diagnostic tests. The company state that the test can detect the *2, *3, *4, *8, *17 and *35 alleles. The technology consists of:

- Genedrive System analyser, which is a rapid thermocycler capable of polymerase chain reaction (PCR) and isothermal-based amplification techniques.
- Genedrive CYP2C19 ID Kit, which includes an assay cartridge containing reagents, a sample collection cheek swab, a transfer capillary and a collection buffer. The cartridges can be stored at room temperature.

2.12 The test uses a single cheek swab to collect the sample. The company states that each cartridge takes less than 1 hour to run. The result of the test is automated. The person's diplotype (their specific pair of CYP2C19 alleles) and metaboliser status are displayed on the device. The company states that results can be transferred electronically to patient records by internet or third-party middleware, or printed with an optional label printer. External controls for all targeted alleles are available in a separate kit to check proper performance of the platform.

Genomadix Cube CYP2C19 system

2.13 The Genomadix Cube CYP2C19 system (Genomadix) is a point-of-care DNA test used to detect the *2, *3 and *17 alleles of the CYP2C19 gene. The technology consists of:

- Genomadix Cube platform, which includes the Genomadix analyser thermal cycling instrument for PCR amplification, the user-interface software and a barcode scanner.
- Genomadix Cube test kit, which includes cheek 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.

2.14 Samples are run on the Genomadix Cube CYP2C19 system, which combines and automates DNA extraction, PCR amplification and fluorescence-based detection of CYP2C19 alleles. The test uses 3 cheek-swab samples, which are inserted into the reagent cartridge. The company states that the test takes 1 hour to run for each cartridge.

2.15 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.

The comparator

2.16 No genotype testing before using clopidogrel.

3 Committee discussion

The diagnostics advisory committee considered evidence on CYP2C19 genotype testing after ischaemic stroke or transient ischaemic attack (TIA) from several sources, including an external assessment report and an overview of that report.

After consultation, the external assessment group (EAG) provided further analyses in 2 addenda and an updated model. Full details are in the project documents for this guidance.

Consent for CYP2C19 genotype testing

3.1 Consent is an important consideration if introducing testing. A patient expert highlighted that people who have had a stroke often have severe cognitive impairment, may have difficulty with their language or speech (aphasia) or may be unconscious. This raises issues with getting consent for testing. They also said that some people or communities may be less likely to give consent for genetic tests. Acceptability and consent for genetic testing may differ according to religious or philosophical beliefs. People may also have concerns about data security and privacy. It is important to consider how the genetic data will be stored, protected, shared, and if necessary deleted. More detail can be found in the Royal College of Physicians' guidance on consent and confidentiality in genomic medicine.

3.2 Clinical experts said that a person's ability to consent is assessed when they are admitted to an acute stroke ward for treatment such as thrombolysis. They explained that healthcare professionals on these wards have experience of assessing capacity to consent. When a person cannot give consent, mechanisms are in place to ask next of kin to give consent on their behalf. Testing could be delayed until a person's capacity to consent returns, particularly if clopidogrel monotherapy is not going to be started immediately.

3.3 Clinical experts highlighted that CYP2C19 loss-of-function variants are common, and their presence would only impact on decisions about which drugs should be used. So, they do not have health implications for the person outside of the context of drugs like clopidogrel. But the committee acknowledged that the CYP2C19 genotype can be relevant for drugs other than clopidogrel, such as some antidepressants. Experts also

commented that consent requirements are similar to other medical tests. The Royal College of Physicians' and British Pharmacological Society's report on personalised prescribing includes detail on consent and ethics for pharmacogenomic testing. It comments that genetic testing in this setting is equivalent to doing renal or liver function tests to guide drug-prescribing decisions. It adds that this analogy could help patient understanding. A committee member also highlighted the Royal College of Physicians' guidance on consent and confidentiality in genomic medicine.

