DIAGNOSTICS ASSESSMENT PROGRAMME

CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack

Draft guidance – Comments

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1	Genomadix	1-5 13 18	1.3 1.4 3.8 3.15	Genomadix notes the recommendation to use the Genedrive CYP2C19 test preferentially over the Genomadix Cube test (both when laboratory testing is not available) despite the following: 1. In the first draft guidance, the Committee recommended not using the Genedrive CYP2C19 test due to a lack of evidence of accuracy of the test. In the most recent draft, the committee changed its recommendation to using the Genedrive test, stating that "Evidence from studies provided by the company, suggests that the Genedrive CYP2C19 ID Kit works well. It can detect more CYP2C19 alleles than the Genomadix Cube point-of-care test." However, according to the information provided in the performance characteristics section of the Genedrive Instructions for Use (Table 8),[1] the Genedrive test accuracy has never been tested in human subjects for 18 of the 27 diplotypes reported by the test, including all of the diplotypes involving the *4, *8 and *35 alleles. The 3 additional alleles that led to the Committee's change in draft recommendation have only ever been tested in contrived specimens created with synthetic DNA rather than human genomic DNA specimens from cheek swabs.	Thank you for your comment which NICE has considered. The EAG's addendum (see section 3.2.1 – [DAP65 EAG Critique_Analyses Stakeholders and GD Data [noACIC] 19092023]) which describes the Genedrive test data stated that the accuracy estimates were based on detection of the *2, *3 and *17 alleles (for example in table 2 in this report). This report was considered by committee in its decision making. While data showing accuracy estimates to detect *4, *8 or *35 alleles using donor specimens was not provided, the test has regulatory approved functionality to detect these alleles. It is therefore considered unlikely that when used on patient derived samples the test would be unable to detect any individuals with the *4, *8 or *35 alleles. In contrast, the Genomadix test does not have the functionality to detect these alleles. As described in section 3.8 of the guidance, the committee considered that tests that only detect the most common loss-of-

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				Because the entire process of running a test, from specimen collection to result, is an important part of assessing the accuracy of the test, it is generally recommended to test the performance of a genotyping device on human subjects whenever possible.	function alleles are more likely to introduce inequalities. This is because less-common loss-of-function alleles are more prevalent in certain ethnic groups. The committee did note that further data on performance and failure rates for the Genedrive test would be beneficial, and it encouraged centres already using this test to take part in data collection (see section 3.23 of the guidance).
2	Genomadix	13	3.8	2. The Genedrive CYP2C19 technology has never been tested in a real world clinical setting that has been published in peer-reviewed journals. In contrast, the Genomadix Cube CYP2C19 technology has been the subject of numerous clinical trials and publications, including the POPular-Genetics Trial (2488 patients)[2], the TAILOR-PCI trial (5302 patients),[3] the IGNITE trial (1815 patients),[4] and a U.S. implementation trial (931 patients),[5] among many others. In total, Genomadix CYP2C19 technology has been tested with well over ten thousand patients in various clinical trials and has been featured in 30 peer reviewed scientific publications (see table 1 below). It is disappointing that the Committee would recommend the Genedrive CYP2C19 test over the Genomadix Cube CYP2C19 test rather than recommending either test, given the very limited data on the performance characteristics of the Genedrive test and the lack of real-world data or peer reviewed publications with the Genedrive test vs. the Genomadix test. The data relating to the Genomadix technology has been attached as an appendix to this document and	Thank you for your comment which NICE has considered. The committee considered the available evidence for the Genomadix Cube test and Genedrive test as described in the EAG's report, which included 11 studies that provided data on test accuracy of the Genomadix Cube CYP2C19 test. Section 3.15 of the guidance describes the committee's rationale for concluding that Genedrive was its preferred point-of-care test. The committee noted that several features of the Genedrive test could offer advantages over the Genomadix Cube. For example, its reagents do not need to be stored in a freezer and it can detect several additional alleles including those that occur in greater frequency in some ethnic groups. The committee also noted that the estimated cost per test for Genedrive was less than for Genomadix, and this remains

