EE614

Evaluating the cost-effectiveness of CYP2C19 genetic testing in patients who have experienced an ischaemic stroke or transient ischaemic attack in England and Wales

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Objectives:

- Anti-platelet therapy with clopidogrel is recommended to prevent further strokes in patients who have had an ischaemic stroke (IS) or transient ischaemic attack (TIA)
- However, clopidogrel can be ineffective in patients with genetic variants of CYP2C19, which can be tested for in laboratories or using point-of-care (POC) tests
- We aimed to assess cost-effectiveness of different CYP2C19 testing strategies in IS and TIA patients for a NICE diagnostic assessment

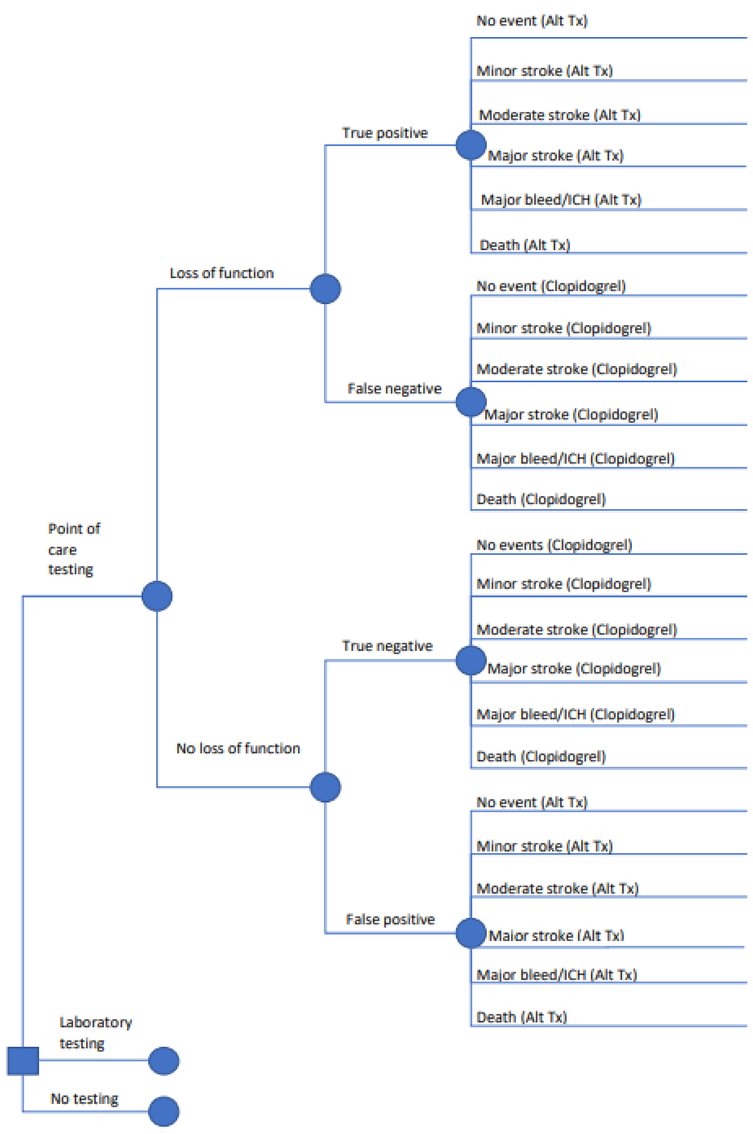
Methods:

- A hybrid decision tree (Fig 1A) and Markov model (Fig 1B) was developed to evaluate the costs and QALYs of testing strategies over a lifetime time horizon, which drew inspiration from an existing CYP2C19 cost-effectiveness model[1].
- Diagnostic strategies evaluated were: Laboratory testing; POC testing; and no testing
- Diagnostic accuracy and treatment effect inputs were obtained from systematic literature reviews of diagnostic accuracy studies and RCTs[2], and other inputs taken from a large UK registry (SSNAP). The laboratory tests were assumed to be a 'gold standard' (sensitivity and specificity of 1)
- Clinical effectiveness of treatments by loss-of-function (LoF) status for strokes and bleeds were synthesized using network meta-analysis (NMA). Two approaches were used to connect the network. The base case NMA used a hazard ratio for LoF vs no-LoF on clopidogrel. The alternative NMA used additional evidence on ticagrelor from a mixed LoF population (THALES) to connect the network.

Figure 1: a) Decision tree branch for the POC tests* and b) Markov model

***L**ab test: identical except no false positives and false negatives. No testing: all patients treated with clopidogrel

A)



B)

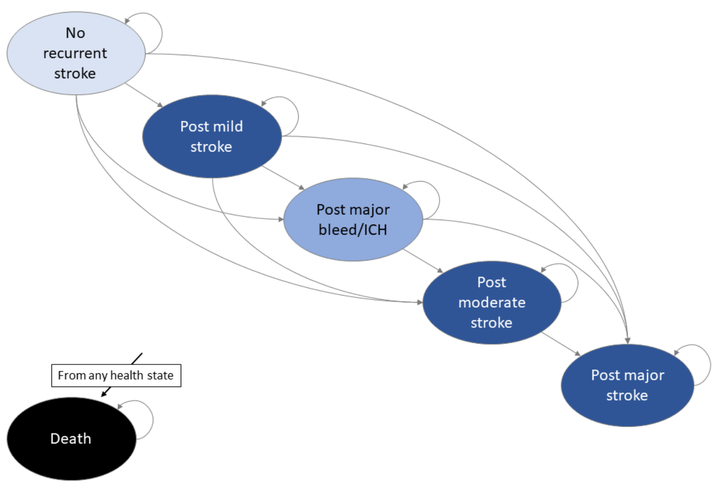


Table 1: Key base case parameters and scenario analyses performed

Model parameters	Base case settings	Source
Treatment if patient tested no LOF	Clopidogrel and aspirin	Assumption
Treatment if patient tested LOF	Dipyridamole and aspirin	Assumption
POCT sensitivity/specificity	Genedrive (0.996/1.0), Genomadix (0.99/1.0)	Our meta-analysis on diagnostic accuracy[2]
Assumed time to receive lab test results	1 week	Laboratory survey[2]
POCT test failure probability	8%	Meta-analysis of studies identified in clinical review for Genomadix[2]
Lab test failure probability	0%	Laboratory survey[2]
Stroke baseline hazards	Lioutas et al. (2021)[3] and SSNAP[4] in the decision tree and Markov model	
POCT and lab test adherence	100%	Assumption
Treatment effects for stroke and major bleeds	NMA, connected using pooled HR for LoF v NoLoF on clopidogrel	CHANCE[5], CHANCE-2[6], PRoFESS[7], meta-analysis LoF v NoLoF on clopidogrel
Key scenario analyses		
Ticagrelor as the alternative treatment in the TIA population		
Alternative baseline hazards sources		
Varying rates of adherence to test results		
Alternative NMA incorporating the THALES[8] study on ticagrelor in a mixed LoF status population		

Results:

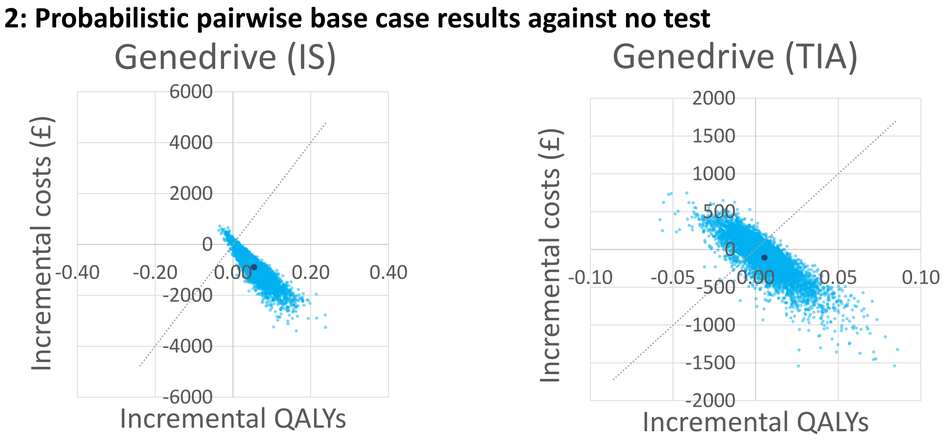
- Both CYP2C19 testing strategies resulted in positive incremental QALYs and lower costs compared with the 'no test' strategy in both IS and TIA populations, with positive net monetary benefit (NMB) at a £20,000 per QALY willingness-to-pay threshold (Table 1). There was a positive NMB for all tests in all the scenario analyses conducted in the IS group

Figure 2: Cost-effectiveness planes for Genedrive vs no testing in minor stroke/TIA and IS populations*

* Average incremental costs and QALYs indicated in dark blue. Genomadix and lab test PSA results appeared similar Genedrive

	Incremental costs (discounted)	Incremental QALYs (discounted)	Net monetary benefit (£20,000 threshold)	Proportion cost-effective (£20,000 threshold)
Non-Minor Ischaemic Stroke				
Genedrive vs no test	-£895	0.05	£1,987	96.2%
Genomadix vs no test	-£802	0.05	£1,894	95.6%
Lab test vs no test	-£824	0.05	£1,884	95.5%
Transient Ischaemic Attack/Minor stroke				
Genedrive vs no test	-£106	0.01	£213	62.3%
Genomadix vs no test	£13	0.01	£120	55.6%
Lab test vs no test	-£26	0.00	£69	52.3%

Table 2: Probabilistic pairwise base case results against no test



- All tests remained cost-effective in both populations when ticagrelor was used as the alternative treatment. When alternative baseline hazard rates were used, higher rates of stroke increased the likelihood of cost-effectiveness for all tests. The scenario using the alternative NMA resulted in no test being the cost-effective strategy in the TIA/Minor stroke group.
- Threshold analysis found in the IS group Genedrive was cost-effective up to 49% non-adherence, Genomadix and lab test up to 46% non-adherence. In the TIA population the tests were cost-effective up to 14%, 9%, and 7% for Genedrive, Genomadix and lab test, respectively

Conclusion:

- Testing for CYP2C19 mutations is cost-effective compared with not testing in the IS/non-minor stroke population, with higher NMB for lab test in the IS population and POC test than in the TIA population. There was higher uncertainty in the minor stroke/population but average results in the probabilistic sensitivity analysis indicated CYP2C19 testing in this population is also cost-effective

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References: 1. Wright et al. (2022) Development of a point-of-care genetic test for effective treatment of patients with ischaemic stroke and transient ischaemic attacks: an early model-based cost-effectiveness analysis. 2. Carroll et al. (2022) Clinical and cost effectiveness of clopidogrel resistance genotype testing after ischaemic stroke or transient ischaemic attack: a systematic review and economic model (accepted by NIHR). 3. Lioutas et al (2021) Incidence of Transient Ischemic Attack and Association With Long-term Risk of Stroke 4. National Guidline Centre and SSNAP (2016) Sentinal Stroke and National Audit Programme. Cost and Cost-effectiveness analysis 5. Wang et al. (2013) Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack. 6. Wang et al. (2021) Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. 7. Deiner et al. (2008) Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study 8. Johnston et al. (2020) Ticagrelor and Aspirin or Aspirin Alone in Acute Ischaemic Stroke or TIA.