Testing locations

3.4 The committee agreed that it should be possible to gather samples for genotype testing at a location that is convenient for the person having the test. This would be particularly relevant if CYP2C19 genotype testing is delayed until after discharge from the acute stroke ward, or when the first test has failed and a second sample is needed for a repeat test. A patient expert noted that people who have had a stroke or TIA are not allowed to drive for at least a month, so may find it difficult to reach centralised testing locations. This could affect uptake of genotype testing. Clinical experts said that the blood sample or cheek swab could be collected at local pharmacies, GP surgeries or even in people's homes. But the committee noted that home testing may not be appropriate if the sample must be added within 24 hours, to reagents that are stored in a freezer.

People currently taking clopidogrel

3.5 The committee acknowledged that there are many people who have had an ischaemic stroke or TIA who are already taking clopidogrel but whose CYP2C19 genotype is unknown. These people may be at increased risk of recurrent stroke if they have loss-of-function alleles. A clinical expert commented that if a person has been taking clopidogrel for a long time without any further events, it is less likely that they have loss-of-function alleles. Clinical experts agreed that it is well documented that risk of

recurrent stroke or TIA is highest in the first 12 weeks after the initial event and then decreases. This aligns with evidence identified by the external assessment group (EAG) for its model, which shows that risk is highest in the first 90 days after stroke or TIA, and then decreases. The committee noted that retrospective testing was outside of the scope of the assessment. But, clinical experts suggested that CYP2C19 genotype testing may be expanded to those who began clopidogrel therapy before this guidance was issued, once testing is more widely available. But, the committee noted that establishing testing for populations who had just had a stroke or TIA would be a considerable challenge (see section 3.19) so the extent of any such capacity is uncertain.

Clinical effectiveness

Clinical benefits of CYP2C19 genotype testing

3.6 The committee said there was strong evidence that people with loss-of-function CYP2C19 alleles had worse outcomes when taking clopidogrel than people without loss-of-function alleles. But the evidence was less clear on the benefits of treatment with other antiplatelets. The committee recalled that clinical experts had said during scoping that dipyridamole plus aspirin was the most likely alternative antiplatelet that would be used in the NHS. But no data was found on the impact on people with loss-of-function alleles if treated with clopidogrel compared with dipyridamole plus aspirin.

3.7 A clinical expert noted that the latest National Clinical Guideline for Stroke recommends ticagrelor as an alternative antiplatelet for people who have had a TIA or minor stroke, but not a major stroke. Ticagrelor does not have a marketing authorisation for TIA or stroke in the UK. The committee recalled that the EAG reported evidence that, compared with clopidogrel, ticagrelor decreased the risk of secondary vascular events in people with loss-of-function CYP2C19 alleles. An alternative network meta-analysis done by the EAG for the second committee meeting, which included

further studies assessing ticagrelor (such as the THALES study), showed a higher risk of major bleed for ticagrelor compared with clopidogrel.

Less-common loss-of-function alleles

3.8 The committee considered that tests that only detect the most common loss-of-function alleles may be more likely to introduce inequalities. This is because less-common loss-of-function alleles are more prevalent in certain ethnic groups (see section 2.7). The EAG estimated that the combined prevalence of the *4, *8 and *35 alleles in the UK stroke population would be around 0.6%. But it noted that the *35 allele has a prevalence of up to 3% in people with sub-Saharan African family background, and that the *4 allele is more common in the Ashkenazi Jewish population. So, tests that detect a smaller range of alleles would likely disproportionately fail to identify people with loss-of-function CYP2C19 alleles in certain ethnic groups. Some clinical experts suggested that commissioners could consider the demographics in their local area when deciding how to do CYP2C19 genotype testing. Other committee members felt that a wide range of alleles should be tested for to minimise potential inequalities. The committee noted that the significance of some CYP2C19 variants, particularly if they are very rare, may be uncertain. Experts highlighted that there is information that could be used to guide decisions on the alleles tested for, such as the Association of Molecular Pathology Pharmacogenetics Working Group's recommendations on minimum and optional sets of alleles, or the Clinical Pharmacogenetics Implementation Consortium's guideline for clopidogrel and CYP2C19. The Association for Molecular Pathology's minimum set of alleles for testing includes the *2 and *3 loss-of-function alleles, with further alleles specified as optional for inclusion in an extended panel. In a survey of genomic laboratories done by the EAG, when asked which alleles would be tested for in a request for a CYP2C19 test, 2* and 3* were the alleles with the highest response. These are also the only loss-of-function alleles tested for when CYP2C19 genotype testing is done in

