Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence

Title of Project: Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

Produced by: Bristol Technology Assessment Group

ADDITIONAL ANALYSES FOLLOWING STAKEHOLDER CONSULTATION AND PERFORMANCE DATA FROM GENE DRIVE

1 Introduction

The EAG has reviewed comments from stakeholders in response to the draft guidance and provided a response in the document "DAP65 Clopidogrel - Collated DG comments for EAG 20230612DB [CIC].docx". The EAG has also been provided with additional data on test performance from Genedrive, received on 6/9/23.

In this document we critique the additional data provided by Genedrive, and provide an updated EAG base-case model in response to comments from stakeholders and the additional data from Genedrive. The EAG has also conducted some additional analyses and modelling scenarios in response to comments received from stakeholders, which we give a rationale for in this document. All results of scenarios are with respect to the EAG updated base-case.

2 EAG Critique of additional data submitted by Genedrive

2.1 Information provided by the company

Genedrive have provided the following additional data for evaluation:

- Performance Data for the Genedrive CYP2C19 ID kit
- Genedrive CYP2C19 ID Kit Instructions for use
- 1 page response to the EAGs request for additional information on the study used to evaluate the Genedrive tests

2.2 Overview of the test

The Genedrive CYP2C19 ID kit is used in conjunction with the Genedrive System to prove a result. Results can be transferred electronically to patient records. The Genedrive requires a buccal swab for evaluation.

The test targets the following CYP2C19 alleles:

- Normal/"wild-type" allele: *1
- Loss of function (LOF) alleles: *2, *3, *4, *8, *35
- Increase function allele: *17

We followed the same approach as in the original EAG report to dichotomise results into alleles that encode for normal function and those that are non-functional. A "positive" test result (non-functional) was defined as the presence of at least one LOF allele.

2.3 Evaluation of test accuracy

Diagnostic test accuracy was evaluated based on 250 donor specimens and 108 contrived specimens. As contrived specimens do not reflect the samples that would be used in practice, data from these specimens were excluded from our review.

2.3.1 QUADAS-2 assessment

The study was judged at unclear risk of bias as there was no information on how test accuracy was evaluated. There was no information on the study population. The EAG

requested additional information on this from Genedrive they state that "Adult donors were used for the non-contrived specimens", but did not provide any information on how they were selected or recruited. The EAG therefore considers the study to be at "Unclear" risk of bias for the patient selection domain. The company provided additional information on the reference standard as part of their response to the EAG request for additional information. They stated that the reference standard was "buccal cell derived gDNA using the Agena MassARRAY and/or Taqman". The EAG consider this to be an acceptable reference standard. Table 1 provide a summary of the QUADAS-2 assessment of risk of bias for this study.

Table 1 Overview of risk of bias in the study evaluating the accuracy of the Genedrive test

Study Details	Patient Selection	Index test	Reference standard	Flow & Timing	Overall	Rationale for Judgement
Gendrive supplementary data	?	☺	☺	☺	?	Insufficient information on selection of study population

2.3.2 Accuracy results

The table below provide an overview of the donor specimens considered in the analysis:

Table 2 Overview of results for Genedrive on the donor specimens

CP2C19 Diplotype	Classification of result (positive = non-functional; negative = normal)	Number of specimens tested	Overall classification
*1/*2	Positive	30	83
*1/*3		12	
*2/*2		24	
*2/*17		17	
*1/*1	Negative	119	167
*1/*17		30	
*17/*17		18	

All samples were reported to have been correctly classified as positive or negative by Genedrive. We calculated exact confidence intervals around estimates of sensitivity and specificity, based on the 250 donor specimens. This gives a sensitivity of 100% with 95% CI (96%, 100%) and specificity of 100% with 95% CI (98%, 100%). Four samples were incorrectly classified by Genedrive – 2 samples with one LOF allele were classified as have 2 LOF alleles, and 2 samples with 2 LOF alleles were classified as having 1 LOF allele. As our dichotomy considers both of these as "positive" test results, this misclassification did not impact on estimates of accuracy.

Table 3 Estimates of accuracy used to inform the economic models a comparison of the estimate of accuracy for Genedrive obtained from the data included in the new submission

with data on the accuracy of Genomadix Cube estimated as part of the original EAG report. These are the accuracy estimates for each test that have been used to inform the economic model.

Table 3 Estimates of accuracy used to inform the economic model

Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Number of studies	Risk of bias
Genedrive	100 (96, 100)	100 (98, 100)	1	Unclear
Genomadix Cube	100 (94, 100)	100 (99, 100)	10	Low

2.4 Technical performance data

Time to results (from specimen collection to result) was reported in the performance data as 69 minutes plus an additional 3 minutes assay set up time. Test failure rate was reported at 0.6% (358/360), but it was unclear whether the two test failures were based on donor or contrived samples and whether this was for the initial run only or after re-testing of failed samples. The EAG notes that for Genomadix cube where data on test failure rate was available for 10 studies, there was substantial variation in test failure rate across studies, from a minimum of 0.4% of tests (1/267) to a maximum of 18.9% (10/53 patients) for the initial run. Studies independent of the test manufacturer reported failure rates from 7% to 18.9%. As there is only one study, conducted by the test manufacturer, that reports information on test failure rate for Genedrive, this should be interpreted with caution. Additional data from independent studies are needed to confirm this result.

3 Updated EAG base-case in response to stakeholder comments and additional data provided by Genedrive

The EAG have updated their base-case in response to stakeholder comments and additional data provided by Genedrive. The changes to the EAG base-case are described below. All results and scenarios in this document are with respect to this updated EAG base-case.

3.1 Test performance data provided by Genedrive

Our analysis of the test performance data provided by Genedrive gives an estimate of 100% with 95%CI (96%, 100%) for sensitivity and 100% with 95% CI (98%, 100%) for specificity (Table 2). The corresponding estimates for Genomadix were sensitivity of 100% (95% CI 94%, 100%) and specificity of 100% (95% CI 99%, 100%)(Table 2). We had previously assumed that the sensitivity and specificity for Genedrive was the same as for Genomadix. Specificity was assumed to be 100%, which is supported by the Genedrive test accuracy data, and so we do not change this assumption in our updated base-case. For specificity we note that Genomadix detects the *2, and *3 alleles, whereas Genedrive detects the *2, *3,

*4, *8, and *35 alleles, and the test accuracy data is only with respect to the alleles detected by each test. In our base-case we assumed a sensitivity of 99% (rather than 100%) to reflect that Genomadix does not test for all LOF alleles. Genedrive does however test for *4, *8, and *35 LOF alleles (but not *5, *6, *7), and so we would expect Genedrive to have a slightly higher sensitivity than Genomadix. Based on the allele frequencies by ethnicity reported in Ionova et al (2020), applying these to the assumed ethnicity distribution in a UK stroke/TIA population (see Prevalence of CYP2C19 LOF subsection of Model Inputs section 5.2.5 of EAG report), we obtain an estimated prevalence of *4, *8, and *35 alleles of 0.6% in a UK population. We therefore assume sensitivity of 99.6% for Genedrive in our updated base-case with and sensitivity unchanged for Genomadix at 99%.

Genedrive state that the estimated time to receive results was 69 minutes plus an additional 3 minutes assay set up time. We assume in our base-case that POCT results would be received prior to discharge, which is supported by these data.

Genedrive state there was a 0.6% test failure rate in their study. As noted in section 2.4, our review found that there was a high variability in test failure rates for Genomadix, ranging from 0.4% to 18.9%, with higher rates in studies not sponsored by the manufacturer. The pooled average rate for Genomadix was 8%, which was used in our base-case. We only have a single estimate from the manufacturers study for Genedrive, but if the variation in test failure rates is similar to that seen for Genomadix, this may be an under-estimate of the failure rates that may occur in practise. We retain an assumed test failure rate of 8% in our base-case, but use a value of 0.6% in a scenario analysis (Scenario 17, section 4).

3.2 Cost of laboratory test mass-array system

The EAG have updated their base-case using an updated calculation for the lifetime cost of the mass-array system, in response to stakeholder comments. We now assume a 5-year device lifetime to better reflect laboratory forecasting for capital equipment replacement costs and estimate a maximum 3,456 samples could be processed by the mass-array system in a 24-hour period (384 plates with a 150min run time). This has a minimal effect on lab test cost as the updated device cost per test is increased to 7p.

3.3 Cost of GP Visit

In the original EAG base-case we did not include the cost of a GP visit when patients switch treatment due to receiving delayed test results or discontinuing a treatment. We now include a 9min GP visit (costing £41 [PSSRU unit costs programme (4)]) for those patients who switch treatments after receiving test results:

- all TIA/minor stroke patients for the lab-test in the EAG updated base-case
- all non-minor stroke patients for the lab-test in the early clopidogrel scenario (Scenario 7)

We also add the cost of a GP visit for all patients discontinuing treatment and switching to aspirin.

3.4 Proportions with TIA or minor-stroke

To obtain the results for a mixed TIA/IS population, we used an estimate of the proportion of patients with TIA or minor stroke. We had calculated this using the NICE Clinical Knowledge Summary, which is based on the PHE briefing document on first incidence of stroke (2007 – 2016) (1). However, we had only included TIAs rather than TIA and minor stroke, and furthermore had assumed that all strokes were ischaemic, whereas only approximately 85% of 1st strokes are ischaemic. The PHE briefing document reports an incidence of first-ever transient ischaemic attack (TIA) of approximately 50 per 100,000 people per year, and a crude incidence rate of first strokes to be 107 per 100,000 population, which gives a crude incidence of first strokes that are ischaemic = 107*0.85 per 100,000 = 90.95 per 100,000. The proportion of initial TIA/ischaemic strokes that are TIA are P(TIA) = 50/(90.95+50) = 0.35. Based on the economics report from SSNAP (Demographics sheet HE-NHSE-RCP-Appendix-1.xlsx), the proportion of initial strokes that are minor stroke (which we define as NIHSS 1-4 for the economic model) is estimated to be 0.486. This gives: P(TIA or minor IS) = 0.35 + 0.486*(1-0.35) = 0.666. We use therefore use a proportion 66.6% with TIA or minor stroke in the EAG updated base-case. Note the proportion with TIA or minor stroke is only used to obtain results for the mixed population and does not affect our results for the TIA/minor stroke and non-minor stroke populations.

3.5 Baseline hazard of recurrent stroke

The committee discussion highlighted that the evidence sources used for the baseline hazards for recurrent stroke would be a mixed population of those with LOF and those with No LOF, whereas we were using these estimates to represent a NoLOF population on clopidogrel. Assuming that the proportion of LOF in these populations are representative of a stroke population in England with 31.8% of patients with LOF alleles (as assumed in our model), then the observed hazard from these sources will be a weighted average of the hazard in the LOF patients and the NoLOF patients. Assuming a hazard ratio of recurrent stroke for LOF relative to NoLOF of 1.46 (from Objective 3 results in the clinical effectiveness section of the original EAG report), then:

$$hazard_{mixed} = hazard_{NoLOF}(0.318*1.46 + 0.682)$$

Rearranging gives:

$$hazard_{NoLOF} = \frac{hazard_{mixed}}{0.318*1.46 + 0.682} = 0.871* hazard_{mixed}$$

We therefore adjust the baseline hazards by a factor of 0.871 in the updated EAG base-case.

3.6 Correction of coding errors

We identified two small coding errors in the computation of treatment costs and in the computation of discontinuations:

1. Treatment costs. The treatment costs in the 90-day decision tree period were double-counted, which has now been corrected. As the costs are largely driven by health state costs, this has a minimal effect on the overall costs.
2. Discontinuation. When patients discontinue on treatment they are modelled to switch treatments. We therefore use discontinuation-adjusted hazard rates to model the state transitions based on hazard rates weighted by the proportion of patients on their 1st and 2nd line treatments. We had calculated the weights based on the proportion of the cohort on each line of treatment, but hadn't accounted for the proportion of the cohort who had died. This has now been corrected to calculate the weight based on the proportion of the cohort that is alive and on treatment in each time cycle. This results in a small change in QALYs and costs.

4 Scenario analyses

We run all the scenario analyses 1 – 9 described in Table 42 from the original EAG report (reproduced in Table 4 below), but do not run the threshold analysis (scenario 10) for Genedrive sensitivity, since we now have data for Genedrive. We also conduct some additional scenarios described below, in response to stakeholder comments and additional data from Genedrive.

Table 4 List of scenario analyses included in original EAG report

Scenario	Description	Model parameters changed	Rationale for analysis
1	Prevalence of clopidogrel resistance	Increased the proportion of patients with LOF variants from 32.1% to 56.8%	Prevalence of LOF variants varies across populations due to differences in ethnicity.
2	Aspirin as Alt Tx for LOF patients	Patients whose test indicates LOF receive aspirin instead of dipyridamole plus aspirin. Costs and hazard ratios for aspirin are used for the alternative treatment.	Dipyridamole may not be used due to tolerability issues.
3	Mean age of cohort	Mean age of cohort reduced to 40 and corresponding life-table values used	This is a long-term treatment, and so costs and benefits of targeted treatment may depend on age at index event
4	Low uptake of alternative therapy after POCT test results	A probability 0.699 of receiving alternative treatment for those with LOF test result is applied.	Swen et al 2023[157] found that physician adoption of pharmacogenetic recommendations was for a range genes including *CYP2C19* was only 69.9%.
5	Extended time to lab-test results	For the lab-test, the time spent on clopidogrel before	Our survey found there is variability between labs in how

Scenario	Description	Model parameters changed	Rationale for analysis
		switching to alternative treatment for LOF patients is varied to 4 weeks	quickly results are produced, and this can change with capacity
6	Ticagrelor (following DAPT ticagrelor + aspirin) as Alt Tx for LOF patients	Patients whose test indicates LOF receive ticagrelor (following DAPT ticagrelor + aspirin) instead of dipyridamole plus aspirin. Costs and hazard ratios for ticagrelor are used for the alternative treatment.	Ticagrelor has not been approved for use in England and Wales but it may be used off-label
7	Early clopidogrel introduction	In the non-minor ischaemic stroke population clopidogrel treatment begins immediately. LOF carriers can benefit from alternative treatment sooner.	Some non-minor ischaemic stroke patients may begin clopidogrel immediately (for example if they are already taking aspirin)
8	Price year 2021	Prices are inflated to 2021 prices instead of 2022	High levels of inflation in 2022 may be impactful
9	Lab-based test costs	The cost of laboratory tests are varied in a threshold analysis	Uncertainty and heterogeneity in labs-costs, which may change with changes in infrastructure

4.1 Network Meta-Analysis for Recurrent Stroke and Major Bleed

4.1.1 Hazard Ratios for Recurrent Stroke

In the EAG base-case we use a network meta-analysis (NMA) based on studies that provide hazard ratios for recurrent stroke by LOF status if possible. We include the following studies (see Figure 1):

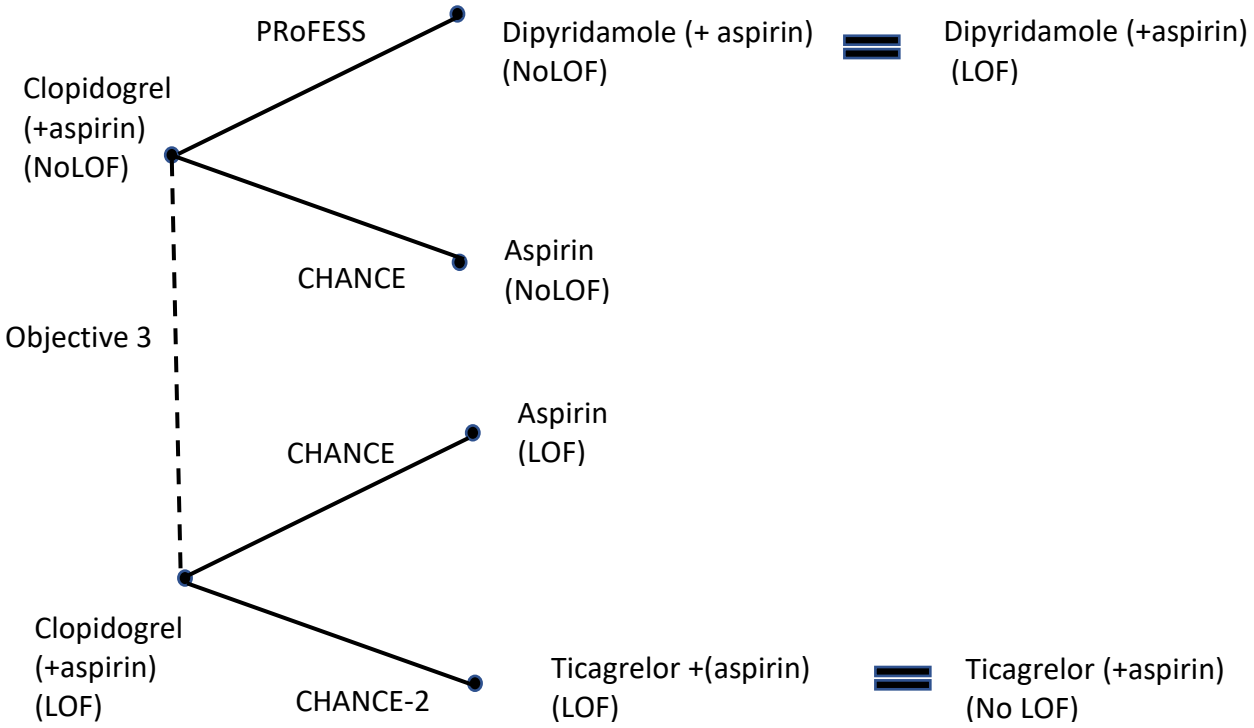
- CHANCE which provides the comparison of Clopidogrel (+Aspirin) vs Aspirin for both LOF and No LOF.
- CHANCE-2 which provides the comparison of Ticagrelor (+Aspirin) vs Clopidogrel (+Aspirin) in LOF patients.
- PRoFESS which compares Dipyridamole(+Aspirin) vs Clopidogrel (+Aspirin), but in a mixed LOF/NoLOF population due to no studies making this comparison by LOF status. We assumed that outcomes for Dipyridamole do not depend on LOF status, and that the PRoFESS study represented a No LOF population (since the majority of patients would be No LOF). In reality the PRoFESS study is a mix of No LOF and LOF patients, which will affect the hazard ratio due to the comparison with clopidogrel where outcomes depend on LOF.
- The hazard ratio for LOF vs NoLOF on clopidogrel from Objective 3 of our review to link outcomes for LOF to those for NoLOF

We excluded two small studies that were under-powered for the outcome of interest:

- PRINCE study (Wang 2019 BMJ) which compares Ticagrelor(+Aspirin) vs Clopidogrel for both LOF and No LOF patients
- POINT study (Meschia 2020 Stroke) which compares Clopidogrel(+Aspirin) vs Aspirin for both LOF and No LOF patients

Excluding these studies is unlikely to impact the estimates due to the very much larger studies making the same comparisons: CHANCE for Clopidogrel(+Aspirin) vs Aspirin by LOF status, and CHANCE-2 for Ticagrelor(+Aspirin) vs Clopidogrel for LOF.

Figure 1 Network diagram indicating studies included in EAG base-case for recurrent stroke. The PRoFESS study is on a mixed population, whereas CHANCE and CHANCE-2 provide results for LOF patients, and CHANCE also gives results for NoLOF patients. The pooled result comparing LOF vs NoLOF from Objective 3 links the populations (dashed line).



Several stakeholders mentioned the THALES study which compares Ticagrelor(+Aspirin) vs Aspirin in a mixed LOF/NoLOF population. We did not include THALES because it does not provide estimates by LOF status, whereas the CHANCE-2 study compared Ticagrelor (+Aspirin) directly with Clopidogrel in LOF patients, which was exactly what was required for our model. However, we do acknowledge that we had included the PRoFESS study to compare dipyridamole+aspirin vs clopidogrel+aspirin, which also does not give results by LOF status. This is because we had no alternative evidence for dipyridamole, whereas CHANCE-2 was available for Ticagrelor.

To explore the impact of including these additional studies, we have conducted an alternative evidence synthesis to include:

- the PRINCE study which compares Ticagrelor(+Aspirin) vs Clopidogrel for both LOF and No LOF (albeit with a small sample size)
- the small POINT study (Meschia 2020) for completeness, although it is unlikely to have a big impact on the results due to the much larger CHANCE study making the same comparison
- the THALES study.

Because THALES and PRoFESS are on a mixed LOF/NoLOF population, we make an adjustment to the estimates from these studies to reflect that the comparison with clopidogrel / aspirin will be affected by the proportion of LOF patients in the studies. To achieve this we assumed that PRoFESS and THALES provide a weighted average of the effects for LOF and NoLOF patients, where the weights were estimated from the baseline characteristics for ethnicity in those studies (using the same LOF proportions as used in our report (section 5.2.5) to estimate LOF prevalence). The estimated percentages of LOF patients were 30.3% for THALES and 31.6% for PRoFESS. As before, we assume that the outcomes for dipyridamole(+aspirin) and ticagrelor(+aspirin) do not depend on LOF. The full network of evidence for this updated evidence synthesis is illustrated in Figure 2.

The results from the alternative evidence synthesis including CHANCE, CHANCE-2, POINT, PRoFESS, PRINCE, and THALES (Figure 2) are provided in

Table 5, reported as hazard ratios (HRs) vs clopidogrel in NoLOF patients. Hazard Ratios are presented relative to clopidogrel NoLOF, because this represents the baseline hazards in our model. However, it is more natural to make treatment comparisons within population, and so the effects for treatments on the LOF patients are also reported relative to clopidogrel LOF, to aide interpretation.
The most important difference between the estimates is that dipyridamole + aspirin is less effective due to adjusting the clopidogrel arm from PRoFESS to allow for a proportion of LOF patients in that study.

Note that both approaches to evidence syntheses make strong assumptions. The EAG base-case NMA (Figure 1) assumes that:

1. The hazard ratio PRoFESS study is representative of the HR for patients with NoLOF
2. The hazard ratio obtained from the meta-analysis of non-randomised comparisons of clopidogrel LOF vs NoLOF from objective 3 is an unbiased estimate
3. Efficacy of dipyridamole and ticagrelor does not depend on LOF status.

The alternative evidence synthesis (Figure 2) relaxes the first of these assumptions, but instead assumes that:

4. The proportion with LOF in THALES and PRoFESS can be estimated based on the reported ethnicity data

5. The hazard ratio for clopidogrel LOF vs NoLOF from objective 3 is applicable in the PRoFESS, THALES, and other study populations.

The EAG retains the NMA used in its base-case, but runs a scenario (Scenario 11) using the alternative evidence synthesis.

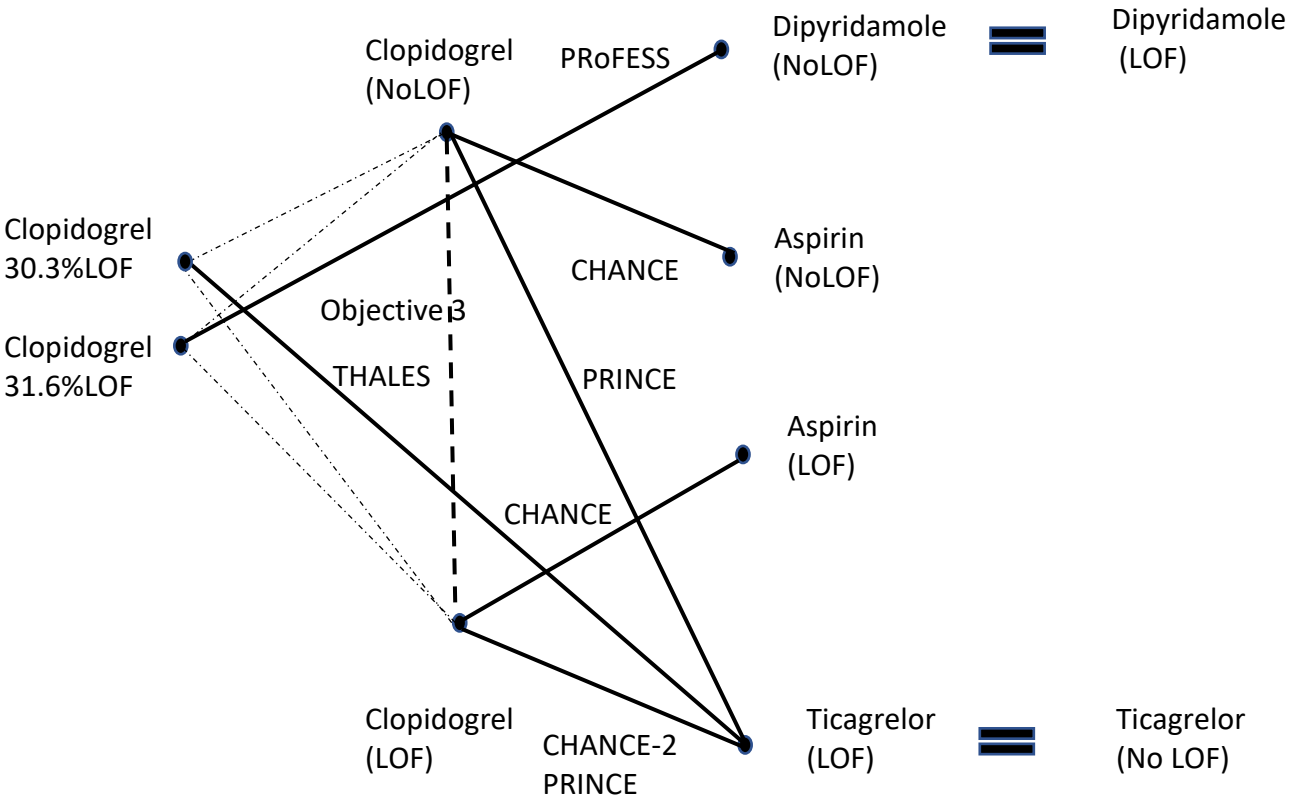


Figure 2 Network diagram indicating studies included in EAG updated network meta-analysis. The PRoFESS and THALES studies are on a mixed population, whereas CHANCE and CHANCE-2 provide results for LOF patients, and CHANCE also gives results for NoLOF patients. The PRoFESS and THALES studies compare with a weighted average of the Clopidogrel effect for LOF and NoLOF based on the estimated proportion LOF in each study (indicated by the light dashed lines). The pooled result comparing LOF vs NoLOF from Objective 3 links the populations (heavy dashed line).