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				given the uncertainty of the use of the GeneDrive technology in a real-world clinical setting, the uncertainty of point (3) below and the additional points raised in comment #4 below, all technologies being cost-effective and the plethora of data for the Genomadix technology compared to a paucity of data for the Genedrive technology, the Committee is requested to consider leaving it to the healthcare institution to determine which point of care test would meet their local requirements, rather than recommending one technology over another, in the instance where laboratory testing is not available or not appropriate.	true even when using the updated cost for the Genomadix test provided in these comments (see comment 4).
3	Genomadix	18	3.15	2. The committee states in its latest draft recommendation that the Genedrive CYP2C19 test was recommended over the Genomadix Cube CYP2C19 test, in part, due to the addition of the *4, *8 and *35 alleles, in addition to the *2, *3 and *17 alleles that both point of care tests include. Genomadix strongly supports the Committee's interest in promoting equality of care for all patients. However, the Committee is also tasked with making evidence based recommendations. Regarding the recommendation of the Genedrive test over the Genomadix Cube test based on the inclusion of the *4, *8 and *35 alleles, Genomadix notes the following: • There is no published data in stroke patients showing the clinical effect of the *4, *8 and *35 alleles in the efficacy of clopidogrel, or the efficacy of using genotype guidance with the *4, *8 and *35 alleles to select antiplatelet treatment.	Thank you for your comment which NICE has considered. As described in the responses above, the committee considered that tests that only detect the most common loss-of-function alleles may be more likely to introduce inequalities. The committee considered that the difference in alleles that the Genedrive and Genomadix tests can detect was significant and a reason to prefer the Genedrive test (as described in section 3.15 of the guidance). The *4, *8 and *35 alleles are designated 'no function' (with limited evidence) according to the PHARMGKB CYP2C19 allele functionality table.

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The strength of evidence for the *4, *8 and *35 alleles with regards to clopidogrel response is inferred rather than ever having been studied and is considered Limited Evidence by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[6] and Association for Molecular Pathology[7], two authoritative sources highlighted in the draft recommendation from the Committee.
Table 1: Comparison of Evidence Levels for Point of Care tests Assessed by NICE Committee
<table>
<tr><th></th><th>Genomadix Cube CYP2C19 T</th></tr>
<tr><td>Percentage of diplotypes that have been tested in human samples in controlled accuracy study</td><td>90%</td></tr>
<tr><td>Number of peer-reviewed scientific papers using technology</td><td>30</td></tr>
<tr><td>Clinical patients tested in published scientific studies</td><td>>10,000</td></tr>
<tr><td>Alleles in test with strong level of evidence by CPIC and AMP</td><td>*2, *3, *17</td></tr>
</table>

1. Genedrive. *Genedrive CYP2C19 ID Kit, Instructions for Use.* Genedrive; 2023 accessed on April 1, 2024.
2. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI. *N Engl J Med*. 2019;381(17):1621-1631. doi:10.1056/NEJMoa1907096

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				3. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA*. 2020;324(8):761-771. doi:10.1001/jama.2020.12443 4. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2018;11(2):181-191. doi:10.1016/j.jcin.2017.07.022 5. Cavallari LH, Franchi F, Rollini F, et al. Clinical implementation of rapid CYP2C19 genotyping to guide antiplatelet therapy after percutaneous coronary intervention. *J Transl Med*. 2018;16(1):92. Published 2018 Apr 11. doi:10.1186/s12967-018-1469-8 6. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther*. 2022;112(5):959-967. doi:10.1002/cpt.2526 Pratt VM, Del Tredici AL, Hachad H, et al. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J Mol Diagn*. 2018;20(3):269-276. doi:10.1016/j.jmoldx.2018.01.011	
4	Genomadix	5 15 16 18	1 3.5 3.11	Regarding the lower cost of the Genedrive test, Genomadix notes that the data used for the Genomadix technology, including in the in the cost effectiveness model was incorrect. On 24th October 2023 Genomadix provided confirmation to NICE that the cost of the device in the UK had been amended to £125 (See NICE Docs document: “Notice of Price Change” submitted	Thank you for your comment which NICE has considered. The revised pricing information was received after the external assessment report and economic model had been