Scotland (see section 3.19). A clinical expert commented that laboratory-based testing is adaptable and can change which alleles are tested for over time, whereas point-of-care tests can only detect certain alleles. Laboratory-based tests can test for a broader range of loss-of-function alleles than point-of-care tests, although this depends on the specific technologies used (see sections 2.10 to 2.15).

Stroke in children and young people

3.9 The committee agreed that CYP2C19 genotype testing would be appropriate for children and young people after an ischaemic stroke, if treatment with clopidogrel was being considered. Clinical experts noted that stroke in children and young people is very rare and normally has a different cause to stroke in adults. They also acknowledged that clopidogrel is not indicated for use in children. Clopidogrel is not normally prescribed except where there are other risk factors for cerebrovascular disease, such as cardiovascular conditions. The EAG did not identify any evidence for children or young people in their review of clinical effectiveness. But, clinical experts said that there is no biological reason why the interaction between drug and genotype would be different in children and young people compared with adults. The Clinical Pharmacogenetics Implementation Consortium states that it is reasonable to extrapolate its recommendations to children and young people if needed (the guidance was also based on data from studies in adults). Experts also said that the benefits from successfully preventing further clotting events by prescribing appropriate antiplatelet therapy would likely be larger for children and young people because of the longer expected remaining lifetime.

People with a recurrent stroke or TIA

3.10 For some people who have a stroke or TIA it will not be their first event (that is, it is a recurrent stroke or TIA) and they will already be taking clopidogrel. The 2023 update to the National Clinical Guideline for Stroke

for the UK and Ireland recommends that if a person has a recurrent cardiovascular event while on clopidogrel, then clopidogrel resistance may be considered. The committee noted that this group was within the scope of the recommendations for using testing, provided continued treatment with clopidogrel is being considered. Clinical experts commented that further investigations are likely to be done for people who have a stroke or TIA while on antiplatelet therapy, for example to check for atrial fibrillation. An alternative antiplatelet treatment is also likely to be considered. Clinical experts said that there is variation in practice in terms of treatment decisions for people who have a recurrent stroke while taking clopidogrel. Treatment may include short-term (3 to 6 weeks) dual antiplatelet therapy (for example, aspirin with clopidogrel) before continuing on a single or dual antiplatelet treatment in the long-term. Or, people may be switched to long-term aspirin or ticagrelor. A clinical expert said that without CYP2C19 genotype testing, people may be returned to long-term clopidogrel monotherapy. A clinical expert commented that, in centres where CYP2C19 genotype testing is done (see section 3.19), people with a loss-of-function allele will be switched to an alternative treatment such as aspirin with dipyridamole. A stakeholder highlighted that non-adherence with prescribed antiplatelet medication may be a cause of apparent clopidogrel resistance. Studies have reported high levels of non-adherence with antiplatelet treatment. But, a patient expert commented that in their experience people prescribed clopidogrel tend to take it. People having a recurrent stroke or TIA while taking clopidogrel are potentially more likely to have a loss-of-function allele, particularly if other causes such as non-adherence with prescribed treatment are ruled out.

