

# Evidence overview: Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the [final scope](#) and the external assessment report.

## 1 Aims and scope

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. The aim of this assessment is to determine whether *CYP2C19* genotype testing after ischaemic stroke or transient ischaemic attack represents a clinically and cost-effective use of NHS resources.

## Background

People who have had a stroke are at increased risk of further occlusive vascular events such as secondary stroke or myocardial infarction. For those with non-cardioembolic ischaemic stroke or TIA, clopidogrel can be considered as an antiplatelet agent to reduce this risk.

## Clopidogrel resistance

The *CYP2C19* gene has many alternative versions or variant forms ([alleles](#)) which produce CYP2C19 enzymes with different levels of activity. Each *CYP2C19* allele is given a star (\*) number for identification. 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 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. 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. 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). Other variants are generally present in less than 1% of people. Further information on the prevalence of different alleles can be found in the results section.

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.

## Current practice

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 \(RCP\) national clinical guideline for stroke](#).

Clopidogrel is an option for preventing further occlusive vascular events in people who have had ischaemic stroke that is not associated with atrial fibrillation. If clopidogrel is contraindicated or not tolerated, modified-release dipyridamole in combination with aspirin, or aspirin alone, are alternative options. For TIA, NICE recommends modified-release dipyridamole (clopidogrel was not approved for this indication at the time of assessment). However, clinical experts commented that clopidogrel is typically used immediately after TIA or minor stroke in the NHS (see [RCP guidance](#)). Aspirin is recommended for up to the first 2 weeks after a non-minor stroke but is typically not used long-term unless other drugs are not tolerated or contraindicated.

Ticagrelor is an antiplatelet therapy that inhibits the same receptor as clopidogrel but does not require metabolism by CYP2C19. It does not have a marketing authorisation for ischaemic stroke or TIA in the UK. Clinical experts suggested that ticagrelor could be used off-label for people with ischaemic stroke or TIA only if other options were unsuitable and if the risk of bleeding was manageable. For more information see section 1.4 of the external assessment report.

A summary of the treatment pathway can be found in section 1.4 (figures 1 and 2) of the external assessment report.

### **CYP2C19 genotype testing**

Genetic testing for loss-of-function *CYP2C19* variants could be done either with a point-of-care test or laboratory-based tests. Point-of-care tests have the potential to deliver results more quickly than standard laboratory-based tests. Laboratory-based tests are done by technicians in a laboratory. In the NHS, genomic testing is generally delivered by a network of 7 Genomic Laboratory Hubs. Testing for *CYP2C19* is not currently included in the [National Genomic Test Directory](#).

Point-of-care tests only detect specific *CYP2C19* variants. Laboratory tests may detect any variant or target a specific subset of variants depending on the technology used. Further information about the potential methods of testing can be found in table 2 in the external assessment report.

## **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.

## **Interventions**

Genetic testing of the *CYP2C19* gene. This can be using:

- A point-of-care test:
  - Genomadix cube *CYP2C19* system
  - Genedrive system *CYP2C19* ID kit (not currently UKCA-marked)
- Laboratory-based testing.

## **Comparator**

No genetic testing before using clopidogrel.

## Healthcare setting

- Specialist acute stroke units
- Secondary care
- Clinical laboratories.

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the [final scope](#).

## 2 Clinical effectiveness evidence

The external assessment group (EAG) did a systematic review to summarise the evidence on the clinical effectiveness of clopidogrel genotype testing after ischaemic stroke, including minor stroke and TIA. They divided the review into 5 objectives. No evidence was found in children for any of the objectives.

Find the full systematic review methods and results from page 36 of the external assessment report.

### **Objective 1: Do people who have genetic testing for clopidogrel resistance, and who are treated based on these results, have a reduced risk of secondary vascular occlusive events compared to those who are not tested and are treated with clopidogrel following standard guidelines?**

In objective 1, the EAG looked for studies where people were either given clopidogrel according to standard practice, or had *CYP2C19* testing and then treated based on their genotype ([personalised treatment](#)). These studies measured differences in outcomes between these 2 groups. Two studies were included, both based in China.

Xia et al. (n=80) allocated patients to either clopidogrel 75 mg per day (with no testing) or *CYP2C19* genotyping (\*1, \*2, \*3 and \*17 alleles) followed by treatment based on *CYP2C19* function:

- Normal function: clopidogrel 75 mg per day
- Intermediate function: clopidogrel 150 mg per day
- Poor function: ticagrelor.

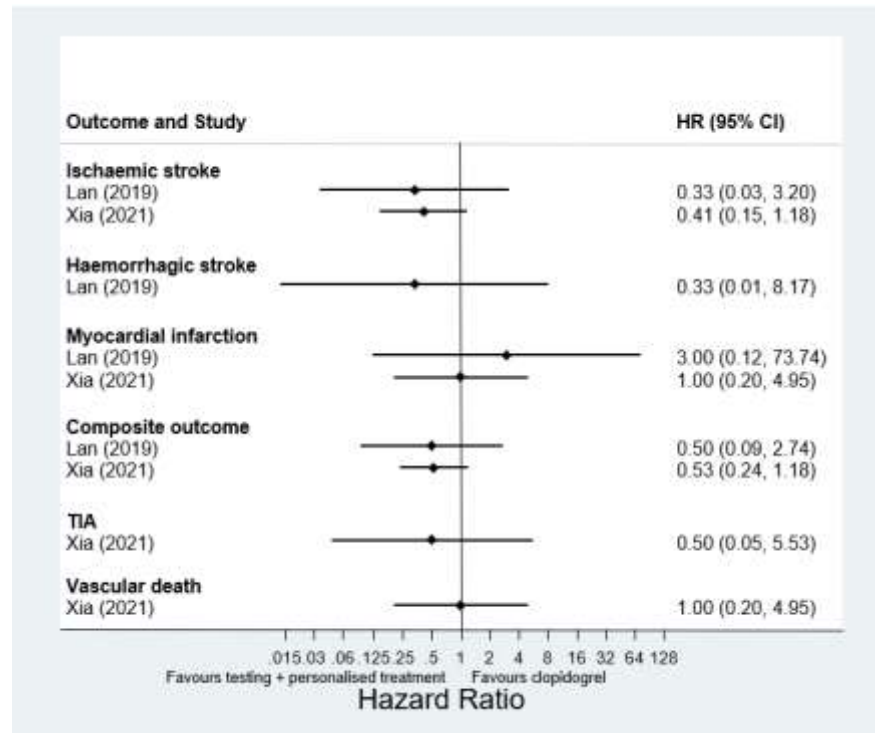
Lan et al. (n=190) genotyped all participants for the \*1, \*2 and \*3 alleles, but then divided the population to either all receive clopidogrel or to receive clopidogrel or aspirin depending on presence of loss-of-function alleles.

Neither study reported study power calculations. The EAG considered both studies to have a high risk of bias, as they were not randomised, there was no pre-registered protocol, and there was no information on the allocation process or potential deviations from the intervention. The Lan et al. study also had a high proportion of loss to follow-up.

## **Results**

Results from Xia et al. and Lan et al. are presented in figure 1.

**Figure 1: Secondary vascular events in people treated with clopidogrel compared with people tested for loss-of-function variants and offered personalised treatment (composite outcome includes stroke, TIA, myocardial infarction and death).**



No significant benefit for personalised treatment was found for any of the outcomes reported, but this may be because of small sample size and lack of power. Find more details in section 4.2.2 of the external assessment report.

**Objective 2: Do people who have loss-of-function alleles associated with clopidogrel resistance have a reduced risk of secondary vascular occlusive events if treated with other antiplatelet therapies?**

For objective 2, the EAG looked for studies where people with loss-of-function alleles were either treated with clopidogrel or an alternative antiplatelet drug and compared these 2 groups. Seven studies (reported in 23 publications) were identified, all of which were randomised controlled trials. Two studies

only included people with loss-of-function alleles who were then randomised to different antiplatelet therapies. The other 5 studies were not restricted based on genotype, but subgroup analyses were done for people with loss-of-function alleles.

