Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Assessment

October 2024

In response to an enquiry from the Accelerated National Innovation Adoption (ANIA) collaborative

Genotype testing to guide clopidogrel use after an ischaemic stroke or transient ischaemic attack (TIA)

Key messages

1. People who have an ischaemic stroke or TIA are often prescribed the antiplatelet medication clopidogrel to reduce their risk of another stroke. Some people are clopidogrel resistant and remain at risk of having another ischaemic stroke while taking clopidogrel.
2. Clopidogrel resistance can be caused by changes in the CYP2C19 gene. Genotype-guided antiplatelet therapy can potentially reduce the risk of stroke recurrence in people who are clopidogrel resistant and have had an ischaemic stroke or TIA.
3. People who are clopidogrel resistant should be prescribed an alternative antiplatelet.
4. Our cost analysis for NHSScotland found that the introduction of laboratory-based genotype-guided antiplatelet therapy for people who have had an ischaemic stroke or TIA led to estimated resource savings of £17.9 million over 5 years, based on 943 fewer people having a recurrent stroke.

What were we asked to look at?

We were asked to review the evidence on CYP2C19 genotype testing to guide antiplatelet therapy for people who have had an ischaemic stroke or TIA and who could be prescribed clopidogrel.

Why is this important?

In Scotland in 2023, there were 9,373 people who had a confirmed ischaemic stroke and an estimated 3,763 people who had a TIA.[1, 2] People who have a non-cardioembolic ischaemic stroke or TIA are at increased risk of having another stroke and are often prescribed antiplatelet medications, such as clopidogrel, to reduce this risk.[3]

In the UK, an estimated 28.7% of people prescribed clopidogrel are unable to metabolise (process) it, meaning it cannot act to reduce their stroke risk.[4] Clopidogrel resistance can be caused by changes in the CYP2C19 gene that can be identified using genotype testing. This allows clinicians to prescribe a more effective antiplatelet medication.[3]

What was our approach?

We reviewed the published literature on the clinical effectiveness, cost effectiveness, safety and patient experience of CYP2C19 genotype testing for people who have had an ischaemic stroke or TIA. We conducted a resource impact analysis using modelling work done by the National Institute for Health and Care Excellence (NICE). More information about SHTG assessments can be found on our website.

What next?

Our assessment will be used to inform an ANIA value case. The value case will inform decision making on the roll out of CYP2C19 genotype testing in NHSScotland.

Key points

Genotype-guided antiplatelet therapy versus usual care

1. Evidence from two randomised controlled trials (RCTs) and two small non-randomised studies, all conducted in China, suggests that CYP2C19 genotype-guided antiplatelet therapy has the potential to reduce the risk of ischaemic stroke recurrence in people who have had an ischaemic stroke or TIA.

Study	n people	Ischaemic stroke recurrence Hazard ratio (HR)	95% confidence interval (CI)
RCT*	2,663	0.96	0.64 to 1.45
RCT	650	0.33	0.09 to 1.22
Non-RCT	190	0.33	0.03 to 3.20
Non-RCT	80	0.41	0.15 to 1.18

**Composite outcome of acute ischaemic stroke or TIA*

2. NICE diagnostic guidance recommends using CYP2C19 genotype testing to determine whether clopidogrel is the most suitable antiplatelet for people who have had an ischaemic stroke or TIA.

3. The results of a NICE economic model show that point of care and laboratory-based genotype testing were more effective and less costly than no testing. Both types of test generated similar cost savings and quality adjusted life years (QALYs).

4. Our cost analysis for NHSScotland found that genotype-guided antiplatelet therapy was resource saving compared with no testing, resulting from a reduction in-hospital and rehabilitation costs associated with fewer people having a recurrent stroke.

    - Laboratory-based genotype-guided antiplatelet therapy was resource saving from the year of implementation. Over a 5-year period, resource savings amounted to £17.9 million, based on 943 fewer people having a recurrent stroke.

    - Point of care genotype testing was cost incurring in the year of implementation and from year two onwards became resource saving. Over a 5-year period, the Genedrive point of care test was associated with £18 million in resource savings and 961 fewer recurrent strokes. Over the same period, the Genomadix Cube point of care test was associated with resource savings of £17.6 million, based on 958 fewer people having a recurrent stroke.

Clopidogrel effectiveness and safety versus alternative antiplatelet therapy

5. A meta-analysis of two RCTs (n=7,087) showed that ticagrelor is more effective at reducing the risk of ischaemic stroke recurrence compared with clopidogrel in people who are clopidogrel resistant: HR 0.77, 95% CI 0.65 to 0.93. Ticagrelor was associated with a statistically significant increase in the risk of bleeding: HR 1.85, 95% CI 1.45 to 2.23.

6. The reduced risk of ischaemic stroke recurrence associated with ticagrelor was maintained at 1 year follow up in one RCT (n=6,412): HR 0.81, 95% CI 0.68 to 0.96. Participants in the trial mostly stopped taking clopidogrel or ticagrelor after the 90-day trial period.

Clopidogrel therapy in people with clopidogrel resistance

7. Two meta-analyses demonstrated that treating people who are clopidogrel resistant with clopidogrel is associated with a significantly increased risk of recurrent stroke compared with people who are not clopidogrel resistant.

    - A meta-analysis of 12 RCTs (n=4,100) reported a significantly increased risk of ischaemic stroke in people with clopidogrel resistance who are treated with clopidogrel: HR 1.99, 95% CI 1.49 to 2.64.

    - A meta-analysis of 25 studies (RCTs and observational studies, n=7,672) reported an increased risk of any stroke in people with clopidogrel resistance treated with clopidogrel: odds ratio (OR) 2.18, 95% CI 1.80 to 2.63.

Diagnostic test accuracy

8. One study (n=250) assessing the diagnostic accuracy of the Genedrive point of care test, reported sensitivity to be 100% (96% to 100%) and specificity to be 100% (98% to 100%).

9. Eleven studies (n=3,895) assessing the diagnostic accuracy of the Genomadix Cube™ point of care test reported sensitivity of 100% (94% to 100%) and specificity of 100% (99% to 100%).

10. CYP2C19 genotype test failure rates are low: 0.6% for the Genedrive system (one study, n=250), 0.4% to 19% for the Genomadix test (10 studies, n=5,000), and <1% in NHS England laboratories.

Patient and social aspects

11. Three studies (n=1,678) in people with cardiac conditions found that most participants felt CYP2C19 genotype testing was important for guiding their care. People's perception of the value of genotype testing was positively correlated with their level of knowledge and confidence in understanding genetic information.

Contents

Definitions

Alleles	The different forms or variants of a gene. Each person inherits two alleles of each gene, one from each parent.[5]
Gene variant	A permanent change in the deoxyribonucleic acid (DNA) sequence of a gene.[6] These were formerly known as gene mutations.
Genotype	The complete set of genes that an individual possesses.[7] It can also refer to the specific variant of a gene that an individual carries, such as their CYP2C19 genotype.
Modified Rankin scale (mRS)	The modified Rankin scale (mRS) measures disability and dependence for activities of daily living in people who have had a stroke.[8] ■ score 0 = no disability or symptoms ■ score 1 = no significant disability despite symptoms ■ score 3-5 = increasing levels of moderate to severe disability ■ score 6 = dead.
Pharmacogenetics / pharmacogenomics	The use of genetic information to optimise medication selection and dosage for individual patients.[9]

Abbreviations are listed in *Appendix 1*. Definitions of terms relating to diagnostic test accuracy are provided in *Appendix 2*.

Introduction

An ischaemic stroke is a potentially life threatening event where a blood clot blocks the flow of blood to parts of the brain.[3, 10] A TIA is a milder, related condition where the brain's blood supply is briefly interrupted. A stroke can cause lasting brain damage, disability or death.

People who have an ischaemic stroke or TIA are at increased risk of having another stroke.[3] They are often prescribed antiplatelet medications to reduce this risk. Antiplatelet medications reduce the risk of a recurrent stroke by preventing blood clots from forming.

The most commonly prescribed antiplatelet medication is clopidogrel which needs to be metabolised (processed) within the body to be effective.[3] Clopidogrel resistance occurs when a person is unable to effectively metabolise clopidogrel.[4] Resistance can be caused by changes in the CYP2C19 gene. The effectiveness of clopidogrel can also be affected by taking omeprazole, obesity, having diabetes or having hypertension.[3]

Relevant CYP2C19 gene variants that affect clopidogrel metabolism can be detected by laboratory or point of care genotype tests.[3] Genotype testing would ensure that people are prescribed the most effective antiplatelet treatment.

Genetics of clopidogrel resistance

Every cell in the human body contains genetic material. Each gene has two copies, one inherited from each parent. These copies are called alleles or variants.

Most genes encode proteins. Enzymes are a type of protein.[3] The CYP2C19 gene encodes an enzyme that metabolises clopidogrel into its active form. Some people have CYP2C19 gene variants that reduce the enzyme's function. These are known as loss of function (LOF) variants or LOF alleles.

Different variants are given a designation, such as *1 or *2, to allow experts to categorise the variants detected. People with two normal CYP2C19 variants (*1/*1) metabolise clopidogrel normally.[3] Those with one normal and one LOF variant (for example, *1/*2) are intermediate metabolisers and metabolise clopidogrel less effectively. People with two LOF variants (for example, *2/*2) are poor metabolisers who gain minimal benefit from taking clopidogrel. The most common LOF variants in people with a white European genetic heritage are *2 and *3. A full list of known CYP2C19 variants and their functional status is given in *Appendix 3*.

Research questions

1. What is the clinical effectiveness and safety of clopidogrel genotype testing compared with no testing after a non-cardioembolic ischaemic stroke or TIA?
2. What are the cost effectiveness and resource impact implications for Scotland of clopidogrel genotype testing compared with no testing after non-cardioembolic ischaemic stroke or TIA?
3. What are patient experiences and preferences in relation to clopidogrel genotype testing after non-cardioembolic ischaemic stroke or TIA?

Literature search

A systematic search of the secondary literature was carried out between 25 and 26 of April 2024 to identify systematic reviews, health technology assessments and other evidence-based reports. The Medline and PsychInfo databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 25 and 26 of April 2024 using the Medline and PsychInfo databases. Results were limited to English language publications.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies. Websites of organisations related to this topic, such as the Picker Institute, Patient Voices and the Kings Fund Patient Experience Blog, were also searched.

Concepts used in all searches include: clopidogrel, genetic testing, pharmacogenomic testing, genotype testing, patient preference, patient perspective, patients view, decision making. A full list of resources searched, and terms used is available on request.

Health technology description

There are two point of care CYP2C19 genotype tests: the Genedrive CYP2C19 ID Kit and the Genomadix Cube™ CYP2C19 System.[3]

The Genedrive CYP2C19 ID Kit can detect the *2, *3, *4, *8, and *35 LOF variants. The technology consists of:

- the Genedrive System analyser
- the Genedrive CYP2C19 ID Kit containing cartridges of reagents, cheek swabs, a transfer capillary and a collection buffer.[3]

A single cheek swab is needed for each test.[3] Reagents for the Genedrive ID Kit can be stored at room temperature. Each test takes 40 minutes to 1 hour to complete. The test results are displayed on the analyser screen, showing the person's two alleles and their metaboliser status.

The Genomadix system can detect the *2 and *3 LOF variants of the CYP2C19 gene. The technology consists of:

- the Genomadix Cube™ platform, consisting of the Genomadix analyser instrument, user interface and barcode scanner
- the Genomadix Cube™ test kit, which includes cheek swabs and cartridges of reagents.[3]

Three cheek swabs are needed for each test.[3] Reagents for the Genomadix system must be stored at −15°C to −80°C and used within 15 minutes of removal from the freezer. The manufacturer will provide a mini-freezer free of charge. Each test takes approximately 1 hour to run.

Laboratory-based CYP2C19 genotype testing uses a range of techniques, including gene sequencing or targeted genotyping assays.[3] Laboratory-based tests use a blood sample instead of a cheek swab. Laboratory tests can potentially identify all CYP2C19 gene variants, but it is likely that commercially available laboratory kits will test for the most common and clinically relevant variants (that is, the same variants as point of care tests).

Epidemiology

In 2023 in Scotland, 9,373 people had a confirmed ischaemic stroke, which accounts for 85% of all strokes that year.[1] An estimated 7,030 (75%) of these people had a non-cardioembolic ischaemic stroke (S Taws, Senior Data Analyst, Public Health Scotland. Personal Communication, 25 July 2024).[11] Approximately 3,763 people had a TIA in Scotland in 2023 (69 TIAs per 100,000 population).[2]

An estimated 12.1% of people who have had a first non-cardioembolic stroke or TIA have a recurrent stroke within 5 years (S Taws, Senior Data Analyst, Public Health Scotland. Personal Communication, 25 July 2024). Routine statistics on stroke recurrence are not available in Scotland. Public Health Scotland analysed national data to estimate the incidence of stroke recurrence after an initial stroke or TIA (*Appendix 4*). In line with published stroke data, the risk of stroke recurrence was highest in the first 3 months after an initial stroke or TIA (*Table 1*).

Table 1: Estimated Scottish stroke recurrence rates after an initial non-cardioembolic stroke or TIA (S Taws, Senior Data Analyst, Public Health Scotland. Personal Communication, 25 July 2024)

Time from initial stroke or TIA	Cumulative percentage recurrence	Cumulative stroke events	Recurrence rate per person-year
90 days	1.84%	543	0.073
1 year	6.84%	1,431	0.051
2 years	14.82%	2,221	0.042
3 years	24.99%	2,775	0.036
4 years	37.05%	3,234	0.033
5 years	50.85%	3,645	0.031

An estimated one in five strokes (of any type) are fatal.[12] In 2021, 2,157 people in Scotland died from a stroke (40.1 stroke deaths per 100,000 population).[2] In the same year, the 30-day mortality rate was 14.7% and 90-day mortality rate was 21.1%.[1]

Strokes are more common in people over 60 years of age.[1] Approximately half of all strokes (51.0%) occur in people aged 60–80 and 32.7% in people aged over 80. Strokes are slightly less common in women (47.9%) compared with men (52.1%).