Cost effectiveness

Cost of testing

3.11 Clinical experts felt that the full cost of laboratory-based testing was likely to be lower than the cost used in the EAG's model (£139 per test). A

scenario run by the EAG that assumed tests would be done in batches, estimated a cost per test of £44. An expert commented that laboratory-based CYP2C19 genotype testing in their region was about £20 to £40 per test (when testing for 3 alleles). The EAG explained that the responses to its survey of genomic laboratory hubs did not express a clear preference for the method of CYP2C19 genotype testing, and there was a lack of agreement on the staff time needed. So, the true cost of laboratory-based testing is uncertain. The cost used for laboratory-based testing in the model was for the Agena Bioscience MassARRAY, with an assumed 1-year lifespan. This was amended to 5 years in an updated base case, in response to consultation comments. The EAG's estimated cost per laboratory test included the cost of the iPlex testing platform, which experts indicated would also be used for tests other than CYP2C19 genotype testing. Some committee members said that the cost of laboratory testing could come down over time because of economies of scale or new technologies. But, the committee noted that costs for laboratory testing may have been underestimated if higher implementation costs were incurred but not captured in the EAG's estimates (see section 3.19). The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920.

3.12 A clinical expert suggested that the costs used for the point-of-care tests may have been underestimated. This is because it is likely that multiple machines would be needed in each centre to handle the volume of testing or as backup in case of failure. The EAG clarified that its cost estimates were based on an average cost per test, which could account for multiple devices. A committee member highlighted that introducing point-of-care tests to stroke services would add new processes such as taking cheek swabs and running tests, which are not currently part of practice. The committee concluded that there is considerable uncertainty about the cost

per test. But it acknowledged that when compared with no testing, costs would have to be much higher (around £1,800 higher for the Genomadix Cube and £1,900 for Genedrive) than those used in the EAG's model, for testing not to be cost effective.

Alternative treatments to clopidogrel and starting antiplatelet treatment

3.13 Several stakeholders questioned how the care pathway had been modelled, stating that it may not reflect current UK practice. The EAG explained that it had provided scenario analyses that varied the modelled care pathway. These included which alternative antiplatelet is used instead of clopidogrel and when antiplatelet treatment is started. The tests were still cost effective when the choice of antiplatelet and timing of treatment were varied.

Longer-term risk of recurrent stroke or TIA

3.14 Testing done for people with minor stroke or TIA generated less net monetary benefit (NMB) than testing done for people with non-minor stroke in the EAG's model. The EAG explained this was because people with non-minor stroke had a higher rate of recurrent stroke in the long term, and so experience greater benefit from appropriate treatment. Experts noted that while recurrence rates were similar in the first 90 days, after that rates in the minor stroke and TIA population were much lower. The EAG explained that the parameter values were from a recent retrospective cohort study using the Framingham Heart Study data. Experts considered that the long-term recurrence rates for non-minor stroke appeared to be in line with their experience, but that those for minor stroke and TIA were too low. Following the second committee meeting, clinical experts suggested alternative evidence sources (4 studies) that they considered better reflected the long-term recurrent stroke rates after a minor stroke or TIA. The EAG did further analyses in the minor stroke and TIA population using these higher rates of recurrent stroke, presented in an addendum to the main report. This increased the

number of incremental quality-adjusted life years (QALYs) for the testing strategies (compared with no testing). This resulted in a higher NMB (ranging from £753 to £1,131) compared with the base case analysis. But, the NMB remained lower than for the non-minor stroke population.

Differences between point-of-care tests

3.15 The committee agreed that the 2 point-of-care tests considered in the assessment are different. So it was not appropriate to use data for the Genomadix Cube to model performance of the Genedrive CYP2C19 ID Kit. The committee recalled that several studies were identified for the Genomadix Cube test, but at the first committee meeting no data on accuracy or failure rate was available for the Genedrive test. By the second committee meeting, the Genedrive test had received its UKCA mark and the company provided data on test performance. The committee acknowledged that this showed that the test performed well. But it noted that further data on performance and failure rates would be beneficial. The company commented that further evidence is being generated. The committee welcomed this and encouraged centres already using this test to take part in data collection (see section 3.21). The committee also noted that several features of the Genedrive test could offer advantages over the Genomadix Cube. For example, its reagents do not need to be stored in a freezer, it can detect several additional alleles including those that occur in greater frequency in some ethnic groups (see section 3.8) and it can interact with patient records (see sections 2.11 to 2.14). The committee also noted that the estimated cost per test for Genedrive is less than for Genomadix. So the committee concluded that Genedrive was its preferred point-of-care test.