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				24th October 2023). The price used in the model appears to be the old price of £175. In addition, Genomadix provides a mini-freezer free of charge to customers for storing cartridges, and so that storage of the Genomadix cartridge presents no obstacle nor does it add any cost to implementation. See also comment #5	completed and committee meeting to discuss the updated assessment had occurred (28th September 2023). When the NICE second consultation period had been set, NICE responded to advise that the price change should be included along with comments on the draft guidance. Many thanks for informing us of the updated cost in this consultation. The updated price information has now been added to section 2.13 of the guidance. Even at this lower price, the test kit for Genomadix still costs more than the estimated cost per test for the Genedrive test (as described in table 38 of the external assesment report). The statement that the cost per test for Genedrive is less than for Genomadix in section 3.15 of the guidance has therefore not been changed. The cost of a freezer was not included in the economic model as an additional cost for the Genomadix Cube CYP2C19 system. Section 2.13 of the guidance has been updated to state that Genomadix provides a mini-freezer free of charge for customers to store cartridges. While this would mean there would be no cost incurred to buy a freezer to store reagents, a remaining impact would be the need to provide for space for the freezer at the point of testing. Also, the Genomadix Cube CYP2C19 instructions for use document, states that

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					after removing the cartridge from the freezer, the test must be started within 15 minutes. Points in the guidance highlighting the need for frozen reagents for the Genomadix as a potential disadvantage to using this test at the point of care, in contrast to the Genedrive, are therefore retained in the guidance.
5	Genomadix	3.15	3.15	Genomadix provides a mini-freezer free of charge to customers for storing cartridges, so that storage of the Genomadix cartridge presents no obstacle nor adds any cost to implementation.	Thank you for your comments which NICE has considered. Please see response to comment 4 above regarding the freezer costs.
6	Genomadix	18	3.15	The Committee highlights three differences between the Genedrive CYP2C19 test and the Genomadix Cube CYP2C19 test, including the lack of requirement to keep cartridges frozen during storage, the ability to import results into electronic health records, and the lower cost of the Genedrive test. Regarding each of these points, Genomadix notes the following: • Genomadix provides a mini-freezer free of charge to customers for storing cartridges, and so that storage of the Genomadix cartridge presents no obstacle nor does it add any cost to implementation. • Regarding transfer of results to patient electronic health records, Genomadix notes that the device can be configured to do so. Upon request, Genomadix Cube users can receive assistance to configure the Genomadix Cube CYP2C19 test for automatic export of CYP2C19 results into their electronic health record system, including an encrypted HL7 file for patient privacy-protected transmission of results into the hospital data systems.	Thank you for your comment which NICE has considered. Please see response to comment 4 above regarding the freezer costs. Thank you for providing detail on how the Genomadix results can be transferred to patient electronic health records. Sections 2.15 and 3.15 of the guidance has been updated to include this detail.

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				The data used in the cost effectiveness model was incorrect. On 24th October 2023 Genomadix provided confirmation to NICE that the cost of the device in the UK had been adjusted to £125 (See NICE Docs document: "Notice of Price Change" submitted 24th October 2023). The price used in the model appears to be the old price of £175.	Regarding the comment about updated pricing, please see response to comment 4.
7	Genomadix	Cost Effectiveness Model	Cost Effectiveness Model and related outputs in the draft guidance	• The data used in the cost effectiveness model is incorrect. On 24th October 2023 Genomadix provided confirmation to NICE that the cost of the device in the UK had been adjusted to £125 (See NICE Docs document: "Notice of Price Change" submitted 24th October 2023). The price used in the model appears to be the old price of £175. • Inputs used in the cost effectiveness model on sensitivity and specificity need to be clarified. The EAG previously clarified that due to lack of data on the test accuracy of Genedrive, they made an assumption that Genedrive and Genomadix would have the same test sensitivity (0.99). However in this current version, the model states Genedrive sensitivity at 1 (and states this is an assumption). • Likewise, the following inputs in the cost effectiveness model are also incorrect: i. *Input Costs Tab: D64, Genomadix Assumed Device Lifetime (tests): 2,000*. This is incorrect. This should read 3,500. ii. *Input Costs Tab: D66, Assumed device lifetime (years): 1.9 years.* This is cited as an assumption assumed equivalent to Genedrive. Please clarify why this assumption was used. Also, this needs recalculating in light of the input errors.	Thank you for your comment which NICE has considered. Regarding the price used in the model please see the response to comment 4. The updated accuracy estimates used for Genedrive in the model are described in the addendum report (DAP65 EAG Critique_Analyses Stakeholders and GD Data [noACIC] 19092023 [section 3.1]) that was provided alongside the model. In the initial report, the EAG 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 this assumption remains in the updated base case. However, for sensitivity the EAG noted that Genomadix detects the *2, and *3 alleles, whereas Genedrive detects the *2, *3, *4, *8, and *35 alleles. In the base case the EAG assumed a sensitivity of 99% (rather than 100%) to reflect that Genomadix does not test for all loss of function alleles (see section 3.1 of the addendum). Because Genedrive does test

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				iii. *Input Costs Tab: D52, Genedrive Assumed Device Lifetime (tests): 6250.* This is cited as an estimate. Please clarify the source. As noted above, Genomadix provides a mini-freezer free of charge to customers for storing cartridges, and so that storage of the Genomadix cartridge presents no obstacle nor does it add any cost to implementation.	for the *4, *8, and *35 loss-of-function alleles, the EAG expected Genedrive to have a slightly higher sensitivity than Genomadix. Based on this and the estimated allele frequencies in the UK population, the EAG assumed a sensitivity of 99.6% in the updated model base case. A full description can be found in the addendum cited above. Regarding the cost effectiveness model inputs, all values and rationales for their use were described in the external assessment report. The assumed device lifetime was taken from the Genomadix response to EAG further information request. This was received by NICE on 19 December 2022 and states that Genomadix cube has a lifetime of "over 2000 uses without failing. However, the design requirement that has been verified is a minimum of 1500 uses". The EAG used this figure to estimate device lifetime in years, assuming the number of tests per year were equivalent to the Genedrive estimate which is based on UK admission rates and assumed an average of 6250 tests over 6 years (see table 38 in section 5.2.5 of the external assessment report).
8	Genomadix	1	1.3	Genomadix has attached the committee consider leaving it up to the healthcare institution to determine which point of care test would meet their local requirements, rather than recommending Genedrive over Genomadix	Thank you for your comment which NICE has considered.

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9	Genomadix	Reference List		DAP65 Genomadix Reference List 20240	Thank you for your comment which NICE has considered.
10	Web Comment		1.1	Dear Sirs I am somewhat surprised that despite there being an excellent POCT that can provide a result within 60-90 minutes so appropriate treatment can be initiated virtually there and then for all strokes/TIA in an acute or OPD setting there will be potentially lengthy delay upto 1-2 weeks to get results back. Some of these will be lost, not communicated effectively or left to the GP to sort out in what limited time they have already with work being transferred inappropriately from hospital. The committee members demonstrate no insight into GP work and it is is really no their role to act as the Stroke Units subsidiary in any way. The test is done in hospital and explaining the whole LOF alleles. etc is the role of the stroke specialists in terms of risks benefits of various medications and not be assumed to be done by the GP. This aside an excellent review of the CHANCE 2 trial which I have not seen referenced https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9214630/#:~:text=In%20this%20secondary%20analysis%20of,21%2Dday%20period%20of%20dual Noted as follows In this secondary analysis of the Ticagrelor or Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events II (CHANCE-2) randomized clinical trial, the benefit with ticagrelor and aspirin was predominately present in the first week and persisted throughout the 21-day period of	Thank you for your comments which NICE has considered. The committee did recommend point-of-care testing and acknowledged the potential benefits. However, the committee stated a preference for laboratory-based testing because it has the potential to detect a broader range of loss-of-function alleles and can be adapted more easily to assess other alleles in the future. Several stakeholders and experts also commented that centralised testing would reduce variability in testing offered across the NHS. Experts raised concerns that if left to local centres to implement testing with point-of-care tests, this would likely lead to considerable variation and could worsen health inequalities. Experts also highlighted that, in the future, pharmacogenomic testing may be reactive when clopidogrel is needed, but pre-emptive pharmacogenomic tests for other treatments could be done at the same time. This would require a panel of tests that would be more easily done in a laboratory. The committee considered that tests that only detect the most common loss-of-function alleles may be more likely to introduce inequalities because less-

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				dual antiplatelet therapy with ticagrelor and aspirin in patients with a minor stroke or TIA who carried CYP2C19 LOF alleles. So the first 1-3 weeks is most important and precisely the time when those early discharges and OPD patients will miss their results. I fear this will predominantly affect the disadvantaged ethnic minorities and those with MH issues and some of these groups are more likely to have LOF alleles. I feel the committee has missed a rare opportunity to put their health at front and centre. The POCT test from analysis is the most cost effective, offers no treatment delay in the golden window and appears easy to administer and surely can be adapted to other alleles if required. I urge the committee to look again at this closely and recommend POCT as first line in all cases both from a clinical effectiveness and from an equality impact assessment point of view I look forward to your response [redacted]	common loss-of-function alleles are more prevalent in certain ethnic groups. These considerations are described in section 3.8 and 3.16 of the updated guidance. The EAG considered evidence from the CHANCE-2 trial and used this to inform some of the economic model parameters. This study is discussed in the external assessment report (see section 5.25). The benefits of point-of-care tests described in the comment were included in the cost effectiveness estimates and considered by committee. For example, point-of-care test results being available sooner than laboratory-based testing, that there is a higher risk of a recurrent stroke in the first 90 days after the initial event and that patients with loss-of-function alleles have an increased stroke risk during the period they are on clopidogrel before switching to alternative treatment. The committee also considered a scenario in which the uptake of alternative treatments following CYP2C19 testing was reduced, based on findings from a recent study that reported physician adoption of alternative treatments following pharmacogenomic testing. The committee acknowledged the potential implementation issues associated with providing laboratory-based testing for

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					everyone who has a stroke or TIA. It noted that testing capacity may need to be scaled up over time. As highlighted in the 'what this means in practice' information box below the recommendations in the guidance, commissioners may wish to consider a phased rollout with testing initially offered to people with a higher risk of stroke recurrence who could benefit most from it, such as people who have had a non-minor stroke (see also section 4 of the guidance). This should help to reduce lengthy delays to getting laboratory-based test results. As noted above and described in the 'What this means in practice' section of the guidance, point-of-care testing is recommended as an alternative if laboratory-based testing is not feasible, or while capacity for laboratory-based testing is increased. Section 3.1 of the guidance outlines the committee's considerations about consent for testing and highlights the Royal College of Physicians' guidance on consent and confidentiality in genomic medicine. This states that as a rule, the process of seeking consent ensures that a person understands the nature and purpose of the procedure or intervention. In the context of CYP2C19 testing in this assesment, as the sample would usually be taken in hospital, in a stroke unit, then the patient should be provided with information about the reason

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					for the test and how the test results (loss of function allele status) may determine subsequent treatment decisions at this point. The information box below the recommendations also states that this guidance does not replace existing guidance on antiplatelet therapy when genotype testing is not available, or when results from testing are not yet received. Starting antiplatelet treatment should not be delayed while waiting for test results.
11	British & Irish Association of Stroke Physicians (BIASP)			Dear NICE, Thank you for your continued work in this area. We welcome the progress in recommendations for more routine testing for clopidogrel resistance. Thank you for considering and responding to the BIASP committee comments and we feel most of these have been addressed in your updated review. The next challenge will be implementation and we look forward to reviewing the tools you are developing to help with this. Yours sincerely, [redacted], BIASP	Thank you for your comments which NICE has considered. NICE are developing a resource impact tool and a case study. More information on these will be available in due course.
12	Inagene Diagnostics UK Ltd		1.1	The requirement for quality assurance processes to be in place for POC tests is an important and welcome recommendation. However it is a specific requirement for POC testing, and therefore would be better placed under the sub-section referring to POC testing. In practice, consideration needs to be given to how quality assurance will be performed for POC tests, and who will be responsible for conducting this? For laboratory tests, quality	Thank you for your comments which NICE has considered. Section 1.1 has been updated to state that quality assurance processes and arrangements are in place for point-of-care tests. Section 3.16 of the guidance has also been updated to state that a stakeholder

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				assurance is clearly the responsibility of the laboratory, but POC tests will be performed in a different organisational environment, and therefore the line of responsibility will not be so obvious.	commented that centres usings point-of care tests would need to have quality-assurance processes in place and consider who is responsible for ensuring these.
13	Inagene Diagnostics UK Ltd		1.1	When interpreting test results, healthcare professionals should take into account The statement that healthcare professionals should take into account that the prevalence of different CYP2C19 genotypes may vary between ethnic groups is relevant. The guidance is currently non-descript, and it would be preferable to give specific guidance on what this means for patients of different ethnic groups, since healthcare professionals cannot be expected to remember the detailed frequencies of alleles and which alleles are tested with the different testing methodologies.	Thank you for your comments which NICE has considered.
14	Inagene Diagnostics UK Ltd		1.2	We agree with the concept that laboratory testing potentially provides a more inclusive service by enabling a greater number of alleles to be tested for. It would be preferable to specify a minimum set of alleles that should be tested in the laboratory setting. Otherwise there is the possibility that a laboratory could simply test for the same minimal set of alleles as covered by one of the POC tests. In America the Association for Molecular Pathology recommended alleles to be tested (see: AMP Recommendations for Clinical CYP2C19 Genotyping Allele Selection), using a two tier system. This was published in 2018, and is possibly due for revision, given the accumulation of data since then and improvements in genotyping technology.	Thank you for your comments NICE has considered. It is outside the scope of this guidance to specify a minimum set of alleles to test for. Section 3.8 in the guidance includes sources that clinical experts have highlighted as sources of information that could be used to guide decisions on the alleles tested for, which, as noted in the comment, may update over time.
15	Inagene Diagnostics UK Ltd		1.4	a phased rollout with testing Re: phased roll outs by prioritization of high risk individuals. This approach is a practical one, while testing capacity is limited. It	Thank you for your comments which NICE has considered.

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				considers the prior risk for each patient, based on clinical history, while the magnitude of benefit is likely a composite of overall risk and genotype-mediated response risk. So, for example, a TIA patient with a poor metaboliser phenotype (as predicted by genotype) may have a higher risk overall than a high risk stroke patient with wild-type genotype. Therefore, it is advisable that a greater emphasis on scalability should be made. Consideration could be given to utilising capacity in commercial genomic laboratories rather than relying on NHS Genomic laboratories which are already stretched with existing workload.	NICE are developing a resource impact tool and a case study. More information on these will be available in due course.
16	Inagene Diagnostics UK Ltd		2.12	Regarding the statement: “External controls for all targeted alleles are available in a separate kit to check proper performance of the platform”. This links to our comment number 1, and the question of who is responsible for quality assurance of POC tests.	Thank you for your comments which NICE has considered. Section 1.1 of the guidance has been updated to state that quality assurance processes and arrangements are in place for point-of-care tests. Section 3.16 of the guidance has also been updated to state that a stakeholder commented that centres usings point-of care tests would need to have quality-assurance processes in place and consider who is responsible for ensuring these.
17	Inagene Diagnostics UK Ltd		2.13	We agree with the conclusions that POC tests offer a rapid and cheap testing solution, but suffer from limited allele detection, and thus introduce ethnic bias. In particular, regarding alleles covered by Genomadix - *35 is missing, and occurs at a frequency of nearly 6% in the UK Biobank. Most of these individuals have African descent. As a result, a notable section of the population may be underserved if tested with this POC device. The table below shows allele frequencies in different ethnic groups and those alleles which will be detected by both POC	Thank you for your comments which NICE has considered. The guidance already describes the committee’s consideration that tests that only detect the most common loss-of-function alleles may be more likely to introduce inequalities and that tests that detect a smaller range of alleles would likely disproportionately fail to identify people with loss-of-function CYP2C19

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				tests (green) and alleles that will be missed (yellow) using one or both POC tests. (from PharmGKB CYP2C19 Frequency Table) Please note the above mentioned table would not load into the comments box - see the added description in its place. The table shows the alleles covered by the two devices as compared to AMP Tier 1&2 guidelines CYP2C19 and frequencies across different populations. As delineated in the table, these point-of-care devices exhibit both strengths and weaknesses, one of which is their limitation on the number of variants that can be tested. Consequently, this limitation may introduce an ethnic bias. For instance, one proposed product encompasses most AMP tier 1 and 2 alleles; however, the alleles omitted are notably prevalent in individuals of African descent. Conversely, the second product exclusively covers tier 1 alleles, thereby posing the risk of misclassifying alleles common across various ethnicities. Consequently, particularly with respect to the second product and/or individuals of African descent, we recommend that samples from individuals identified as harbouring ancestral alleles be submitted for comprehensive screening. ** https://www.jmdjournal.org/article/S1525-1578(17)30519-6/fulltext"	alleles in certain ethnic groups (see section 3.8 of the guidance), so no further change to the guidance has been made.
18	Inagene Diagnostics UK Ltd		2.15	Regarding the statement: “Optional external controls are available to check proper performance of the platform as per local requirements for accreditation”. Referring to POC testing, it is unclear what external accreditation is being referred to. Laboratories would be accredited, but healthcare organisations (clinics?) providing POC testing would not be accredited to laboratory standards (ISO15189) and thus the reference to accreditation in this context is unclear. This links to our comment	Thank you for your comments which the committee considered. This information was provided by the company. Section 2.15 in the guidance has been updated to clarify this. The UK Accreditation Service (UKAS) states that ISO 15189:2022, now incorporates requirements for point of care testing when carried out in hospitals, clinics

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				number ref 1.1, and the question of who is responsible for quality assurance of POC tests.	and by healthcare organisations offering ambulatory care. Section 1.1 of the guidance has been updated to state that quality assurance processes are in place for point-of-care tests. Section 3.16 of the guidance has also been updated to state that a stakeholder commented that centres using point-of care tests would need to have quality-assurance processes in place and consider who is responsible for ensuring these.
19	Inagene Diagnostics UK Ltd		3.10	It is reassuring to see that all forms of CYP2C19 testing that were evaluated were cost effective when compared to no testing, if the cost per test is less than £1920. This price bracket opens the possibility to provide large pharmacogenomic panel tests and enable pre-emptive testing for a wide range of medications, since such panel testing could be provided at a considerably lower price than £1920. We appreciate that pre-emptive PGx testing was not in the remit for this evaluation, but this conclusion opens the way for further consideration towards replacing single gene PGx testing of CYP2C19 with a large PGx panel. Such a panel would include additional medications that are commonly prescribed to stroke patients, including those for pain and mental health, thus potentially offering increased clinical benefit while still being cost effective. This possibility is referred to in point 3.16 of the guidance.	Thank you for your comment which NICE has considered. As noted in the comment, pre-emptive genetic testing and the testing of *CYP2C19* or other genes to guide use of drugs other than clopidogrel were outside of the scope of this assessment, and no recommendations for these uses are made in the guidance.
20	Inagene Diagnostics UK Ltd		3.20	We support empiric clopidogrel treatment while awaiting genotype results, and treatment modification as necessary. This is the approach used with antibiotics while C&S results are pending.	Thank you for your comment which NICE has considered.

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21	NHS England			Page number 23 - Section number 4 - Comment: The intention to develop tools is welcomed and within these it is suggested that worked examples and pathways – released at the same time as the guidance - will be essential to enable implementation within current service provision. Co-development from an early stage is recommended.	Thank you for your comment which NICE has considered. NICE are developing a resource impact tool and a case study. More information on these will be available in due course.
22	NHS England			Page number 10 - Section number 3.2 - Comment: It is important to differentiate the potential scenarios noted, which include the provision of both consent and assent.	Thank you for your comment which NICE has considered. Section 3.2 of the guidance has now been updated based on advice from stroke physicians on the committee.
23	NHS England			Page number 25 - Section number 3.10 - Comment: PPV involvement in the process is welcomed. Consideration of the weight articulated to anecdotal views on adherence is suggested.	Thank you for your comments which NICE has considered.