The trials were predominantly in Asian populations, although 1 was international and included a majority white (67%) mixed ethnicity population. Six studies investigated the 2 main loss-of-function alleles (\*2 and \*3) and 1 study only genotyped the \*2 allele.

The treatment comparisons were varied between trials. Only one study used clopidogrel alone in the comparator arm (Han et al. 2017), all others used aspirin as well as clopidogrel for at least 21 days. No studies included an arm that corresponds to UK clinical practice (see [section 1](#)). For more details on the characteristics of the included trials, see table 6 in the external assessment report.

Four of the 7 studies (Chen et al. 2019; Han et al. 2017; Wang et al. 2021; Wang et al. 2016) were judged to be at low risk of bias. One had some concerns because of lack of information on allocation concealment (Wu et al. 2020). Two studies were at high risk of bias, 1 because of lack of information on loss to follow-up (Meschia et al. 2020), and the other due to missing detail on the randomisation process and potential deviations from the intended intervention (Yi et al. 2018). For more detail see table 7 in the external assessment report.

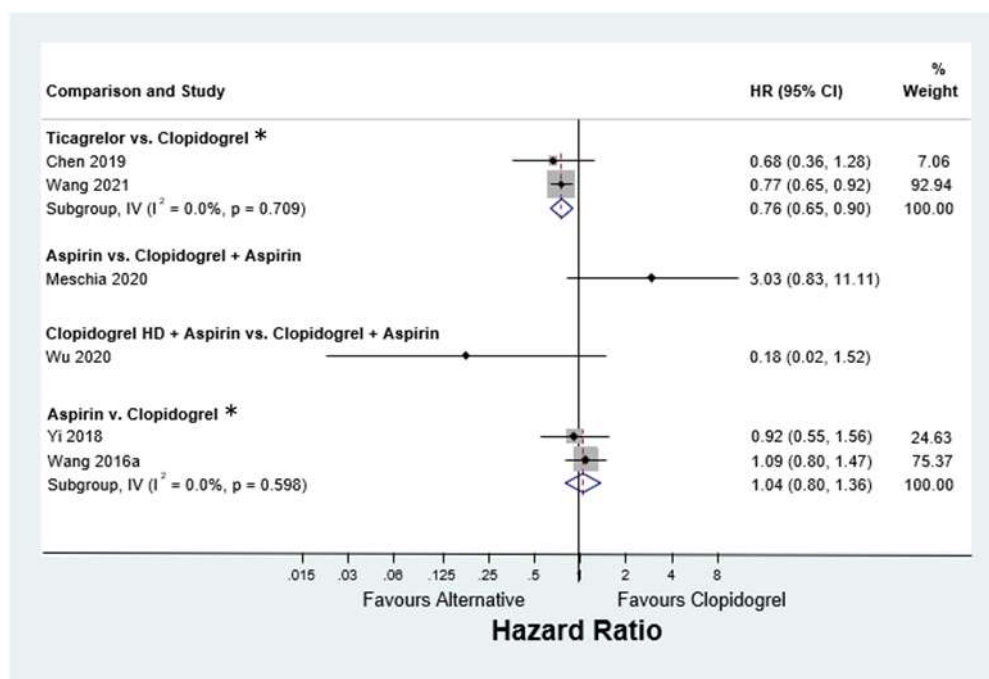
## Results

For secondary vascular occlusive events, 6 of the 7 studies reported a composite endpoint (stroke, TIA, myocardial infarction and vascular death) as well as incidence of individual secondary outcomes. A composite endpoint was not reported for the study that used clopidogrel alone in the comparator arm. Network meta-analyses were not possible (for more detail see figure 6 in the external assessment report).



Two studies provided evidence that treatment with ticagrelor significantly reduced the risk of secondary vascular events in those with loss-of-function alleles, compared to treatment with clopidogrel (pooled hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.65 to 0.90). Both groups received aspirin for the first 21 days. No other alternative treatment resulted in a significant difference in the incidence of secondary vascular occlusive events for loss-of-function carriers (figure 2).

**Figure 2: Incidence of a composite outcome of secondary vascular events in people with loss-of-function *CYP2C19* alleles receiving clopidogrel, compared with an alternative antiplatelet treatment**



\*Short-term aspirin was given alongside clopidogrel in these studies.

Similar results were seen for the risk of secondary stroke and ischaemic stroke (see figures 8 and 9 in the external assessment report). No significant effects on risk of other secondary events (TIA, myocardial infarction, vascular death and mortality) were reported, although the absolute number of events was low.

All 7 studies reported incidence of bleeding events. In Wang et al. (2021), an increased risk of bleeding was observed with ticagrelor compared to clopidogrel (HR 2.18, 95% CI 1.66 to 2.86), but this was not shown in the other study of ticagrelor. There was no statistically significant difference between other antiplatelet treatment strategies for bleeding outcomes. Risk of other adverse events were similar between all treatment strategies. For more detail see page 56 of the external assessment report.

**Objective 3: Do people who have loss-of-function *CYP2C19* variants have an increased risk of secondary vascular occlusive events when treated with clopidogrel compared to people without loss-of-function variants?**

For objective 3, the EAG looked for studies where people with stroke or TIA were treated with clopidogrel, and reported comparisons of outcomes between those with and without loss-of-function alleles. Twenty-five studies (reported in 45 publications) were identified. There were 13 prospective cohorts, 7 retrospective cohorts, and 5 studies where a single arm of a randomised trial was used as a cohort. Participants were either given clopidogrel (15 studies), clopidogrel and aspirin (long-term aspirin 3 studies, short-term aspirin 5 studies), or clopidogrel with or without other antiplatelets (2 studies). Most studies enrolled people with stroke (14 studies) or stroke and TIA (10 studies), with 1 study only enrolling people with TIA. Random effects meta-analysis was used to produce summary HRs for each outcome where possible.

The majority of studies were done in Asia (13 in China, 2 in Japan and 1 in Korea), 4 in the USA, with single studies from other countries or regions (Tornio et al. 2018 set in Scotland). No study used a point-of-care test to determine *CYP2C19* status. Sixteen studies looked for the \*2 and \*3 alleles, 5 studies tested for \*2 only, 2 did not report which alleles were tested for, and 2

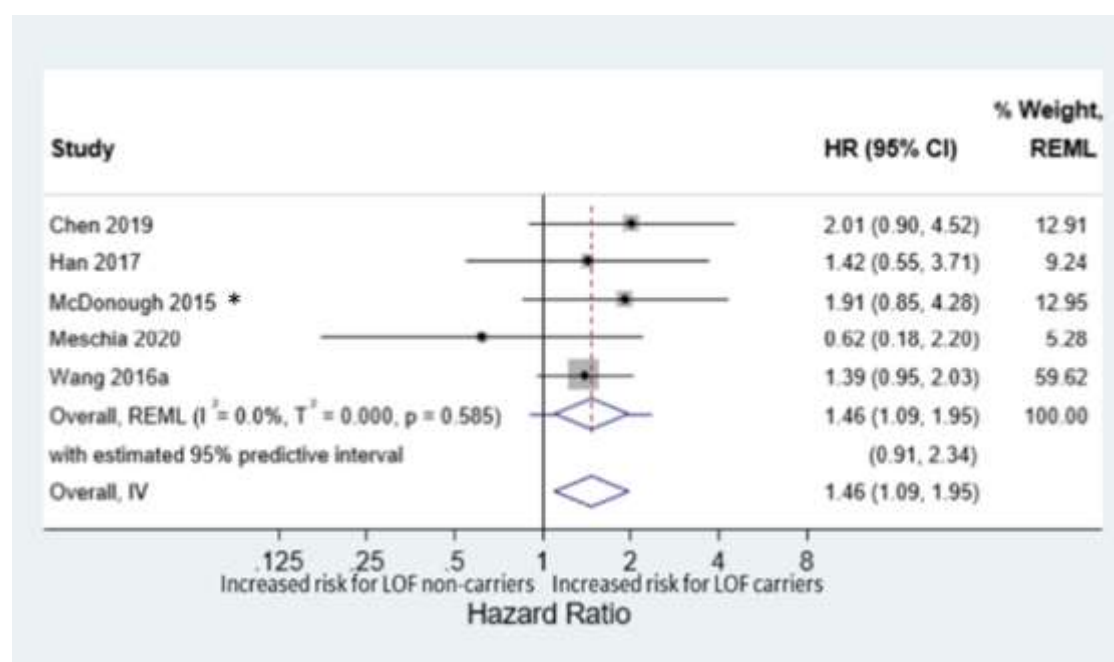
tested for additional alleles: \*8 in 1 study and \*4 to \*8 in the other. Full study characteristics can be found in table 8 of the external assessment report.

