NICE National Institute for Health and Care Excellence

Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

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Genedrive	1	9, 80, 81, 168, 178	Background 4.6.1 Table 18 7.1, 7.3	The time to result for Genedrive POCT was stated as 40 minutes in the early feasibility published at ESHG[92] **The time to result for the current product design is approximately 1 hour, as communicated directly to NICE at the start of the DAP.**	In Table 2 – we have this as "less than 1 hour" which is what was shared by NICE in the NICE scope. In section 7.1 and Table18 we are referring specifically to the study that evaluated Genedrive and so we think this is factually correct – this is the only available data that we had on the Genedrive test.
Genedrive	2	168/169	7.1	The early study[92] used a previous version of the Genedrive test targeted * alleles (*2,*3,*4,*8 and *17). The final product design targets *2,*3,*4,*8,*17 and *35 (correctly listed in Table 2 section 1.3 and on page 178). **We would like to highlight the differences and ensure consistency for the current review and discussion of our POCT (test targets *2, *3, *4, *8, *17 and *35)**	In section 7.1 we are referring specifically to the study that evaluated Genedrive and so we think this is factually correct. We acknowledge the current product design can identify *35, and as noted describe the alleles targeted by the current product correctly in Table 2. The economic model is based on detection of *2 and *3 LOF alleles, which is what the diagnostic test accuracy data that we had available were based upon, as well as much of the prevalence data. We note in the report that this may overestimate the sensitivity of the Genomadix cube test, and this is why we set the sensitivity to 0.99 rather than 1. We

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					also note that Genomadix may have lower sensitivity than Genedrive because it does not detect as many alleles as Genedrive, although we apologise that we did not highlight the *35 allele in this discussion. However, the prevalence of *4, *8, and *35 is very low, particularly after taking into account the ethnicity in the stroke population reported in the PHE briefing document. We therefore think it unlikely that including this would have had any impact on our conclusions. We have added a threshold analysis to the sensitivity of the POCTs in response to comment 12 below to explore this.
Genedrive	3	169	7.1	The genomic hubs stated their turnaround time for a result range from 24-72 hours up to 1-2 weeks **We would like to highlight that a POCT would be the only feasible test option in the following scenario - Patients in the treatment pathway for TIA/minor IS in Figure 1 on page 33 who require treatment to commence in first 24 hours and therefore would not get a result from a lab-based test before they need to start clopidogrel.**	For TIA/minor IS patients we heard that what would happen in practice for the lab-test is that they would start on clopidogrel whilst awaiting test results, and then would switch to dipyridamole when results become available. There would therefore be a short period of inappropriate treatment, with increased event rates. So, POCT is not the only feasible option for these patients, but does have an advantage in avoiding this period of inappropriate

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				Is this clinically relevant in terms of patient outcome? What % of patients (those who cannot take aspirin and/or have had minor stroke or TIA) would require a result in <24 hours Vs 1 week. Can the EAG triangulate these points in the EAR with regards to the requirement of a POCT, the time restraints and the size of the patient population affected?	treatment. This advantage of POCT is included in our model for the TIA/non-minor patients. There is also a risk that the lab-test results won't get picked up on when they arrive, and that is modelled in our scenarios on uptake of results and time to receive lab-test results. Furthermore, we have provided additional threshold analyses for test sensitivity, in response to a query from the NICE Technical team (comment 12 below). Our model does not capture patients who have a non-minor IS but cannot take aspirin. For these patients, immediate treatment with clopidogrel would be indicated, and there would be a small advantage of POCT over laboratory testing in the 1-2 week period whilst awaiting test results. We estimate prevalence of aspirin sensitivity of 2.26% based on the control group of the UK National Chronic Rhinosinusitis Epidemiology Study (N=221), which when applied to the 68.2% of first strokes that are non-minor IS gives 1.54% of all first strokes, which is 1.6 per 100,000 population. We note however, that there may be more patients unwilling to receive aspirin than just those with aspirin sensitivity.

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Genedrive	4	174, 176	7.2, 7.3	The sentence states 'Genedrive also detects *4 and *8' **For consistency, this should also state *35 throughout.**	Apologies, we acknowledge that this should also have included *35.
Genedrive	5	178, 182	7.3, 8.2	*The manufacturer confirmed that there were no studies currently ongoing, but these were planned to start from the first quarter of 2023. No details were provided on what these studies would evaluate.* [redacted]	Thank you for providing this information, which was not available at the time the report was written.
Genedrive	6	178	7.3	The Genedrive System has been reviewed by NICE for an alternative assay. And is currently under review as an EVA, currently in progress. **We would like to highlight that the NICE EVA recommendation for our alternative assay is due to be published by NICE on 30th March.**	Noted.
Genedrive	7	181	8.1	We would like to highlight that one advantage of POCT not included in the Conclusion is the same as outlined above in comment 3. Patients in the treatment pathway for TIA/minor IS in Figure 1 on page 33 would not get a result before they need to start clopidogrel. A POCT would be the only feasible test option in this scenario.	As explained in our response to comment 3, this advantage of POCT is captured in our economic model for TIA/minor IS patients. Those who are tested using POCT proceed to appropriate treatment immediately as per the treatment pathway. For patients tested with non-POCTs, they are assumed to initiate

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					clopidogrel until the test results arrive. Patients would then switch to alternative treatment if necessary after the results are received. In these patients who switch treatment there is a cost due to higher event rates in the period on inappropriate treatment prior to receiving lab-test results.
Genedrive	8	178	7.3	When discussing the impact of testing other LOF * alleles and their frequencies, we would like to highlight that whilst LOF * alleles other than *2 and *3 are less frequent overall, they are of higher frequency in specific ethnic groups (eg.*4 LOF allele in Jewish populations) and as a minimum are very relevant for the purposes of ethnic equality. Scott SA, Martis S, Peter I, Kasai Y, Kornreich R, Desnick RJ. Identification of CYP2C19*4B: pharmacogenetic implications for drug metabolism including clopidogrel responsiveness. *Pharmacogenomics J*. 2012;12(4):297-305. doi:10.1038/tpj.2011.5)	We acknowledge that around 2% of Jewish populations have *4, and that *35 is only found in African American and Sub-Saharan Afrian populations. This may therefore be an equality issue with the use of Genomadix. Note however that the overall proportions with *4, *8, and *35 alleles are very small. It is difficult to obtain accurate data on allele frequency, particularly on the UK stroke population. Based on the frequency table from Ionova et al. and then applying these frequencies to the ethnicity data on the stroke population from the PHE briefing document (92% white, 4% Asian, 2.5% Black, 1.5% other) and grouping the Black/ Other together, gives the total proportions of each LOF allele in the UK stroke population as follows: *2 15.37% *3 0.45%

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					*4 0. 22% *8 0.31% *35 0.06% (3% in Sub-Saharan African and 1.6% in African American/Afro-Caribbean populations) The *4, *8, and *35 alleles are therefore found in <0.6% of all stroke patients. Ref: Ionova Y, Ashenhurst J, Zhan J, Nhan H, Kosinski C, Tamraz B, Chubb A. CYP2C19 allele frequencies in over 2.2 million direct-to-consumer genetics research participants and the potential implication for prescriptions in a large health system. Clinical and translational science. 2020 Nov;13(6):1298-306.
SCM applicant	9	87		Testing capacity and turnaround time: Estimate for the first year 150,000 based on annual stroke/ TIA incidence. No comment on stroke/TIA patients who are already started on clopidogrel and whether they should be tested and have treatment altered if found to be LOF (this is noted later in the report). Is it possible to model for patients who have started clopidogrel for e.g. within the last 90 days?	Our economic model considers new patients with a first stroke. If testing is adopted for this group of patients, then going forwards all patients would be tested at the time of their first stroke. However, we acknowledge that currently there will be patients already taking clopidogrel due to previous TIA or IS, who would potentially benefit from testing. This would be the case regardless of whether they have a subsequent stroke. We would argue that if testing is considered cost-effective at the point at which patients have a first stroke,

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					then it would have been cost-effective for those already taking clopidogrel when they had their initial stroke. It seems only fair for those patients to be offered testing after the event of their first stroke. We do not think incorporating this group in the model will change the findings, and consider this question to be mainly one of implementation and equity.
SCM applicant	10	111		Decision Tree. The proportion of the modelled population that are LOF carriers is the same regardless of the test. Why is this? The proportion of the population that is identified as LOF carrier and therefore will have treatment changes is variable depending on the alleles tested for by the particular test. Additional variants tested should result in a higher rate of LOF carriers being picked up (dependent on prevalence of variants tested).and receiving targeted DAPT. Or has this been reflected in the False negative population for each test? E.g. if POCT test is testing for less variants, a *8 allele carrier may not be identified by the test. It would not be a FN, since the test is not claiming to identify these individuals as positive, but they would not receive targeted tx, so essentially treated as a FN – and remain on clopidogrel.	This is correct, the model assumes a general LOF rate based on population norms of ischaemic stroke patients. Changing the test does not change the underlying prevalence. However, we think that what you meant to say here is that the proportion of LOF patients **detected** would vary by each test. This is captured with the sensitivity of the tests (ie the False Negative rate, as you suggest). The sensitivity is assumed to be perfect for the lab-test, and estimated from diagnostic test accuracy studies for POCTs. Unfortunately the diagnostic test accuracy data that we have is reliant on which alleles were included in the definitions of true positives. Furthermore we only have diagnostic test accuracy data for Genomadix cube and not Genedrive, so although Genedrive does test for

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					more alleles, we have no data on the test accuracy of Genedrive. For this reason we made the simplifying assumption that Genedrive and Genomadix have the same test sensitivity. The diagnostic test accuracy data for Genomadix showed a very high sensitivity (close to 1), but of course, as you highlight, this was only with respect to the *2 and *3 alleles. The other alleles are very rare and so we do not expect the sensitivity of the tests to change much by incorporating the additional alleles. For this reason we used a sensitivity of 0.99 in the model (rather than 1) for Genomadix. Based on the proportions reported in Ionova et al, applied to the ethnicity proportions in an English stroke population reported in the PHE briefing report, we estimate that 0.6% of stroke patients would have *4, *8, or *35 alleles (see response to comment 8 above). The impact on sensitivity would therefore be at most 0.006 difference between Genomadix cube and Genedrive. We do not expect that including this will change the results substantially, however we have run an additional threshold analysis varying the

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					sensitivity of the POCTs. (See response to comment 12 below from the NICE technical team).
SCM applicant	11	176	7.3	Uncertainties. No reference made throughout to the fact that laboratory testing as modelled being provided by genomic lab hubs would require addition of CYP2C19 testing to the NHSE national genomic test directory. Unclear whether it would be possible for hospitals/ providers to directly commission local GLH service to provide their CYP2C19 testing in the same way they could deliver POCT at the hospital.	This is an issue about implementation of the tests, and is not something that we considered as part of our assessment.
NICE Technical Team (query in e-mail of 15/3/2023)	12			Would it be possible to do another threshold analysis on the value of sensitivity that the POCTs need to drop to where they are no longer cost effective versus lab testing (keeping specificity fixed to 100%)? This would help committee understand how many variants (or prevalence of LOF variants not tested for) POCT would need to miss versus lab testing to not be cost effective.	See below for the requested threshold analyses.

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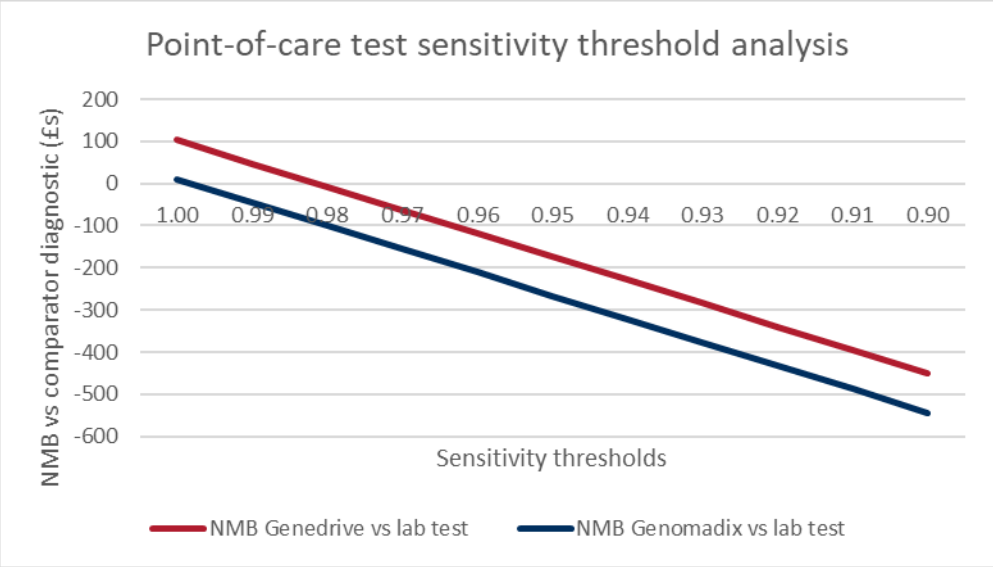
In the first figure, the net monetary benefit of Genedrive and Genomadix vs lab test are plotted for each value of the sensitivity of the POCT between 0.9-1.0. As there is uncertainty surrounding our estimates of the costs of Genedrive, Genomadix, and lab tests, we also included a two-way analysis displayed in the next 2 figures where the incremental costs per test (Genedrive – Lab test and Gemodadix – Lab test) are varied +£100 or -£100 from the Base-Case (BC) in order to present the sensitivity of the threshold analyses to changes in the cost estimation of the diagnostic tests.

We report figures separately for the IS and TIA populations.

IS population



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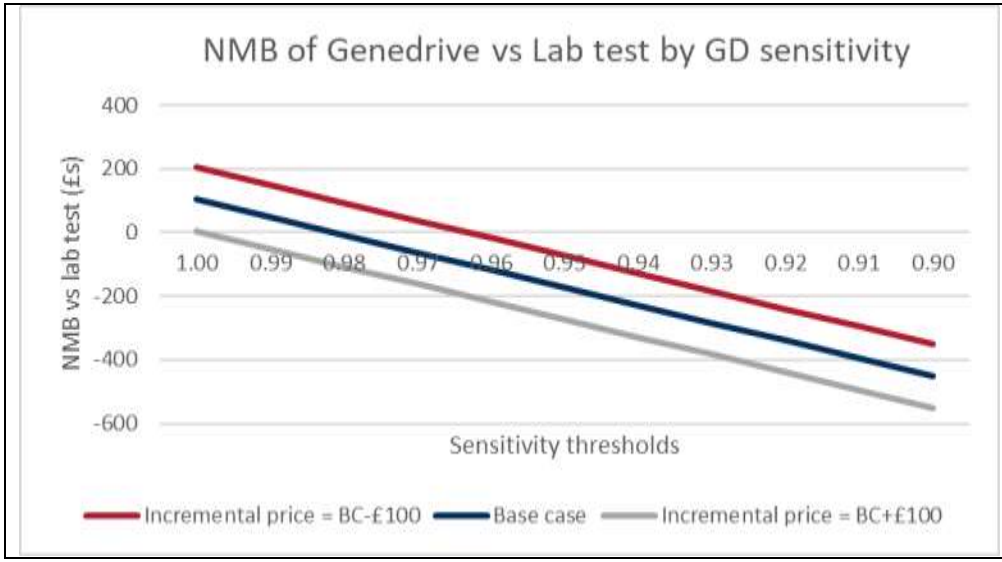

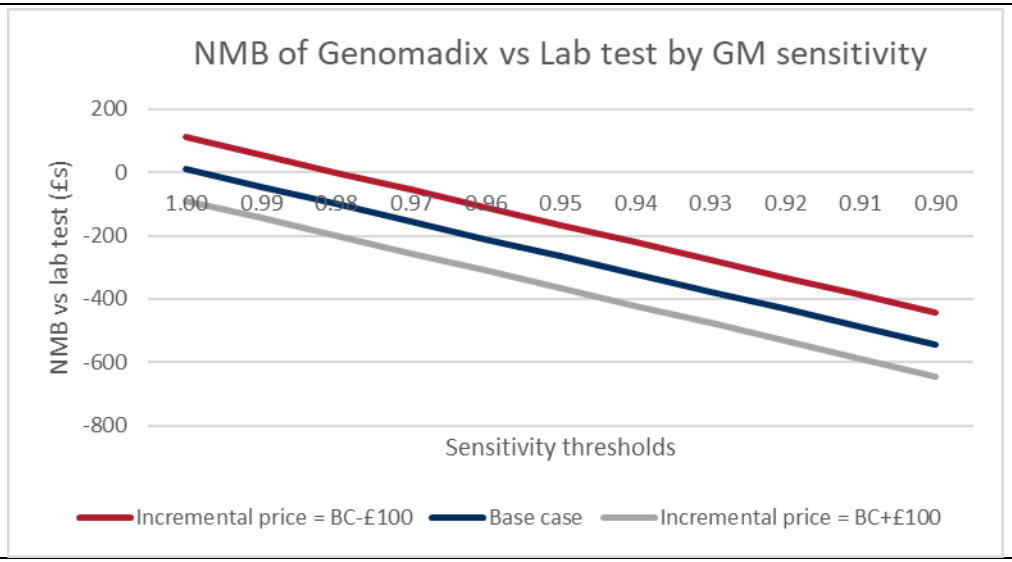

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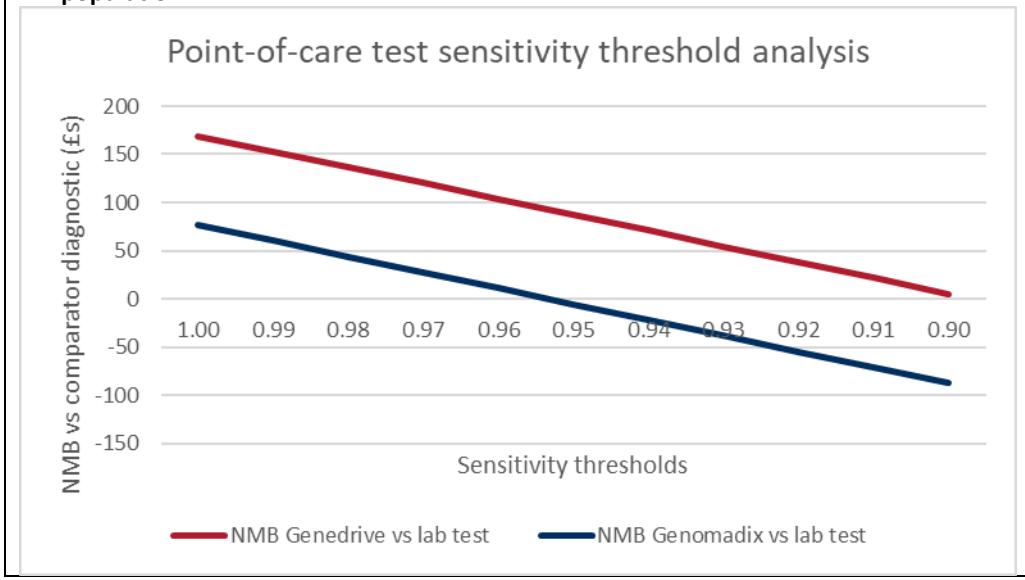
TIA population



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