Laboratory-based tests compared with point-of-care tests

3.16 The committee stated a preference for laboratory-based tests over point-of-care tests. It noted that there was very little difference in the QALYs generated in the EAG's model by the different methods of testing. The

committee had previously concluded that tests that detected fewer loss-of-function alleles would likely disproportionately affect certain ethnic groups (see section 3.8). While Genedrive detects more alleles than Genomadix, laboratory-based testing has the potential to detect an even broader range. Also, if needed, laboratory testing can be adapted more easily to assess other alleles in the future. Several stakeholders and experts also commented that centralised testing would reduce variability in testing offered across the NHS. Experts raised concerns that if left to local centres to implement testing with point-of-care tests, this would likely lead to considerable variation and could worsen health inequalities. Some committee members stated that existing infrastructure should be preferentially used over investing in new single-purpose technologies. Experts also highlighted that, in the future, pharmacogenomic testing may be reactive when clopidogrel is needed, but pre-emptive pharmacogenomic tests for other treatments could be done at the same time. This would require a panel of tests that would be more easily done in a laboratory. There was also relatively little evidence for Genedrive (see section 3.15). So, despite Genedrive having the highest net benefit of the 3 tests assessed in modelling, the committee concluded that laboratory-based testing was its preferred method. But the committee also acknowledged that there are barriers to implementing laboratory-based testing (see section 3.19). If laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used.

CYP2C19 genotype testing is likely to be cost effective

3.17 The committee agreed that CYP2C19 genotype testing was likely to be cost effective. It recalled that in the EAG's updated base-case analysis, provided for the second committee meeting, testing dominated no testing in probabilistic analysis (it cost less and produced more QALYs). Testing had positive net monetary benefit for all scenario analyses for the non-minor stroke population. This was including all alternative antiplatelet

agents modelled (dipyridamole plus aspirin, ticagrelor plus aspirin or aspirin alone), based on potential variation in UK practice. Net monetary benefit was lower for the minor stroke and TIA population, and not positive in all scenario analyses. But the committee recalled that NMB estimates for this population were increased (although remained lower than for non-minor stroke) in the EAG's additional analysis that used higher long-term recurrent stroke rates (see section 3.14).

3.18 The committee also considered that CYP2C19 genotype testing was likely to be cost effective for children or young people. The committee recognised that there was no data for children or young people, and that clopidogrel is rarely used in this population. But, clinical experts advised that, if clopidogrel was being considered, information on CYP2C19 genotype would still be useful (see section 3.9). The committee noted that CYP2C19 genotype testing was more cost effective in the EAG's scenario analysis, which used a younger cohort of adults (average age 40) than in the base case (average age 71). Clinical experts suggested that this would be more pronounced in children and young people because of their longer expected remaining lifetime.

Implementation challenges

3.19 Several stakeholders highlighted that there would be considerable challenges to implementing a new laboratory-based test for all people who have a stroke or TIA. This included the need to expand testing capacity. The committee noted that CYP2C19 genotype testing was being done by NHS Tayside in Scotland. An expert commented that this was now being considered for roll out nationally in Scotland. But they also highlighted that rolling out testing over a much larger number of people would have considerable additional challenges. Experts further highlighted a shortage of clinical scientists, which would impact on the possibility of increasing laboratory testing capacity. The committee acknowledged that implementing testing for everyone who has a stroke or TIA could be done

in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The 2023 update to the National Clinical Guideline for Stroke for the UK and Ireland recommends considering testing for clopidogrel resistance only for a subset of people who have had a stroke or TIA (a recurrent TIA or stroke while taking clopidogrel; see section 3.10).

The committee recalled that, compared to no testing, CYP2C19 testing after a non-minor stroke generated more NMB than testing after a minor stroke or TIA. This was the case even when higher recurrent stroke rates for the minor stroke and TIA population were considered (see section 3.14). Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population.