The EAG judged 19 studies to have a low risk of bias. Seven studies were considered to have a high risk of bias because of lack of information on follow-up or a high proportion of participants being lost to follow-up, because ethnicity was not described in detail or considered in a population that was likely to be diverse, or because of concerns with the participant selection process. For more detail see table 9 in the external assessment report.

## Results

The EAG considered there was strong evidence that people with loss-of-function alleles treated with clopidogrel (with or without aspirin) have a higher incidence of secondary vascular events (stroke, TIA, myocardial infarction or vascular death combined), stroke and ischaemic stroke than those without loss-of-function alleles (see figure 3 and table 1). The pooled outcome for stroke was used as an input in the EAG's economic model (see [model inputs](#)). There was also some evidence that risk of vascular death is increased in people with loss-of-function alleles. There was little evidence that mortality or TIA incidence were associated with *CYP2C19* status, but these were only evaluated in single studies and the number of events was low. For more detail see section 4.4.2 of the external assessment report.

**Figure 3: Incidence of any stroke in carriers of *CYP2C19* loss-of-function variants alleles receiving clopidogrel (with or without aspirin) compared with non-carriers**



\*The EAG considered this study to have a high risk of bias due to lack of information on follow-up.

**Table 1: Difference in risk of secondary vascular events and mortality between people with and without loss-of-function *CYP2C19* variants (hazard ratio over 1 indicates lower occurrence in group without loss-of-function variants)**

Outcome	Number of studies	Summary hazard ratio (95% CI)
Composite outcome – secondary vascular events	18	1.72 (1.46 to 2.03)
Stroke	5	1.46 (1.09 to 1.95)
Ischaemic stroke	12	1.88 (1.46 to 2.39)
Vascular death	2	5.07 (1.26, 20.39)
TIA	1	0.86 (0.14 to 5.12)
Mortality	1	3.67 (0.18 to 76.49)

The EAG investigated the effects of factors including ethnicity, clopidogrel regimen and primary event on the pooled outcomes from studies identified for objective 3. The negative effect of loss-of-function alleles for people taking

clopidogrel was reduced when a loading dose of clopidogrel was given (ratio of hazard ratios [RHR] 0.64, 95% CI 0.43 to 0.96), and for people who had long-term aspirin alongside clopidogrel compared with clopidogrel alone or clopidogrel with short-term aspirin (RHR 0.47, 95% CI 0.22 to 0.96). The effect was also reduced in studies that included both stroke and TIA as primary events compared with those that only included stroke (RHR 0.62, 95% CI 0.44 to 0.86). There was a lot of uncertainty in the estimates for the effect of ethnicity, and no statistical difference in the effect of loss-of-function alleles by ethnicity was found. For more detail see table 10 in the external assessment report.

The EAG stated there was no evidence of a difference in the risk of bleeding under clopidogrel treatment for people with or without loss-of-function alleles for any category of bleeding assessed (any bleeding HR 0.98, 95%CI 0.68 to 1.40)). For more detail see page 67 of the external assessment report.

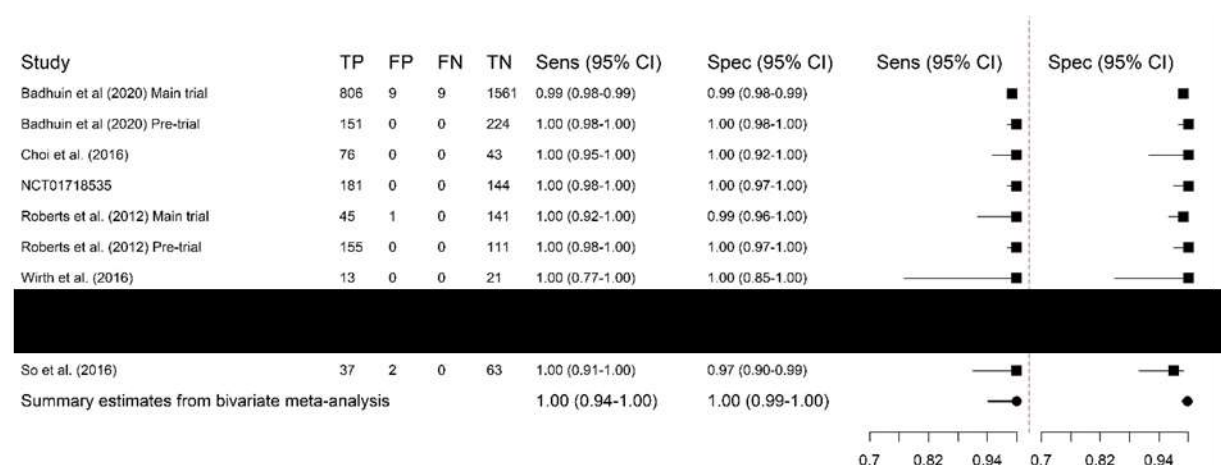
#### **Objective 4: What is the accuracy of point-of-care genotype tests for detecting variants associated with clopidogrel resistance?**

The EAG found 11 studies (in 12 publications) reporting data on test accuracy for the Genomadix Cube CYP2C19 system. All studies evaluated the test under a previous name or version (Spartan Cube, Spartan RX or Spartan FRX). No data was available for the Genedrive CYP2C19 ID kit. No studies were conducted specifically in people with stroke or TIA. However, the EAG did not think that this was likely to affect accuracy as the presence or absence of different alleles would not be affected by factors such as comorbidities, age or sex. Six of the studies were based in Canada, 2 in Europe, 1 in South Korea and 2 were multinational. All studies were considered at low risk of bias.

## Results

All studies used a laboratory-based reference standard to measure accuracy for detection of the alleles that the Genomadix Cube tests for. The EAG's meta-analysis produced a summary estimate of 100% sensitivity and specificity for the Genomadix Cube system (figure 4).

**Figure 4: Individual study and overall summary estimates of sensitivity and specificity for the Genomadix Cube**



The proportion of discordant results between the Genomadix Cube and the laboratory reference standard ranged from 0 to 2.9% and was less than 1% in 9 studies.

## Objective 5: What is the technical performance (other than accuracy) and cost of the different *CYP2C19* genetic tests?

The EAG found 20 studies (in 24 publications) that reported on the technical performance of point-of-care *CYP2C19* tests, of which 16 reported on the Genomadix Cube and 1 on an early version of the Genedrive test. Study populations were varied, with 1 in people with stroke and the rest in people with percutaneous coronary intervention or other cardiological conditions, healthy volunteers, or condition not reported. Five studies took place in Europe, 11 studies in North America, 1 in South Korea, 1 in Saudi Arabia, and 2 studies were international.

NICE

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March 2023

The EAG also sent a survey to 10 UK genomic laboratories asking for information about how *CYP2C19* testing might be implemented in NHS clinical practice. Responses were received from 5 English genomic laboratory hubs, and from the Scottish Strategic Network for Genomic Medicine, the All Wales Medical Genomics Services, and the Northern Ireland Regional Genetics Service.

## **Results**

### **Test failure rate**

There was substantial variation in the reported test failure rate from 10 studies of the Genomadix Cube, from 0.4% to 18.9% for the initial run. Test failures included producing inconclusive results (or not identifying a genotype) and device errors or failures during the amplification process. Where studies reported post-failure action, most said they repeated the test where possible. For more detail see table 15 in the external assessment report.

### **Ease of use**

Five studies of the Genomadix Cube reported experience of using the system. Overall the studies suggested that the device was simple, user-friendly and required minimal training. Limitations included the storage conditions of reagents, and that only one sample can be run at a time. Other studies highlighted that the test is restricted to the \*2, \*3 and \*17 alleles, and there can be issues with sample collection.

One study of Genedrive described the device as portable, rapid, and not requiring freezers to store reagents.

### **Number of people with *CYP2C19* loss-of-function variants**

The proportion of participants with any loss-of-function variant ranged from 15% to 64%, including people with 1 loss of function allele (intermediate metabolisers, for example \*2/\*1) or 2 loss of function alleles (poor metabolisers, for example \*2/\*2). No studies were done in the UK. Most

studies did not report ethnicity, so it was not possible to investigate how with the prevalence of *CYP2C19* variants differed between ethnic groups. The study with the highest proportion of people with variant forms (64%) did not report on ethnicity but was conducted in South Korea and so is likely to have included a mainly Asian population. For more detail see table 16 in the external assessment report.

## **UK laboratory survey results**

A selection of the survey results is given below. For full detail, see section 4.6.2 of the external assessment report.

### **Testing platform**

Table 2 provides an overview of the test platforms that the responding laboratories had available and preferred for implementing *CYP2C19* testing. Only 1 lab did not report any sequencing technology ([Sanger](#) or [next-generation sequencing](#)). All had some form of targeted *CYP2C19* variant detection system, most commonly polymerase chain reaction (PCR)-based single nucleotide polymorphism (SNP) assays such as TaqMan (ThermoFisher). Mass spectrometry and loop-mediated isothermal amplification (LAMP) were the most commonly preferred technologies, both of which are for targeted variant detection. Reasons given for preferring certain technologies included volume of throughput, cost, availability of commercial *CYP2C19* kits, staff time and ease of reporting.



**Table 2: Available and preferred *CYP2C19* testing technologies in UK laboratories**

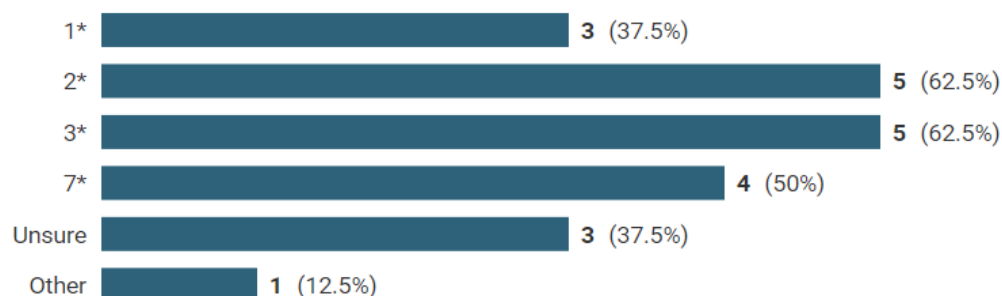
Technology	Technology Available	Preferred Technology
Sanger <i>CYP2C19</i> sequencing	7	0
Next-generation <i>CYP2C19</i> gene sequencing	6	2
PCR-based SNP genotyping assays using fluorescent reporter systems, for example TaqMan (ThermoFisher)	6	1
Other PCR-based genotyping panels that use proprietary detection methods, for example xTAG <i>CYP2C19</i> Kit v3 (Luminex)	1	0
Variant detection using mass spectrometry, for example MassARRAY (Agena Bioscience)	4	3
LAMP, for example LAMP human <i>CYP2C19</i> mutation kit (LaCAR MDx Technologies)	4	3
QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System	1	1

Abbreviations: LAMP, loop-mediated isothermal amplification; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

### Alleles targeted

Figure 5 provides an overview of responses to the question, “Which alleles would you test for in a request for a *CYP2C19* test”. The ‘other’ response stated that next-generation sequencing would be able to detect all variants.

**Figure 5: Responses to question “Which alleles would you test for in a request for a *CYP2C19* test?”**



Please note that \*7 was mistakenly included on the survey instead of \*17.

Four laboratories stated that the number of alleles tested for could affect test performance, although 2 highlighted that this would depend on the

technology. Potential impacts included increased cost and increased turnaround time.

## Ongoing studies

The EAG identified 3 ongoing studies, 1 trial for objective 1 and 2 trials for objective 3. [REDACTED]

[REDACTED]

## 3 Cost effectiveness evidence

### Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify any published economic evaluations of *CYP2C19* genetic tests for guiding treatment after ischaemic stroke or TIA. The full review methods can be found in section 5.1.1 and 5.1.3 of the external assessment report.

### Cost effectiveness of *CYP2C19* testing strategies

Five studies were identified as relevant by the EAG. For full detail of the included studies see tables 22 to 24 in the assessment report. The EAG considered the studies to be generally of high quality, although how unit costs were estimated was not clear for any study. All models found that *CYP2C19* testing is likely to be cost effective.

The EAG considered Wright et al. (2022) to be the most relevant study. This was an early evaluation from a UK NHS perspective, modelling the Genedrive point-of-care test to determine genotype after stroke. People with loss-of-function alleles were assumed to be treated with modified-release dipyridamole and aspirin rather than clopidogrel. In this study, the Genedrive

test was found to dominate the no testing strategy (it generated more quality-adjusted life years [QALYs] and lower costs), with a probability of being cost effective of 0.77 at a maximum acceptable ICER of £20,000 per QALY. However, the EAG noted that the model inputs were based on older data that doesn't include more recent relevant evidence. For more detail see section 5.1.2 of the external assessment report.

### **Cost effectiveness of secondary prevention of ischaemic stroke**

The EAG also searched for cost effectiveness studies of secondary prevention of ischaemic stroke in a general population to inform their model. For full details see section 5.1.3 and tables 25 and 26 of the external assessment report.

### **Economic analysis**

The EAG developed a de novo economic model to estimate the incremental costs and quality-adjusted life years (QALYs) for *CYP2C19* genetic testing for clopidogrel resistance in people who have had a non-cardioembolic ischaemic stroke or TIA where treatment with clopidogrel is being considered, compared with no genetic testing.

The interventions evaluated in the model were the Genomadix Cube and Genedrive *CYP2C19* point-of-care tests, and a laboratory-based *CYP2C19* test based on one of the most commonly preferred devices (Agena Bioscience MassARRAY) from the survey of genomic laboratory hubs (see [objective 5 results](#)).

### **Model structure**

The model uses a hybrid decision tree and Markov structure. Diagnostic decisions and short-term 90-day outcomes were modelled using a decision tree, and long-term lifetime outcomes used a 5-state Markov model. For full detail, see section 5.2 of the external assessment report.

## Decision tree

The decision tree differed by test type. Point-of-care tests could have true positive, true negative, false positive, or false negative results. Laboratory-based testing was assumed to have perfect sensitivity and specificity (no false results). A test failure rate was also modelled, where failed tests were repeated. People who got a negative test result were assumed to have clopidogrel, and people with positive test result (for a loss-of-function allele) were assumed to have an alternative treatment (modified-release dipyridamole with aspirin in the base case, varied in scenario analyses). If no test was modelled, everyone was assumed to have clopidogrel.

Following testing (or no testing for the comparator) and assignment to treatment, the decision tree modelled the 90-day clinical outcomes. The possible outcomes were the same for each branch of the diagnostic decision tree, but had different probabilities of happening depending on the treatment and loss-of-function status (see figures 23 to 25 in the external assessment report):

- No further event
- Further minor stroke
- Major bleed or intracerebral haemorrhage
- Further moderate stroke
- Further major stroke
- Death.

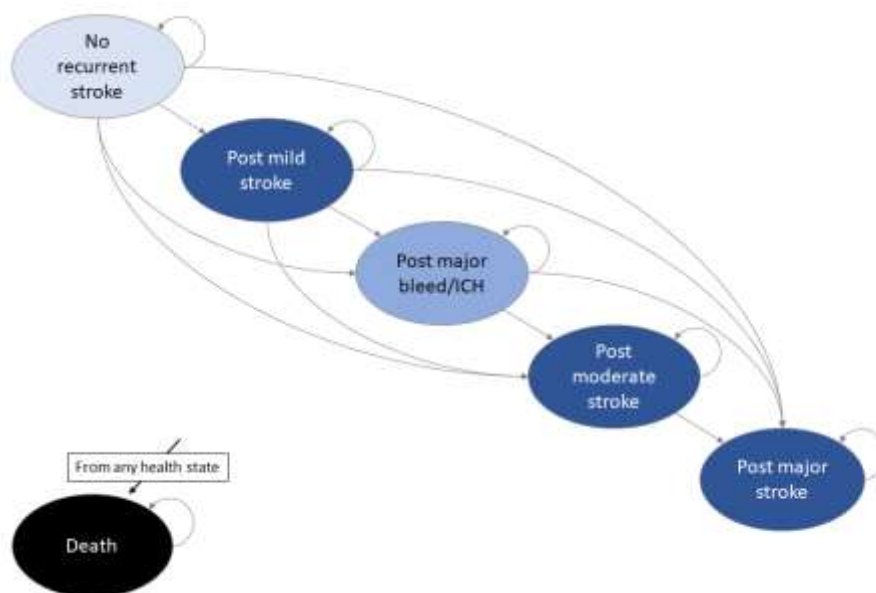
Laboratory-based testing may introduce a delay in receiving test results, after which those identified as loss-of-function carriers switch from clopidogrel to the alternative treatment.

In all branches, side effects could lead to treatment discontinuation. The EAG assumed that people discontinuing would switch to low-dose aspirin monotherapy.

## Markov model

Following the decision tree, a Markov model was used to evaluate long-term outcomes. The model used annual cycles (minus the 90-day decision tree period for year 1) with a lifetime time horizon (up to age 100). Figure 6 illustrates the structure of the Markov model, which had 5 transition states and 1 absorbing death state. People entered the model based on the proportions of each treatment and genotype combination in each health state at the end of the 90-day decision tree period.

**Figure 6: The EAG's long-term Markov model structure (ICH, intracerebral haemorrhage)**



Each state was associated with differing costs, health-related quality of life, mortality rate and recurrent event rates. The health states were ordered by severity from no further event to major stroke. The severity of major bleed or intracerebral haemorrhage was placed between mild stroke and moderate stroke based on advice from clinical experts. People were categorised by the most severe event that they had experienced.

The EAG assumed that people stayed on the treatment they were receiving at the end of the decision tree unless they experience a bleeding event.

## **Population**

Two versions of the model were developed, one for adults with non-minor ischaemic stroke and the other for adults with TIA or minor stroke. This was done to reflect the differences in the treatment pathways for these 2 populations (see [section 1](#)). The model structure was the same for each population, but some parameter values were different. Results were reported for the 2 groups separately, and for a combined population using a weighted average based on condition prevalence. The mean age of the population in the base case was 71 years.

The EAG commented there was not enough evidence to run the model with parameters for children or young people, but a scenario was done for adults who were younger at the time of first stroke or TIA (see [scenario analyses](#)).

## **Comparator**

The comparator was no testing in which all people were assumed to be treated according to the treatment pathways outlined in figure 1 in the external assessment report.

## **Model inputs**

Find the full detail on model parameters and inputs in section 5.2.5 of the external assessment report.

## **Test performance**

The meta-analysis for the Genomadix Cube from the clinical review estimated 100% sensitivity and specificity (see [section 2, objective 4](#)). However, these figures are for detection of the \*2 and \*3 only, as these are the loss-of-function alleles that the Genomadix Cube tests for. Other loss-of-function variants would not be detected by the test, but these are rare across all ethnicities (see

[section 1](#) and [section 2](#)). So, the EAG assumed a sensitivity of 99% to account for alleles that would not be detected.

No delay between testing and receiving personalised therapy was used for point-of-care tests, as they were reported to provide results within hours (see [section 2, objective 5](#)). Based on the survey of laboratories, the EAG assumed a 1-week delay in the base case for laboratory-based testing.

The test failure rate for the Genomadx Cube was estimated at 8% based on meta-analysis from the clinical review (see [section 2, objective 5](#)). For laboratory-based testing, the EAG assumed that the test failure rate was 0%. However, the impact of test failure in a laboratory setting was examined in scenario analyses on the cost of testing (see [scenario analyses](#)).

There was no data on diagnostic test accuracy or test performance for the Genedrive *CYP2C19* test. For the model, the EAG used the same inputs as for the Genomadx Cube, but highlighted that this is uncertain.

**Table 3: Test performance parameters used in the EAG's base case**

Parameter	Genomadx Cube and Genedrive	Laboratory-based testing
Sensitivity	99%	100%
Specificity	100%	100%
Time to receive test results	–	1 week
Test failure rate	8%	0%

### Cohort characteristics

There was limited UK-based data available on the prevalence of *CYP2C19* loss-of-function alleles that also reflected UK demographics. So, the EAG used estimates from a US-based study (Ionova et al. 2020). When weighted by ethnicity figures reported by Public Health England (Amin et al. 2018), the EAG's estimate for loss-of-function allele prevalence in the UK used in the base case was 32.1%. This assumes that the prevalence of loss-of-function alleles in the non-European, non-Asian UK population is the same as

observed in the US African American population (31.9%, Ionova et al. 2020). The EAG also examined a higher prevalence of 56.8% in a scenario analysis, based on the prevalence in the East Asian population from Ionova et al.

For more information on the cohort characteristics, see page 118 of the external assessment report.

### **Transition probabilities**

The EAG identified event rates for further stroke, bleeding or mortality for people without loss-of-function *CYP2C19* alleles who are taking clopidogrel only (baseline rates; see pages 118 to 123 in the external assessment report). Mortality rates were based on data from the Sentinel Stroke National Audit Programme (SSNAP), the South London Stroke Registry (Mohan et al. 2009), and the Office for National Statistics. The EAG assumed that people with TIA had a mortality rate equal to people with a [modified Rankin Score](#) (mRS) of 0.

For the non-minor stroke population, stroke recurrence rates were from SSNAP and Mohan et al. (2009). For TIA, recurrence rates were from Lioutas et al. 2021. The rate of major bleed or intracerebral haemorrhage was based on the PRoFESS trial (Sacco et al. 2008).

The EAG then used hazard ratios to derive event rates (recurrent stroke and major bleed or intracerebral haemorrhage) for people in other groups relative to the baseline rates (see table 4 below, and table 34 in the external assessment report). As limited data for objective 1 was available, the hazard ratios were based on studies identified for objective 2 (CHANCE and CHANCE-2) and objective 3 (meta-analysis). As no evidence on dipyridamole with aspirin was found that included loss-of-function status, the EAG based the hazard ratio for recurrent stroke on the PRoFESS randomised controlled trial (Sacco et al. 2008), assuming that outcomes for people taking this therapy would not differ according to loss-of-function status. The EAG assumed that event rates depended on the severity of primary stroke experienced, but that relative treatment effects (hazard ratios) did not vary by



stroke severity. For more detail see pages 123 to 125 of the external assessment report.

**Table 4: Hazard ratios for recurrent stroke for each treatment and loss-of-function combination relative to people with no loss-of-function alleles who are taking clopidogrel only**

Treatment and loss-of-function status	HR for recurrent stroke	Source
Clopidogrel only, no loss-of-function	1	-
Clopidogrel only, loss-of-function	1.46 95% CI (1.09, 1.95)	<a href="#">Objective 3</a> (see figure 3)
Dipyridamole + aspirin, any genotype	1.01 95% CI (0.92, 1.11)	PRoFESS (Sacco et al. 2008)
Aspirin, no loss-of-function	1.96 95% CI (1.33, 2.857)	CHANCE (Wang et al. 2016)
Aspirin, loss-of-function	1.387 95% CI (0.8947, 2.054)	CHANCE with HR from Objective 3 applied
Ticagrelor, any genotype	1.142 95% CI (0.7967, 1.587)	CHANCE-2 (Wang et al. 2021) with HR from Objective 3 applied

## Costs

Find the full detail of costs used in the model on pages 127 to 131 of the external assessment report.

### Point-of-care testing costs

The cost per test for the point-of-care tests was £197 for the Genomadix Cube and £104 for the Genedrive *CYP2C19* test. These costs were based on device, test and control kit costs, extended warranty costs and device lifetime provided by the respective manufacturers. Both tests were stated to take 10 minutes, and were assumed to be done by a Band 5 nurse. These per test costs did not include training costs or reagent storage costs, which the EAG assumed to be negligible.

## Laboratory-based testing costs

The EAG's survey of UK genomic laboratories found wide variation in the methods each laboratory would prefer to use to test for *CYP2C19* variants (see [objective 5](#)). Estimated costs per test varied from around £15 to £250. The 2 most common preferred test platforms were the Agena Bioscience MassARRAY and loop-mediated isothermal amplification (LAMP). In its base case, the EAG used costs for the MassARRAY assuming a 1-year lifespan, but explored the effect of laboratory-based test cost with [threshold analysis](#). Incorporating the platform, reagent and staff costs, the EAG estimated the total cost to be £139 per laboratory test.

## Health state costs

Health state costs were based on a study from the Sentinel Stroke National Audit Programme (SSNAP) representing stroke hospitalisations in the UK in 2016. These costs include both NHS and social costs, and are stratified by stroke severity. Overall costs were lower for the TIA or minor stroke population compared to those for non-minor stroke.

For people with no recurrent stroke, only social care costs were used. For people in the TIA or minor stroke population, social care costs after a secondary minor stroke were lower than for the non-minor stroke population. After a secondary moderate or major stroke, all populations incurred the same social care costs.

Major bleed and intracerebral haemorrhage costs were modelled as a one-off cost in the cycle that the event happened, and was added onto the cost of the stroke-related health state. The value for this cost was taken from an assessment carried out for NICE's original guidance on clopidogrel and dipyridamole for secondary prevention (Jones et al. 2004).

The costs the EAG used in 2014 prices are shown in tables 40 and 41 of the external assessment report. These were inflated to 2022 prices in the model.

## Health-related quality of life and QALY decrements

The EAG modelled the utilities according to the [modified Rankin Scale](#) (mRS) using EQ-5D results from Whynes et al. 2012 (see table 36 in the external assessment report). Each health state was given an mRS range (table 5). The utility values for each health state were an average of the utilities for the relevant mRS scores. For major bleed or intracerebral haemorrhage, the utility was taken from Micieli et al. 2022. The value was similar to that for moderate stroke, which the EAG considered consistent with feedback from clinical experts.

**Table 5: Utilities associated with modelled health states in the EAG's base case**

Health State	mRS range	Utility value
TIA	0	0.89
Minor stroke	0 to 1	0.89
Major bleed or intracerebral haemorrhage	1 to 2	0.62
Moderate stroke	2 to 3	0.63
Major stroke	4 to 5	0.065

A utility decrement of  $-0.145$  was applied for all people who had ischaemic stroke either as a first event or during the course of the model, to account for the impact on quality of life for carers. This was based on utilities reported in the TRACS trial (Forster et al. 2013) which evaluated carers of inpatients after stroke enrolled on a structured training programme.

## Base case results

Results of the model were reported separately for the TIA or minor stroke population and the non-minor ischaemic stroke population. For some key outputs the EAG also provided results for the whole population (that is, both these populations combined) as a weighted average using the proportions of each group in the overall population. Net monetary benefit was calculated

using a willingness-to-pay threshold of £20,000 per QALY. For full base case results, see section 5.3.1 of the external assessment report.

As noted in the [model inputs section](#), test performance characteristics for the Genedrive *CYP2C19* test were assumed to be the same as the Genomadix Cube as there was no data available for the Genedrive. The EAG stated that these results should be considered exploratory only.

### **Cost effectiveness of *CYP2C19* genotype testing versus no testing**

In all populations and testing strategies, *CYP2C19* genotype testing dominated no testing (testing produced more QALYs and had lower costs). The EAG's base case deterministic pairwise comparisons are shown in tables 6 to 8. QALYs generated by the 3 tests in all populations were very similar. Probabilistic outcomes were very close to the deterministic results (see tables 55 to 57 in the external assessment report).

**Table 6: Deterministic pairwise comparisons versus no testing for the non-minor ischaemic stroke population**

<b>Intervention versus no test</b>	<b>Incremental costs (discounted)</b>	<b>Incremental QALYs (discounted)</b>	<b>Net monetary benefit</b>
Genedrive	-£1,915	0.21	£6,159
Genomadix Cube	-£1,823	0.21	£6,066
Laboratory test	-£1,909	0.21	£6,112

**Table 7: Deterministic pairwise comparisons versus no testing for the TIA or minor stroke population**

<b>Intervention versus no test</b>	<b>Incremental costs (discounted)</b>	<b>Incremental QALYs (discounted)</b>	<b>Net monetary benefit</b>
Genedrive	-£1,141	0.08	£2,737
Genomadix Cube	-£1,048	0.08	£2,644
Laboratory test	-£1,069	0.08	£2,584

**Table 8: Deterministic pairwise comparisons versus no testing for the mixed TIA or ischaemic stroke population**

<b>Intervention versus no test</b>	<b>Incremental costs (discounted)</b>	<b>Incremental QALYs (discounted)</b>	<b>Net monetary benefit</b>
Genedrive	-£1,669	0.17	£5,069
Genomadix Cube	-£1,576	0.17	£4,976
Laboratory test	-£1,641	0.17	£4,988

Abbreviations: QALY, quality-adjusted life-year.

### **Fully incremental analysis**

Fully incremental results are shown in tables 44 to 46 of the external assessment report. Genedrive dominated both laboratory-based testing and the Genomadix Cube. The incremental cost-effectiveness ratio (ICER) for the Genomadix Cube compared to laboratory-based testing was £42,123 in the non-minor stroke population, £5,023 in the TIA or minor stroke population, and £24,387 in the overall population.

### **Sensitivity analyses**

#### **Deterministic sensitivity analysis**

The EAG did deterministic sensitivity analysis to assess which parameters had the largest impact on model results (see section 5.3.2 and table 43 in the external assessment report). In all analyses, no testing remained dominated by the genetic testing strategies (figures 27 to 30 in the external assessment report).

#### **Probabilistic sensitivity analysis**

Full details of the probabilistic sensitivity analysis can be found in section 5.3.3 and table 43 of the external assessment report.

As in the deterministic analysis, the probabilistic analysis found that all testing strategies dominated no testing. Net monetary benefits were slightly larger in the probabilistic analysis, but overall results were similar (see tables 55 to 57 in the external assessment report).

In all cases, the probability of no testing being cost effective was close to 0 across all willingness-to-pay thresholds. Genedrive had the highest probability of being cost-effective in all populations, but was assumed to have the same parameters as the Genomadix Cube (except a lower cost). The laboratory-based test had a much lower probability of being cost effective in the TIA or minor stroke population, compared to the non-minor stroke population (compare figures 33 and 36 in the external assessment report). The EAG stated that this was driven by the delay in receiving test results, as people with TIA or minor stroke typically start antiplatelet therapy immediately rather than 2 weeks after the initial stroke.

### **Threshold analyses**

The EAG did 2 threshold analyses. See the full results in section 5.3.5 of the external assessment report.

In the first analysis, the EAG varied the cost of laboratory testing. In the non-minor ischaemic stroke population, the laboratory test was cost-effective versus Genedrive at costs per test below £29, versus the Genomadix Cube below £184, and versus no test below £6,251. In the TIA or minor stroke population, the laboratory test was cost-effective at costs per test below £79 versus the Genomadix Cube, below £2,723 vs no test, but was dominated at all costs against the Genedrive test.

The EAG also examined the impact of the accuracy of the Genedrive *CYP2C19* test by varying sensitivity and specificity (set to the same value) in a one-way threshold analysis. In both populations, the Genedrive test was more cost-effective than the Genomadix Cube at sensitivity and specificity of 99% or more, and more cost effective than laboratory testing at sensitivity and specificity of 98% or more.

## **Analysis of alternative scenarios**

Find the full list of the EAG's scenario analyses in table 42 of the external assessment report on page 133. Results can be found in tables 58 and 59 in the external assessment report.

*CYP2C19* testing was found to be cost saving and generated more QALYs compared with no testing across all scenarios explored. Scenarios with the highest net benefit were those where the prevalence of *CYP2C19* loss-of-function alleles was high and for a younger cohort. The lowest net benefit scenarios were those with 69.9% uptake of personalised treatment and where ticagrelor or aspirin were used as the alternative antiplatelet therapy.

## **4 Summary**

### **Clinical effectiveness**

Two small studies were identified that evaluated a testing and treatment strategy directly relevant to the decision question. The EAG considered both to have a high risk of bias. Neither study found significant differences in clinical outcomes for people who were tested and treated based on their *CYP2C19* genotype compared to people who were universally treated with clopidogrel. The EAG stated there was a suggestion that testing plus treating based on loss-of-function status was associated with a reduced incidence of ischaemic stroke, TIA and a composite outcome of secondary vascular events, but confidence intervals were wide.

Seven studies were identified that investigated whether people with loss-of-function alleles have better clinical outcomes when treated with an alternative antiplatelet therapy compared to those treated with clopidogrel. No studies used clopidogrel as it would be used in the NHS (starting 2 weeks after stroke onset). No studies used dipyridamole and aspirin as the alternative therapy, which the EAG considered is most likely to be offered as an alternative to clopidogrel in NHS clinical practice. Two studies provided evidence that

treatment with ticagrelor with aspirin significantly reduced the risk of secondary vascular events (HR 0.76, 95% CI 0.65 to 0.90) and stroke in those with loss-of-function alleles, compared to treatment with clopidogrel with aspirin. Ticagrelor does not have a marketing authorisation for ischaemic stroke or TIA in the UK. No significant difference in outcomes was found for other comparisons between treatments.

The EAG stated there was strong evidence from 25 studies that people with loss-of-function alleles treated with clopidogrel (with or without aspirin) were at higher risk of secondary vascular events (HR 1.72, 95% CI 1.43 to 2.08), stroke (HR 1.46, 95% CI 1.09 to 1.95) and ischaemic stroke (HR 1.99, 95% CI 1.49 to 2.64) than those without loss-of-function alleles. This effect was reduced in studies where a loading dose of clopidogrel was given, where long-term aspirin was given alongside clopidogrel, and in studies where people with TIA were included rather than only stroke.

Summary estimates of sensitivity and specificity for the Genomadix Cube (from 11 studies) were both 100% for the detection of the \*2 or \*3 alleles (the test does not detect other loss-of-function variants). No diagnostic accuracy studies of the Genedrive *CYP2C19* test were found.

There was wide variation in the test failure rate for the Genomadix Cube (0.4% to 19%). Some studies provided data on the prevalence of the different variant forms of *CYP2C19*, but these were relatively small samples with little information on ethnicity to show how prevalence of variant forms (particularly other than \*2 or \*3) differ by family background.

Eight genomic laboratory hubs responded to the EAG's survey about how *CYP2C19* testing could be implemented in NHS laboratories. Most labs said that they would test for the \*2 and \*3 alleles, with 1 saying that they would test for all using next-generation sequencing.



## Cost effectiveness

In the EAG's base case, all testing strategies dominated no testing (*CYP2C19* testing produced more QALYs and cost less than no testing). This finding was robust to deterministic and scenario analyses.

There were very small differences in the QALYs generated by the EAG's model for each testing strategy (less than 0.01 QALYs).

The probability that laboratory testing was cost effective was much lower in the minor stroke or TIA compared to the non-minor stroke population. This was because of the 1-week delay between taking the sample and getting the test result for laboratory-based testing (there was no delay for the point of care tests). In the overall population (that is, all stroke and TIA) more people had non-minor stroke (68.2% based on data from Public Health England).

The cost of laboratory testing was uncertain as the method of testing that would be used in different laboratories was also uncertain. Threshold analysis found that laboratory testing would be cost-effective in the non-minor stroke population up to a cost per test of £184 versus the Genomadix Cube, or up to £29 versus the Genedrive test.

As there was limited information on the Genedrive test, the EAG assumed that the test performance parameters were the same as for the Genomadix Cube. Since the Genedrive test has a lower cost per test, Genedrive was the more cost-effective option. The EAG emphasised that this should be considered exploratory, and it did a threshold analysis in which the sensitivity and specificity of the Genedrive test were reduced (but kept equal). This analysis found that the Genedrive test would be cost effective at sensitivity and specificity of 99% or more versus the Genomadix Cube, and 98% or more versus laboratory testing.

## 5 Issues for consideration

### Clinical effectiveness

Less data was identified using the EAG's preferred study designs, and what was identified had high risk of bias (objective 1), or included care that didn't reflect NHS practice to show how using an alternative treatment to clopidogrel for people with loss-of-function alleles changes risk of future clinical events (objective 2). The EAG stated that a major limitation of the review was that none of the studies for objectives 1 or 2 evaluated dipyridamole with aspirin, the most likely alternative treatment to clopidogrel that would be offered in the NHS. Most evidence on the effect of personalised antiplatelet therapy based on *CYP2C19* genotype was from differences in outcomes for people with and without loss-of-function variants who were treated with clopidogrel (see [objective 3](#)). This difference in effect was used in the economic model (see [model inputs](#)).

No data for any of the tests was identified in children or young people.

The accuracy of the Genomadix Cube reported in the literature was very high (see [objective 4](#)). However, the reference standard for these studies was laboratory testing only for those alleles that the point-of-care test detects (\*2, \*3 and \*17). Other loss-of-function alleles are rarer but would be missed by this test and this is not reflected in these estimates of accuracy. The true accuracy is therefore likely to be lower than reported. Laboratory-based tests can detect all alleles (depending on which method is used) but for some methods this could increase time or cost of testing. The EAG stated that it is also unclear exactly which alleles should be tested for. While some alleles such as \*2, \*3, \*4 and \*8 have been clearly linked to loss-of-function, for others such as \*9 and \*10 the evidence base is still evolving, and these alleles are currently categorised as "indeterminate" or "likely loss-of-function". It concluded that the value of testing for additional alleles beyond \*2 and \*3 is unclear.

The Genedrive test detects more *CYP2C19* alleles than Genomadix Cube (\*4, \*8 and \*35) which the EAG stated may be of particular value for people with Asian or Ashkenazi Jewish family backgrounds where these alleles are found at higher frequencies. But no data on accuracy were identified. This test also does not currently have regulatory approval. The EAG highlighted a further benefit of this test is that it does not require the frozen storage of test kits that is required for Genomadix Cube. It also allows data to be uploaded directly into patient records, whereas data are only stored locally with Genomadix Cube.

### **Cost effectiveness**

The EAG stated that the main conclusion is that *CYP2C19* testing is cost saving and generates additional QALYs, and this was robust to assumptions made. It also said that cost-effectiveness acceptability curves showed that there is a high probability that one of the testing strategies is cost-effective. The EAG stated that because the different testing strategies (point-of-care test or laboratory test) had similar QALYs under its model assumptions, choice between them is largely one of reducing cost and ease of implementation.

Clinical advice to the EAG was that modified-release dipyridamole with aspirin would be the first choice of alternative antiplatelet therapy for people with loss-of-function alleles in the NHS. No studies were identified that compared the clinical outcomes of people with loss-of-function alleles when treated with clopidogrel versus treatment with dipyridamole with aspirin (see [objective 2](#)). The EAG identified 1 study that compared dipyridamole plus aspirin with clopidogrel monotherapy (the P<sub>Ro</sub>FESS trial). It assumed that the effect of dipyridamole with aspirin was the same regardless of loss-of-function status.

Point-of-care tests may be more likely to be cost effective (compared to laboratory-based testing) in the non-minor stroke and TIA population, rather than the non-minor stroke population.

The point-of-care tests do not detect all loss-of-function alleles, and may detect fewer alleles than laboratory-based testing (this depends on the method of testing used in a laboratory, which may vary across the country). In the economic model, the EAG assumed a slightly lower sensitivity for the Genomadix Cube than was found in the clinical effectiveness review; assuming 1 in 100 people with a loss of function alleles would have a variant that the point-of-care tests would not detect. But the true value of this is uncertain, and it may vary by family background (see the equalities section).

The Genedrive test detects more loss of function alleles than the Genomadix Cube (\*4, \*8 and \*35 alleles in addition to \*2 and \*3), and the EAG highlighted several further advantages for this technology. But no accuracy data or data on test failure rate was available, so to model this test EAG made a strong assumption that the tests would have same accuracy and failure rate as the Genomadix Cube, with no evidence to support this. A threshold analysis showed that the Genedrive would need to have high sensitivity and specificity (98% or higher) to be cost effective compared to laboratory-based testing.

The EAG found no evidence for children or young people. It was therefore unable to model this population in the economic evaluation. The EAG did a scenario using a younger adult cohort (aged 40) which increased net monetary benefit by around £3,000 (54%) in the non-minor stroke population, and by around £1,500 (56 to 58%) in the TIA or minor stroke population. Clopidogrel is not normally recommended for children to prevent secondary stroke (see section 1.4 in the external assessment report), but if it was offered the EAG suggested that genetic testing may be a cost-effective option.

## **6 Equality considerations**

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

Loss-of-function alleles are more prevalent in some populations than others, for example in Asian populations. The EAG investigated whether ethnicity had an effect on the response to clopidogrel for people with or without loss-of-function alleles. No statistically significant effect was observed (see [objective 3](#)).

Rarer loss-of-function alleles may be more prevalent in certain ethnic groups. 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. Studies identified in the EAG's clinical effectiveness review only reported on the prevalence of \*2, \*3 and \*17 alleles (see [objective 5](#)), and many did not report ethnicity, so the impact of these alleles is unclear.

## 7 Implementation

### **Laboratory hub anticipated barriers to implementing *CYP2C19* testing**

In the EAG's survey, the expected volume of testing was highlighted as a major barrier to implementing *CYP2C19* testing in the NHS, with one centre noting that they do not currently perform any tests on this scale and so do not have the necessary infrastructure. Staffing was also seen as an important concern. The Scottish Tayside lab, which is currently piloting *CYP2C19* testing highlighted the following as barriers to implementing testing:

- Fixed budget for pilot so limited requests to stroke unit and cardiology
- Unable to accept requests from GPs
- Difficulty for some medical disciplines to understand output of genetic results
- Separate requesting and reporting systems for acute and primary care.

## Reporting of results and uptake of personalised treatment

The EAG noted that the way that test results are recorded for future reference could affect the cost effectiveness of testing. If test results are not appropriately added to a person's medical record, personalised treatment may not be possible. In a scenario analysis, the EAG found that reducing the uptake of personalised treatment to 69.9% reduced the cost effectiveness of testing (although testing still dominated no testing). The EAG noted that the Genedrive test allows data to be uploaded directly into patient records, where data are only stored locally on the Genomadix Cube.

The uptake of personalised treatment could also be affected by the time to get test results. Point-of-care tests provide results in around 1 hour, which could allow alternative treatment to be given before a person is discharged. For laboratory-based tests, a turnaround time of 1 week could mean that results are not communicated before discharge and there is a risk that treatment is not changed for loss-of-function carriers.

## People currently taking clopidogrel

Many people who have had ischaemic stroke or TIA are currently taking clopidogrel for secondary prevention, of whom a proportion will have loss-of-function *CYP2C19* variants. If testing for *CYP2C19* variants after stroke becomes NHS clinical practice, people already taking clopidogrel may also wish to be tested.

## *CYP2C19* and non-clopidogrel drugs

Many drugs other than clopidogrel are also metabolised by the *CYP2C19* enzyme. The Clinical Pharmacogenetics Implementation Consortium (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](#)). Knowing *CYP2C19* genotype may affect treatment of non-stroke conditions, including those already present

before genotyping. Recording genotyping results into patient records would be important to ensure that this information is not lost.

### **Future pharmacogenetic panel testing**

There are proposals to implement pre-emptive pharmacogenetic panel testing in the NHS, which would likely include *CYP2C19*. Pilot projects are ongoing, but if this were to become common practice then the benefits of targeted genotyping would be reduced.

### **Implementation of point-of-care tests in laboratories**

Six respondents to the EAG's survey said that it should be possible to use a point-of-care test in a central laboratory workflow. However, 1 said that it would not be efficient given the required volume of testing, and another that there is no precedent in their lab. Additional resources needed included staff and freezers. Two laboratories said that they would not be able to use point-of-care tests, with 1 saying that staff would have to regularly interrupt their duties to perform this test.

The EAG excluded some costs in their model because they were negligible when evaluated per test. These included cost of freezers to store the Genomadix Cube reagents, staff training costs, and changes to processes to ensure results are recorded in patient records. However, the EAG noted that these requirements would represent an up-front investment if testing is adopted in the NHS.

## **8 Authors**

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## Glossary

### Allele

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.

### CYP2C19

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.

### Modified Rankin Scale (mRS)

A 6-point disability scale often used as an outcome measure in clinical trials of stroke. The scale ranges from 0 (no residual symptoms) to 5 (severe disability). A score of 6 is sometimes used to signify death.

### Next-generation sequencing

Next-generation sequencing technologies sequence millions of short DNA sequences in parallel. This offers several advantages over Sanger sequencing, such as higher sensitivity, quicker turnaround for large sample numbers and a lower limit of detection.

### P2Y12

P2Y12 is a receptor involved in blood clotting.

### Personalised treatment

Treatment based on specific patient characteristics such as genotype. For example, people without loss-of-function *CYP2C19* alleles could be given clopidogrel while people with loss-of-function alleles would be given an alternative antiplatelet therapy.



## **Sanger sequencing**

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.