Table 5 Hazard Ratios (HR) for recurrent stroke for each treatment and LOF combination relative to NoLOF on Clopidogrel from the evidence synthesis in the original EAG base-case (Figure 1) and from the updated evidence synthesis (Figure 2).

Treatment, LOF Status	Alternative Evidence Synthesis	Original EAG Base-Case
HR vs Clopidogrel NoLOF		
Clopidogrel, NoLOF	1	1
Aspirin, No LOF	1.733 (1.241, 2.36)	1.96 95%CI (1.33, 2.857)
Dipyridamole, No LOF	1.316 (1.058, 1.612)	1.01 95%CI (0.92, 1.11)
Ticagrelor, No LOF	1.191 (0.879, 1.574)	1.142 95%CI (0.797, 1.587)

Clopidogrel, LOF	1.475 (1.109, 1.923)	1.46 95%CI (1.09, 1.95)
Aspirin, LOF	1.492 (0.9851, 2.167)	1.387 95%CI (0.895, 2.054)
Dipyridamole, LOF	1.316 (1.058, 1.612)	1.01 95%CI (0.92, 1.11)
Ticagrelor, LOF	1.191 (0.879, 1.574)	1.142 95%CI (0.797, 1.587)
HR vs Clopidogrel LOF		
Clopidogrel, LOF	1	1
Aspirin, LOF	1.008 (0.7917, 1.266)	1.075 (0.794, 1.449)
Dipyridamole + Aspirin, LOF	0.8978 (0.7883, 1.018)	0.700 (0.509, 0.935)
Ticagrelor, LOF	0.809 (0.6911, 0.941)	0.77 (0.64, 0.94)

4.1.2 Major Bleeds

In the EAG base-case we included the same studies for the major bleed outcome as were included for recurrent stroke (CHANCE, CHANCE-2, and PRoFESS), using studies with results by LOF status where possible. We have explored the impact of including studies on mixed LOF/NoLOF populations in an alternative NMA for major bleed/ICH, under the assumption that bleeds do not depend on LOF status. To ensure we include all such studies on a mixed population we included studies identified in the network meta-analysis by Del Giovane et al (2) on treatments relevant for our model (see Figure 3 for the network diagram). This analysis identified one study (ESPIRIT which compared dipyridamole+aspirin vs aspirin)) as an outlier with a relative effect estimate in the opposite direction from other studies making this comparison. Excluding ESPIRIT substantially improved model fit and reduced heterogeneity so that a fixed effect model was adequate. The results from the alternative network meta-analysis for major bleed are provided in Table 6. The main impact of including more studies in the network meta-analysis is to increase the HR for ticagrelor + Aspirin vs clopidogrel + aspirin. This was previously based on the CHANCE-2 study alone, which had a very uncertain estimate consistent with both a reduced or an increased risk of bleeding for ticagrelor. The alternative network meta-analysis results indicate an increased risk of major bleed / ICH for ticagrelor vs clopdigrel, although the 95% credible interval still includes 1 (Table 6). We run a scenario analysis to using the alternative NMA for major bleed / ICH.

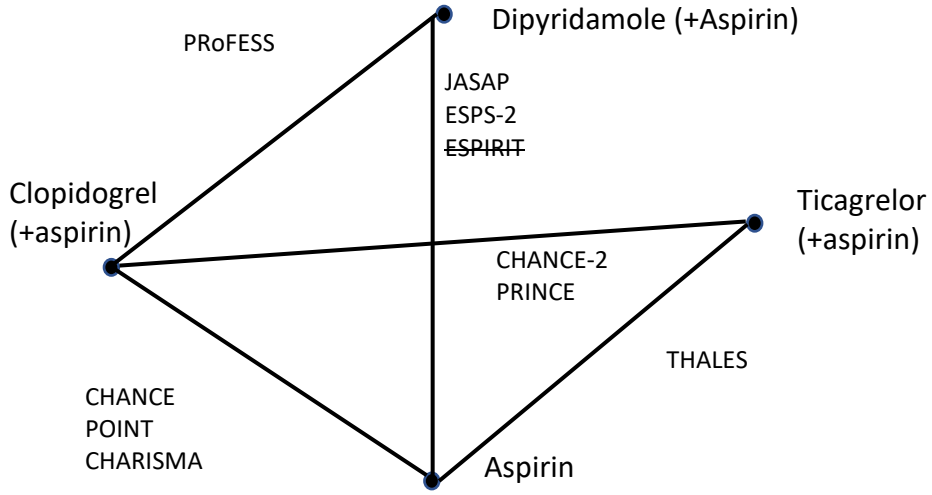


Figure 3 Network diagram indicating studies in EAG updated network meta-analysis for major bleed / ICH in a mixed population (combined LOF and NoLOF).

Table 6 Hazard Ratios for major bleed/ICH for each treatment relative Clopidogrel, assumed not to depend on LOF status

HR major bleed/ICH relative to Clopidogrel	Alternative NMA	Original EAG Base-Case
Clopidogrel (LOF or NoLOF)	1	1
Aspirin + Dipyridamole (LOF or No LOF)	1.139 (0.994, 1.300)	1.15 95%CI (1, 1.32)
Aspirin (LOF or No LOF)	0.6726 (0.466, 0.940)	0.637 95%CI (1.087, 0.373)
Ticagrelor (LOF or No LOF)	1.536 (0.829, 2.606)	0.82 95%CI (0.34, 1.98)

Scenario 11: EAG base case using (a) the hazard ratios from the alternative NMA for recurrent stroke; (b) the hazard ratios from the alternative NMA and major bleeds; (c) both alternative NMAs for recurrent stroke and major bleed.

4.2 No Testing (Ticagrelor) vs Testing (Clopidogrel/Ticagrelor)

The RCP recently updated guidance to recommend ticagrelor as an option for people with TIA/minor stroke. Therefore, not testing and using ticagrelor for all TIA/minor stroke patients is now an option. We have therefore added a scenario for the TIA/minor stroke where we compare the strategy “No test and use ticagrelor for all” with testing strategies where ticagrelor is the alternative treatment for those with LOF alleles get ticagrelor and those with NoLOF alleles get clopidogrel. This Scenario is run using (i) the hazard ratios for recurrent stroke and major bleeds from the EAG base-case and (ii) the hazard ratios for recurrent stroke and major bleeds in Scenario 11 above (see section 4.1).

Scenario 12: No test with ticagrelor vs Test and ticagrelor for LoF and clpidogrel for No LOF (TIA / minor stroke population), (i) with EAG base-case HRs, (ii) with HRs from Scenario 11

4.3 Laboratory Costs

The stakeholder comments and committee discussion highlighted the uncertainty around the laboratory costs, including whether these may be lower due to efficiencies such as running tests in batches. We have explored this in a "high efficiency" lab-test scenario where lab tests were assumed to be processed in batches of 55 tests per batch. A batch of 55 was chosen assuming 100,000 tests per year and assuming 400 tests per working day. It is assumed that each of the 7 current NHS GLH laboratories would process these 400 tests each day. The cost of reagent, per test cost of the machine, and nursing costs were kept the same of the base case. When using a batch size of 55 samples the overall lab test cost used in Scenario 13 was £44.

Scenario 13: Assuming lower laboratory costs due to efficiency savings.

We also run two threshold analyses. The first varies the cost per lab-test, reporting the net monetary benefit (NMB) of the lab test against all other tests across a range of costs per lab test. The range of this threshold analysis begins at £40 per test, based on the committee discussion.

The second threshold analysis varies the batch-size of the lab-test and reports the NMB of the lab test vs Genedrive.

Scenario 14: Threshold analysis showing the net monetary benefit (NMB) of lab-test vs no test by varying the lab-test cost

Scenario 15: Threshold analysis showing the net monetary benefit (NMB) of lab-test vs Genedrive by varying batch size of the lab-test

4.4 Uptake of Alternative Treatment

Some of the stakeholder comments related to practicalities of implementing the POCT tests, suggesting that some patients may be prescribed clopidogrel and discharged before test results are available. Our model accounts for this for the lab-test in the TIA/minor stroke population where all patients are initially prescribed clopidogrel and then switched to an alternative treatment when lab-test results become available if they have LOF alleles. Those with LOF have a heightened stroke risk during the period they are on clopidogrel before switching to alternative treatment. We also provided a scenario (for both populations) where not all patients will receive the alternative treatment by modelling uptake of alternative treatment, which could be due to a variety of reasons including the test results not being made available in time.

The most recent annual report from SSNAP (3) provides modelled estimates of length of stay by MRS state:

MRS 0 = 2.5 days (TIA/Minor stroke)

MRS 1 = 2.9 days (Minor Stroke)

MRS 2 = 5.15 days (Moderate Stroke)
MRS 3 = 13.85 days (Moderate Stroke)
MRS 4 = 28.6 days (Major Stroke)
MRS 5 = 32.9 days (Major Stroke)

There may be barriers to implementing the POCTs, but if implemented then POCT results should be available within 24 hours. Based on the length-of-stay figures above, patients should in principle be able to receive their POCT test result prior to discharge, although TIA patients may be discharged sooner. For the lab-tests, all TIA/non-minor stroke patients are likely to be discharged prior to receiving the lab-test result, as assumed in our base-case model, but most of the non-minor stroke will be discharged after 7 days when lab-test results are available. In the EAG report we conducted a scenario to all non-minor patients initiating clopidogrel immediately (Scenario 7), and switching to alternative treatment at a later time when lab-results are available.

We now have added threshold analyses for both populations and for both lab-tests and POCTs to further explore the impact of low uptake of alternative treatments, which may be due to delays with test results.

Scenario 16: Threshold analysis on uptake of alternative treatment for both lab-test and POCT, for both populations.

4.5 Test failure rate for Genedrive

In our base-case we have retained the test failure rate for Genedrive to be 8% based on the variation in test failure rates seen across studies for Genomadix. We run a scenario (Scenario15) using a test failure rate of 0.6% as reported in the study by Genedrive.

Scenario 17: Test failure rate of 0.6% for Genedrive

5 Results

The results for the EAG updated base-case (described in section 3) are shown in Sections 5.1.1 (deterministic results) and 5.1.2 (probabilistic results), with scenario analyses reported in section 5.2. All calculations of net monetary benefit were calculated using a willingness to pay threshold of £20,000 per QALY.

5.1 EAG updated base-case

For the non-minor ischaemic stroke population all diagnostic strategies dominated No test, with all diagnostic strategies offering lower costs and higher QALYs over the lifetime time horizon (Table 7, Table 9). The fully incremental analysis found the Genedrive test to dominate all other diagnostic strategies in the deterministic results (Table 7), and similar findings for the probabilistic results except there is a very high ICER for Genomadix vs Genedrive (Table 9). The probabilistic sensitivity analysis (PSA) found most iterations to be

cost-effective against No test for all diagnostic tests (Figure 4, Figure 5 , and Figure 6). The cost-effectiveness acceptability curve shows Genedrive to have the highest probability of being the most cost-effective strategy across the WTP thresholds analysed (Figure 7). Net monetary benefit at £20,000 WTP is highest for Genedrive, followed by Genomadix, then Lab-test (Table 8). The incremental costs and benefits are lower in the EAG updated base-case compared to the original EAG base-case due to the adjusted baseline hazards which results in a lower incidence of stroke events in the model.

In the TIA/minor stroke population the Genedrive test dominated the other testing strategies in both the deterministic (Table 7) and probabilistic (Table 9) results. The incremental costs and QALYs between the strategies were small (Table 8, Table 10), but incremental net monetary benefit was highest for Genedrive. The cost-effective planes (Figure 8, Figure 9, Figure 10) show the high uncertainty around cost-effectiveness estimates in the TIA/minor stroke population due to the small differences in incremental costs and QALYs between the strategies. Genedrive has the highest probability of being cost-effective (approx. 60%) (Figure 11). No test has the next highest probability of being cost-effective, however note there was also a high probability that No test was least cost-effective, indicating the high level of uncertainty associated with these results.