The committee also recalled that it considered that point-of-care tests could be recommended for use if laboratory-based testing is not available (see section 3.16). It noted that point-of-care tests may have less potential to detect a wider array of loss-of-function alleles, although this will depend on how many alleles laboratory-based testing includes; for example, if it goes beyond *2 and *3 alleles (see section 3.8). This could disproportionately affect certain ethnic groups. But, if the alternative is no testing, all groups will benefit from some form of testing; the loss-of-function allele that is most common across all groups is the *2 allele, which is included in both point of care tests assessed. The committee considered the implementation challenges and delays associated with laboratory-based testing. It agreed that point-of-care testing should be

considered as an alternative if laboratory-based testing is not feasible at this scale, or while capacity for laboratory-based testing is increased.

Impact on antiplatelet prescribing

3.20 Stakeholders highlighted concern that waiting for test results may mean that starting antiplatelet treatment is delayed inappropriately. The EAG's model included starting initial clopidogrel treatment and changing to an alternative antiplatelet treatment later if genotype testing indicated a loss-of-function allele was present. The committee agreed that this was appropriate, and that starting antiplatelet treatment should not be delayed while waiting for test results. Stakeholders also raised concern that if testing was recommended but not available, alternatives to clopidogrel may be used more often, including ticagrelor, which is more expensive. The committee noted that many publications already highlight the prevalence of CYP2C19 loss-of-function alleles, and that this is higher in some groups. For example, a recently published study reported that 57% of a cohort of people in the UK from Bangladeshi and Pakistani backgrounds had at least 1 loss-of-function allele (Magavern et al. 2023). Recommendations to use CYP2C19 genotype testing to inform choices about antiplatelet treatment already exist, for example from the Clinical Pharmacogenetics Implementation Consortium. Testing that is already being used in the NHS in Tayside (see section 3.19) has also been publicised. So, the incidence of loss-of-function alleles and their impact would already be widely known. The committee noted that this guidance does not replace any existing guidance on using antiplatelet therapy if genotype testing is not available. Experts also strongly emphasised the importance of shared decision making with people when deciding which treatment to use, and the important role stroke pharmacists can play here.

Research considerations

3.21 The committee encouraged centres using the Genedrive CYP2C19 ID Kit test to take part in data collection to further determine the accuracy and failure rate.

4 Implementation

The committee acknowledged that implementing laboratory-based testing for everyone who has a stroke or TIA could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity is established. Testing could be initially started in groups of people who could benefit most from it, because of higher risk of stroke recurrence, such as people with non-minor stroke. Alternatively, point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or while capacity for laboratory-based testing is increased. See section 3.19 for further discussion of these issues.

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

5 Review

NICE will regularly monitor its published technology guidance to check for any new evidence or information that could affect the recommendations. Guidance will not have a fixed review date.

Brian Shine

Chair, diagnostics advisory committee

March 2024

6 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Daniel Burrage

Consultant in clinical pharmacology, St George's University Hospitals NHS Foundation Trust

Mark Cadman

Specialist lay committee member

Alexander Doney

Senior clinical lecturer and honorary consultant physician, University of Dundee

Salim Elyas

Consultant stroke physician, University of Exeter and Royal Devon University Healthcare NHS Foundation Trust

Albert Ferro

Professor of cardiovascular clinical pharmacology, King's College London

Dheeraj Kalladka

Consultant neurologist and stroke physician, Imperial College London

Dagan Lonsdale

Senior lecturer in clinical pharmacology and honorary consultant intensivist, St George's, University of London

Paresh Parmar

Lead pharmacist for stroke and older people, Northwick Park Hospital, London North West University Healthcare NHS Trust

Michelle Wood

Principal clinical scientist, All Wales Medical Genomics Service, University Hospital of Wales

NICE project team

Each diagnostics evaluation is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Simon Webster and Jacob Grant

Topic leads

Thomas Walker

Technical adviser

Harriet Wilson and Donna Barnes

Project managers

ISBN: