NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Draft guidance

Clopidogrel genotype testing 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: May 2023

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.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

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

Key dates:

Closing date for comments: 9 June 2023

Second diagnostics advisory committee meeting: 27 July 2023

1 Recommendations

1.1 Offer laboratory-based clopidogrel genotype testing, or the Genomadix Cube point-of-care test if laboratory testing is not possible, to people who have had an ischaemic stroke or transient ischaemic attack if treatment with clopidogrel is being considered.

1.2 Healthcare professionals should take into account that the prevalence of different CYP2C19 genotypes may vary between ethnic groups.

1.3 There is not enough evidence to recommend the Genedrive CYP2C19 ID Kit. It should only be used in the context of research.

1.4 Further research is recommended on the Genedrive CYP2C19 ID Kit to determine its accuracy and failure rate (see the section on further research).

Why the committee made these recommendations

Clopidogrel is an antiplatelet drug used after ischaemic stroke or transient ischaemic attack (sometimes called a 'mini stroke') to reduce the risk of blood clots that can cause further strokes or heart attacks. But clopidogrel does not work as well in some people because they have variations in a gene called CYP2C19 (known as 'loss-of-function variants'). Clopidogrel genotype testing can identify these people 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 variants who have clopidogrel are more likely to have further blood clots compared with people without loss-of-function CYP2C19 variants. Clinical experts agreed that it would be beneficial to treat people with loss-of-function CYP2C19 variants with alternative antiplatelet treatment, but the evidence was less clear on the size of this benefit. The economic evidence shows that clopidogrel genotype testing is cost effective compared with not testing, regardless of which alternative antiplatelet therapy people have. So clopidogrel genotype testing is recommended.

There is good evidence that the Genomadix Cube point-of-care test can accurately detect 2 of the most common loss-of-function CYP2C19 variants. But it does not detect other less common variants. It is also more expensive per test than laboratory testing.

The long-term health benefits of laboratory-based and point-of-care clopidogrel genotype testing are very similar. But, some less common loss-of-function CYP2C19 variants occur at a higher rate in certain ethnic groups. This means that tests that only identify the most common variants may disproportionately misdiagnose people in these groups. So, because they can detect a wider range of variants and are likely to cost less, laboratory tests should be used if possible.

There is no data on the Genedrive CYP2C19 ID Kit. More evidence is needed on how well it works. It does not yet have regulatory approval and is only recommended for further research in this draft guidance because the company indicated that approval is expected in the next 12 months. This test will only be included in the final guidance if it has appropriate regulatory approval by the date of final guidance publication.

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.

Clopidogrel resistance

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

2.4 The CYP2C19 gene has many alternative versions or variant forms (alleles) that produce CYP2C19 enzymes 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, cannot activate clopidogrel to its active form and are classed as 'poor metabolisers'. People with only 1 loss-of-function allele are classed as 'intermediate metabolisers' with significantly reduced enzyme activity.

2.7 Loss-of-function alleles are more common in certain ethnic populations, 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 genotyping

2.8 CYP2C19 genotype testing can identify variants in the CYP2C19 gene. 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 using laboratory-based testing or a point-of-care test.

Genomadix Cube CYP2C19 system

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

- Genomadix Cube platform, which contains the Genomadix analyser thermal cycling instrument for polymerase chain reaction (PCR) amplification, the software user interface, and 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.

2.11 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 cheek 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.

2.12 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.

Genedrive CYP2C19 ID Kit

2.13 The Genedrive System is a point-of-care gene amplification device used for qualitative in vitro molecular diagnostic tests. At the time of issuing this

draft guidance, the technology does not have regulatory approval for use in the UK. The company state that the test will be able to detect the *2, *3, *4, *8, *17 and *35 alleles. The test will consist of:

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

2.14 The test will use a single cheek 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. The diplotype and metaboliser status will be displayed on the device. The company states that 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

2.15 Clinical experts indicated that there are several methods that diagnostic genetic laboratories could use to implement CYP2C19 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.

The comparator

2.16 No genotype testing before using clopidogrel.

3 Committee discussion

The diagnostics advisory committee considered evidence on clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack (TIA) from several sources, including an external assessment report and an overview of that report. 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 on admittance 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 people 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 medications should be used. So, they do not have health implications for the person outside of the context of medications such as 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.