Deterministic sensitivity analysis results are summarised in Appendix 1: One-way sensitivity analysis results). These show that results are most sensitive to the hazard ratio for stroke in patients with LOF relative to NoLOF on clopidogrel plus aspirin, which was based on the results of our clinical review Objective 3. Results were also sensitive to the hazard ratios for stroke and bleeds for dipyridamole plus aspirin.

5.1.1 Deterministic results tables

Table 7 Updated EAG base-case (Section 3) following stakeholder comments and additional data from Genedrive: deterministic results

Testing Strategies	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	96,415	6.68					
Laboratory genetic test	96,487	6.68	Yes	N/A	Dominated		
PoC test - Genomadix cube	96,505	6.68	Yes	N/A	Dominated	8,745	
No test	97,236	6.63	Yes	N/A	Dominated	Dominated	Dominated
Transient Ischaemic Attack/Minor stroke							
					Vs Genedrive	**Vs Lab test**	**Vs No test**
PoC test - Genedrive	45,688	8.53					
Laboratory genetic test	45,767	8.52	Yes	N/A	Dominated		
No test	45,769	8.52	Yes	N/A	Dominated	Dominated	
PoC test - Genomadix cube	45,773	8.53	Yes	N/A	Dominated	1,885	471

Table 8 Updated EAG base-case (Section 3) following stakeholder comments and additional data from Genedrive: Pairwise results vs no test: incremental costs and QALYs, and Net Monetary Benefit (Willingness to pay £20,000 per QALY). Deterministic results

	Incremental costs (discounted)	Incremental QALYs (discounted)	Net monetary benefit (£20,000 threshold)
Non-Minor Ischaemic Stroke			
Genedrive vs no test	-821	0.05	1,901
Genomadix vs no test	-731	0.05	1,804
Laboratory genetic test vs no test	-749	0.05	1,781

Transient Ischaemic Attack/Minor stroke			
Genedrive vs no test	-82	0.01	249
Genomadix vs no test	4	0.01	162
Laboratory genetic test vs no test	-3	0.00	98

5.1.2 Probabilistic results

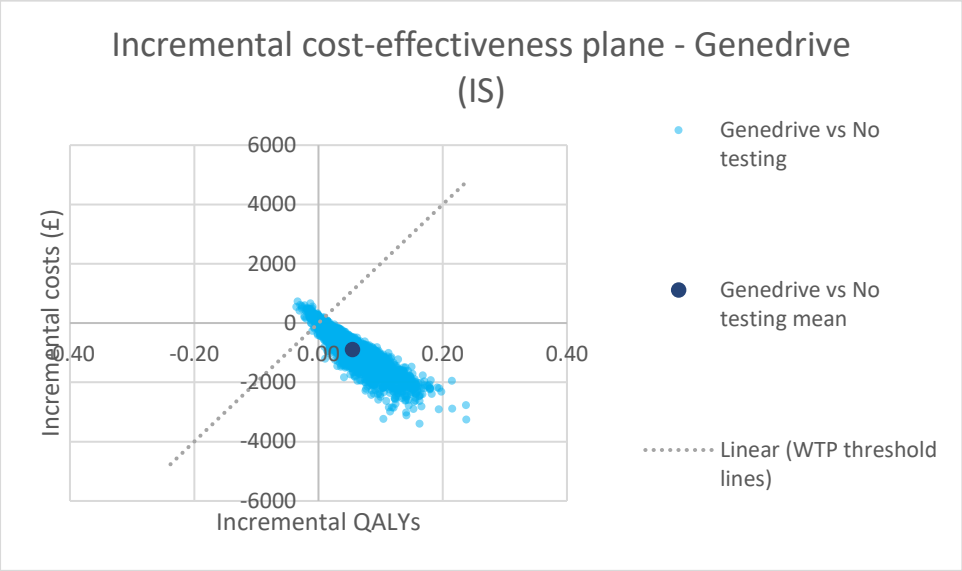
Table 9 Updated EAG base-case (Section 3) following stakeholder comments and additional data from Genedrive: probabilistic results

Testing Strategies	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	96,322	6.67					
Laboratory genetic test	96,393	6.67	Yes	N/A	Dominated		
PoC test - Genomadix cube	96,415	6.67	No	No	7051447	13417	
No test	97,217	6.61	Yes	N/A	Dominated	Dominated	Dominated
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	45,709	8.50					
Laboratory genetic test	45,789	8.50	Yes	N/A	Dominated		
PoC test - Genomadix cube	45,802	8.50	Yes	N/A	Dominated	4124	
No test	45,815	8.50	Yes	N/A	Dominated	Dominated	Dominated

Table 10 Updated EAG base-case (Section 3) following stakeholder comments and additional data from Genedrive: Pairwise results vs no test: incremental costs and QALYs, and Net Monetary Benefit (Willingness to pay £20,000 per QALY). Probabilistic results

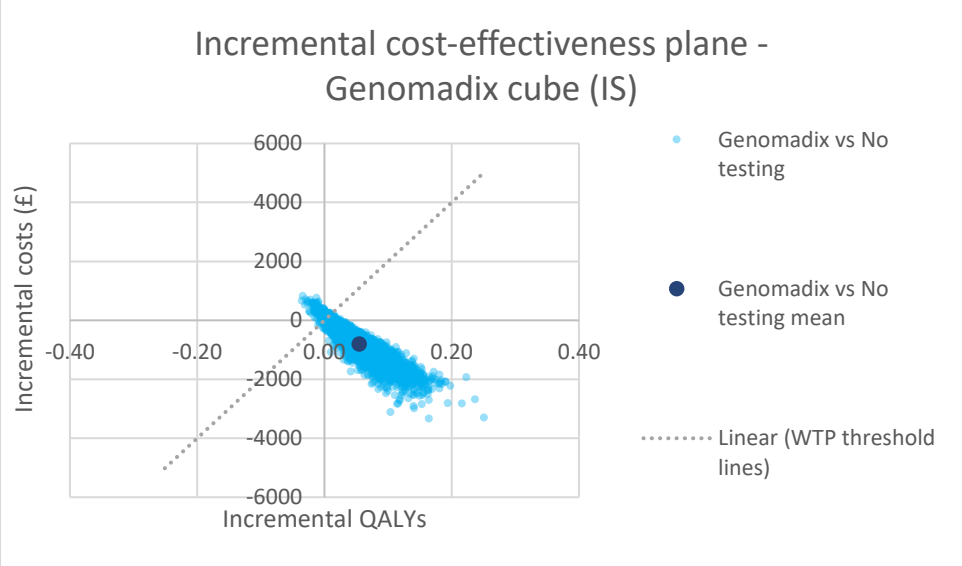
	Incremental costs (discounted)	Incremental QALYs (discounted)	Net monetary benefit (£20,000 threshold)
Non-Minor Ischaemic Stroke			
Genedrive vs no test	-895	0.05	1,987
Genomadix vs no test	-802	0.05	1,894
Laboratory genetic test vs no test	-824	0.05	1,884
Transient Ischaemic Attack/Minor stroke			
Genedrive vs no test	-106	0.01	213
Genomadix vs no test	-13	0.01	120
Laboratory genetic test vs no test	-26	0.00	69

Figure 4 Genedrive incremental cost-effectiveness plane: Non-minor ischaemic stroke population



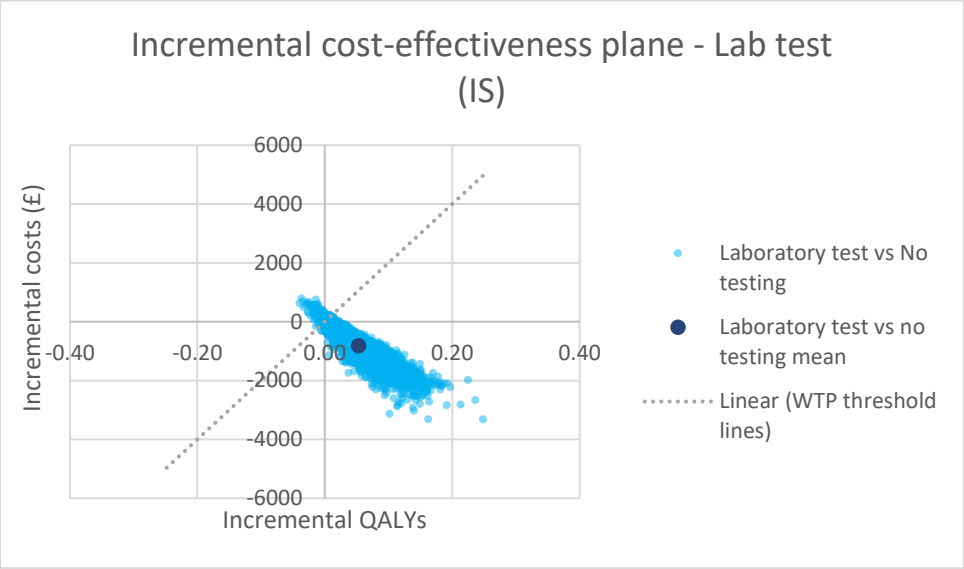
Pairwise comparisons of Genedrive vs no test in the IS population found 96.2% of iterations were cost-effective at a £20,000 WTP threshold.

Figure 5 Genomadix incremental cost-effectiveness plane: Non-minor ischaemic stroke population



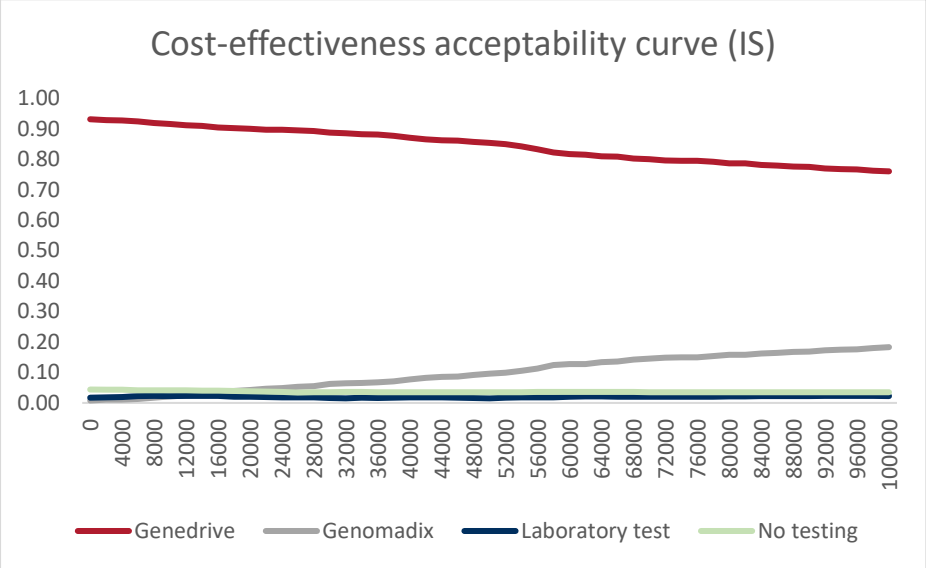
Pairwise comparisons of the Genomadix cube vs no test in the IS population found 95.6% of iterations were cost-effective at a £20,000 WTP threshold.

Figure 6 Lab test incremental cost-effectiveness plane: Non-minor ischaemic stroke population



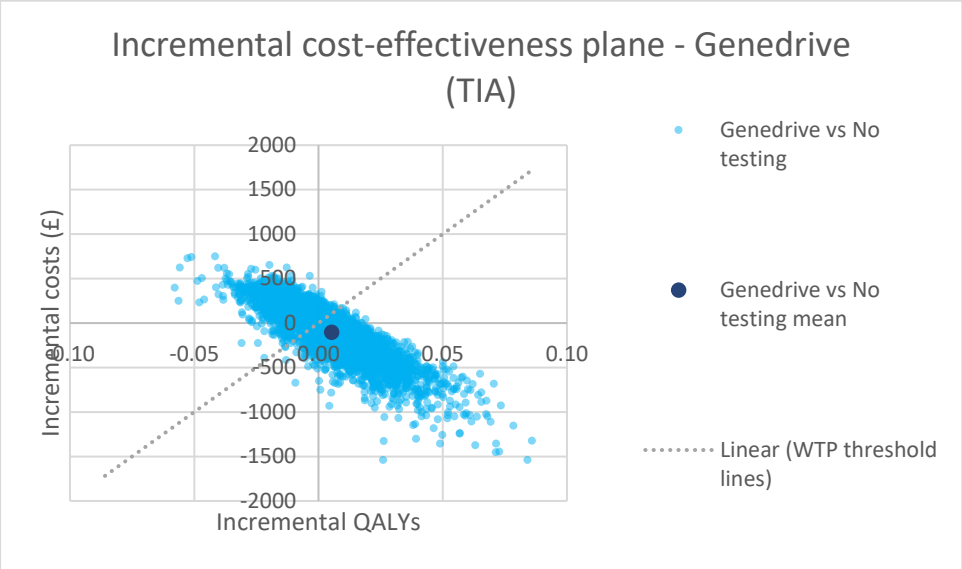
Pairwise comparisons of the lab test vs no test in the IS population found 95.5% of iterations were cost-effective at a £20,000 WTP threshold.

Figure 7 Cost-effectiveness acceptability curve: Non-minor ischaemic stroke population



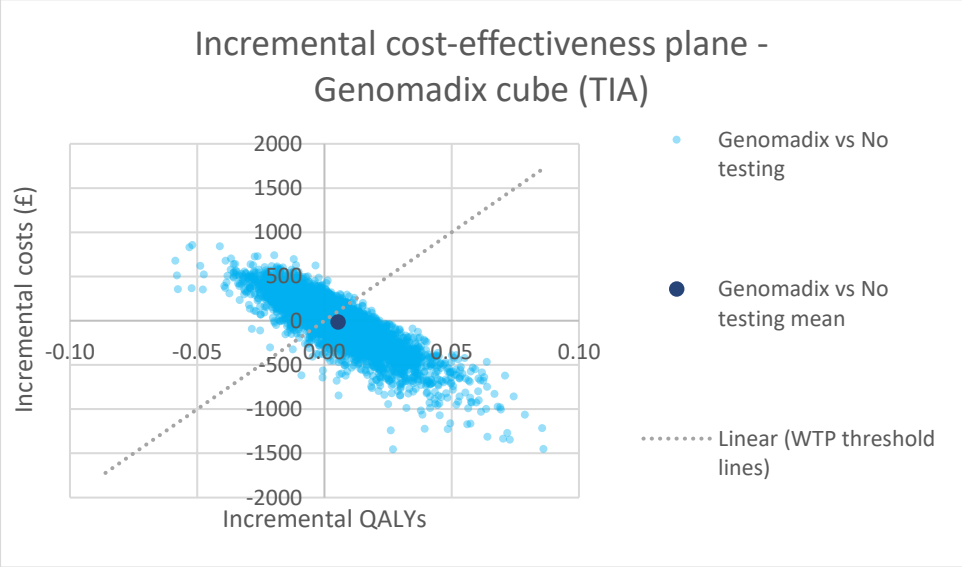
In the non-minor ischaemic stroke population the Genedrive test was most likely to be the cost-effectiveness strategy in all WTP thresholds analysed.

Figure 8 Genedrive incremental cost-effectiveness plane – TIA/minor stroke population



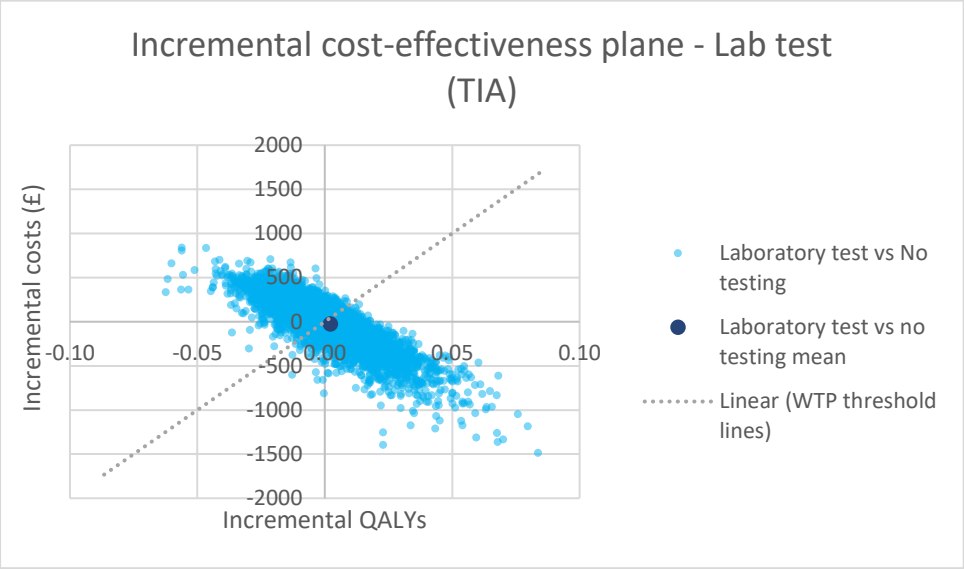
Pairwise comparisons of Genedrive vs no test in the TIA/minor stroke population found 62.3% of iterations were cost-effective at a £20,000 WTP threshold.

Figure 9 Genomadix incremental cost-effectiveness plane: TIA/minor stroke population



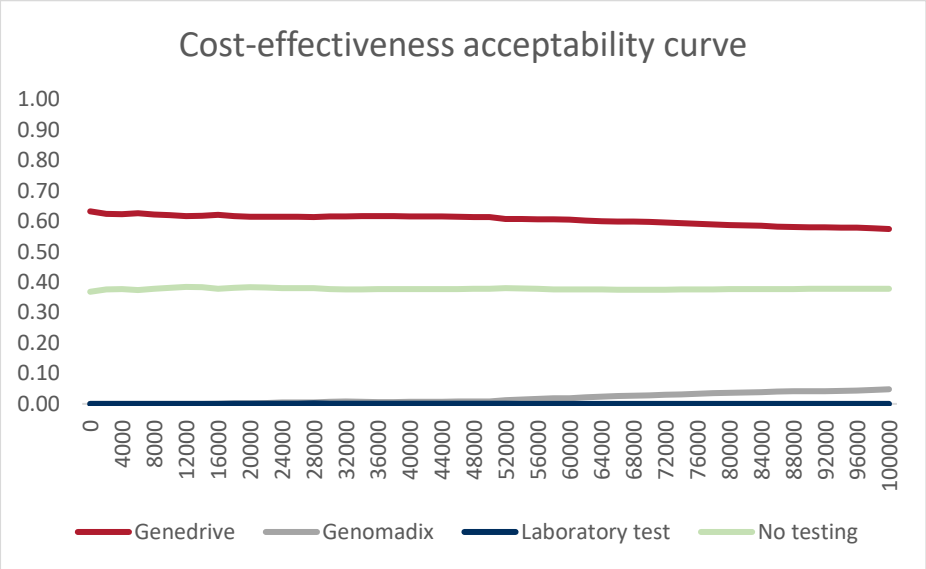
Pairwise comparisons of the Genomadix cube vs no test in the TIA / minor stroke population found 55.6% of iterations were cost-effective at a £20,000 WTP threshold.

Figure 10 Lab test incremental cost-effectiveness plane: TIA/minor stroke population



Pairwise comparisons of the Lab test vs no test in the TIA/minor stroke population found 52.3% of iterations were cost-effective at a £20,000 WTP threshold

Figure 11 Cost-effectiveness acceptability curve: TIA/minor stroke population



Genedrive was most likely to be cost-effective at all WTP thresholds in the TIA/minor stroke population. No test had just under a 40% chance of being the cost-effective strategy across the WTP thresholds analysed. Note however, that there was a high degree of uncertainty whether testing was cost-effective, but on the iterations where testing was cost-effective, then Genedrive had the highest net monetary benefit.

5.2 Results from Scenario Analyses from original EAG report

Results for Scenarios 1- 9 (Table 4) and additional Scenarios 11-17 (Section 4) in response to stake-holder comments and additional Genedrive data are presented in Table 11 and Table 12. All results shown are for the deterministic analysis.

For the non-minor ischaemic stroke population we found that all testing strategies had a positive net monetary benefit compared with No test (Table 11), and Genedrive had the highest net monetary benefit in all of Scenarios 1- 9. The results were also robust for all additional scenarios, with the exception of Scenario 13 (low lab-costs) where the lab-test dominates No test, and the ICERs for Genedrive and Genomadix relative to Lab-test are £9,570 and £55,572 resp. (Table 18).

For the TIA / minor stroke population Scenarios 1-9, all testing strategies had a positive net monetary benefit compared with No test, with the exception of Scenario 4 (low uptake of POCT) where the POCTs have a negative net monetary benefit compared with No test (Table 11). Genedrive had the highest net monetary benefit in Scenarios 1-4, and 6- 9. In Scenarios 11a and 11c where the alternative NMA was used for hazard ratios for recurrent stroke, No test dominates the testing strategies for the TIA/minor stroke population (Table 13, Table 15). In Scenario 12 (No test ticagrelor vs test and use ticagrelor or clopidogrel) then testing strategies dominate No test, regardless of the NMA approach used, with Genedrive the most cost-effective test (Table 16, Table 17). In Scenario 13 (low lab-costs) the lab-test dominates No test, and the ICERs for Genedrive and Genomadix relative to Lab-test are £4,433 and £28,738 resp. (Table 18).

Table 11 Results for Scenarios 1-9 (Table 4) in the updated EAG base case: Non-minor ischaemic stroke population

	Genomadix Cube vs No testing				Laboratory test vs No testing				Genedrive vs No testing			
	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)
Non-Minor Ischaemic Stroke												
Deterministic updated EAG base-case	-731	0.05	-13,630	1,804	-749	0.05	-14,507	1,781	-821	0.05	-15,217	1,901
1. Prevalence of clopidogrel resistance of 56.8%	-1450	0.10	-15230	3355	-1437	0.09	-15682	3270	-1545	0.10	-16124	3460
2. Aspirin as Alt Tx for LOF patients	-149	0.04	-3,637	969	-166	0.04	-4,315	936	-236	0.04	-5,716	1,061
3. Mean age of cohort (including a scenario for young people) - 40 years old	-1146	0.08	-13819	2805	-1167	0.08	-14454	2781	-1239	0.08	-14846	2908
4. Low uptake of alternative therapy after PoC test results	-224	0.02	-10847	638					-313	0.02	-14963	731
5. Extended time to lab-test results	-731	0.05	-13,630	1,804	-722	0.05	-14266	1733	-821	0.05	-15,217	1,901
6. Ticagrelor + aspirin as Alt Tx for LOF patients	363	0.05	6,677	725	347	0.05	6,451	729	280	0.05	5,114	815
7. Early clopidogrel introduction	-713	0.05	-13320	1784	-749	0.05	-14509	1781	-803	0.05	-14911	1880
8. Price year 2021	-678	0.05	-12641	1751	-693	0.05	-13416	1725	-762	0.05	-14111	1841

Table 12 Results for Scenarios 1-9 (Table 4) in the updated EAG base case: TIA/minor stroke population

	Genomadix Cube vs No testing				Laboratory test vs No testing				Genedrive vs No testing			
	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)	Inc. costs (£)	Inc. QALYs	ICER (£)	NMB (£)
Transient Ischaemic Attack/Minor stroke												
Deterministic updated EAG base-case	4	0.01	469	162	-3	0.00	-574	98	-82	0.01	-9,773	249
1. Prevalence of clopidogrel resistance of 56.8%	-145	0.01	-9853	441	-113	0.01	-13243	282	-232	0.01	-15625	529
2. Aspirin as Alt Tx for LOF patients	-328	0.06	-5,952	1,429	-341	0.05	-6,611	1,373	-416	0.06	-7,500	1,524
3. Mean age of cohort (including a scenario for young people) - 40 years old	-120	0.01	-11191	335	-120	0.01	-18723	249	-207	0.01	-19124	423
4. Low uptake of alternative therapy after PoC test results	287	0.00	-61740	-380					202	0.00	-43683	-294
5. Extended time to lab-test results	4	0.01	469	162	44	0.00	14601	16	-82	0.01	-9,773	249
6. Ticagrelor + aspirin as Alt Tx for LOF patients	688	0.04	18,558	53	668	0.04	18,709	46	606	0.04	16,267	139
7. Early clopidogrel introduction	4	0.01	469	162	-3	0.00	-574	98	-82	0.01	-9773	249
8. Price year 2021	4	0.01	437	163	-2	0.00	-320	97	-76	0.01	-9049	243

5.2.1 Scenario 11a: EAG base case using the hazard ratios from the alternative network meta-analyses for recurrent stroke

Table 13 EAG base case using the hazard ratios from the alternative network meta-analyses for recurrent stroke

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					Vs Genedrive	Vs No test	Vs Lab test
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	97,052	6.65					
No test	97,110	6.64	Yes	N/A	Dominated		
Laboratory genetic test	97,119	6.65	Yes	N/A	Dominated	691	
PoC test - Genomadix cube	97,137	6.65	Yes	N/A	Dominated	2,000	11,823

Transient Ischaemic Attack/Minor stroke							
					Vs No test	Vs Genedrive	Vs Lab test
No test	45740	8.52					
PoC test - Genedrive	45985	8.51	Yes	N/A	Dominated		
Laboratory genetic test	46048	8.51	Yes	N/A	Dominated	Dominated	
PoC test - Genomadix cube	46068	8.51	Yes	N/A	Dominated	1786696	8114

5.2.2 Scenario 11b: EAG base case using the hazard ratios from the alternative network meta-analyses for major bleeds

Table 14 EAG base case using the hazard ratios from the alternative network meta-analyses for major bleeds

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					Vs Genedrive	Vs Lab test	Vs Genomadix cube
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	96,416	6.68					
Laboratory genetic test	96,489	6.68	Yes	N/A	Dominated		
PoC test - Genomadix cube	96,506	6.68	Yes	N/A	Dominated	8,947	
No test	97,239	6.63	Yes	N/A	Dominated	Dominated	Dominated
Transient Ischaemic Attack/Minor stroke							
					Vs Genedrive	Vs Lab test	Vs Genomadix cube
PoC test - Genedrive	45,697	8.52					
Laboratory genetic test	45,775	8.52	Yes	N/A	Dominated		
PoC test - Genomadix cube	45,782	8.52	Yes	N/A	Dominated	2,011	
No test	45,784	8.52	Yes	N/A	Dominated	Dominated	Dominated

5.2.3 Scenario 11c: EAG base case using the hazard ratios from the alternative network meta-analyses for recurrent stroke and major bleeds

Table 15 EAG base case using the hazard ratios from the alternative network meta-analyses for recurrent stroke and major bleeds

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs No test	vs Lab test
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	97,054	6.65					
No test	97,113	6.63	Yes	N/A	Dominated		
Laboratory genetic test	97,120	6.65	Yes	N/A	Dominated	593	
PoC test - Genomadix cube	97,139	6.65	Yes	N/A	Dominated	1,879	12,129
Transient Ischaemic Attack/Minor stroke							
					vs No test	**vs Genedrive**	**Vs Lab test**
No test	45755	8.52					
PoC test - Genedrive	45994	8.51	Yes	N/A	Dominated		
Laboratory genetic test	46057	8.51	Yes	N/A	Dominated	Dominated	
PoC test - Genomadix cube	46077	8.51	Yes	N/A	Dominated	1997145	8420

5.2.4 Scenario 12: No test with ticagrelor vs Test and ticagrelor for LoF and clopidogrel for No LOF (TIA / minor stroke population)

Table 16: No test with ticagrelor vs Test and ticagrelor for LoF and clopidogrel for No LOF (i) using hazard ratios the NMA in the original and updated EAG base case: TIA / minor stroke population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	46,042	8.60					
Laboratory genetic test	46,111	8.60	Yes	N/A	Dominated		
PoC test - Genomadix cube	46,132	8.60	Yes	N/A	Dominated	14,668	
No test	49,247	8.59	Yes	N/A	Dominated	Dominated	Dominated

Table 17 No test with ticagrelor vs Test and ticagrelor for LoF and clopidogrel for No LOF (ii) using hazard ratios from the alternative NMA (Scenario 11): TIA / minor stroke population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Genomadix cube	vs Lab test
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	47,852	8.36					
PoC test - Genomadix cube	47,938	8.36	No	No	372,267		
Laboratory genetic test	47,946	8.35	Yes	N/A	Dominated	Dominated	
No test	50,847	8.36	Yes	N/A	Dominated	Dominated	872,203

5.2.5 Scenario 13: Assuming lower laboratory costs due to efficiency savings

Table 18: Scenario assuming lower laboratory costs due to efficiency savings

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Lab-test	vs Genedrive	vs PoC test - Genomadix
Non-Minor Ischaemic Stroke							
Laboratory genetic test	96,392	6.68					
PoC test - Genedrive	96,415	6.68	No	No	9,570		
PoC test - Genomadix cube	96,505	6.68	Yes	N/A	55,572	Dominated	
No test	97,236	6.63	Yes	N/A	Dominated	Dominated	Dominated
Transient Ischaemic Attack/Minor stroke							
					vs Lab test	**vs Genedrive**	**vs No test**
Laboratory genetic test	45,672	8.52					
PoC test - Genedrive	45,688	8.53	No	No	4,433		
No test	45,769	8.52	Yes	N/A	Dominated	Dominated	
PoC test - Genomadix cube	45,773	8.53	Yes	N/A	28,738	Dominated	469

5.2.6 Scenario 14: Threshold analysis showing the NMB of Lab test by varying the cost per test

Figure 12 and Figure 13 show the thresholds at which the lab test becomes a cost-effective strategy using a £20,000 per QALY WTP threshold for the two population. In the non-minor ischaemic stroke population the lab test is cost-effective vs Genedrive at a cost of below £11 per test, against Genomadix at a cost below £116 per test and against no testing at a cost below £1920 per test (Figure 12). In the TIA/minor stroke population there is no cost per test where the lab test is cost-effective against Genedrive, the lab test is cost-effective against Genomadix at cost per test below £75, and cost-effective against no test at costs below £237.

Figure 12 Laboratory test cost per test threshold analysis (non-minor ischaemic stroke population)

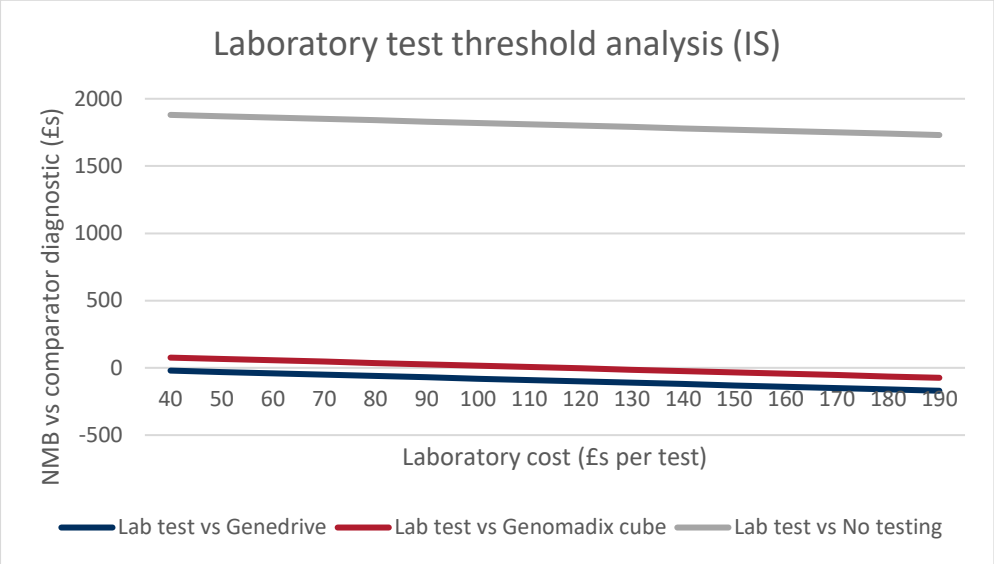
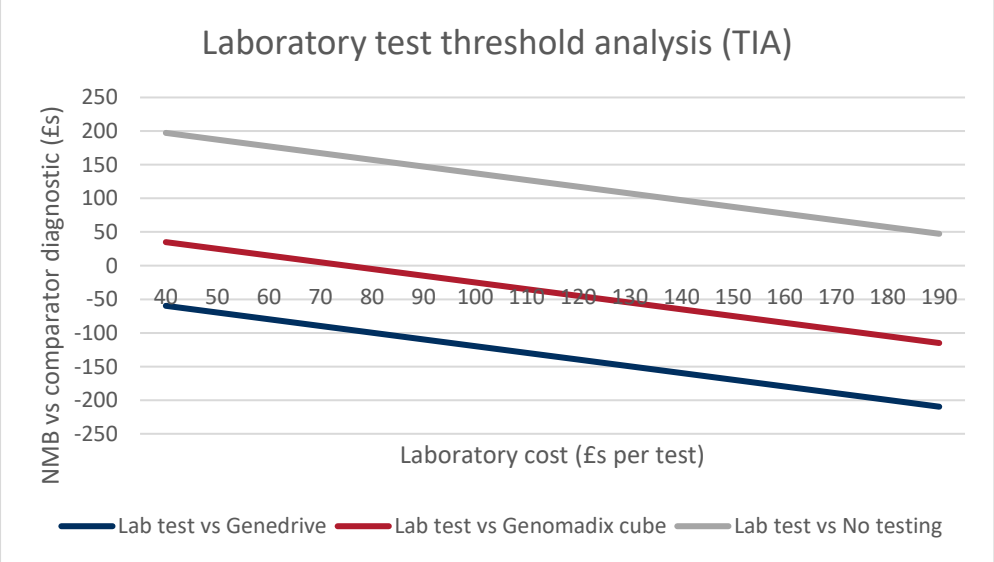


Figure 13 Laboratory test cost per test threshold analysis: TIA/minor stroke population



5.2.7 Scenario 15: Threshold analysis of lab test vs Genedrive varying batch size of the lab-test

When increasing the batch size of the lab test, the Genedrive test remained cost-effective in both populations (Figure 14, Figure 15), including the batch size of 55 used in scenario 12. At

this batch size the total costs of the lab test are cheaper than the Genedrive test, but the Genedrive test has an ICER lower than the WTP threshold in both populations.

Figure 14 Threshold analysis showing the NMB of lab test vs Genedrive by lab test batch size: non-minor ischaemic stroke population

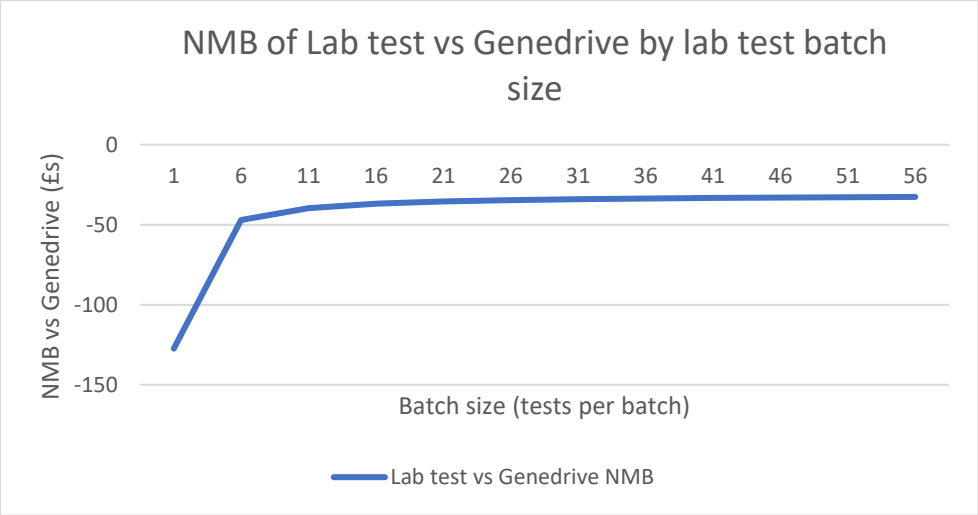
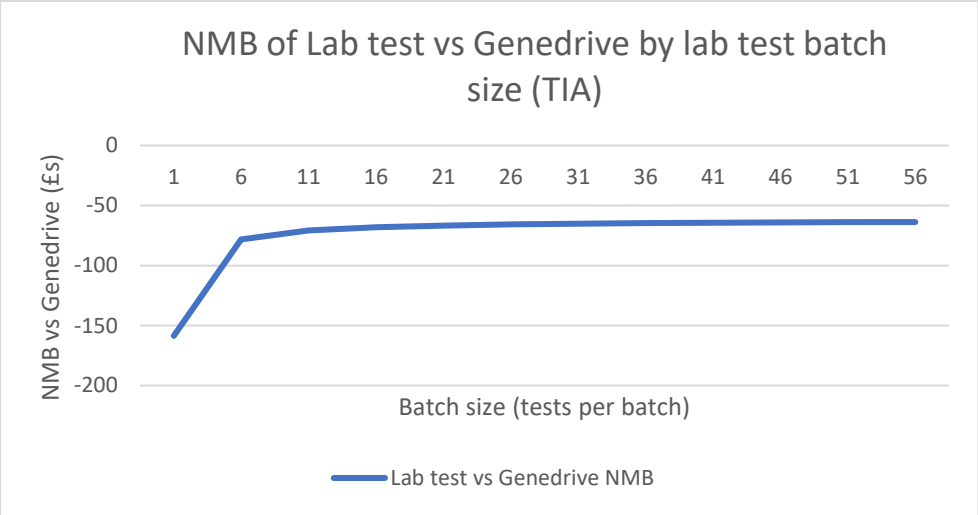


Figure 15 Threshold analysis showing the NMB of lab test vs Genedrive by lab test batch size: TIA/minor stroke population



5.2.8 Scenario 16: Threshold analysis on uptake of alternative treatment for both lab-test and POCT, for both populations

Figure 16 shows that in the updated base-case for the non-minor stroke population the lab test was cost-effective vs no testing when non-adherence was below 46%, Genedrive was cost-effective vs no testing when non-adherence was below 49% and the Genomadix cube was cost-effective against no testing when non-adherence was below 46%.

Figure 16: EAG base case with threshold analysis on uptake of alternative treatment for both lab-test and POCT, non-minor ischaemic stroke population

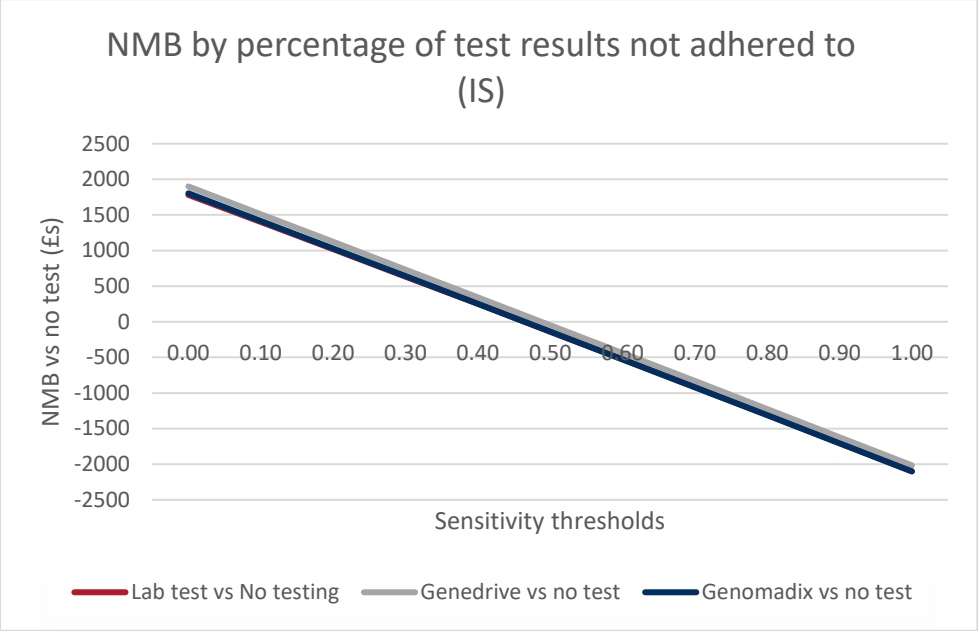
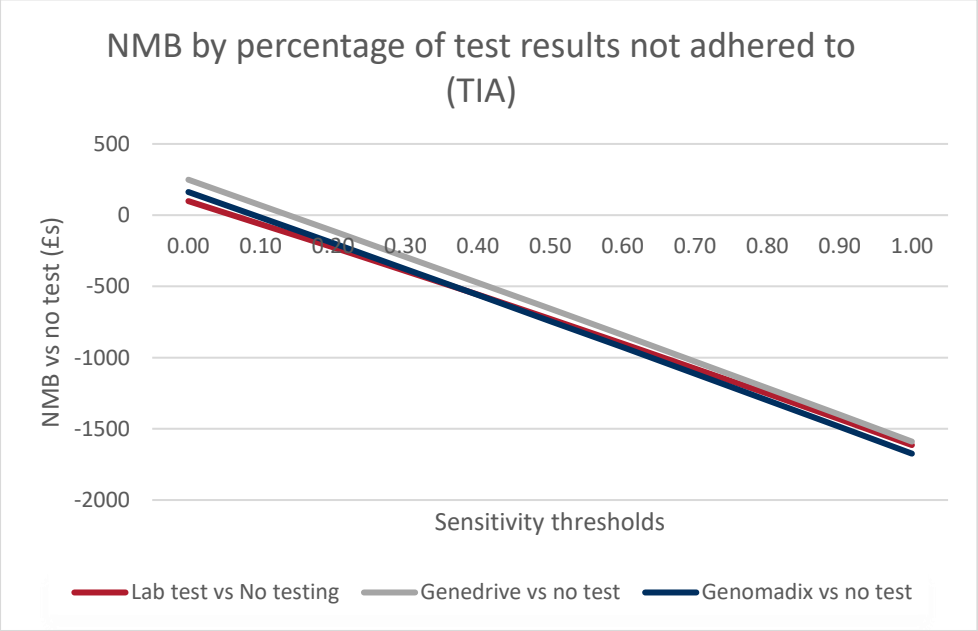


Figure 17 shows that in the updated base case for the TIA/minor-stroke population the lab test was cost-effective vs no testing in when non-adherence was below 7%, Genedrive was cost-effective vs no testing when non-adherence was below 14% and the Genomadix cube was cost-effective against no testing when non adherence was below 9%.

Figure 17: EAG base case with threshold analysis on uptake of alternative treatment for both lab-test and POCT, TIA/minor stroke population



5.2.9 Scenario 17: Assuming a test failure rate of 0.6% for Genedrive

Table 19 Fully incremental results in a scenario analysis where the Genedrive failure rate is set to 0.6%

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Non-Minor Ischaemic Stroke							
PoC test - Genedrive	96,407	6.68					
Laboratory genetic test	96,487	6.68	Yes	N/A	Dominated		
PoC test - Genomadix cube	96,505	6.68	Yes	N/A	Dominated	8745	
No test	97,236	6.63	Yes	N/A	Dominated	Dominated	Dominated
Transient Ischaemic Attack/Minor stroke							
					vs Genedrive	vs Lab test	vs No test
PoC test - Genedrive	45,680	8.53					
Laboratory genetic test	45,767	8.52	Yes	N/A	Dominated		
No test	45,769	8.52	Yes	N/A	Dominated	Dominated	
PoC test - Genomadix cube	45,773	8.53	Yes	N/A	Dominated	1884	469

6 References

1. Evans T. Briefing document: First Incidence of Stroke: Estimates for England 2007 to 2016. PHE publications: Public Health England; 2018.
2. Del Giovane C, Boncoraglio GB, Bertu L, Banzi R, Tramacere I. Antiplatelet drugs for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. BMC neurology. 2021;21(1):319.
3. Bhalla AM, E; Afsar, A. The Road to Recovery: The Ninth SSNAP Annual Report. King's College London; 2022.
4. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022 Manual. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2023. Contract No.: technical_report.

7 Appendix 1: One-way sensitivity analysis results

Table 20 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genedrive vs No Test for the Non-Minor Ischaemic Stroke Population

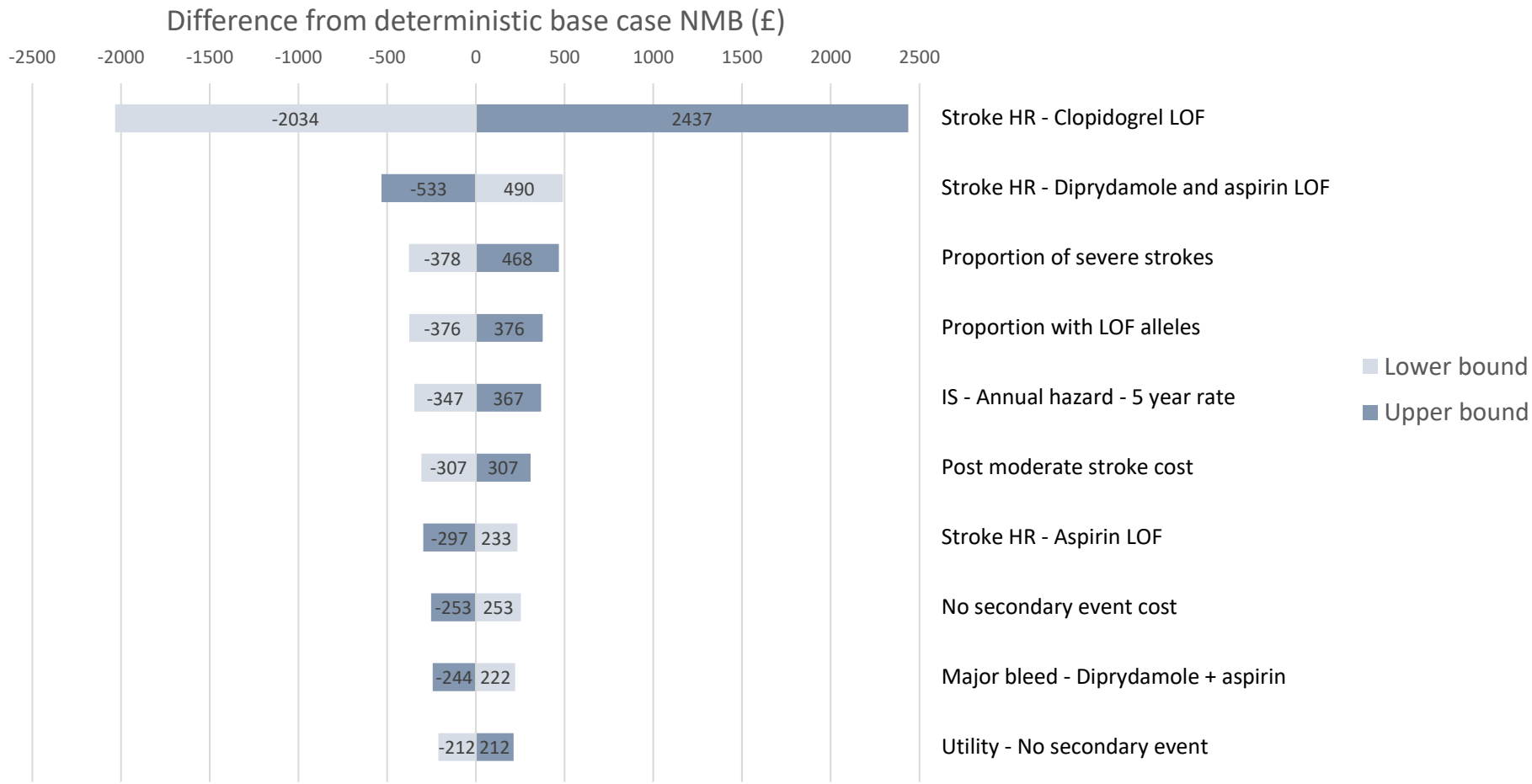


Table 21 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genomadix vs No Test for the Non-Minor Ischaemic Stroke Population

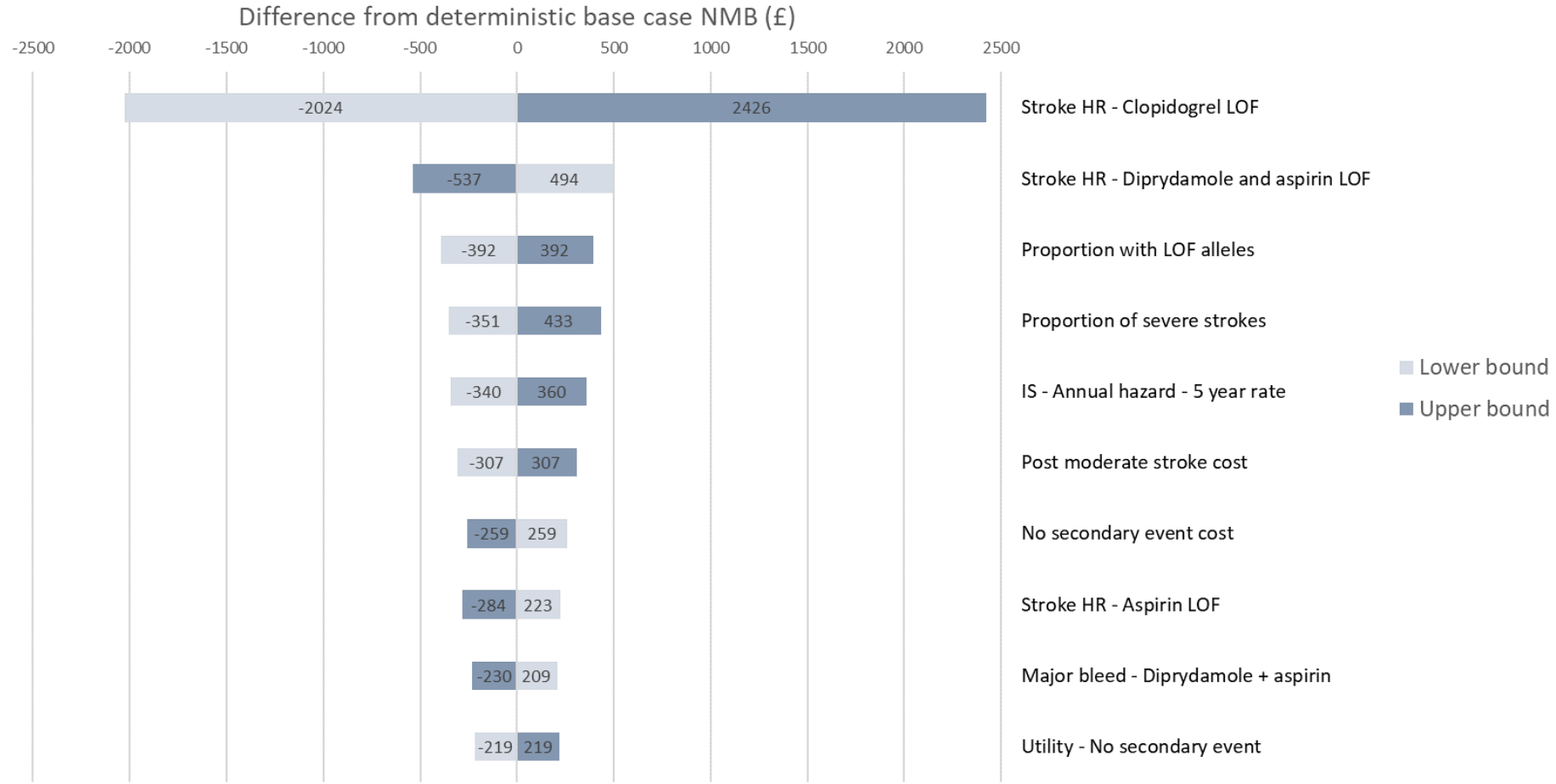


Table 22 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Lab test vs No Test for the Non-Minor Ischaemic Stroke Population

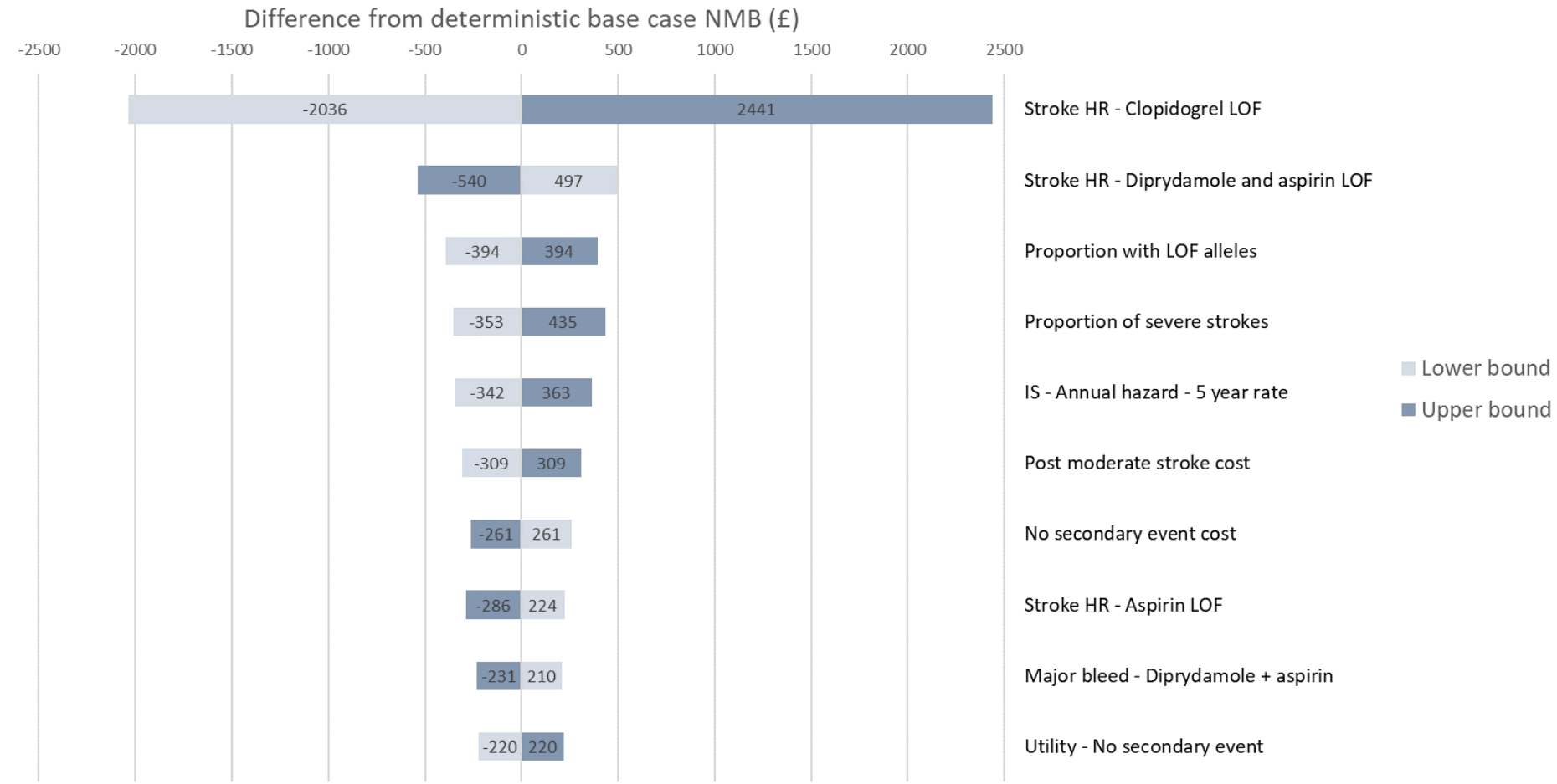


Table 23 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genedrive vs No Test for the TIA / Minor Stroke Population

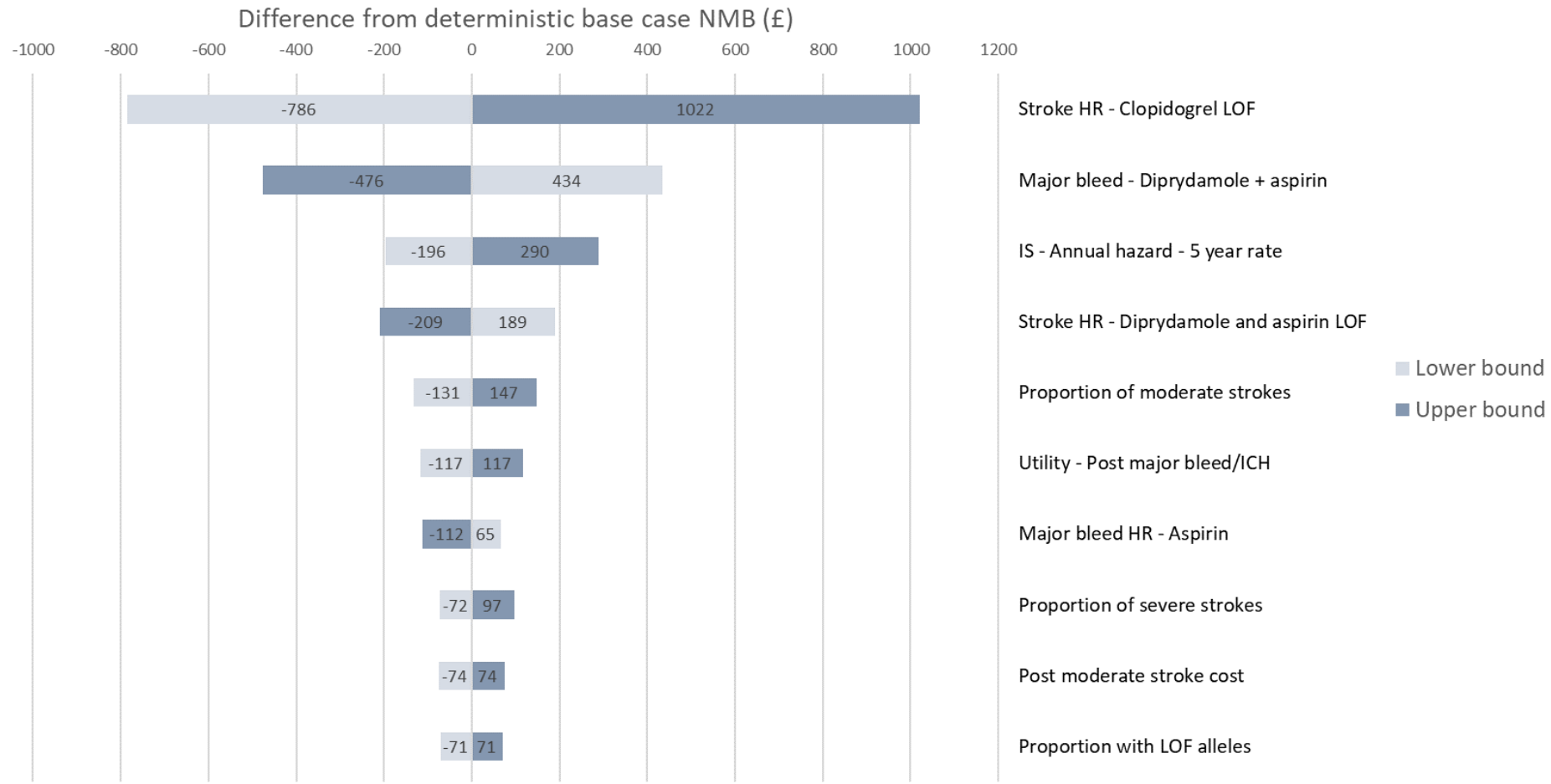


Table 24 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genomadix vs No Test for the TIA / Minor Stroke Population

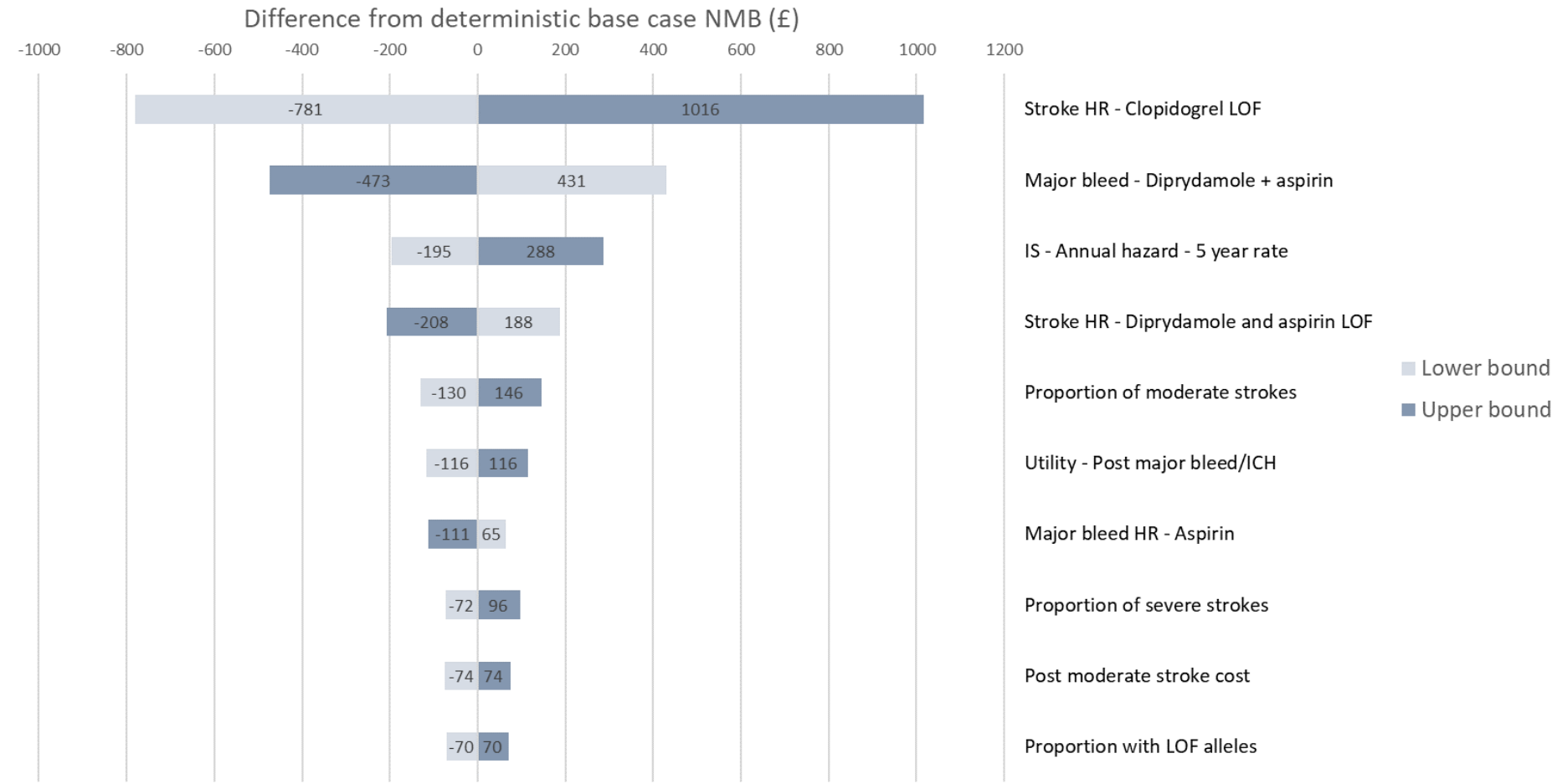


Table 25 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Laboratory Test vs No Test for the TIA / Minor Stroke Population