In the UK, an estimated 28.7% of people prescribed clopidogrel have at least one LOF variant associated with clopidogrel resistance.[13]

Inequalities

Stroke risk

People living in the most deprived areas of Scotland (defined based on the Scottish Index of Multiple Deprivation) have more strokes than people living in the least deprived areas (23.5% versus 16.4% in 2022).[1] The odds of having a stroke are 15% greater among people living in the most deprived areas compared with the least deprived areas (OR 1.15, 95% CI 1.02 to 1.30).[13]

In a UK cohort of people, patients from an ethnic minority background* (n=95) had an earlier age of stroke onset and a two- to four-fold increase in stroke related mortality compared with patients with Caucasian ancestry.[14] The odds of a stroke before age 69 were higher (OR 2.91, 95% CI 1.86 to 4.54) for people living in the UK who have an ethnic minority background compared with people from a white background. People from an ethnic minority background who had an acute stroke had

* People were grouped into a category of 'ethnic minority background' if they were reported to be from a white or black Caribbean, white or black African, any mixed, Indian, Pakistani, any Asian, African, any black, Chinese or any other ethnic background. Most people in the study were from a south Asian background.

significantly higher odds of needing palliative care within the first 72 hours (OR 3.88, 95% CI 1.92 to 7.83) and of dying in hospital (OR 2.50, 95% CI 1.41 to 4.44) compared with people from a white background.

Prevalence of LOF variants

The prevalence of CYP2C19 LOF variants varies significantly between people with ancestry from different geographical areas (*Table 2*).[15, 16] People with an east Asian (59%) or central or south Asian (49%) genetic heritage have a higher prevalence of one or two LOF alleles compared with people with a white European (28%) genetic heritage. In a UK cohort of people with Bangladeshi or Pakistani ancestry (n=44,396), 57% were found to have at least one CYP2C19 LOF allele.[3] This variation indicates that some populations are disproportionately affected by clopidogrel resistance.

Based on the latest census, 12.9% of people living in Scotland describe themselves as having an ethnic minority background. We applied this proportion to estimate the percentage of poor and intermediate metabolisers from these population groups (*Table 2*).

Table 2: Estimated prevalence of poor and intermediate metabolism of clopidogrel by geographical ancestry[15, 16]

Biogeographical region[†]	Poor metaboliser	Intermediate metaboliser	Normal metaboliser	% Scottish population[*]
White European	2%	26%	40%	5.64%
Sub-Saharan Africa	5%	34%	37%	1.08%
African American or Afro-Caribbean	5%	34%	33%	0.12%
North American	1%	21%	63%	-
Latino	1%	19%	53%	-
East Asian	13%	46%	38%	1.46%
Central or south Asian	8%	41%	29%	2.44%
Near eastern	2%	23%	45%	0.41%
Oceanian	57%	37%	4%	-

[†] White European = people living in European countries, travellers or gypsies. Sub-Saharan Africa = people living in sub-Saharan African countries, such as Zimbabwe, Ethiopia, Tanzania, Ghana, Uganda and Nigeria. African American/ Afro-Caribbean = people of African descent who are living in North America or Barbados. American = people living in the United States of America, Mexico, Canada or Brazil. Latino = people living in central and south America, including Bolivia, Columbia, Puerto Rica, Brazil, Ecuador and Peru. East Asian = people living in China, Japan, Korea, Taiwan, Indonesia, Philippines, Thailand, Vietnam or Siberia. Central/south Asian = people living in India, Pakistan or Sri Lanka. Near eastern = people living in Turkey, Egypt or the Middle East. Oceania = people living in New Zealand and other Oceanian islands.

**Estimated based on Scottish census returns. Not all categories on the census could be matched to the biographical regions listed in the table.*

The prevalences of specific CYP2C19 LOF variants varies among people with ancestry from different geographical areas.[3] For example, the prevalence of *4, *8 and *35 LOF variants in the UK stroke population is estimated to be 0.6%. In contrast, the *35 allele has a prevalence of up to 3% in people with a sub-Saharan African heritage and the *4 allele has been found to be common in Ashkenazi Jewish populations. For this reason, tests that focus only on a few LOF alleles could introduce inequalities by failing to identify people with other variants.

Effects of LOF variants on risk of recurrent stroke

NICE found evidence that suggests that the effects of LOF variants on the risk of a recurrent vascular event varies by ethnic background (*Table 3*).[3] The ethnic groups listed in *Table 3* are not well defined in the source documents and may not accurately describe genetic populations.

Table 3: Ethnicity subgroup (as defined by NICE) analysis on the risk of secondary vascular events in people with LOF variants compared with people without LOF variants[3]

Ethnic group	n studies	HR (95% CI)
White	4	2.66 (1.68 to 4.21)
East Asian	16	1.80 (1.50 to 2.15)
Mixed	4	1.27 (0.35 to 4.69)
Black	1	1.93 (0.59 to 6.33)
Hispanic	1	0.27 (0.02 to 4.59)

A meta-analysis comparing stroke recurrence rates in people with and without CYP2C19 LOF alleles who were treated with clopidogrel, conducted subgroup analyses based on the ethnicity of study participants.[17] It is unclear how the ethnic groups were defined in this analysis and they may not accurately describe genetic populations.

There are 28 studies included in the meta-analysis. The risk of recurrent ischaemic stroke in people with LOF alleles compared to people without them was only significantly different in people with Asian ancestry (predominantly Chinese populations):

- Asian populations OR 2.29, 95% CI 1.88 to 2.80, p<0.00001, 22 studies, n=6,533
- Europeans and Americans OR 1.47, 95% CI 0.71 to 3.04, p=0.30, four studies, n=824
- African populations OR 1.93, 95% CI 0.58 to 6.43, two studies, n=97
- other ethnicities OR 0.22, 95% CI 0.02 to 2.32, p=0.21, two studies, n=249.

These results should be interpreted with caution since there were very few studies and participants in the non-Asian subgroup analyses.

Another meta-analysis compared outcomes for people with and without CYP2C19 LOF variants treated with clopidogrel in populations other than east Asians.[18] There were eight studies in this meta-analysis (n=1,673). The studies were conducted in Europe (three studies), the USA (two studies), Turkey (one study) and two studies were multiregional.

The results of this meta-analysis suggest that CYP2C19 LOF variants have a similar impact on the efficacy and safety of clopidogrel in people from different geographical areas (*Table 4*). Subgroup analyses looking specifically at people with European ancestry had similar results to all non-east Asian populations combined.

Table 4: Results from a meta-analysis comparing outcomes in people with CYP2C19 LOF variants and people without LOF variants in non-east Asian populations[18]

Outcome	Group	n patients (n studies)	Relative risk (95% CI)	p-value	GRADE
Stroke	All	1,391 (6)	1.68 (1.04 to 2.71)	0.03	Moderate
	European	367 (3)	2.69 (1.11 to 6.51)	0.03	-
Composite vascular events	All	842 (4)	1.15 (0.58 to 2.28)	0.70	Very low
	European	224 (2)	1.63 (0.91 to 2.93)	0.10	-
Bleeding	All	1,053 (3)	0.84 (0.38 to 1.86)	0.67	Very low
	European	306 (2)	1.74 (0.58 to 5.23)	0.32	-

A meta-analysis of 15 studies (n=4,762) compared recurrent stroke risk in people who were clopidogrel resistant with people who were not.[19] Study populations included people with east Asian (85%), European (8%), African (2%) or other (5%) ancestry. A subgroup analysis based on ancestry found a significantly increased risk of stroke recurrence in people with LOF alleles who had Asian (Relative risk (RR) 1.93, 95% CI 1.55 to 2.39) or European (RR 2.46, 95% CI 1.06 to 5.72) ancestry, but not in people with African ancestry (RR 1.74, 95% CI 0.63 to 4.79), compared with people with similar ancestry but no LOF alleles.

Clinical effectiveness and safety

Genotype-guided antiplatelet therapy versus usual care

Two RCTs and two small non-randomised studies compared genotype-guided antiplatelet therapy with usual care in people who have had an ischaemic stroke or TIA.[3, 20, 21]

Randomised studies

A multicentre RCT, conducted across 14 hospitals in China, compared genotype testing with usual care in people who had an acute ischaemic stroke or TIA.[20] The study was open label, meaning participants knew what medication they were taking. The randomisation process for assigning participants to the intervention and control groups was not clearly described and may have introduced bias to the study.

People in the intervention group were genotyped for *2 or *3 LOF variants using laboratory-based testing. Individuals with any LOF alleles were prescribed aspirin. If they were aspirin resistant, they received clopidogrel. People who were resistant to both clopidogrel and aspirin were prescribed ticagrelor or cilostazol. Control group participants were treated with clopidogrel or aspirin as per Chinese national guidelines.

A total of 2,663 people were randomised. Trial participants had a median age of 64 years and 65% were male. Almost all participants were ethnic Han Chinese (99.65%). Most participants had had an acute ischaemic stroke (97.2%). Around a fifth of study participants (21.9%) had a medical history of a previous ischaemic stroke. Baseline characteristics were balanced and comparable between the two groups. In the intervention group, 60.6% of participants had at least one CYP2C19 LOF variant. The control group were not genotyped, making it unclear if the groups were well matched in terms of genotypes, potentially introducing bias to the comparisons.

There was no statistically significant difference between groups for the primary outcome of recurrent ischaemic stroke or TIA (*Table 5*). People receiving genotype-guided antiplatelet therapy had a significantly better functional prognosis compared with the control group. The risk of a bleeding event was estimated to be 34% greater in the control group.

Table 5: Results of an RCT in China comparing genotype-guided antiplatelet therapy with usual care in patients who had an acute ischaemic stroke or TIA[20]

Outcome	n events Intervention group (n=1,344)	n events Control group (n=1,319)	HR (95% CI)	p-value
Acute ischaemic stroke or TIA	46	48	0.96 (0.64 to 1.45)	0.843
Poor functional prognosis (mRS 3-6)	200	240	0.77 (0.63 to 0.95)	0.012
Severe, moderate or mild bleeding	49	72	0.66 (0.45 to 0.95)	0.025

A single centre RCT at a hospital in China compared genotype-guided antiplatelet therapy with usual care in people who had a mild-to-moderate acute ischaemic stroke or moderate-to-high risk of a TIA.[21] The trial was open label, so participants knew what medication they were taking. Participants randomised to the intervention group were genotyped using laboratory-based testing (*2 or *3 alleles). Intermediate metabolisers (one LOF allele) were prescribed aspirin plus high dose clopidogrel, while poor metabolisers (two LOF alleles) received aspirin plus ticagrelor. The control group were treated with aspirin plus clopidogrel. Participants were followed up for 90 days.

A total of 650 people were randomised after having an ischaemic stroke or TIA. The study enrolled fewer participants than required based on the power calculation, which reduces the statistical power and reliability of the findings. Recruitment was limited by funding restrictions. Most participants presented with an ischaemic stroke (89.69%). The mean age of participants was 68 years and 73% were male. It is assumed all participants were Chinese.

Around a quarter of participants (27.4%) were taking aspirin or clopidogrel prior to randomisation. Almost half the participants (45.5%) in the intervention group were intermediate metabolisers and 15.7% were poor metabolisers. The control group was not genotyped, so it is unclear if the two groups were well matched in terms of their genotypes.

The genotype-guided therapy group had a statistically significantly lower risk of any stroke or a composite of vascular events (*Table 6*). There were no significant differences between groups for recurrent ischaemic stroke or TIA. There were no significant differences between groups for the safety outcomes of major, minor and any bleeding. It is possible that the lack of statistical significance for the individual outcomes is because the study is underpowered or because there were low event rates in both groups.

Table 6: Results of an RCT in China comparing genotype-guided antiplatelet therapy with usual care in patients who had an acute ischaemic stroke or TIA[21]

Outcome	n events intervention group (n=325)	n events control group (n=325)	HR (95% CI)	p-value
Stroke (ischaemic or haemorrhagic)	3	11	0.27 (0.08 to 0.97)	0.04
Ischaemic stroke	3	9	0.33 (0.09 to 1.22)	0.10
TIA	1	2	0.50 (0.05 to 5.49)	0.57
All-cause mortality	2	6	0.33 (0.07 to 1.65)	0.18
Composite outcome*	7	18	0.38 (0.16 to 0.92)	0.03
Major bleeding	3	2	1.50 (0.25 to 8.95)	0.66
Minor bleeding	8	11	0.72 (0.29 to 1.79)	0.48
Any bleeding	26	22	1.18 (0.67 to 2.09)	0.56

**Composite of ischaemic stroke, haemorrhagic stroke, myocardial infarction and vascular death.*

Non-randomised studies

NICE diagnostic guidance identified two small (total n=270), non-randomised studies that compared CYP2C19 genotype-guided antiplatelet therapy with usual care in people who had a previous stroke.[3] Both studies had a high risk of bias because there was no clear information on the allocation process and a lack of randomisation, which affects the reliability of their findings. The small sample sizes and high risk of bias make their results less reliable than the RCTs described in the previous section. Both studies used laboratory-based testing to determine CYP2C19 genotype (*2 and *3 variants).

Both studies were conducted in a Chinese population. Mean age of study participants was 69 years and 38% were female. One study (n=80) treated people with one LOF function allele with a higher dose of clopidogrel and people with two LOF alleles with ticagrelor.[22] The other study (n=190) genotyped all participants but treated the control group as if their genotype was unknown.[23] Everyone who had one or more LOF alleles in the intervention group was given aspirin.

Effect size estimates suggest that genotype-guided therapy could reduce the risk of ischaemic stroke or TIA compared with usual care. There were no statistically significant differences in the risk of ischaemic stroke recurrence or other secondary vascular events in either study (*Table 7*).

Table 7: Results from two non-randomised studies in China comparing genotype-guided antiplatelet therapy with usual care in people who had a previous stroke[3, 22, 23]

Outcome and study	n patients	HR (95% CI)
Ischaemic stroke		
Lan 2019	190	0.33 (0.03 to 3.20)
Xia 2021	80	0.41 (0.15 to 1.18)
Composite outcome*		
Lan 2019	190	0.50 (0.09 to 2.74)
Xia 2021	80	0.53 (0.24 to 1.18)
TIA		
Xia 2021	80	0.50 (0.05 to 5.56)
Vascular death		
Xia 2021	80	1.00 (0.20 to 4.95)

**Composite of stroke, TIA, myocardial infarction and death.*

Guideline recommendations

NICE diagnostic guidance recommends clopidogrel genotype testing after an ischaemic stroke or TIA.[3]

> 'Use CYP2C19 genotype testing to assess if clopidogrel is a suitable antiplatelet drug for people who have just had an ischaemic stroke or transient ischaemic attack (TIA). CYP2C19 genotype testing is only recommended if:
>
> - quality-assurance processes and arrangements are in place for point of care tests
> - shared decision making for doing the test is established.
>
> When interpreting test results, healthcare professionals should take into account that the prevalence of different CYP2C19 genotypes may vary between ethnic groups.
>
> Use laboratory-based testing for CYP2C19 genotype testing.
>
> Use the Genedrive CYP2C19 ID Kit point of care test for CYP2C19 genotype testing when laboratory-based testing is not available.
>
> Use the Genomadix Cube point of care test when laboratory-based testing and the Genedrive CYP2C19 ID Kit point of care test are not available.'[3]

The NICE recommendations are not intended to replace existing guidance on antiplatelet therapy when genotype testing is not available or when awaiting test results.[3] Starting antiplatelet therapy should not be delayed while waiting for genotype test results.

These recommendations only apply to people who have recently had an ischaemic stroke or TIA.[3] People already taking clopidogrel before the guidance was published are advised to continue taking their medication.

The Clinical Pharmacogenetics Implementation Consortium (CPIC)[‡] guideline on CYP2C19 genotype testing makes recommendations on antiplatelet therapies for people who are intermediate or poor clopidogrel metabolisers (*Table 8*).

[‡] CPIC is an international consortium of volunteers who are interested in facilitating pharmacogenomic testing for patient care.

Table 8: CPIC recommendations for antiplatelet therapy in people with normal, intermediate or poor clopidogrel metaboliser status[15]

Metaboliser status	Example genotypes	Treatment recommendation	Strength of recommendation
Normal	*1/*1	Standard dose clopidogrel 75 mg/day	Strong
Intermediate (one LOF allele)	*1/*2, *1/*3	Consider an alternative antiplatelet at standard dose if clinically indicated and no contraindications	Moderate
Poor (two LOF alleles)	*2/*2, *3/*3, *2/*3	Avoid clopidogrel if possible. Consider an alternative antiplatelet at standard dose if clinically indicated and no contraindications	Moderate

The national guideline for stroke in the UK makes recommendations relating to antiplatelet prescribing and clopidogrel resistance:[24]

- 'For patients within 24 hours of onset of TIA or minor ischaemic stroke and with a low risk of bleeding, the following dual antiplatelet therapy should be given:
    - Clopidogrel (initial dose 300 mg followed by 75 mg per day) plus aspirin (initial dose 300 mg followed by 75 mg per day for 21 days) followed by monotherapy with clopidogrel 75 mg once daily

      OR

      Ticagrelor (initial dose 180 mg followed by 90 mg twice daily) plus aspirin (300 mg followed by 75 mg daily for 30 days) followed by antiplatelet monotherapy with ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily at the discretion of the prescriber.
- For patients with recurrent TIA or stroke whilst taking clopidogrel, consideration should be given to clopidogrel resistance.'

The guideline also states (but does not make an associated recommendation) that 'comparative trials…. show that aspirin plus modified-release dipyridamole and clopidogrel monotherapy are equally effective, with both options superior to aspirin monotherapy.'[24]

Clopidogrel versus alternative antiplatelet therapy in people with LOF variants (clopidogrel resistance)

Evidence on the effectiveness of clopidogrel compared with other antiplatelets in people with CYP2C19 LOF variants who had a stroke or TIA comes from seven RCTs (n=10,051) included in the

NICE diagnostic guidance,[3] and three secondary analyses (n=6,412) published after the NICE literature search.[25-27]

The RCTs included in the NICE guidance compared clopidogrel with alternative antiplatelets in people resistant to clopidogrel (with one or more LOF alleles) who had a stroke or TIA.[3] NICE judged four of the seven trials to be low risk of bias. Two studies had a high risk of bias because of a lack of information on loss to follow up or the randomisation process. Five trials were conducted in China, one in Korea and one in an international setting (67% of participants were of white north American heritage).

Mean age of trial participants ranged from 60.8 (standard deviation (SD) 8.7) to 64.8 (SD not reported) years. Female participants ranged from 34% to 45%. Genotyping methods varied across the studies. Four trials determined participant genotype using laboratory-based testing, one used a point of care test and two studies did not report how genotype was determined. All studies checked only for the *2 or *3 variants.

A maximum of two RCTs reported each outcome in the NICE analysis (*Table 9*). Evidence from two RCTs suggests that ticagrelor is associated with a lower risk of stroke recurrence compared with clopidogrel. Treatment with ticagrelor may also be associated with an increased risk of bleeding. None of the other antiplatelets tested significantly reduced stroke recurrence risk compared with clopidogrel in people with LOF alleles.

Table 9: Alternative antiplatelets compared with clopidogrel in people who are clopidogrel resistant[3]

Comparison	n patients (n studies)	Any stroke HR (95% CI)	Ischaemic stroke HR (95% CI)	Any bleeding event HR (95% CI)
Ticagrelor vs. clopidogrel	7,087 (2)	0.76 (0.63 to 0.92)	0.77 (0.65 to 0.93)	1.85 (1.45 to 2.35)
Triflusal vs. clopidogrel	784 (1)	1.23 (0.55 to 2.75)	1.37 (0.62 to 3.02)	0.97 (0.45 to 2.10)
Aspirin vs. clopidogrel + aspirin	4,881 (1)	3.03 (0.83 to 11.11)	3.03 (0.83 to 11.11)	NR
Aspirin vs. clopidogrel	2,933 (1)	1.08 (0.80 to 1.45)	1.18 (0.87 to 1.59)	0.62 (0.29 to 1.25)
Clopidogrel high dose + aspirin vs. clopidogrel + aspirin	131 (1)	NR	0.37 (0.04 to 3.57)	0.37 (0.02 to 9.08)

All three secondary analyses published since the NICE guidance are based on the Ticagrelor or Clopidogrel with Aspirin in High Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial.[25-27] The CHANCE-2 trial was a multicentre (202 hospitals in China), randomised, double blind, placebo controlled trial that compared dual antiplatelet therapies in people who had a minor stroke or TIA and one or more CYP2C19 LOF alleles. The CHANCE-2 trial results at 90 days follow up, for the whole cohort, were included in the NICE analysis described in *Table 9*.[3]

People enrolled in the CHANCE-2 trial had their genotype assessed using the GMEX point of care test within 24 hours of symptom onset. One group received ticagrelor, aspirin and a placebo version of clopidogrel. The other group were given clopidogrel, aspirin and a placebo version of ticagrelor. Participants had a median age of 64.8 years and 33.8% were female. Approximately 78% of participants were intermediate metabolisers (had one LOF allele). Around 80% of participants presented with a minor ischaemic stroke.

The most recent prespecified secondary analysis followed up participants in the CHANCE-2 trial at 1 year (2024).[25] After day 90 in the trial, each participant's (n=6,412) antiplatelet treatment was determined by their preferences and their clinician's opinion.

There were no statistically significant differences in the proportion of study participants from the ticagrelor and clopidogrel groups who were taking antiplatelets beyond 90 days (p=0.86). At 1 year follow up, approximately 73% of trial participants were taking aspirin, 22% were not taking any antiplatelet medication and 2.6% were taking clopidogrel despite having impaired metabolism. The high proportion of people taking aspirin may be because Chinese stroke guidelines recommend aspirin as the first choice for preventing stroke recurrence.

The trial results at 1 year were consistent with the results at 90 days follow up. Initial treatment with ticagrelor plus aspirin was associated with a statistically significant reduction in recurrent stroke, ischaemic stroke, vascular events and mortality that was sustained at 1 year follow up (*Table 10*).

In exploratory subgroup analyses, there was a significantly reduced rate of stroke recurrence for ticagrelor compared with clopidogrel in people who had no history of ischaemic stroke or TIA before enrolment (HR 0.72, 95% CI 0.59 to 0.87). This difference was not statistically significant in people who had a history of ischaemic stroke or TIA.

Treatment with ticagrelor was associated with a significantly increased risk of any bleeding event at 1 year follow up compared with clopidogrel. This result is likely driven by the number of mild bleeding events.

Table 10: Results from 1 year follow up in the CHANCE-2 trial comparing clopidogrel with ticagrelor in people who have CYP2C19 LOF variants[25]

Outcome	n events ticagrelor (n=3,205)	n events clopidogrel (n=3,207)	HR (95% CI)	p-value
Stroke (ischaemic or haemorrhagic)	252	310	0.80 (0.68 to 0.94)	0.008
Vascular events*	302	380	0.78 (0.67 to 0.91)	0.001
Ischaemic stroke	247	300	0.81 (0.68 to 0.96)	0.01
Severe or moderate bleeding	17	20	0.85 (0.44 to 1.61)	0.61
Fatal bleeding	4	4	0.96 (0.24 to 3.82)	0.95
Any bleeding event	185	93	2.04 (1.58 to 2.62)	<0.001
Death	33	56	0.59 (0.38 to 0.91)	0.02

**Composite of ischaemic stroke, haemorrhagic stroke, myocardial infarction, TIA and vascular death.*

A prespecified subgroup analysis of the CHANCE-2 trial compared outcomes between intermediate metabolisers (one LOF allele) and poor metabolisers (two LOF alleles).[27] In the trial, 6.8% of intermediate metabolisers (341 of 5,001) and 6.6% of poor metabolisers (93 of 1,411) had a recurrent stroke within 90 days. The beneficial effects of ticagrelor compared with clopidogrel in reducing stroke recurrence were similar regardless of metaboliser status (*Table 11*). Similarly, the increased risk of bleeding associated with ticagrelor was present in both intermediate and poor metabolisers.

Another subgroup analysis explored the effects of ticagrelor compared with clopidogrel in the CHANCE-2 trial when participants were stratified by baseline risk of a recurrent stroke.[26] Participants' baseline risk of stroke recurrence was calculated using the Essen Stroke Risk Score (ESRS). This tool gives people a score between 0 and 9. People scoring <3 are classed as low risk. People scoring ≥3 are classed as high risk.

In the CHANCE-2 trial, 3,899 (60.8%) people were classed as low risk and 2,513 (39.2%) as high risk using the ESRS score. The relationship between treatment assignment in the trial (ticagrelor or clopidogrel) and the risk of a recurrent stroke or bleeding differed by baseline risk (*Table 12*). Compared with clopidogrel, ticagrelor was associated with a reduced risk of new strokes in people at low baseline risk, but not people who were at high risk. Participants at low risk treated with ticagrelor had the lowest risk of a new stroke within 90 days (p<0.001). The incidence of bleeding was higher in the ticagrelor group compared with the clopidogrel group in people at low risk, but not high risk.

Table 11: Results of CHANCE-2 trial stratified by metaboliser status[27]

Outcome	Intermediate metabolisers			Poor metabolisers			p-value for interaction
	n events ticagrelor (n=2,486)	n events clopidogrel (n=2,512)	HR (95% CI)	n events ticagrelor (n=719)	n events clopidogrel (n=692)	HR (95% CI)	
Stroke (ischaemic or haemorrhagic)	150 (6.0%)	191 (7.6%)	0.78 (0.63 to 0.97)	41 (5.7%)	52 (7.5%)	0.77 (0.50 to 1.18)	0.88
Any bleeding	134 (5.4%)	66 (2.6%)	2.14 (1.59 to 2.89)	36 (5.0%)	14 (2.0%)	2.99 (1.51 to 5.93)	0.66

Table 12: Results of CHANCE-2 trial stratified by risk of stroke recurrence[26]

Outcome	Low risk, ESRS<3			High risk, ESRS ≥3			p-value for interaction
	n events ticagrelor (n=1,940)	n events clopidogrel (n=1,959)	HR (95% CI)	n events ticagrelor (n=1,265)	n events clopidogrel (n=1,248)	HR (95% CI)	
Stroke (ischaemic or haemorrhagic)	92 (4.7%)	144 (7.4%)	0.63 (0.48 to 0.82)	99 (7.8%)	99 (7.9%)	0.97 (0.73 to 1.29)	0.02
Any bleeding	112 (5.8%)	37 (1.9%)	3.27 (2.24 to 4.79)	58 (4.6%)	43 (3.4%)	1.26 (0.83 to 1.90)	0.01

Treatment with clopidogrel in people who are resistant compared with people who are not resistant

Evidence on the effectiveness and safety of clopidogrel in people who have CYP2C19 LOF variants compared with people who process clopidogrel normally, comes from two meta-analyses.[3, 17]

The NICE diagnostic guidance included 20 cohort studies and five RCTs (total n=7,672) in a meta-analysis comparing outcomes in people with and without CYP2C19 LOF variants who were treated with clopidogrel.[3] Six studies were at high risk of bias because they had high loss to follow up that could be related to the meta-analysis outcomes. Of the 25 studies included, 16 were conducted in east Asia (13 in China, two in Japan and one in Korea). All studies assessed CYP2C19 genotype using laboratory-based testing.

The NICE guidance concluded there was strong evidence that people with clopidogrel resistance who are treated with clopidogrel have a significantly greater risk of secondary vascular events, stroke and ischaemic stroke compared with people without LOF variants (*Table 13*). There was no difference in the risk of bleeding events between people with and without LOF variants treated with clopidogrel.

Table 13: Outcomes in patients without CYP2C19 LOF variants compared with people who have clopidogrel resistance when everyone is treated with clopidogrel[3]

Outcome	n studies	HR (95% CI)
Composite outcome	18	1.72 (1.43 to 2.08)
Any stroke	5	1.46 (1.09 to 1.95)
Ischaemic stroke	12	1.99 (1.49 to 2.64)
TIA	1	0.86 (0.14 to 5.12)
Mortality	1	3.67 (0.18 to 76.49)
Vascular death	2	5.07 (1.26 to 20.39)
Any bleeding	5	1.02 (0.71 to 1.47)

A second meta-analysis compared outcomes of clopidogrel therapy in people with and without clopidogrel resistance who had experienced an ischaemic stroke or TIA.[17] Despite covering a similar time period as the NICE diagnostic guidance, there are 11 studies in this meta-analysis that were not included by NICE. All included studies were rated as high quality.

The 28 studies included in the meta-analysis (22 observational studies and six RCTs) had a total of 9,443 participants. Study participants had a mean age of 65.7 years (SD 11.1) and 34% were female. Like the NICE guidance, this meta-analysis found a significantly increased risk of stroke recurrence in people who were clopidogrel resistant and were treated with clopidogrel compared with people without LOF variants (OR 2.18, 95% CI 1.80 to 2.63, p<0.00001, 25 studies, n=7,672). There was no

statistically significant difference in risk of bleeding events (OR 0.86, 95% CI 0.62 to 1.19, p=0.37, 13 studies, n=5,656).

In subgroup analyses based on study design, the estimated odds of recurrent stroke were considerably higher in the meta-analysis of 19 observational studies compared with the meta-analysis of six RCTs (OR 2.83 vs OR 1.48). The direction of effect and statistical significance of the difference were the same in both subgroups.

Diagnostic accuracy and test performance

Diagnostic accuracy estimates of the Genomadix Cube™ and Genedrive point of care tests were calculated by NICE based on the assumption that the laboratory-based tests (reference standard) were always correct.[3]

Eleven studies (n=3,895) reported diagnostic accuracy measures for the Genomadix Cube™ point of care test compared with a laboratory reference standard.[3] All studies were at low risk of bias based on the QUADAS-2 tool. No studies were conducted in a stroke population (six recruited people having percutaneous coronary interventions, two recruited healthy volunteers and data were not provided for three studies).

The Genomadix Cube™ test had sensitivity of 100% (95% CI 94% to 100%) and specificity of 100% (95% CI 99% to 100%) for detecting *2 and *3 LOF variants. The proportion of results that were discordant (the point of care and laboratory tests did not agree) ranged from 0 to 2.7% and was less than 1% in nine studies. The discordance in results only affected estimates of accuracy in two studies because the other results did not change the person's overall metaboliser status.

One study (n=250), conducted by the manufacturer, reported diagnostic accuracy for the Genedrive point of care test.[3] The study was judged to have an unclear risk of bias based on the QUADAS-2 tool. No information was provided about the study population. NICE calculated the sensitivity and specificity of the Genedrive test to be 100% (95% CI 96% to 100%) and 100% (95% CI 98% to 100%), respectively. Four samples were incorrectly classified by the point of care test. None of these discordant results affected the individual's assigned metaboliser status.

Test failure rates for the Genomadix point of care test ranged from 0.4% to 19% in 10 studies (n=5,000).[3] Only one study was in a stroke population. Test failure rates for the Genedrive point of care test were reported to be 0.6% in the manufacturer study described above. Most NHS England laboratories estimated their genotype test failure rate to be less than 1%.

Patient and social aspects

Three primary studies (n=1,678) provide evidence about people's views on CYP2C19 genotype testing.[9, 13, 28] None of the evidence is from a stroke population.

In a qualitative study, face-to-face interviews explored views on CYP2C19 genotype testing among people in Singapore who were admitted to hospital with an acute coronary syndrome.[28] A series of open-ended questions explored factors that could affect people's decision on whether to have CYP2C19 genotype testing. Participants were given a brief explanation about antiplatelet treatment options and the role of genotype testing in deciding which treatment was best for them. No patient's treatment was changed as a result of the interviews.

Fourteen people were interviewed. Eight were of Chinese descent, four were of Malay descent, one of Indian descent and one was described as 'other'. There were 11 males and three females. Ages ranged from 36 to 80 years.

Thematic analysis identified 11 factors that could affect the uptake of CYP2C19 genotype testing. The most common was the recommendation of the patient's physician (n=11). Other factors that were cited by more than one person included the convenience of rapid genotype testing (n=4), the influence of family opinions (n=3), fears about being prescribed ineffective medications (n=3), the accuracy of the genotype test (n=3) and an explanation from medical staff about genotype testing (n=5).

An international survey within an RCT explored people's perceptions of genetic testing and whether there were geographical differences in these perceptions.[29] The sub-study involved point of care CYP2C19 genotype testing in people who had a percutaneous coronary intervention and needed at least 12 months antiplatelet therapy. Recruiting trial participants to complete the survey may have biased the results if people who enrolled in the trial were predisposed to genetic testing. The survey was administered before and 6 months after randomisation.

There were 1,353 people enrolled in the sub-study. The 6 month follow up survey was completed by 860 people. Most participants (77%) were male. Mean participant age was 63 years. Respondents to the survey were living in Canada (29%), the USA (43%) or Korea (28%). Approximately two-thirds of participants described themselves as white (65%) and 30% as east or south Asian.

Most survey respondents (97%) did not have any prior experience of genetic testing. Approximately three-quarters were interested in finding out if they had pharmacogenetic variants (77%) or other genetic variants related to their health (73%). Seventy-five percent of participants were comfortable with their physician recommending genetic testing to guide their healthcare. Sixty-four percent of respondents were confident in their ability to understand genetic information.

The perceived importance of genetic variants was higher among people living in the USA (89%) and Canada (91%) compared with Korea (44%). This difference in perceptions may be related to lower confidence in understanding genetic information. In people from Korea, only 21% felt confident in their understanding of genetic information, compared with 86% of Canadians and 77% of Americans.

More men than women felt that pharmacogenetics (78% vs 72%, p=0.026) and genetic variants associated with health (75% vs 66%, p=0.002) were important. These differences were more apparent among Korean respondents.

A similar study conducted a survey among participants in a different trial of antiplatelet therapy in Americans who had percutaneous coronary interventions.[9] All participants in the trial (n=504) were invited to complete a 33-item questionnaire at baseline. In total, 311 people completed the survey (61.7% response rate). Most respondents were male (73.5%) and self-identified as white (79.2%). The mean age of respondents was 63.4 years.

Most respondents (74%) were unaware that genetic testing could predict their response to medications. Most participants felt it was important to know about genetic effects on medication side effects (75%) and how genes could predict medication efficacy (79%).

The level of existing knowledge about genetics and pharmacogenetics varied between participants. Higher genetics knowledge scores were positively correlated with higher income (p=0.008) and higher levels of education (p=0.0001). People in this study who self-identified as white had higher genetics knowledge scores compared with people who self-identified as black (p=0.0008).

Attitudes about pharmacogenetic testing were generally positive for all participants. Higher genetics knowledge scores were correlated with positive attitudes to pharmacogenetic testing (p=0.002). This suggests that people who understood the role of genetics in health had a more positive attitude towards testing. Most respondents preferred to be informed before a genotype test was ordered (83.1%) and wanted a separate consent process for genotype testing (68.8%).

Organisational issues/context

CYP2C19 genotype testing in Scotland

Clopidogrel genotype testing is not routine practice in NHSScotland. The exception is within NHS Tayside, where there is an established programme of genotype testing for clopidogrel resistance for people diagnosed with a non-cardioembolic ischaemic stroke or TIA (A Doney, Honorary Consultant Physician, Ninewells Hospital and Medical School. Personal Communication, 14 August 2023).

NHS Tayside ran a pilot of their genotype testing service (P4Me Clopidogrel) from April 2022 to March 2023. Laboratory-based genotype test results were available to clinicians within 7 days of the request in more than 98% of cases. For people identified as impaired clopidogrel metabolisers (*2 or *3 alleles) general practitioners were advised to prescribe an alternative antiplatelet from the local formulary.

During the pilot, 723 people were genotype tested, of which 204 (28.2%) had impaired clopidogrel metabolism. Of these people, 168 were prescribed an alternative antiplatelet. Thirty-six people were

not prescribed an alternative antiplatelet for a range of reasons, including a change in diagnosis or death.

Implementing CYP2C19 genotype testing

Experts identified four main barriers to implementing national genotype testing in Scotland. They were concerned that the benefits of antiplatelet therapy are maximised when the patient is started on treatment within 24 hours of the initial stroke or TIA. Laboratory-based testing, which can take up to one week to provide results, could result in patient harm if treatment is delayed until the test results are available. Many patients could be discharged from hospital by the time laboratory test results are available and it would be difficult for clinicians and patients to coordinate changing a prescription after the patient has left hospital.

Clinical staff may find it difficult to understand genotype test results. With both point of care and laboratory-based testing, clinical staff could incorrectly interpret the results they receive for an individual, risking patients being given the wrong antiplatelet for their genotype.

Smaller hospitals serving remote and rural areas, such as island communities, could experience problems accessing laboratory-based genotype testing. These include difficulties around logistics and delays associated with sending blood samples to laboratories in different health board areas, particularly over weekends.

Laboratory capacity and staffing problems currently affect most hospital-based laboratories in Scotland. There are four regional genetic testing centres in Scotland: Aberdeen, Dundee, Edinburgh and Glasgow. These regional centres are under pressure to deliver urgent cancer genetic testing priorities. Experts were concerned that using regional genetic testing centres would result in inequalities in care across Scotland.

Facilitators of CYP2C19 genotype testing include:

- strong support from stroke clinicians, specialist pharmacists and senior managers
- existing knowledge of pharmacogenomics testing within NHS laboratory services
- providing training and awareness raising for multidisciplinary teams working in relevant specialties
- availability of appropriate equipment.[3]

Cost effectiveness

NICE cost effectiveness model

NICE conducted a cost-utility analysis comparing genotype-guided antiplatelet therapy (point of care or laboratory-based testing) with usual care in people who have had a non-cardioembolic ischaemic

stroke or TIA.[3] The analysis uses a hybrid decision tree Markov model. Three cohorts were considered: people who had a non-minor ischaemic stroke, people who had a TIA or minor ischaemic stoke and people who had any severity of ischaemic stroke or TIA.

Current practice for people who have a non-minor ischaemic stroke was assumed to be aspirin 300mg daily for 2 weeks, followed a loading dose of 300mg clopidogrel, then 75mg clopidogrel daily. After a minor stroke or TIA, people were assumed to be treated with a loading dose of 300mg clopidogrel, followed by 75mg aspirin plus 75mg clopidogrel daily for 90 days, then 75mg of clopidogrel daily. In the model, people who were found to have clopidogrel resistance were given 75mg aspirin daily plus dipyridamole 200mg twice daily, in place of clopidogrel.

The decision tree portion of the model (*Appendix 5*) stratified people based on their LOF allele status (genotype test result). An individual's CYP2C19 LOF status only affected treatment decisions in the genotype testing arm of the model.

Laboratory-based genotype tests were assumed to have 100% sensitivity and specificity. People in the point of care test arms of the model could receive an inaccurate result. Sensitivity for the Genedrive (99.6%) and Genomadix Cube (99.0%) point of care tests were based on the number of LOF variants detected by the respective test. Both point of care tests were assumed to have 100% specificity. People were treated based on their point of care test result, even if it was incorrect. Point of care tests also had a test failure rate, whereas the laboratory-based tests did not.

The decision tree outcomes at 90 days were no recurrent stroke, recurrent mild, moderate or major stroke, major bleeding including intracranial haemorrhage (ICH), and death. The health states in the Markov portion of the model (*Appendix 5*) were the same as the 90-day decision tree outcomes. People entered the Markov model at 91-days in proportions that depended on their outcomes at 90-days in the decision tree.

The first model cycle was 275.25 days. Subsequent model cycles were 1 year for the remaining 30-year (lifetime) model horizon. People could only transition to more severe stroke health states and the death health state was absorptive. The major bleeding health state severity was assumed to be between mild stroke and moderate stroke. In other words, people could only transition to major bleeding from the no event or mild stroke health states, and from the major bleeding health state to major stroke or death.

Data to inform the model parameters came from a variety of sources. Demographic data, including UK population ethnic ancestry distribution, were taken from registry data provided by Public Health England. The prevalence of CYP2C19 LOF alleles was calculated using prevalence by ethnic group as described in the literature.

The baseline rates of recurrent stroke for people who had a non-minor ischaemic stroke were based on data from the Sentinel Stroke National Audit Programme (SSNAP) and the South London Stroke Register (SLSR). For people who had a minor stroke or TIA these data were from the Framingham

Heart study. These rates were observed in a mixed population with and without LOF variants, adjusted using a weighted average of the hazards in each population.

The probability of a recurrent stroke was higher in the first 90 days and then remained constant for the remainder of the model. The proportion of recurrent strokes that were of each severity was taken from SSNAP data. The baseline rate of major bleeding, the proportion of bleeds that were ICH and the proportion of ICH that were fatal, were taken from the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) study.[30]

Genotype test results affected patient outcomes by adjusting the rates of recurrent stroke which were determined by their LOF status and prescribed antiplatelet. The baseline rate of recurrent stroke was applied to people without LOF alleles (No LOF) taking clopidogrel. For people who had clopidogrel resistance (LOF variants) and were taking clopidogrel, the baseline rate of recurrent stroke was adjusted using the hazard ratio from the NICE meta-analyses (HR 1.46). For people receiving an alternative antiplatelet, hazard ratios for stroke recurrence were taken from the literature and applied to the baseline rate of stroke recurrence. For people with LOF variants in the base case analysis, the alternative antiplatelet therapy was dipyridamole plus aspirin (HR 1.01).

The baseline rate of major bleeding was applied to everyone receiving clopidogrel and was adjusted depending on alternative antiplatelets. It did not depend on an individual's LOF status.

People changed treatments in the genotype testing arms of the model if they were found to have clopidogrel resistance. In the point of care arm of the model, test results were assumed to be immediate, whereas in the laboratory-based testing arm this depended on turnaround time. If people switched treatments, they experienced event probabilities proportional to the time spent taking each medication. People could change treatment in any arm of the model if they experienced intolerance to treatment. Patients in the model who discontinued clopidogrel or dipyridamole switched to long-term low dose aspirin (75mg daily).

Mortality rates for the mild, moderate and major recurrent stroke health states were based on rates reported by SSNAP and the SLSR.

Health state utilities were taken from the literature and based on the modified Rankin scale (mRs), a measure of disability after a stroke. The utility for patients in the no recurrent stroke health state varied by cohort. Carer disutilities were included in the base case for all patients in the non-minor stroke population and all patients who experienced a minor, moderate or severe stroke in the TIA and minor stroke population.

Costs in the model included the genotype tests, medication, treatment switching (requiring a general practitioner (GP) visit) and health state costs. Laboratory-based testing costs included a device unit cost, reagent cost per test and costs for staff time. Point of care test costs included device unit cost, test kit costs, control kit costs, annual warranty and staff time. An additional cost was applied per point of care test to account for the test failure rate.

Health state costs covered NHS and social care costs associated with the management of stroke according to the severity of the stroke modelled (non-minor stroke or minor stroke/TIA). Health state costs were based on the SSNAP study that reported costs incurred for in-hospital stay (NHS costs) and out of hospital rehabilitation (social care costs). The 'no recurrent stroke' health state incurred rehabilitation costs only. The major bleeding or ICH health state incurred a one-off cost.

In-hospital (NHS) health state costs from the SSNAP study included ambulance transport, magnetic resonance imaging (MRI), computed tomography (CT) scans, thrombolysis, acute stroke unit care, general medical ward care and stroke unit care. Out of hospital costs (social care) included those associated with early supported discharge (for example, occupational therapist, physiotherapist, speech and language therapist and psychologist visits), community rehabilitation, GP visits, home help care packages, meals on wheels and social service day centre visits. Care home costs were only included for patients who resided in a care home prior to their recurrent stroke.

NICE analysis results

In all populations, the Genedrive point of care test and laboratory-based testing dominated the no testing strategy. In other words, genotype testing generated more QALYs at a lower cost. The Genomadix test dominated the no testing strategy in the non-minor ischaemic stroke population and was associated with an incremental cost effectiveness ratio (ICER) of £471 per QALY gained in the minor stroke and TIA population. Differences in incremental costs and QALYs between testing strategies (that is, between the two point of care tests and laboratory-based test) were very small, as was the difference in net monetary benefit. In a fully incremental deterministic analysis, the Genedrive test dominated all other testing strategies.

In the non-minor ischaemic stroke population, compared with no testing, laboratory-based testing was associated with an incremental cost saving of £749. For the Genedrive test the saving was £821 and for the Genomadix test it was £731. All testing strategies were associated with an incremental QALY gain of 0.05 compared with no testing.

In the minor ischaemic stroke and TIA population, compared with no testing, laboratory-based testing was associated with a cost saving of £2, for the Genedrive test the saving was £81. The Genomadix test was associated with an incremental cost of £4 compared with no testing. Laboratory-based testing, the Genedrive test and the Genomadix test were associated with a QALY gain of >0.01, 0.01 and 0.01 respectively, compared with no testing.

An analysis that considered a mixed population of people who had a minor ischaemic stroke or TIA or a non-minor ischaemic stroke found that all the testing strategies dominated the no testing strategy.

The QALY gain and cost savings associated with the CYP2C19 genotype tests were driven by a reduction in costs associated with fewer people entering the recurrent stroke health states.

The results of the analysis were robust to a wide range of sensitivity analyses. These included extending the laboratory-based testing turnaround time to 4 weeks and an alternative usual care strategy whereby everyone who had a non-minor stroke or TIA received ticagrelor versus people with LOF variants receiving ticagrelor and people with no LOF variants receiving clopidogrel. The assumptions that had the most impact on the results were when ticagrelor plus aspirin or aspirin monotherapy were used as alternative treatments to clopidogrel for people with LOF variants, or there was a low uptake of alternative therapy after point of care test results.

The main limitation of the analysis was an absence of test-and-treat studies to provide efficacy data for the testing and no testing arms of the model. As a result, the model relied on indirect evidence to estimate the treatment effects of alternative antiplatelet therapies depending on LOF status (see *Treatment with clopidogrel in people who are resistant compared with people who are not resistant*).

SHTG resource impact analysis

We conducted a cost analysis to estimate the effects of introducing genotype-guided antiplatelet therapy in NHSScotland. We compared genotype testing using either laboratory-based or point of care testing with usual care (no genotype testing). The population was defined as people who have had a non-cardioembolic ischaemic stroke or TIA. The cost analysis was conducted from the perspective of NHSScotland and personal social care over a 5-year time horizon.

We adopted the model structure used in the NICE economic evaluation described above. The model was run twice, once for people who had a non-minor stroke and once for people who had a minor stroke or TIA. The results were combined with upfront and recurring fixed costs.

Input data for the cost analysis were assumed to be the same as those used in the NICE economic evaluation except where Scotland-specific data were available. Differences between the NICE work and our analysis are described below and a full list of model parameters are available in *Appendix 6.*

Eligible population

The population considered eligible for genotype-guided antiplatelet therapy was everyone in Scotland who had a non-cardioembolic ischaemic stroke or TIA. In year 1 of the model, the eligible population was estimated using the total number of ischaemic strokes or TIAs in Scotland 2022–2023, adjusted for the proportion considered likely to be cardioembolic according to the literature.[1, 2, 11] The number of people who entered the model each year from year 2 onwards, was assumed to be those who had a first non-cardioembolic ischaemic stroke. This approach was chosen because it was assumed that in the first year of implementation everyone would receive the test even if presenting with a recurrent stroke.

The number of people who had a non-minor stroke in the first year of the model was calculated by applying the proportion of ischaemic strokes that were non-minor from the literature to the number of people who had a non-cardioembolic ischaemic stroke in Scotland.[31] The proportion of strokes that were assumed to be minor were added to the number of people who had a TIA.

For years 2–5 of the model, the eligible population was estimated according to the average annual number of non-cardioembolic ischaemic strokes or TIAs recorded by Public Health Scotland for the years 2012 to 2017 (S Taws, Senior Data Analyst, Public Health Scotland. Personal Communication, 25 July 2024). These were the only data available for annual rates of non-cardioembolic ischaemic stroke in Scotland. The baseline stroke recurrence rates used in the economic model were also derived from these data. The number of people in each cohort was assumed to remain constant in each year of the model thereafter (*Table 14*).

Table 14: Eligible population with non-cardioembolic stroke or TIA in Scotland

Model period	Population	n	Source
Year 1	TIA	3,763	Public Health Scotland, 2022–2023
	Ischaemic stroke	9,373	
	Non-cardioembolic ischaemic stroke	7,030	Calculation (proportion of strokes that are cardioembolic = 0.25)[11]
	Minor stroke or TIA	6,758	Calculation (proportion of strokes that are minor = 0.4257)[31]
	Non-minor stroke	4,035	
Years 2–5	TIA	1,842	Per year average, Public Health Scotland 2012–17
	Non-cardioembolic ischaemic stroke	4,169	
	Minor stroke or TIA	3,618	Calculation (proportion of strokes that are minor = 0.4257)[31]
	Non-minor stroke	2,393	

Prevalence of CYP2C19 LOF alleles

The prevalence of CYP2C19 LOF variants in the Scottish stroke and TIA population was estimated according to the ethnic ancestry of the Scottish population and the prevalence of LOF alleles in different ethnic groups.[15, 16] This resulted in an estimated prevalence of 28.7%, which is similar to that reported by the UK Biobank study but lower than the prevalence estimated in the UK population by NICE (32.1%).[3, 13] As the ethnic ancestry of the Scottish stroke and TIA population may differ from that of the general population, the true prevalence of LOF variants is uncertain.

Baseline event rates

Baseline rates of ischaemic stroke in the TIA population and recurrent stroke in the stroke population were based on the recurrence rates reported by Public Health Scotland for 2012–2017. Recurrence rates in the NICE model were adjusted according to the estimated prevalence of LOF alleles in the Scottish population (*Table 15*).

Table 15: Baseline stroke event rates for the Scottish cost analysis (including changes made to the NICE model)

Parameter	Stroke rate per person-year		Source
	NICE	SHTG	
Risk of stroke 0–90 days after TIA	0.073	–	Lioutas et al adjusted for estimated UK LOF allele prevalence
	–	0.049	Public Health Scotland 2012–2017 data adjusted for estimated Scottish LOF allele prevalence
Risk of stroke >90 days after TIA	0.0055	–	Lioutas et al adjusted for estimated UK LOF allele prevalence
	–	0.028	Public Health Scotland 2012–2017 data adjusted for estimated Scottish LOF allele prevalence
Risk of recurrent stroke 0–90 days after stroke	0.0804	–	SSNAP adjusted for estimated UK LOF allele prevalence
	–	0.084	Public Health Scotland 2012–2017 data adjusted for estimated Scottish LOF allele prevalence
Risk of recurrent stroke >90 days after stroke	0.0490	–	SLSR adjusted for estimated UK LOF allele prevalence
	–	0.0436	Public Health Scotland 2012–2017 data adjusted for estimated Scottish LOF allele prevalence

Laboratory-based genotype testing costs

Costs for laboratory-based genotype testing (*Table 16*) were based on a business case provided by the Centre for Sustainable Delivery (CfSD).

Capital and initial machine validation costs were for repurposing Quant Studio 7 machines already owned by NHSScotland. These are based on a quote provided by a genetics laboratory in Dundee. Machine maintenance and laboratory staff costs were assumed to be fixed and annually recurring. Transportation costs were applied as a cost per test and are based on the average per test transportation cost in the CfSD business case. Reagents and consumables costs were applied per test according to the per test costs provided by CfSD.

Costs were estimated for the time taken to collect the test sample (assumed to be 10 minutes per sample) at NHSScotland Agenda for Change pay grade band 5 nurse.

Table 16: Laboratory-based genotype testing cost inputs

Parameter	Cost (£)	Quantity	Total (£)	Source
Year 1 fixed costs				
Cost per machine	8,750	4	35,000	CfSD
Machine validation	7,434	1	7,434	
Total			**42,434**	
Fixed costs per year				
Staff costs	Band 2: 33,321 Band 3: 36,208 Band 4: 39,660 Band 5: 50,080 Band 6: 61,579 Band 7: 72,059	1 2 2 1 2 1	33,321 72,416 79,320 50,080 123,158 72,059	CfSD
Machine maintenance (rising 5% per year)	8,475	4	33,900	
Total			**464,254**	
Per test costs (year 1)				
Transportation of samples	0.83	10,793	8,958	National average per test (CfSD)
Reagents and consumables	11		118,723	CfSD
Band 5 nurse time to collect sample (10 minutes)	8.67		93,575	PSSRU, 2022[32]
Total	**20.5**		**221,256**	-

Point of care genotype testing costs

Costs for the Genedrive and Genomadix Cube point of care genotype tests (*Table 17*) were based on the NICE economic evaluation because these are the only publicly available costs for these tests.

The number of point of care machines required by NHSScotland was assumed to be 30 as per an estimate provided by CfSD, which was the same as the number of Scottish hospitals with an emergency department. The total capital and operational costs associated with the procurement of point of care testing are not known because published estimates exclude several components of implementation, such as delivery charges, installation costs, annual maintenance costs and staff training costs.

Table 17: Point of care genotype testing cost inputs

Parameter	Cost (£)		Quantity	Total (£)		Source
	Genedrive	Genomadix		Genedrive	Genomadix	
Year 1 fixed costs						
Device price	4,500	3,500	30	135,000	105,000	NICE[3]
Fixed costs per year						
Warranty	750	700	30	22,500	21,000	NICE[3]
Control kit (1 kit per machine per month)	100	50	360	36,000	18,000	
Per test costs (year 1)						
Price per test kit	100	125	10,793	1,079,300	1,349,125	NICE[3]
Test failure rate	8%			86,344	107,930	NICE[3]
Band 5 nurse time to collect sample (10 minutes)	8.67			93,575		PSSRU, 2022[32]
Total				**1,259,219**	**1,550,630**	

Cost analysis results

The base case results from our resource impact analysis are presented in *Table 18*. The results indicate that genotype-guided antiplatelet therapy for people who have had a stroke or TIA in Scotland using laboratory-based testing is associated with a cumulative resource saving of £17.9 million over 5 years compared with no genotype testing. The Genedrive point of care genotype test is associated with a cumulative resource saving of £18 million over 5 years. The Genomadix Cube point of care genotype test is associated with a cumulative resource saving of £17.3 million over 5 years.

Laboratory-based genotype testing is cost saving in year 1 compared with no testing, with a net resource saving of £400,000. Each year, from year 2 onwards, laboratory-based testing is increasingly resource saving compared with current practice, with resource savings of £8.5 million in year 5 (*Table 18*).

The Genedrive point of care test is cost incurring in year 1 compared with no testing, with an additional net cost of £415,985 in year 1. From year 2 onwards, point of care testing with the Genedrive device is resource saving compared with current practice, with resource savings of £9 million in year 5.

The Genomadix Cube point of care test is cost incurring in year 1 compared with no testing, with an additional net cost of £1 million in year 1. From year 2 onwards, point of care testing with the Genomadix Cube device is resource saving compared with current practice, with resource savings of £8.9 million in year 5.

The resource savings associated with all three tests in the model are driven by a reduction in the number of people having a recurrent stroke. Savings include resources such as staff and hospital resources (for example MRI and CT scanners) and these resources are likely to be fixed over the short term; staff are likely to still be employed within the NHS and hospital equipment is still likely to be used. A relatively small proportion of the savings may be cash releasing over a shorter time period, such as costs associated with thrombolysis and rehabilitation.

Care home costs were not included in the analysis for patients who lived independently prior to their recurrent stroke because of a lack of data. These additional costs could be substantial and a proportion of these could be cash releasing for local authorities.

The 5-year resource impact analysis results were disaggregated to explore the distribution of resource cost impact across each diagnostic strategy (*Table 19*). Genotype testing was associated with resource savings from out of hospital rehabilitation after recurrent stroke, with savings of £13.5 million for each testing strategy. In-hospital resource costs after a recurrent stoke were lower with genotype testing; laboratory-based testing saving £14.3 million and point of care tests saving £15 million.

Point of care tests were associated with lower fixed costs (£500,000 and £200,000 for Genedrive and Genomadix Cube, respectively) than laboratory-based testing (£2.4 million). Laboratory-based testing was associated with lower per test costs (£700,000) than either point of care test (£4.1 million and £5 million for Genedrive and Genomadix Cube, respectively). The cost of GP appointments for switching antiplatelet treatment was lower for the point of care tests (£1.2 million) compared with a no testing strategy (£1.4 million) or laboratory-based testing (£1.9 million). The difference in costs for GP appointments for people switching antiplatelets is driven by people being prescribed alternative antiplatelet therapy immediately in the point of care test arm, whereas in the laboratory-based test arm those with clopidogrel resistance switched from clopidogrel to dipyridamole at a later date. The cost of antiplatelet medication was lower with no testing (£1.4 million) compared with all three testing strategies (£7.6 million) because the cost of dipyridamole was higher than the cost of clopidogrel.

The model found that the number of recurrent strokes were lower in people who have had a stroke or TIA in Scotland and received genotype-guided antiplatelet therapy. The number of recurrent strokes prevented in the first year was 82 with laboratory-based testing and 84 with the Genedrive or Genomadix point of care tests (*Table 20*) The number of recurrent strokes prevented increased over the 5-year period because people continue to remain at risk over time and new people become eligible for the test in each subsequent year. The cumulative number of recurrent strokes prevented over 5-years was 943, 961 and 958 for the laboratory-based, Genedrive and Genomadix tests, respectively.

Table 18: Base case cost analysis results for NHSScotland years 1–5

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	88.2	106.2	137.6	219.4	382.7	934
Genedrive point of care testing	88.4	104.4	135	214.6	373.7	916
Genomadix Cube point of care testing	88.6	104.5	135.1	214.7	373.8	916.7
Laboratory-based testing	87.8	104.4	135	214.8	374.2	916.1
Net change: Genedrive vs no testing	0.2	-1.8	-2.6	-4.8	-6.9	-18
Net change: Genomadix vs no testing	1.0	-1.3	-2.2	-4.7	-8.9	-17.3
Net change: laboratory-based vs no testing	-0.4	-1.8	-2.6	-4.6	-8.5	-17.9

Table 19: 5 year disaggregated base case cost analysis results for NHSScotland

Pathway	Costs (£ million)					
	In-hospital	Out of hospital	Genotype test: fixed	Genotype test: per test	GP appointments	Antiplatelet medications
Current pathway (no genotype testing)	91.0	840.2	-	-	1.4	1.4
Genedrive point of care testing	76.0	826.7	0.5	4.1	1.2	7.6
Genomadix Cube point of care testing	76.0	826.7	0.2	5.0	1.2	7.6
Laboratory-based testing	76.7	826.8	2.4	0.7	1.9	7.6
Net change: Genedrive vs no testing	-15.0	-13.5	0.5	4.1	-0.3	6.3
Net change: Genomadix vs no testing	-15.0	-13.5	0.2	5.0	-0.3	6.2
Net change: laboratory-based vs no testing	-14.3	-13.5	2.4	0.7	0.5	6.2

Table 20: Base case recurrent stroke results for NHSScotland years 1–5

Pathway	n recurrent strokes					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	443	581	701	1,119	1,941	4,785
Genedrive point of care testing	359	452	576	894	1,544	3,825
Genomadix Cube point of care testing	359	452	577	895	1,545	3,827
Laboratory-based testing	361	454	579	898	1,551	3,843
Net change: Genedrive vs no testing	-84	-129	-125	-226	-398	-961
Net change: Genomadix vs no testing	-84	-129	-124	-225	-397	-958
Net change: laboratory-based vs no testing	-82	-127	-122	-222	-390	-943

Sensitivity analyses

Sensitivity analyses were conducted to explore the effects of changing input parameters in the model (*Appendix 7*). The scenarios involved doubling the per test cost of laboratory-based testing, reducing health state costs by 20%, reducing the clopidogrel HR for LOF versus no LOF variants, doubling fixed costs for the point of care tests and an analysis from the perspective of a rural health board.

In all scenarios, genotype-guided antiplatelet therapy was resource saving compared with not testing from year 2 onwards. The magnitude of cost savings was most sensitive to lowering the clopidogrel HR.

Conclusion

Three meta-analyses have shown that giving clopidogrel to people who have had an ischaemic stroke or TIA and who have CYP2C19 LOF variants (clopidogrel resistance) is associated with a significantly increased risk of stroke recurrence. Genotype-guided antiplatelet therapy has the potential to reduce the risk of stroke recurrence for these people.

Four trials (two randomised and two non-randomised) comparing genotype-guided antiplatelet therapy with usual care report effect point estimates (HR, RR, etc) that suggest a reduction in the risk of recurrent ischaemic stroke in the genotype-guided group. These results are not statistically significant because the confidence intervals all overlap the null (a HR of 1, meaning that there may be no difference in stroke recurrence between the groups). A range of factors, including low event rates, clopidogrel resistance in the usual care groups and inadequate sample sizes, may explain the lack of statistical significance in these studies. Further research is needed.

Evidence suggests that people with CYP2C19 LOF variants should be treated with an alternative antiplatelet. A meta-analysis of two RCTs showed that ticagrelor is more effective at reducing the risk of stroke recurrence compared with clopidogrel in people who have clopidogrel resistance. This reduced risk was maintained at 1 year follow up in one trial. However, ticagrelor is associated with an increased risk of bleeding and is currently only recommended for patients who have had a minor ischaemic stroke or TIA. No other antiplatelets that have been compared with clopidogrel in people with LOF alleles were found to significantly reduce stroke recurrence risk.

Three qualitative studies in people with cardiac conditions found that most people believed that CYP2C19 genotype testing was important for informing their care. The perceived value of genetic testing was correlated with people's level of knowledge and confidence in understanding genetic information.

The results of the NICE cost effectiveness analysis suggests that genotype-guided antiplatelet therapy is likely to be cost effective for people who have had an ischaemic stroke or TIA. Laboratory-

based testing and point of care testing generated more QALY benefits and resource savings compared with no testing, driven by a reduction in the number of people having a recurrent stroke.

The results of our cost analysis for Scotland found that implementing laboratory-based genotype-guided antiplatelet therapy would be resource saving in the first year. Point of care genotype testing was cost incurring in the first year. Resource savings associated with reduced recurrent stroke rates were greater than the ongoing costs associated with each strategy of genotype testing from year 2 onwards. Over 5 years, all testing strategies were associated with significant resource savings of around £17.8 million.

Identified research gaps

Since most existing evidence on CYP2C19 genotype testing, alternative antiplatelet therapies and stroke risk in people with clopidogrel resistance, comes from Chinese populations, it would be beneficial for future RCTs to be conducted in a wider range of populations, including European or UK groups, to increase the generalisability of findings. Larger study sample sizes may help to increase the statistical power of these trials.

There is a need for comparative, long-term studies that:

- compare dipyridamole plus aspirin with clopidogrel and other antiplatelet medications
- evaluate the efficacy and safety of alternative antiplatelet therapies, such as ticagrelor or dipyridamole plus aspirin, beyond 1 year follow up
- explore how genotype testing influences clinical decision making and whether it leads to changes in patient treatment or outcomes.

Evidence on perspectives and preferences around genotype testing from a stroke population would be valuable for informing the future use of CYP2C19 testing in NHSScotland. Understanding how to effectively communicate genetic information to patients to improve knowledge and confidence (as well as timely access to testing and integration of genotype results into clinical practice) is important.

Acknowledgements

Healthcare Improvement Scotland assessment development team

- Mr James Chappell, Senior Health Economist
- Ms Hilda Emengo, Health Services Researcher
- Ms Jenny Harbour, Lead Author/Health Services Researcher
- Mr Paul Herbert, Health Information Scientist
- Ms Tammy Nicol, Senior Project Officer

Public Health Scotland contributors to the assessment

- Dr Fatim Lakha, Consultant Public Health Medicine
- Mr Andrew Lee, Service Manager
- Ms Sarah Taws, Senior Information Analyst

Peer reviewers

SHTG would like to thank the following individuals who took part in the peer review and provided comments on the draft document:

- Dr Mark Barber, Geriatrician and Stroke Physician, NHS Lanarkshire
- Mr Jeremy Bridge-Cook, Chief Scientific Officer, Genomadix Inc
- Dr Anthony Byrne, Consultant Physician, NHS Forth Valley
- Dr Alexander Doney, Clinical Reader and Honorary NHS Consultant, University of Dundee
- Mr Peter Kerr, Advanced Nurse Practitioner in Stroke, NHS Greater Glasgow & Clyde
- Mr Alexandre Matos, Specialist Clinical Pharmacist, NHS Tayside
- Prof Zofia Miedzybrodzka, Professor of Medical Genetics/Service Clinical Director Genetics, University of Aberdeen/NHS Grampian
- Dr Mark Redpath, Consultant Biochemist, NHS Borders
- Mr Austin Willett, Chief Executive Officer, Different Strokes

Declarations of interest from all reviewers are published alongside the review on our website. Reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Suggested citation: Harbour J, Chappell J, Emengo H, Herbert P, Lakha F, Lee A, Nicol T, Taws S. Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack (TIA). 2024; Available from: https://shtg.scot/our-advice/clopidogrel-genotype-testing-after-ischaemic-stroke-or-transient-ischaemic-attack-tia/

Published October 2024

References

1. Public Health Scotland. Scottish stroke improvement programme: annual report 2023. 2023 [cited 2023 Oct 30]; Available from: https://www.publichealthscotland.scot/publications/scottish-stroke-improvement-programme/scottish-stroke-improvement-programme-annual-report-2023/.
2. Public Health Scotland. Scottish stroke statistics. 2023 [cited 2023 Oct 30]; Available from: https://publichealthscotland.scot/publications/scottish-stroke-statistics/scottish-stroke-statistics-year-ending-31-march-2022/.
3. National Institute for Health and Care Excellence (NICE). Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack. 2023 [cited 2023 Oct 26]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-dg10054.
4. MedlinePlus. Clopidogrel resistance. 2015 [cited 2023 Oct 26]; Available from: https://medlineplus.gov/genetics/condition/clopidogrel-resistance/.
5. National Human Genome Research Institute. Talking glossary of genomic and genetic terms: allele. 2024 [cited 2024 Jun 28]; Available from: https://www.genome.gov/genetics-glossary/Allele?id=4.
6. MedlinePlus. What is a gene variant and how do variants occur? 2021 [cited 2024 Jun 11]; Available from: https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/.
7. Scitable. Genotype definition. 2014 [cited 2024 Jun 11]; Available from: https://www.nature.com/scitable/definition/genotype-234/.
8. van Swieten J. Modified Rankin Scale for neurologic disability. [cited 2024 Jun 19]; Available from: https://www.mdcalc.com/calc/1890/modified-rankin-scale-neurologic-disability.
9. Lee G, Varaghese LA, Conway L, Stojinski C, Ashokkumar S, Monono K, et al. Attitudes toward pharmacogenetics in patients undergoing CYP2C19 testing following percutaneous coronary intervention. Per Med. 2022;19(2):93-101.
10. NHS. Stroke: overview. 2022 [cited 2023 Oct 26]; Available from: https://www.nhs.uk/conditions/stroke/.
11. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429-38.
12. Stroke Association. Stroke statistics. 2013 [cited 2023 Oct 31]; Available from: https://www.thepossibilities.co.uk/assets/downloads/stroke-statistics.pdf.
13. Pilling LC, Turkman D, Fullalove H, Atkins JL, Delgado J, Kuo CL, et al. Analysis of CYP2C19 genetic variants with ischaemic events in UK patients prescribed clopidogrel in primary care: a retrospective cohort study. BMJ Open. 2021;11(12):e053905.
14. Fluck D, Fry CH, Gulli G, Affley B, Robin J, Kakar P, et al. Adverse stroke outcomes amongst UK ethnic minorities: a multi-centre registry-based cohort study of acute stroke. Neurol Sci. 2023;44(6):2071-80.

15. Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC guideline for clopidogrel and CYP2C19. 2022 [cited 2024 Jun 13]; Available from: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/.

16. Nguyen AB, Cavallari LH, Rossi JS, Stouffer GA, Lee CR. Evaluation of race and ethnicity disparities in outcome studies of CYP2C19 genotype-guided antiplatelet therapy. Front Cardiovasc Med. 2022;9:991646.

17. Biswas M, Hossain MS, Rupok TA, Hossain MS, Sukasem C. The association of CYP2C19 LoF alleles with adverse clinical outcomes in stroke patients taking clopidogrel: an updated meta-analysis. Clin Transl Sci. 2024;17(4):e13792.

18. Cargnin S, Ferrari F, Terrazzino S. Impact of CYP2C19 genotype on efficacy and safety of clopidogrel-based antiplatelet therapy in stroke or transient ischemic attack patients: an updated systematic review and meta-analysis of non-east Asian studies. Cardiovasc Drugs Ther. 2023 [In press].

19. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation. 2016;135(1):21-33.

20. Han M, Jia W, Wu Y, Kuang J, Tu J, Yin S, et al. Short-term efficacy and safety of personalized antiplatelet therapy for patients with acute ischaemic stroke or transient ischaemic attack: a randomized clinical trial. Br J Clin Pharmacol. 2023;89(9):2813-24.

21. Zhang X, Jiang S, Xue J, Ding Y, Gu J, Hu L, et al. Personalized antiplatelet therapy guided by clopidogrel pharmacogenomics in acute ischemic stroke and transient ischemic attack: a prospective randomized controlled trial. Front Pharmacol. 2023;13:931405.

22. Xia C, Zhang Z, He X, Liu J, Li X, Chang Q, et al. Correlation between CYP2C19 gene polymorphism and individualized medication in patients with ischemic stroke. Chin J Clin Pharmacol Therap. 2021;26(3):318-23.

23. Lan H, Ying T, Xi-Hua S, Yi L. Anti-platelet therapy in mild cerebral infarction patients on the basis of CYP2C19 metaboliser status. Cell Transplant. 2019;28(8):1039-44.

24. Scottish Intercollegiate Guidelines Network (SIGN), Royal College of Physicians of Ireland, Royal College of Physicians. National clinical guideline for stroke for the United Kingdom and Ireland. 2023 [cited 2023 Oct 31]; Available from: https://www.strokeguideline.org/contents/.

25. Meng X, Wang A, Tian X, Johnston C, Li H, Bath PM, et al. One-year outcomes of early therapy with ticagelor vs clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA trial. Neurology. 2024;102(3):e207809.

26. Wang A, Meng X, Tian X, Zuo Y, Bath PM, Li H, et al. Ticagrelor aspirin vs clopidogrel aspirin in CYP2C19 loss-of-function carriers with minor stroke or TIA stratified by risk profile. Neurology. 2023;100(5):e497-504.

27. Xie X, Jonston C, Wang A, Xu Q, Bath PM, Pan Y, et al. Association of CYP2C19 loss-of-function metabolizer status with stroke risk among Chinese patients treated with ticagrelor-aspirin vs clopidogrel-aspirin: a prespecified secondary analysis of a randomized clinical trial. JAMA Netw Open. 2023;6(6):e2317037.

28. Png WY, Wong XY, Kwan YH, Lin YY, Tan DS. Perspective on CYP2C19 genotyping test among patients with acute coronary syndrome: a qualitative study. Future Cardiol. 2020;16(6):655-62.

29. Pereira NL, So D, Bae JH, Chavez I, Jeong MH, Kim SW, et al. International survey of patients undergoing percutaneous coronary intervention and their attitudes toward pharmacogenetic testing. Pharmacogenet Genomics. 2019;29(4):76-83.

30. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359(12):1238-51.

31. National Guideline Centre, SSNAP. Sentinel stroke national audit programme: cost and cost-effectiveness analysis - technical report. 2016 [cited 2024 Aug 02]; Available from: https://www.strokeaudit.org/SupportFiles/Documents/Health-Economics/Health-economic-report-2016.aspx.

32. Jones K, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit costs of health and social care 2022 manual. 2023 [cited 2024 Jul 24]; Available from: https://www.pssru.ac.uk/pub/uc/uc2022/Unit_Costs_of_Health_and_Social_Care_2022.pdf.

33. Last J. A dictionary of epidemiology. 4th ed. New York: Oxford University Press; 2001.

34. National Institute for Health and Care Excellence (NICE). Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events: TA210. 2010 [cited 2024 Aug 1]; Available from: https://www.nice.org.uk/guidance/ta210.

Appendix 1: Abbreviations

ANIA	Accelerated National Innovation Adoption
BNF	British national formulary
CfSD	Centre for Sustainable Delivery
CHANCE-2	ticagrelor or clopidogrel with aspirin in high risk patients with acute nondisabling cerebrovascular events ii
CI	confidence interval
CPIC	Clinical Pharmacogenetics Implementation Consortium
CT	computed tomography
DNA	deoxyribonucleic acid
ESRS	Essen stroke risk score
GP	general practitioner
GRADE	grading of recommendations, assessment, development and evaluations
HR	hazard ratio
ICD-10	international classification of disease tenth revision
ICER	incremental cost effectiveness ratio
ICH	intracranial haemorrhage
LOF	loss of function
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
OR	odds ratio
PPY	people per year
PRofESS	prevention regimen for effectively avoiding second strokes
PSSRU	personal social services research unit
QALY	quality adjusted life years
RCT	randomised controlled trial

RR	relative risk
SD	standard deviation
SHTG	Scottish Health Technologies Group
SLSR	south London stroke register
SMR01	Scottish morbidity records 01
SSNAP	Sentinel Stroke National Audit Programme
TIA	transient ischaemic attack
UK	United Kingdom
USA	United States of America

Appendix 2: Definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease[33].

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease[33].

Appendix 3: CYP2C19 variants and their functional status

Table A: CYP2C19 variants and their functional status[15]

CYP2C19 allele numbers				
Normal function	**LOF**	**Decreased function**	**Increased function**	**Uncertain function**
*1	*2	*9	*17	*12
*11	*3	*10		*14
*13	*4	*16		*23
*15	*5	*19		*29
*18	*6	*25		*30
*28	*7	*26		*31
*38	*8			*32
	*22			*33
	*24			*34
	*35			*39
	*36			
	*37			

Appendix 4: Public Health Scotland data analysis

There are no routinely gathered statistics published on the incidence of recurrent stroke in Scotland.

This analysis of Public Health Scotland data aimed to:

1. identify the number of people in Scotland who experienced a first non-cardioembolic ischaemic stroke or TIA between 1 January 2012 and 31 December 2017
2. identify the number of people in Scotland who experienced a recurrent stroke event (ischaemic stroke, intracerebral haemorrhage or subarachnoid haemorrhage) within 5 years of their initial stroke.

The results of the analysis were used to inform the SHTG cost analysis.

Methods

Frequency of stroke recurrence

Data were collected from the Scottish Morbidity Records 01 (SMR01), which covers episode based data for all general and acute hospital inpatient admissions and day cases. Episodes were aggregated to hospital inpatient stay level for individual patients based on their unique identifier. Each stay was treated as a single event or occurrence.

Event types (index or recurrent) were defined according to the International Classification of Disease Tenth Revision (ICD-10) diagnostic codes (*Table A*). Event types were classified based on the first episode recorded during a hospital stay, prioritising the primary discharge diagnosis. The first relevant discharge code was taken as the defining diagnosis for that hospital stay.

Table A: ICD-10 codes and definitions used to classify event types and occurrence

Event type	Index or recurrent event	ICD-10 code	Definition
Intracerebral haemorrhage	Recurrent	1610-9	Intracerebral haemorrhage
		1620-9	Other non-traumatic ICH
Ischaemic stroke	Both	1630-9	Cerebral infarction
		164X	Stroke, not specified as haemorrhage or infarction
Subarachnoid haemorrhage	Recurrent	1600-9	Subarachnoid haemorrhage
Transient ischaemic attack	Index	G450-3, 8-9	Transient cerebral ischaemic attacks and related syndromes

As a result of limitations of ICD-10 codes in distinguishing between non-cardioembolic and cardioembolic events, data were linked with prescribing records. Patients prescribed antiplatelet medications within 90 days of hospital discharge were assumed to have had a non-cardioembolic ischaemic stroke.

An initial cohort of 43,520 first ischaemic strokes or TIAs was identified from the ICD-10 and prescribing data. We refined this cohort by excluding cases without prescribing information (12.7%), cases where only anticoagulant medications were prescribed (13.9%) and cases where both anticoagulants and antiplatelets were prescribed, unless the anticoagulant came after the recurrent event (4.4%). There is currently no standardised approach to defining stroke recurrence. We adapted a methodology reported in previous studies.[34] An event was considered a recurrence if:

- the event occurred ≥21 days after the first event

  OR

- the event occurred before 21 days after the first event but was considered a different event type according to ICD-10.

Recurrence events were limited to the first recurrent stroke up to a maximum of 5 years after an index hospital admission and needed to be linked to a separate hospital stay. To avoid implausible values and ensure inclusion of a representative population, the length of hospital stay was capped at the 90th percentile, limiting the maximum index hospital stay to 63 days.

In 2010, NICE guidelines were updated to recommend clopidogrel for preventing occlusive vascular events, replacing the previous recommendation of a combination of aspirin and dipyridamole.[34] To

ensure our analysis reflected this change in clinical practice, our analysis was restricted to first ever stroke or TIA events from 2012 onwards.

Statistical analysis

We conducted a univariate time to event analysis to estimate the cumulative risk of stroke recurrence up to 5 years after an initial event. We did not adjust for multiple variables.

Data preparation and calculation steps:

1. Interval definition: intervals were set at 0.25, 1, 2, 3, 4 and 5 years after the index event.
2. Follow up time and event calculation: for each interval, we calculated the follow up time and number of events. The follow up time was truncated at the end of each interval. Patients were censored at the time of their first recurrent event, death or at 5 years after the index event.
3. Recurrence rate calculation: the recurrence rate per person-year was calculated for each interval by dividing the total number of events by the total person-years of follow up. This generates a standardised incidence rate that accounts for varying follow up durations.

Results

There were a total of 30,054 first non-cardioembolic ischaemic strokes or TIAs between January 2012 and December 2017, resulting in a total of 116,193 person-years of follow up with 3,645 individuals experiencing a recurrent event (12.1%).

As with previously published analyses, risk of stroke recurrence was highest in the first 3 months after an incident event (*Table B*). Overall, in 79,645 person-years of follow up for first non-cardioembolic ischaemic strokes, 2,802 all recurrent strokes were observed. In 36,548 person-years of follow up for TIA events, 843 all stroke recurrences were observed.

Table B: Stroke recurrence estimates based on SMR01 following index non-cardioembolic ischaemic stroke or TIA.

Time from index event (years)	Cumulative percentage recurrence	Cumulative stroke events	Time period (interval)	Recurrence rate per person-year
After index non-cardioembolic ischaemic stroke or TIA				
0.25	1.84	543	0–0.25 (0.25 years)	0.073
1	6.84	1,431	0.25–1 (0.75 years)	0.051
2	14.82	2,221	1–2 (1 year)	0.042
3	24.99	2,775	2–3 (1 year)	0.036
4	37.05	3,234	3–4 (1 year)	0.033
5	50.85	3,645	4–5 (1 year)	0.031
After index non-cardioembolic ischaemic stroke				
0.25	2.12	432	0–0.25 (0.25 years)	0.084
1	7.83	1,127	0.25–1 (0.75 years)	0.058
2	16.81	1718	1–2 (1 year)	0.047
3	28.19	2,130	2–3 (1 year)	0.041
4	41.61	2,467	3–4 (1 year)	0.037
5	57.14	2,802	4–5 (1 year)	0.035
After index TIA				
0.25	1.22	111	0–0.25 (0.25 years)	0.049
1	4.63	304	0.25–1 (0.75 years)	0.035

2	10.41	503	1–2 (1 year)	0.030
3	17.95	645	2–3 (1 year)	0.027
4	27.03	767	3–4 (1 year)	0.025
5	37.11	843	4–5 (1 year)	0.023

Appendix 5: NICE cost effectiveness analysis model structure

All figures in this appendix have been replicated by SHTG based on the published NICE model.[3]

Figure 1: Decision tree no testing branch

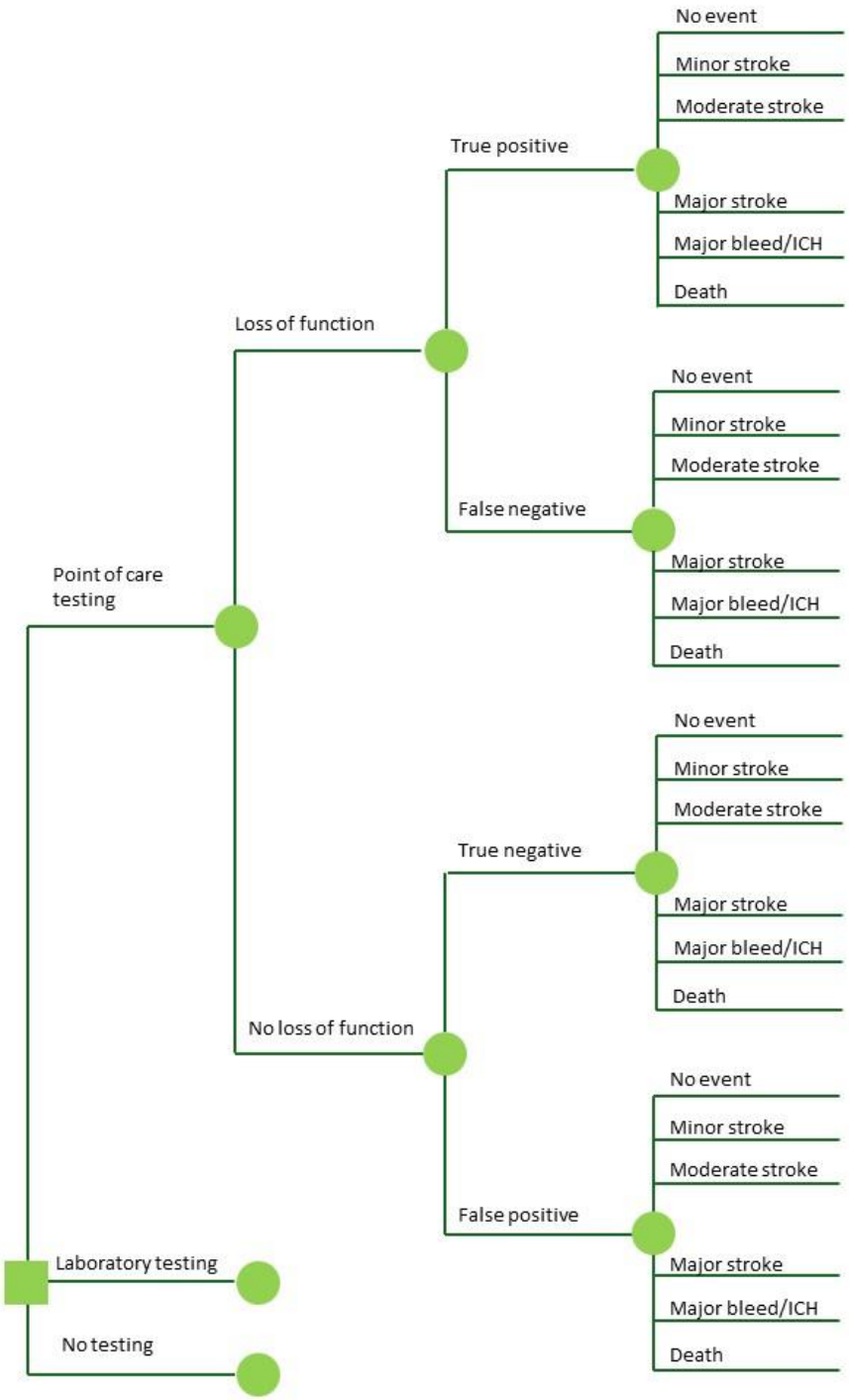


Figure 2: Decision tree point of care testing branch

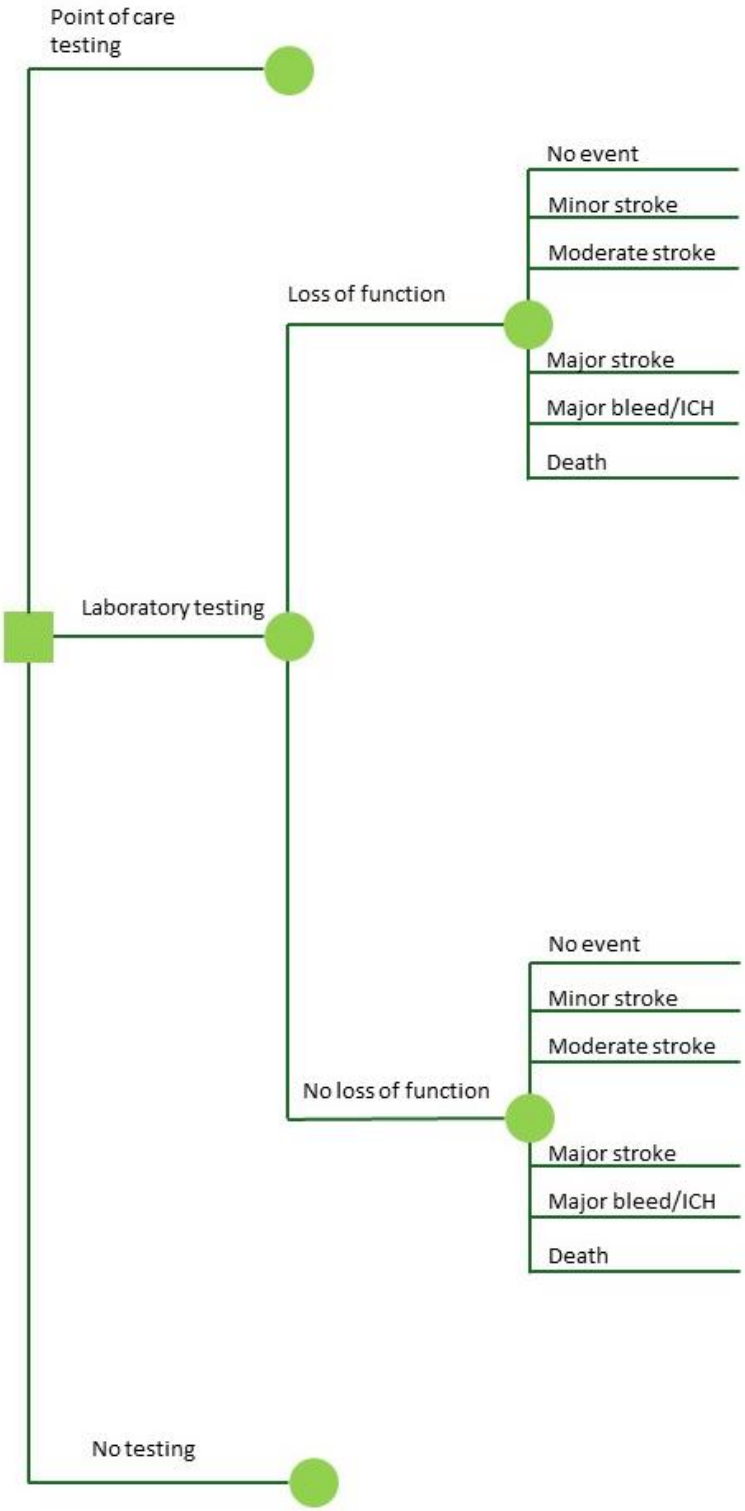


Figure 3: Decision tree laboratory testing branch

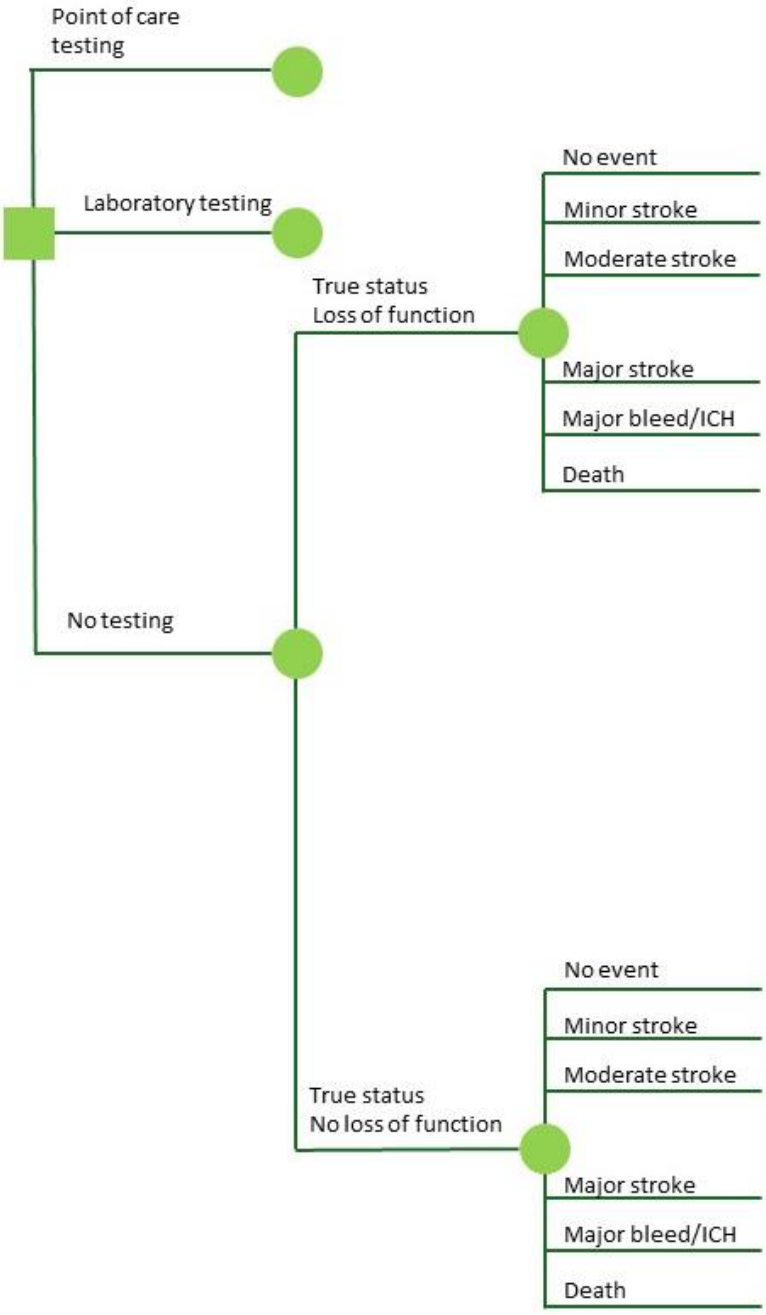
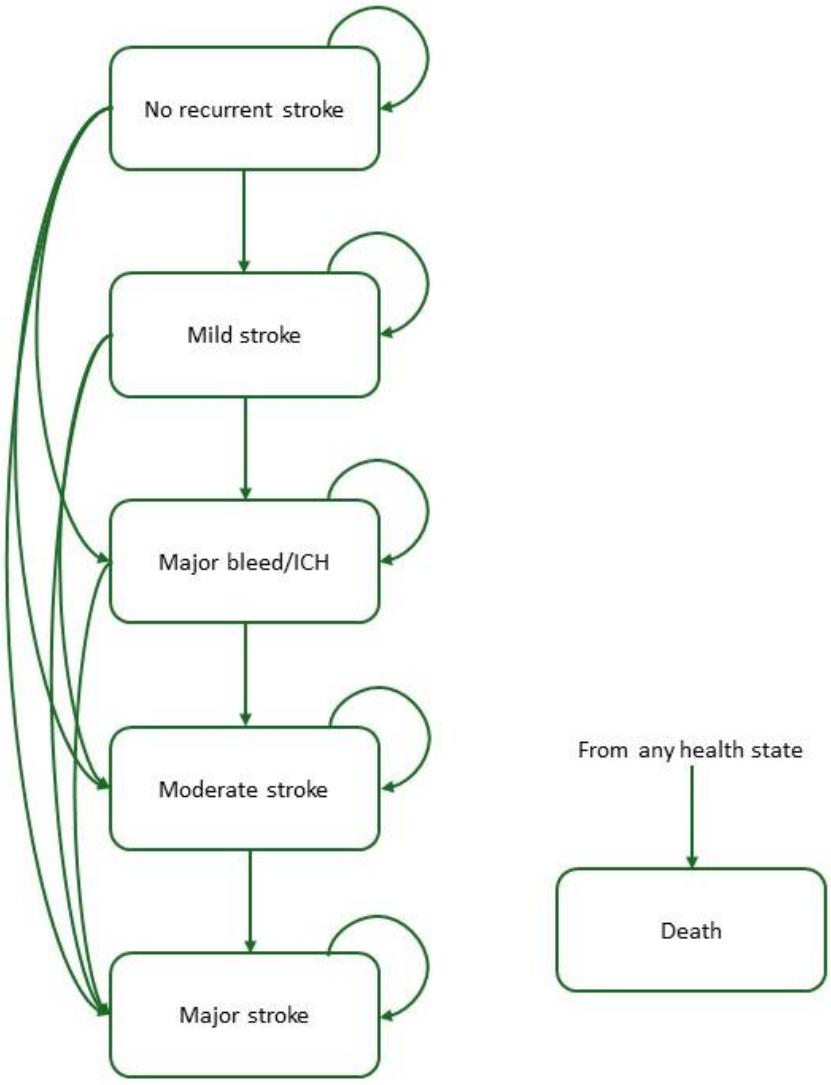


Figure 4: Markov model



Appendix 6: Cost analysis model parameters

Table A: Model input data for the SHTG cost analysis

Parameter	Value	Evidence source
Proportion of recurrent stroke by severity	Minor 0.426 Moderate 0.475 Major 0.0495	SSNAP
Mortality rate by time for mRS 0–3	0–30 days 0.0128 31–90 days 0.0467 >90 days 0.0331	SSNAP and SLSR
Mortality rate by time for mRS 4–5	0–30 days 0.0157 31–90 days 0.0574 >90 days 0.0407	SSNAP and SLSR
Major bleeding or ICH (ppy)	0.0144	PRoFESS trial
Proportion of major bleeds that are ICH	0.282	
Proportion of ICH that are fatal	0.527	
Treatment effects (HR relative to clopidogrel treatment with no LOF)		
Recurrent stroke		
Clopidogrel, LOF	1.46	NICE (objective 3, figure 14)
Dipyridamole + aspirin, no LOF	1.01	PRoFESS
Dipyridamole + aspirin, LOF	1.01	
Aspirin, no LOF	1.96	CHANCE
Aspirin, LOF	1.387	CHANCE with HR from NICE (objective 3, figure 14) applied
Major bleeding or ICH		
Clopidogrel (LOF or no LOF)	1	Assumption as per NICE
Aspirin + Dipyridamole (LOF or no LOF)	1.15	PRoFESS
Aspirin (LOF or no LOF)	0.637	CHANCE
Treatment discontinuation probabilities		
Clopidogrel	0.106	PRoFESS
Dipyridamole + aspirin	0.164	
Test performance		
Genedrive	Sensitivity 99.6% Specificity 100%	NICE
Genomadix cube	Sensitivity 99% Specificity 100%	NICE
Laboratory test	Sensitivity 100% Specificity 100%	NICE
Point of care test failure rate	8%	NICE
Treatment costs		

Clopidogrel 75mg per day (annualised)	£16.04	BNF
Dipyridamole 400mg per day (annualised)	£160.10	
Aspirin 75mg per day (annualised)	£9.78	
Health state costs		
After major bleed or ICH (one-off cost when event occurs)	£2,010	NICE TA90
Ischaemic stroke population (annual, first year)		
No secondary event	£9,741	SSNAP
After secondary minor stroke	£19,776	
After secondary moderate stroke	£26,160	
After secondary major stroke	£33,445	
TIA population (annual, first year)		
No secondary event	£4,085	SSNAP
After secondary minor stroke	£15,864	
After secondary moderate stroke	£26,160	
After secondary major stroke	£33,445	
Ischaemic stroke population (annual, subsequent years)		
No secondary event	£5,944	SSNAP
After secondary minor stroke	£9,015	
After secondary moderate stroke	£10,154	
After secondary major stroke	£13,035	
TIA population (annual, subsequent years)		
No secondary event	£2,841	SSNAP
After secondary minor stroke	£6,869	
After secondary moderate stroke	£10,154	
After secondary major stroke	£13,035	
Other costs		
Treatment switching cost	£42	Cost of GP visit (PSSRU)

ppy = per person-year

Appendix 7: Sensitivity analyses

Table A: Scenario 1 – doubling the per test cost for laboratory-based testing

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	88.2	106.2	137.6	219.4	382.7	934
Laboratory-based testing	88.1	104.5	135.1	214.9	374.3	916.9
Net change: laboratory-based vs no testing	-0.2	-1.7	-2.5	-4.5	-8.4	-17.2

Table B: Scenario 2 – decreasing health state costs by 20%

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	70.7	85.0	110.1	175.6	306.4	747.8
Genedrive point of care testing	71.2	83.9	108.4	172.2	299.8	735.5
Genomadix point of care testing	71.4	84.0	108.5	172.3	300.0	736.2
Laboratory-based testing	70.6	83.9	108.4	172.4	300.2	735.4
Net change: Genedrive vs no testing	0.5	-1.1	-1.8	-3.4	-6.5	-12.3
Net change: Genomadix vs no testing	0.7	-1.0	-1.6	-3.3	-6.4	-11.6
Net change: laboratory-based vs no testing	-0.1	-1.1	-1.7	-3.3	-6.1	-12.3

Table C: Scenario 3 – lowering the LOF versus no LOF (HR = 1.09)

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	88.4	106.5	138.1	220.1	384.0	937.1
Genedrive point of care testing	89.0	105.1	136.0	216.4	376.9	923.4
Genomadix point of care testing	89.2	105.2	136.1	216.5	377.0	924.1
Laboratory-based testing	88.5	105.1	136.1	216.5	377.3	923.5
Net change: Genedrive vs no testing	0.6	-1.4	-2.0	-3.8	-7.1	-13.7
Net change: Genomadix vs no testing	0.8	-1.3	-1.9	-3.7	-7.0	-13.1
Net change: laboratory-based vs no testing	0.04	-1.4	-2.0	-3.6	-6.7	-13.6

Table D: Scenario 4 – rural health board perspective (6% of stroke and TIA population; 10 day laboratory-based testing turnaround time; 6% of laboratory-based testing fixed costs)

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	5.3	3.7	3.9	4.4	5.4	22.7
Genedrive point of care testing	5.3	3.6	3.8	4.3	5.2	22.1
Genomadix point of care testing	5.3	3.6	3.8	4.3	5.2	22.2
Laboratory-based testing	5.3	3.6	3.8	4.3	5.2	22.1
Net change: Genedrive vs no testing	0.01	-0.1	-0.1	-0.1	-0.2	-0.5
Net change: Genomadix vs no testing	0.02	-0.1	-0.1	-0.1	-0.2	-0.5
Net change: laboratory-based vs no testing	-0.02	-0.1	-0.1	-0.2	-0.2	-0.6

Table E: Scenario 5 – point of care test fixed costs doubled

Pathway	Annual costs (£ million)					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current pathway (no genotype testing)	88.2	106.2	137.6	219.4	382.7	934
Genedrive point of care testing	88.6	104.5	135.0	214.6	373.8	916.4
Genomadix point of care testing	88.7	104.5	135.1	214.7	373.9	916.9
Net change: Genedrive vs no testing	0.4	-1.8	-2.6	-4.6	-8.5	-17.6
Net change: Genomadix vs no testing	0.5	-1.6	-2.5	-4.7	-8.8	-17.1