Location of testing

3.4 The committee agreed that it should be possible to get samples for genotype testing at a location that is convenient for the person who has had a stroke. This would be particularly relevant if CYP2C19 testing is delayed until after discharge from the acute stroke ward, or when the initial 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.

People currently taking clopidogrel

3.5 The committee acknowledged that there are many people who have had ischaemic stroke or TIA who are already taking clopidogrel but do not know their CYP2C19 genotype. 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. Therefore, the population would be different to people starting clopidogrel. The committee noted that retrospective testing was outside of the scope of the assessment. However, 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.

Clinical effectiveness

Clinical benefit 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 variants. But the evidence was less clear on the benefits of treatment with alternative antiplatelets. The committee recalled that clinical experts had said during scoping that dipyridamole with 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 with TIA or minor stroke, but not major stroke. Ticagrelor does not have a marketing authorisation for TIA or stroke in the UK. The committee recalled that the external assessment group (EAG) reported evidence that ticagrelor

significantly decreased the risk of secondary vascular events in people with loss-of-function CYP2C19 alleles 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 are 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%. However, 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 affect 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 alleles, 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. 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 are also likely to 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 2.11 to 2.15).

Children and young people with stroke

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 aetiology 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. However, 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 paediatric patients 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.

Cost effectiveness

Cost of testing

3.10 Clinical experts felt that the true cost of laboratory-based testing was likely lower than the cost used in the EAG's model (£139 per test). An expert commented that laboratory-based CYP2C19 testing in their region was about £20 to £40 per test (when detecting 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 testing, and there was a lack of agreement on the staff time required. Therefore, 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. 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. Some committee members said that the cost of laboratory testing could reduce over time because of economies of scale or new technologies.

3.11 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 the tests, which are not currently part of practice. Cost per laboratory test could therefore be less than cost per point-of-care test (the test costs were very similar in the EAG's base case model).

Differences between point-of-care tests

3.12 The committee agreed that the 2 point-of-care tests considered in the assessment are different and that it was not appropriate to use data for the Genomadix Cube to model performance of the Genedrive CYP2C19 ID Kit. It recalled that several studies were identified for the Genomadix Cube test, but no data on accuracy or failure rate was available for the Genedrive test. More data would be needed for the Genedrive test on these outcomes (see section 4) for the committee to consider recommending its use. The committee also noted that several features of the Genedrive test could offer advantages over the Genomadix Cube, such as reagent storage (Genedrive reagents do not require storage in a freezer), the range of alleles tested for (the Genedrive test detects several additional alleles) and interaction with patient records (see sections 2.11 to 2.14). However, the committee recalled that the Genedrive CYP2C19

ID Kit does not have regulatory approval for use in the UK. A company representative stated that this was being sought.

Laboratory testing versus point-of-care testing

3.13 The committee stated a preference for laboratory testing over the available point-of-care test (the Genomadix Cube). It noted that there was very little difference in the quality-adjusted life years (QALYs) generated by the different methods of testing in the EAG's model. 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). The cost per test in the EAG's base case model was lower for laboratory-based testing (£139) than for the Genomadix Cube (£197). The committee had also concluded that the true cost of laboratory testing would be lower than this (see section 3.10), and the true cost of point-of-care tests could be higher. Some committee members stated that existing infrastructure should be preferentially used over investing in new single purpose technologies.

CYP2C19 genotype testing is likely to be cost effective

3.14 The committee agreed that CYP2C19 genotype testing was likely to be cost effective. It recalled that in the EAG's base case analysis and in all sensitivity and scenario analyses, genotype testing dominated no testing (it cost less and produced more QALYs). This was true for all alternative antiplatelet agents modelled (dipyridamole with aspirin, ticagrelor with aspirin or aspirin alone), based on potential variation in UK practice.

3.15 The committee also considered that CYP2C19 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. However, 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.

4 Recommendations for further research

4.1 Further research is recommended to determine the accuracy and failure rate of the Genedrive CYP2C19 ID Kit.

5 Implementation

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

In addition NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendation in section 4 into its guidance research recommendations database and highlight the recommendation to public research bodies.

6 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

May 2023

7 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.

Jacob Grant

Topic lead

Thomas Walker

Technical adviser

Harriet Wilson

Project manager

ISBN: