DIAGNOSTICS ASSESSMENT PROGRAMME

Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

Draft guidance – Themed comments

Diagnostics Advisory Committee date: 28 September 2023

THEME: Laboratory based testing: Capacity, costs and benefits

Comment number	Name and organisation	Section number	Comment	NICE Response
1	Royal College of Physicians	General	We would like to endorse the response submitted by the British and Irish Association of Stroke Physicians (BIASP).	Thank you for your comments which the committee considered.
2	British and Irish Association of Stroke Physicians (BIASP)	8	We note that there will need to be a huge increase in capacity in genotype testing and may be expensive and impractical for some peripheral stroke services. Only 600,000 genotype tests are carried out in England per annum. There would need to be an increase in capacity of over 15% just to complete the genotype testing for clopidogrel resistance alone (approx.100,000 ischaemic stroke and TIA pts in England per annum).	Thank you for your comments which the committee considered. The committee acknowledged that implementing testing for everyone who has a stroke or transient ischaemic attack (TIA) could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee recalled that, compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit (NMB) than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate

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				implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added below the recommendations to highlight these implementation considerations (see 'What this means in practice').
3	Web Comment	General	we currently have significant resource issues in the lab genetic testing service in our regions and are unable to access timely results and the additional pressures from testing in the large numbers of new strokes and TIAs at the current time will make getting results in a clinically relevant time frame not possible. current waiting times for WGS is 6-12 months in Yorkshire.	Thank you for your comments which the committee considered. The committee acknowledged that implementing testing for everyone who has a stroke or transient ischaemic attack (TIA) could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee recalled that, compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate

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4	Web Comment	2.15	A benefit of laboratory-based testing is that in England this is commissioned nationally via the Genomic Medicine Service and delivered through the NHS Genomic Laboratory Hubs. This provides an opportunity to ensure better equity of access to testing when compared to POCT which is likely to need funding and implementation at a local level.	Thank you for your comments which the committee considered. Several stakeholders and experts 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. Some committee members said that existing infrastructure should be preferentially used over investing in new single purpose technologies. The committee concluded that laboratory-based tested was its preferred method to implement testing. These considerations are in section 3.16 of the updated guidance.
5	Web Comment	2.15	From the full diagnostics assessment report one of the major barriers to implementing laboratory based *CYP2C19* testing was the scale of the predicted activity and current capacity in the NHS Genomics Laboratory Hubs (GLHs). The NHS GLHs do	Thank you for your comments which the committee considered. The committee acknowledged that implementing testing

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			not currently perform any tests of this scale in the NHS and so do not currently have the infrastructure for this. This information would be helpful to include in the final guidance document as will be an important consideration for the choice of test to be adopted, and will impact the timescale before which testing could be routinely provided as there will be a considerable amount of time and resource required in order to upscale capacity to meet this demand.	for everyone who had a stroke or TIA could be done in a stepwise process, with a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee noted that compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added below the recommendations to highlight these implementation considerations (see 'What this means in practice').
6	UK Clinical Pharmacy Association (UKCPA)	5	We agree and wish to highlight the importance in objective 5 of the expert review that there is no precedent for implementing a genetic test at this scale, and roll-out would need to be carefully planned in order to avoid swamping laboratories with *CYP2C19* requests.	Thank you for your comments which the committee considered. The committee acknowledged that implementing testing for everyone who had a stroke or TIA could be done in a

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				stepwise process, with a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee noted that compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added below the recommendations to highlight these implementation considerations (see 'What this means in practice').
7	UK Clinical Pharmacy Association (UKCPA)	3.10	We would like to see the evidence that testing 3 alleles costs £20-40 in a laboratory, particularly when this is not running at scale. Limited experience with pharmacogenomic panels suggests that costs are higher than this, especially when running tests at low volume with a reduced number of genes tested or reported.	Thank you for your comments which the committee considered. These figures were reported by a committee member based on their experience of clopidogrel genotyping. In the base case analysis the EAG used a laboratory test

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				cost of £139 per test, which assumed no batching of samples. This was varied in further analysis provided in an addendum, a batch testing scenario analysis assumed batches of 55 samples per run and used a reduced cost of £44 per test. The EAG acknowledged the uncertainty about test costs, and provided this further analysis to show how varying test costs impacts on cost effectiveness estimates. It further highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920. See section 3.11 of the updated guidance.
8	Genomadix	3.10 & 3.13 (Cost effectiveness - Laboratory testing versus point-of-care testing)	**Committee Discussion: Estimation of Cost of Laboratory Testing** We agree that there is little difference in QALYs between laboratory and point-of-care testing in the EAG model, and that the true cost of laboratory-based testing us uncertain. However, the committee papers highlighted several major barriers that exist which indicate that these costs may in fact also be underestimated (p88) but no comment to this effect is included in the guidance. The committee noted that: Major barriers include staffing, capacity and need to scale as barriers existing knowledge to implement tests of this scale in the NHS is lacking One laboratory undertaking these tests highlighted several other barriers including the inability to accept requests from GPs, separate requesting and reporting systems for acute and primary care, and fixed budgets being in place which meant requests for tests were restricted.	Thank you for your comments which the committee considered. The EAG said that the estimated costs for laboratory testing in the model did not account for any efficiencies due to batching samples. In response to stakeholder comments the EAG added a batch testing scenario analysis which assumed batches of 55 samples per run and used a reduced cost of £44 per test. The committee noted that costs for laboratory testing may have been underestimated if higher implementation costs were incurred but not captured in the EAG's estimates (see section 3.19 of the updated guidance). The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920. See section 3.11 of the updated guidance. 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

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			additional resources may also be required. In addition to the above, given the fact that some patients require results rapidly, it is possible that laboratory testing that is batch-based might have to be run in small batches or even singly to obtain timely results, which could increase the cost of testing.	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. However, the committee also stated that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in section 3.16 of the updated guidance
9	ICSWP	1.1	ICSWP members were not convinced that sufficient consideration had been given by the committee to the resource implications of their recommendations. In particular, it would result in the need for as many as 100,000 additional laboratory genotype tests per year in labs that are currently providing 600,000 genotype tests per year, with many already reporting capacity issues. This may mean that, in the health economic analysis, the relatively simplistic assumptions that expansion of capacity could be achieved solely on a cost-per-test basis, and that the cost per test would correspondingly be reduced by laboratory efficiencies, would not apply, and this would significantly affect the cost-effectiveness analysis.	Thank you for your comments which the committee considered. The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920. See section 3.11 of the updated guidance. The committee acknowledged that implementing testing for everyone who has a stroke or TIA could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee noted that compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people

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				per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added below the recommendations to highlight these implementation considerations (see 'What this means in practice).
10	ICSWP	3.10, 3.11	The ICSWP's health economics expert noted that the modelling is based on a lower cost for lab based testing (£139) versus point of care testing (£197). The committee's experts thought lab testing costs could be lower and could even reduce over time due to economies of scale or new technologies. However, this line of argument is based on costs under an assumption of available capacity. If labs were in fact at full capacity – and common knowledge would tell us this is the case, as confirmed in the lab survey findings in the EAR report which point towards various capacity hurdles – they will either not be able to meet demand (i.e. the treatment strategy could not be implemented as intended) or there will need to be further investment to meet the demand. Either of those real-world scenarios could be expected to increase overall costs for this treatment strategy, and therefore the average cost of a test. As a result, test costs may be underestimated.	Thank you for your comments which the committee considered. The committee noted that costs for laboratory testing may have been underestimated if higher implementation costs were incurred but not captured in the EAG's estimates (see section 3.19 of the updated guidance). The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920 See section 3.11 of the updated guidance. However, the committee also stated that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used (see section 3.16 of the

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				updated guidance).
11	ICSWP	7	ICSWP members thought that by considering the tests as specific interventions, rather than as treatment strategies in a wider care context, estimates of costs and outcomes were too narrowly focused. For example, pages 37-38 of the Evidence Overview document includes a specific section related to implementation, which describes various pragmatic implementation issues, but many of these are not accounted for in the modelling/assessment. Given how narrow the cost differences were between treatment strategies, accounting for the real world implications to a greater extent may have suggested different costs and conclusions.	Thank you for your comments which the committee considered. The committee noted that costs for laboratory testing may have been underestimated if higher implementation costs were incurred but not captured in the EAG's estimates (see section 3.19 of the updated guidance). The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920 See section 3.11 of the updated guidance.
12	NHS England	Cost of testing – 3.10	The figures for (including type of) laboratory testing was taken from individual survey responses from laboratories across the UK. A more standardised and facilitated approach with multi (rather than individual) stakeholder engagement to discuss implementation may have been beneficial in reaching likely agreed numbers and testing approaches particularly since NHS England is introducing cost pricing for genomic testing.	Thank you for your comments which the committee considered. The EAG agreed that there was uncertainty in their calculations and that the introduction of standardised cost pricing for genomic testing would be welcome. A threshold analysis done by the EAG showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920 See section 3.11 of the updated guidance.
13	Inagene Diagnostics	General	The Technology Assessment Report has done a good job of assessing and including factors that impact on the costs of testing. The laboratory testing in particular is complex to assess accurately, since some of the data is unknown or has been based on estimates. However, there are some inaccuracies in the costing assumptions for laboratory testing, as detailed below: 1. Number of laboratory tests per day	Thank you for your comments which the committee considered. In the EAG's updated base case, the lifespan of the MassARRAY system was amended to 5 years. It also estimated a maximum 3,456 samples could be processed by the mass-array system in a 24-hour period. The EAG said that this had a minimal effect on lab test cost as the updated device cost per test is increased to

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			In Table 39 of the Technology Assessment Report, the number of MassArray tests per machine per day is quoted at 40,000. This is an overestimate for one machine. The Agena website (The MassARRAY System from Agena Bioscience) quotes a run time of 150 minutes for a 384 well plate. Therefore, within a 24 hour period, the maximum number of 384 well plates that could be analysed is 24hrs x 60 minutes / 150 minutes = 9.6. Additional time between runs is required, so an absolute maximum of 9 plates could be analysed in 24 hours, allowing 9 x 384 = 3,456 samples to be processed in 24 hours. However, using this maximum number of tests would be inappropriate for one machine, since a single laboratory would not receive this number of tests per day. If 100,000 tests are performed annually (the predicted number of tests to be performed after year 1), this equates to only 100,000 / 52 = 1,923 tests per week, or 385 tests per day (assuming a 5 day working week). If the tests are shared equally among the 7 GLH laboratories, this equates to approximately 55 tests per lab per day. Therefore the machine cost per test would increase if this figure is used in the calculations. 2. Lifespan of MassArray machine In the laboratory testing costing model, an estimated lifetime of 1 year has been assumed for the Agena Bioscience MassARRAY instrument The predicted device lifetime for a MassArray or for any similar molecular biology analyser is generally assumed to be 5 years when NHS laboratories are forecasting budget requirements for capital equipment replacement costs. Therefore if a 5 year lifetime is used in the calculations, the machine cost element of the test cost would increase.	7p. In response to stakeholder comments the EAG added a batch testing scenario analysis which assumed laboratory tests were processed in batches of 55 tests. 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 as the base case. This reduced the cost to £44 per test. The committee noted that costs for laboratory testing may have been underestimated if higher implementation costs were incurred but not captured in the EAG's estimates (see section 3.19 of the updated guidance). The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less than £1,920. See section 3.11 of the updated guidance.

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			3. Laboratory testing time The laboratory survey question on staff time required to carry out testing has been answered ambiguously and differently by different responders, and thus the times used in table 39 of the Technology Assessment Report are not appropriate for single sample testing; the times quoted in table 39 appear to be more appropriate for testing a batch of samples, which could be a batch of approx. 55 samples per day - as would be the likely predicted number of samples received per lab, as discussed in point 1 above. Therefore if the hands on times used in the calculations are applied to testing a batch of 55 samples rather than a single sample, the staff costs per test would decrease.	
14	Inagene Diagnostics	3.10	there was a lack of agreement on the staff time required The laboratory survey question on staff time required to carry out testing has been answered ambiguously and differently by different responders, and thus the times used in table 39 of the Technology Assessment Report are not appropriate for single sample testing; the times quoted in table 39 appear to be more appropriate for testing a batch of samples, which could be a batch of approx. 55 samples per day - as would likely be received per lab, assuming 100,000 tests pa (after year 1), which equates to approx 400 tests per day nationally (assuming 5 working days per week), and assuming tests are divided across the 7 GLH laboratories.	Thank you for your comments which the committee considered. In response to stakeholder comments the EAG added a batch testing scenario analysis which assumed laboratory tests were processed in batches of 55 tests. 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 as the base case. This reduced the cost to £44 per test. See section 3.11 of the updated guidance.
15	Inagene Diagnostics	3.10	Therefore, the true cost of laboratory-based testing is uncertain. Using a multi-gene panel that tests for evidence-based drug-gene relationships can impact multiple outcomes, thereby "spreading the overhead costs" of single gene laboratory testing. The cost per gene, cost per drug, or cost per variant could be used as the basis for an "apples-to-apples"	Thank you for your comments which the committee considered. The EAG acknowledged the uncertainty about test costs. But it highlighted that a threshold analysis it had done showed that laboratory-based testing was cost effective compared with no testing if the cost per test was less

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			comparison.	than £1,920. See section 3.11 of the updated guidance.
16	Inagene Diagnostics	3.10	based testing in the model was for the Agena Bioscience MassARRAY In Table 39 of the Technology Assessment Report, the number of MassArray tests per day is quoted at 40,000. This number is the estimated throughput of MassArray testing if a machine was working at full capacity for 24 hours per day. In reality, a single machine in one laboratory would not be testing this sort of numbers per day, because a single laboratory would be unlikely to receive this number of samples per day, and NHS GLH laboratories do not currently work 24/7 hours. If 100,000 tests are performed annually (the predicted number of tests to be performed after year 1), this equates to less than 400 tests per day nationally (assuming 5 working days per week), and approximately 55 samples per day per GLH (assuming 7 GLHs provide testing).	Thank you for your comments which the committee considered. Please see the response to comment 13.
17	Inagene Diagnostics	3.10	was for the Agena Bioscience MassARRAY with an assumed 1-year lifespan. Can this be elaborated upon? It is unclear what the ramifications of this statement are. Is the cost of an entire Agena MassARRAY an annual expense thereby increasing the cost of laboratory testing? Is the cost being depreciated over a year? Does it implicate purchase of reagents?	Thank you for your comments which the committee considered. In the EAG's updated base case, the lifespan of the MassARRAY system was amended to 5 years.
18	Inagene Diagnostics	3.10	an assumed 1-year lifespan. In the laboratory testing costing model, a lifetime of 1 year has been assumed for the Agena Bioscience MassARRAY instrument The predicted device lifetime for a MassArray or any similar molecular biology analyser is generally assumed to be 5	Thank you for your comments which the committee considered. In the EAG's updated base case, the lifespan of the MassARRAY system was amended to 5 years.

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			years when laboratories are forecasting budget requirements for capital equipment replacement costs. Therefore the machine cost element of the test cost should be lower than used in the model.	
19	Inagene Diagnostics	3.13	existing infrastructure should be preferentially used over investing in new single purpose technologies. Using existing infrastructure to provide *CYP2C19* testing has an additional advantage over investing in new single purpose technologies, since it prepares the infrastructure for (a) increasing sample volume numbers and (b) commissioning of more pharmacogenomic tests. The range of pharmacogenomic tests that NHS will commission is likely to increase over time. Currently, point of care devices are limited in the number of tests they can perform. If single point of care devices are used, health care providers will need to keep a stock of several different devices for performing numerous different tests for different medicines. This is not practical in terms of storage of the devices and selection of the appropriate device to ensure the correct test is performed. Laboratory testing can readily be scaled up to test for additional medicines, and larger number of tests, making laboratory testing a more practical and efficient means of providing pharmacogenomic testing in the long term.	Thank you for your comments which the committee considered. The committee considered the potential benefits of laboratory-based testing. 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. These considerations are in section 3.16 of the updated guidance.
20	Inagene Diagnostics	1.4	So, because they can detect a wider range of variants and are likely to cost less, laboratory tests should be used if possible. The other advantage of lab testing is that other relevant gene-drug relationships may be explored with the same/similar inputs (i.e., one sample and associated staff time). Some of these agents include proton pump inhibitors used to provide cytoprotection from anti-platelet agents, and statins, used to manage global vascular risk.	Thank you for your comments which the committee considered.

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21	Inagene Diagnostics	3.13	The committee stated a preference for laboratory testing over the available point-of-care test A further advantage of laboratory testing is that GLH laboratories are accredited to ISO 15189 standards, and carry out numerous quality control checks as part of routine testing. This level of quality control would not be present for point of care testing.	Thank you for your comments which the committee considered. The recommendations have been updated to state that *CYP2C19* genotype testing is only recommended if quality assurance processes are in place for point of care tests. See recommendation 1.1 in the updated guidance.
22	Inagene Diagnostics	3.8	A clinical expert commented that laboratory-based testing is adaptable and can change which alleles are tested for over time, whereas point-of-care tests can only detect certain alleles. This approach also relies on the initial sample and consent (consent once), thereby reducing costs associated with collecting a new sample. Furthermore, clinical recommendations based on established genotypes may also change over time based on the accumulation of new data and review by expert committees such as CPIC.	Thank you for your comments which the committee considered. The committee stated a preference for laboratory-based tests over point-of-care tests. It also noted that, if needed, laboratory testing can be adapted more easily to assess other alleles in the future. These considerations are in section 3.16 of the updated guidance.

THEME: Populations tested

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23	BIASP	3.5	Could testing be expanded to those who return to stroke services with a further stroke/TIA whilst taking clopidogrel. It also raises the question as to whether we should be testing all those on clopidogrel to ensure they are on an effective drug for	Thank you for your comments which the committee considered. People who have a recurrent stroke or TIA whilst taking

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			stroke prevention.	clopidogrel are within the scope of the recommendations for using testing, provided continued treatment with clopidogrel is being considered. These considerations are described in section 3.10 of the updated guidance. The committee noted that retrospective testing was outside of the scope of the assessment. Further considerations are described in section 3.5 of the updated guidance.
24	NHS England	People currently taking clopidogrel – 3.5	The capacity and capability to genetically test an additional 100,000 stroke / TIA patients per annum will take some time to create as well as developing a model of provision. There are an additional 1.3 million stroke survivors in the UK. Although this guidance focuses on new starters on this medication only, this population will need to be planned for and a substantial proportion may actively request this as will those who take this medication for other cardiovascular conditions – some clinicians have already fed back that since the publication of this draft guidance GPs are writing to stroke services regarding genetic testing requests from patients.	Thank you for your comments which the committee considered. The committee noted that retrospective testing was outside of the scope of the assessment. For clarification, an information box has been added below the recommendations in the updated guidance (see 'What this means in practice'). This states that this guidance is not intended to affect treatment with clopidogrel that was started in the NHS before this guidance was published. People already having clopidogrel should continue until they and their NHS clinician consider it appropriate to stop. The guidance recommends testing only for people just after they have had a stroke or TIA. This is because the risk of another event is higher at this time and therefore so is the potential benefit of testing. But, as risk of recurrent stroke or TIA reduces over time, so does the benefit of testing. For this reason, retrospective testing for people already taking clopidogrel was outside of the scope of this assessment. Further considerations are described in section 3.5 of the updated guidance.

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25	NHS England	General Comments	Numbers estimated do not reflect potential demand due to the very high volume of stroke survivors on clopidogrel as noted above. This requires a clear and structured approach to the establishment of infrastructure and introduction of testing that was highlighted in the EAR, but not reflected in the final draft recommendations. It is important to introduce processes that can be clearly explained and communicated with our patients and public to reduce any potential distress regarding concern about their current treatment or inconvenience in trying to access services that are not yet in place.	Thank you for your comments which the committee considered. The committee noted that retrospective testing was outside of the scope of the assessment. For clarification, an information box has been added below the recommendations in the updated guidance. This 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. This guidance is not intended to affect treatment with clopidogrel that was started in the NHS before this guidance was published. People already having clopidogrel should continue until they and their NHS clinician consider it appropriate to stop. The guidance recommends testing only for people just after they have had a stroke or TIA. This is because the risk of another event is higher at this time and therefore so is the potential benefit of testing. But, as risk of recurrent stroke or TIA reduces over time, so does the benefit of testing. For this reason, retrospective testing for people already taking clopidogrel was outside of the scope of this assessment. Further considerations are described in section 3.5 of the updated guidance.
26	Inagene Diagnostics	3.5	A clinical expert commented that if a person has been taking clopidogrel for a long time without any further events, it is less likely that they have loss-of-function alleles. Therefore, the population would be different to people starting clopidogrel. The "survivorship" noted by the expert relies on the notion that a disproportionate number of long term users will have experienced clopidogrel's benefit. This doesn't seem likely when	Thank you for your comments which the committee considered. Clinical experts commented that it is well documented that risk of recurrent stroke or TIA is highest in the first 12 weeks after the initial event and then decreases. This aligns with evidence identified by the EAG for its model, which shows that risk is highest in the first 90 days after stroke or TIA, and then decreases. These considerations

Comment number	Name and organisation	Section number	Comment	NICE Response
			considering NNT = 40 (https://thennt.com/nnt/antiplatelet-agents-preventing-early-recurrence-ischemic-stroke-transient-ischemic-attack/)	are in section 3.5 of the updated guidance.
27	Web Comment	General	Stroke and TIA survivors in addition to newly presenting patients will be asking for testing creating additional consultation and testing time which again needs economic health cost benefit analysis These are crucial areas for us to gain additional understanding before wholescale recommendation of testing To the best of my knowledge no current stroke services in England are offering/undertaking genotyping at all. It is important going forward to gain more knowledge of the clinical benefit especially in those patients with recurrent events on clopidogrel but we are struggling with resources to manage care where there is robust evidence and diversion of resource to genotyping every patient when we don't currently have robust evidence of clinical benefit in our population would be inappropriate. Patients are starting to ask to have genetic testing and am very keen to have access to testing in patients who have had recurrent events or in high risk group but have concerns current data not robust enough to recommend wholescale implementation currently.	Thank you for your comments which the committee considered. People who have a recurrent stroke or TIA whilst taking clopidogrel are within the scope of the recommendations for use of testing, provided continued treatment with clopidogrel is being considered. These considerations are in section 3.10 of the updated guidance. The committee noted that retrospective testing was outside of the scope of the assessment. Further considerations are described in section 3.5 of the updated guidance. The committee acknowledged that implementing testing for everyone who has a stroke or TIA could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee noted that compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be

Comment number	Name and organisation	Section number	Comment	NICE Response
				started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population.
28	Web Comment	3.5	Although a person who has been taking clopidogrel for a long time without further events may be less likely to have loss-of-function alleles, it is important to state that this is not definitive and to consider other groups such as patients who have only been on clopidogrel for a short time, or those that have had further events despite being on clopidogrel.	Thank you for your comments which the committee considered. People who have a recurrent stroke or TIA whilst taking clopidogrel are within the scope of the recommendations for using testing, provided continued treatment with clopidogrel is being considered. Clinical experts commented that it is well documented that risk of recurrent stroke or TIA is highest in the first 12 weeks after the initial event and then decreases. This aligns with evidence identified by the EAG for its model, which shows that risk is highest in the first 90 days after stroke or TIA, and then decreases. These considerations are in section 3.5 of the updated guidance.
29	UK Clinical Pharmacy Association (UKCPA)	1	Retrospective testing was outside of scope for the assessment but may be used "once testing is more widely available" which is a vague status and open to significantly variable interpretation. See comments in recommendations for further research (section 4) and implementation (section 5); as a wider testing strategy is required for patients who will receive further benefits.	Thank you for your comments which the committee considered.
30	UK Clinical Pharmacy Association (UKCPA)	1.1	Does this apply to people who are already on clopidogrel? Anecdotally, we are already receiving queries from patients who are being started on clopidogrel right now. Further consideration on whether testing would be extended retrospectively is required, and if so, how far?	Thank you for your comments which the committee considered. The committee noted that retrospective testing was outside of the scope of the assessment. For clarification, an information box has been added below the recommendations in the updated guidance. This states that this guidance is not intended to affect treatment with clopidogrel that was started in the NHS before this guidance was published. People already having clopidogrel should continue until they and their NHS clinician consider it appropriate to stop. The guidance

Comment number	Name and organisation	Section number	Comment	NICE Response
				recommends testing only for people just after they have had a stroke or TIA. This is because the risk of another event is higher at this time and therefore so is the potential benefit of testing. But, as risk of recurrent stroke or TIA reduces over time, so does the benefit of testing. For this reason, retrospective testing for people already taking clopidogrel was outside of the scope of this assessment. Further considerations are described in section 3.5 of the updated guidance.
31	UK Clinical Pharmacy Association (UKCPA)	3.5	The evidence shows that possession of LOF variants will increase risk for that part of the patient population receiving clopidogrel for secondary prevention. Is there evidence to support the assertion that a certain amount of time elapsing without an event is protective? If not, it would be worrying to rule out testing for that population on the basis that they were 'treated too soon', and we would support expanding testing to patients previously started on clopidogrel as soon as is practical.	Thank you for your comments which the committee considered. Clinical experts agreed that it is well documented that risk of recurrent stroke or TIA is highest in the first 12 weeks after the initial event and then decreases. This aligns with evidence identified by the EAG for its model, which shows that risk is highest in the first 90 days after stroke or TIA, and then decreases (see section 3.5 of the updated guidance). Further detail on the rationale for the difference in rates of recurrent stroke are in section 5.2.5 of the external assessment report (pages 121 to 125). Clinical experts suggested that *CYP2C19* genotype testing may be expanded to those who began clopidogrel therapy before this guidance was issued, once testing is more widely available. But, the committee noted that establishing testing for populations who had just had a stroke or TIA would be a considerable challenge (as highlighted in several consultation comments elsewhere in this document) so the extent of any such capacity is uncertain. These considerations are in section 3.5 of the updated guidance.

THEME: Antiplatelet treatment

Comment number	Name and organisation	Section number	Comment	NICE Response
32	BIASP	General	Update to be in line with up to date evidence summarised in National Stroke Clinical Guideline update April 2023	Thank you for your comments which the committee considered. The EAG did further analyses in the addendum to reflect changes to care in line with the National Stroke Clinical Guideline update 2023. These analyses were discussed by the committee in sections 3.7 and 3.10 of the updated guidance.
33	BIASP	General	Support in theory for increased access to genotype testing, but major reservations about this draft guidance based on several inaccuracies within the document. This includes incorrect assumptions about when clopidogrel is initiated, use of dipyridamole and evidence-based guidelines for alternative antiplatelet use.	Thank you for your comments which the committee considered. The time at which clopidogrel is initiated was varied in analyses run in the EAG's model to assess impact on cost effectiveness estimates. In the EAG's base case model, the TIA/minor stroke population is assumed to start clopidogrel within 24 hours. For the non-minor stroke population, clopidogrel was assumed to be started 2 weeks after a stroke. The EAG also ran a scenario analysis (scenario 7) which explored the impact of starting clopidogrel within 24 hours in the non-minor stroke group. See section 5.2 in the addendum for results of these analyses and section 3.13 in the updated guidance for committee discussion.
34	BIASP	3.3	Not in line with update national clinical guidelines and not in line with current clinical practice. https://www.strokeguideline.org/contents/	Thank you for your comments which the committee considered. The EAG did further analysis in the addendum to reflect changes to care in line with the National Stroke Clinical Guideline update 2023. These analyses were discussed by the committee in sections 3.7 and 3.10 of the updated

Comment number	Name and organisation	Section number	Comment	NICE Response
				guidance.
35	BIASP	3.6	Given recent updated national clinical guidelines we would ask that a recommendation is made which antiplatelet should be used in the event of a positive loss-of-function *CYP2C19* variant test. It is also worth noting that the new National Stroke Guidelines recommend the use of ticagrelor, this drug however does not have a marketing authorisation to be used for this purpose in the UK currently.	Thank you for your comments which the committee considered. Recommendations on which antiplatelet agent to use are outside the scope of this guidance. In modelling done to assess cost effectiveness, in the event of a loss-of-function *CYP2C19* variant being detected the EAG modelled use of different antiplatelet agents (dipyridamole plus aspirin, ticagrelor plus aspirin, or low dose aspirin monotherapy) to assess how this impacted on cost effectiveness estimates. Results can be found in section 5.3 of the external assessment report and this is discussed in the updated guidance document in sections 3.6, 3.7 and 3.13. The choice of antiplatelet was based on existing guidance, including the updated National Stroke Guidelines which as noted recommends the use of ticagrelor.
36	BIASP	6.5	Needs updating with THALES trial and new national stroke guideline	Thank you for your comments which the committee considered. The EAG did an alternative network meta-analysis for the second committee meeting, which included the THALES trial. The EAG also did a further analysis in the addendum to reflect changes to care in line with the National Stroke Clinical Guideline update 2023. These analyses were discussed by the committee in sections 3.7 and 3.10 of the updated guidance.
37	BIASP	6.1	We are concerned that the test will not be widely available and may discourage clinicians from prescribing clopidogrel. If there is a genetic test to inform prescribing of a specific drug, and that	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			test is not obtainable or doesn't fit with the workflow for the service, clinicians may choose another option. It might lead to people not using clopidogrel or not commencing clopidogrel instead of aspirin for long term secondary prevention until the clopidogrel genotype test result is available.	The EAG's model included starting initial clopidogrel treatment and changing to an alternative antiplatelet treatment later if genotype testing indicated a loss-of-function allele was present. The committee agreed that this was appropriate, and that starting antiplatelet treatment should not be delayed while waiting for test results. The committee noted that this guidance does not replace any existing guidance on use of antiplatelet therapy if genotype testing is not available (see section 3.20 of the updated guidance). An information box has also been added below the recommendations in the updated guidance. This 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.
38	NHS England	Clinical benefit of *CYP2C19* testing – 3.6, 3.7	National clinical experts state dipyridamole is rarely used as an alternative. As noted, clinical outcomes are based on use of medications not in current first-line treatment pathway as no data is available on use of aspirin and dipyridamole in patients with these genetic variants. As noted, in 3.7, the current alternative antiplatelet recommended in the recently published National Clinical Guidelines for Stroke (www.strokeguidelines.org) is ticagrelor; this drug does not currently have marketing authorisation for use in TIA/minor stroke in this country.	Thank you for your comments which the committee considered. The EAG noted that clinical experts had advised that in current practice dipyridamole plus aspirin was the most likely alternative antiplatelet that would be used in the NHS. A stakeholder response to this consultation (comment 41) also described that aspirin and dipyridamole are considered in people who are unable to tolerate or in those who we think treatment has failed. The EAG also modelled alternative antiplatelet treatments (ticagrelor plus aspirin, or low dose aspirin monotherapy) in scenario analyses. To derive hazard ratios for stroke in people with loss-of-function alleles (relative to no loss-of-function) treated with clopidogrel, the EAG used the random effects meta-analysis (objective 3, figure 14 in the external assessment

Comment number	Name and organisation	Section number	Comment	NICE Response
				report).
39	NHS England	General comments	There are some concerns about the assumptions made on clinical practice currently and likely next steps following *CYP2C19* testing – national clinical experts have noted they have not been directly consulted and that there was no representation from the Integrated Stroke Delivery Networks. Many assumptions are felt to be inaccurate. Overall review of clinical guidance may be required alongside to ensure the use of genomic testing aligns with current clinical practice and relevant guidelines nationally/locally. Any recommendations for genetic testing should be aligned with current practice/treatment, taking account of both efficacy and potential harms.	Thank you for your comments which the committee considered. The EAG explained that it had provided scenario analyses that varied the modelled care pathway. These included which alternative antiplatelet to clopidogrel is used and when antiplatelet treatment is initiated. An addendum provided by the EAG included scenario analyses that varied parameters including the time to testing and antiplatelet treatment used. This was considered by the committee at the second committee meeting. Model outputs were robust, in terms of cost effectiveness, to these variations. These considerations are in section 3.13 of the updated guidance.
40	NHS England	General comments	If clinical teams decided to move towards an alternative antiplatelet, there has within this guidance been no assessment of the cost implications for this transition. These could be significant and with a population of 100,000 patients per annum potentially being prescribed an alternative antiplatelet to clopidogrel in the absence of rapidly accessible, timely genetic testing, this may make this guideline no longer value for money to the NHS.	Thank you for your comments which the committee considered. For clarification, an information box has been added below the recommendations in the updated guidance. This 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.
41	Web Comment		We are aware of the emerging role of ticagrelor in acute stroke and there may be a role in people with *CYP2C19* polymorphism but until a validated, simple, point-of-care genetic test becomes available, we don't think there is a strong case for us to change local practice in a big way. A colleague in the East Midlands has a major interest and published in this area (https://www.ahajournals.org/doi/full/10.1161/SVIN.122.000576;	Thank you for your comments which the committee 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

Comment number	Name and organisation	Section number	Comment	NICE Response
			https://www.rcpjournals.org/content/clinmedicine/22/5/449/tab-article-info) so we have basis to support our rationale. We use clopidogrel for patients with stroke and TIA but consider aspirin and dipyridamole in people who are unable to tolerate or in those who we think treatment has failed. Ticagrelor is potent but there are concerns regarding bleeding and long-term data is sparse. We think that if treatment was still to be considered, it would be in a very small group and agreed in an MDT. Last but not least, Ticagrelor is expensive and we are not aware of it coming off patent for sometime	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. However, the committee also stated that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are described in section 3.16 of the updated guidance.
42	ICSWP	1.1	The ICSWP was not convinced that the full implications of a blanket recommendation for genotype testing prior to any clopidogrel use had been fully considered by the committee. The consensus of clinical experts on the ICSWP was that, in the absence of a practically implementable and immediate genotype test in emergency situations, most centres and clinicians seeing TIA/minor stroke patients would resort to the most practical alternative – most likely to be the combination of Ticagrelor with Aspirin as used in the THALES trial (Johnston et al, 2020) and as recommended in the recent 2023 National Clinical Guideline for Stroke. Thus the committee's recommendation of blanket testing for all patients prior to clopidogrel use may in reality have the unintended consequence of effectively eliminating the use of clopidogrel in emergency/urgent clinical situations and its replacement with a far more costly alternative. This consideration appears to be lacking from the health economic analysis in the External Assessment report, and left the ICSWP with the impression that the committee had considered the evidence in isolation from the clinical context in which their guidance would in fact be implemented.	Thank you for your comments which the committee considered. For clarification, an information box has been added below the recommendations in the updated guidance. This 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. This guidance is not intended to affect treatment with clopidogrel that was started in the NHS before this guidance was published. People already having clopidogrel should continue until they and their NHS clinician consider it appropriate to stop. The guidance recommends testing only for people just after they have had a stroke or TIA. This is because the risk of another event is higher at this time and therefore so is the potential benefit of testing. But, as risk of recurrent stroke or TIA reduces over time, so does the benefit of testing. For this reason, retrospective testing for people already taking clopidogrel was outside of the

Comment number	Name and organisation	Section number	Comment	NICE Response
			Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y; THALES Investigators. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. N Engl J Med. 2020 Jul 16;383(3):207-217. doi: 10.1056/NEJMoa1916870. PMID: 32668111.	scope of this assessment. The EAG did an alternative network meta-analysis for the second committee meeting, which included the THALES trial (see section 4.1 in the addendum). The EAG also did a further analysis in the addendum to reflect changes to care in line with the National Stroke Clinical Guideline update 2023. The EAG also added a scenario in which everyone in the comparator arm for TIA or minor stroke received ticagrelor rather than clopidogrel. In the testing arm, people without loss-of-function alleles had clopidogrel and people with loss-of function alleles kept being treated with ticagrelor. In this scenario no testing was dominated when using the original network meta-analysis and either dominated or had a very high ICER when using the alternative network meta-analysis (see section 5.2.4, table 17 in the addendum). That is, in a scenario where, in the absence of testing, everyone was treated with ticagrelor it would still be cost effective to adopt testing to identify people who could be treated with clopidogrel.
43	UK Clinical Pharmacy Association (UKCPA)	3.7	It is important to recognise the limitations in evidence supporting the effects of changing from clopidogrel to one of the alternatives used in the UK, and the outcomes of any such change in practice should be monitored, both from clinical efficacy and adverse events standpoints (e.g. increased risk of bleeding with ticagrelor)	Thank you for your comments which the committee considered. The EAG did an alternative network meta-analysis for the second committee meeting, which included the THALES trial (see section 4.1 in the addendum). The EAG also did a further analysis in the addendum to reflect changes to care in line with the National Stroke Clinical Guideline update 2023. The EAG also added a scenario in which everyone in the comparator arm for TIA or minor stroke received

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				ticagrelor rather than clopidogrel. In the testing arm, people without loss-of-function alleles had clopidogrel and people with loss-of function alleles kept being treated with ticagrelor. In this scenario no testing was dominated when using the original network meta-analysis and either dominated or had a very high ICER when using the alternative network meta-analysis (see section 5.2.4, table 17 in the addendum). That is, in a scenario where, in the absence of testing, everyone was treated with ticagrelor it would still be cost effective to adopt testing to identify people who could be treated with clopidogrel.

THEME: Timing and uptake of genetic testing and treatment

Comment number	Name and organisation	Section number	Comment	NICE Response
44	NHS England	Less common loss-of-function alleles – 3.8 Laboratory testing versus point-of-care testing – 3.13	Recommending clinicians wait for test results before starting clopidogrel when indicated to be started within 24-48 hours would be against current empirical evidence and national clinical guidance, and risks putting patients at much higher risk of recurrence of stroke in the high-risk period post-index event.	Thank you for your comments which the committee considered. The draft guidance did not suggest that treatment should be delayed until test results were available. For clarification, an information box has been added below the recommendations in the updated guidance. This 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

Comment number	Name and organisation	Section number	Comment	NICE Response
				delayed while waiting for test results. The EAG's model included starting initial clopidogrel treatment and changing to an alternative antiplatelet treatment later if genotype testing indicated a loss-of-function allele was present. The committee agreed that this was appropriate, and that starting antiplatelet treatment should not be delayed while waiting for test results. These considerations are in section 3.20 of the updated guidance.
45	NHS England	Clinical need and practice – point 2.2	There are several statements regarding current practice and acute stroke management that are not universally representative of practice in the NHS in England e.g. most stroke units start clopidogrel within 24-48 hours of the acute stroke event, and almost always at the point of discharge, which is usually before 2 weeks.	Thank you for your comments which the committee considered. In the EAGs model, the TIA/minor stroke population is assumed to start clopidogrel within 24 hours. For the non-minor stroke population, clopidogrel was assumed to be started 2 weeks after a stroke. The EAG ran a scenario analysis which explored the impact of starting clopidogrel within 24 hours in the non-minor stroke group which had very little impact on cost effectiveness results. Committee consideration of these results are described in section 3.13 of the updated guidance.
46	Genomadix	3.6 (Clinical effectiveness) & 1 (Recommendation)	**Pathway for TIA and minor stroke: patient safety concerns with laboratory testing delays** The laboratory hubs stated that the turnaround time for test results ranged from 24-72 hours to as much as 2 weeks. Laboratories also stated that investment and resources would be required to allow for adoption and scale of undertaking these tests. The point-of-care test delivers results within one hour. The treatment pathway for TIA/minor stroke recommends that clopidogrel is given within the first 24 hours. The committee	Thank you for your comments which the committee considered. The EAG's model included starting initial clopidogrel treatment and changing to an alternative antiplatelet treatment later if genotype testing indicated a loss-of-function allele was present. The committee agreed that this was appropriate, and that starting antiplatelet treatment should not be delayed while waiting for test results. These considerations are in section 3.20 of the updated guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
			discussed that in practice, while awaiting test results, patients would be started on clopidogrel then switched to dipyridamole if necessary, when test results came back. In the comments section of the committee report, it is stated that the committee discussed that this could mean "short period of inappropriate treatment, with increased event rates." This puts this particular group of patients at risk, if laboratory tests are unlikely to deliver a result in a timely manner. This was further demonstrated in Yuesong et al "Time course for benefit and risk with ticagrelor and aspirin in individuals with acute ischemic stroke or transient ischemic attach who carry *CYP2C19* loss-of-function alleles. A secondary analysis of the CHANCE-2 RCT". JAMA Neurol. 2022;79(8):739-745. doi:10.1001/jamaneurol.2022.1457. In this analysis, the data show that the majority of the benefit from *CYP2C19*-guided therapy occurs in the first week after symptom onset. The recently updated UK Stroke Organization updated recommendation, includes ticagrelor as an alternate to clopidogrel, and discussed the possibility of clopidogrel resistance. Note also that recommendation highlights that for minor stroke and TIA, the greatest risk of a secondary event is in the first few days after the primary event. As such, POCT would be preferable in minor stroke/TIA patients where laboratories are unable to provide results in a timely manner, preferably within 24 hours or less of symptom onset.	The EAG said that the economic model took into account the difference in time to results between point-of-care tests and laboratory test results. It also included the increased risk of event for minor stroke and TIA patients in the short-term (90 days post minor stroke or TIA). 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. However, the committee also stated that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are described in section 3.16 of the updated guidance
47	Genomadix	3.6 (Clinical effectiveness) & 1 (Recommendati	**Pathway for TIA and minor stroke: patient safety concerns with laboratory testing delays (additional reference provided)**	Thank you for your comments which the committee considered. Please see response to comment 46.

Comment number	Name and organisation	Section number	Comment	NICE Response
		on)	An analysis of the time course of recurrent strokes in the POINT trial, a large, randomized controlled trial comparing aspirin plus clopidogrel to aspirin alone. The benefit of adding clopidogrel was seen in a reduction of adverse events (recurrent strokes, heart attacks, or death due to a thrombotic event) within the first week. The study showed that the highest rate of recurrence was seen at 12 hours after symptom onset. By hour 54 (2.25 days) after symptom onset, the rate of recurrent stroke is lower but still significant. The benefit of adding clopidogrel to aspirin was seen only in the first week—after that, the benefit of reduced strokes/heart attacks/death was offset by the risk of major bleeds. Given the noted time delays for laboratory tests, this further supports that POCT would be preferable in minor stroke/TIA patients where laboratories are unable to provide results in a timely manner, i.e. within 24 hours or less of symptom onset. REF: S. Claiborne Johnston et al. "Time Course for Benefit and Risk of Clopidogrel and Aspirin After Acute Transient Ischemic Attack and Minor Ischemic Stroke. A Secondary Analysis from the POINT Randomized Trial." Circulation AHN: August 20, 2019; Vol 140, Issue 8	
48	BIASP	6.2	There may be delays in initiating definitive secondary prevention treatment prior to discharge resulting in increased follow-up/workload for secondary care. (i.e.. Coordinating test results and switching in the community). The current guidelines suggesting switch on discharge were formulated in part to help this issue and to reduce risk of gaps in treatment.	Thank you for your comments which the committee considered. The EAG provided a scenario analysis where the availability of laboratory test results was delayed from 1 week to 4 weeks. This resulted in a small reduction in net monetary benefit (NMB) for lab-based testing (from £1,781 to £1,733). Also in the updated base case, the model included the cost of a GP visit for switching treatment due to receiving delayed test results or discontinuing a treatment. The EAG did a further scenario analysis based on the findings of a recent

Comment number	Name and organisation	Section number	Comment	NICE Response
				study by Swen et al. 2023, in which only 69.9% of patients switch treatment following the point-of-care test results. Full results are presented in section 5.2, tables 11 and 12 in the addendum).
49	ICSWP	1.1	ICSWP members were not reassured that the committee had given sufficient consideration to the real world circumstances under which clopidogrel would be prescribed. It is frequently given in the emergency/urgent situation including the diagnosis of TIA or minor stroke in, for example, an emergency department where the practicalities of the first use of point-of-care genotype testing would be a considerable obstacle to proper implementation. Clearly in an emergency situation waiting for laboratory-based genotype testing is out of the question, but these aspects of the practical clinical use of clopidogrel do not appear to have been considered by the committee.	Thank you for your comments which the committee considered. The EAG said that the model accounts for this for the laboratory-test in the TIA/minor stroke population where all patients are initially prescribed clopidogrel and then switched to an alternative treatment when laboratory-test results become available if they have loss of function alleles. Those with loss of function alleles have a heightened stroke risk during the period they are on clopidogrel before switching to alternative treatment. The draft guidance does not recommend that treatment should be delayed while waiting for test results. For clarification, an information box has been added below the recommendations in the updated guidance. This 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. The EAG also provided a scenario for both populations where not all patients will receive the alternative treatment (reduced uptake of alternative treatment). In this scenario 69.9% of patients switched treatment, based on the findings of a recent study by Swen et al. (2023). The EAG also commented that the most recent annual report from the Sentinel Stroke National Audit Programme (SSNAP) provides modelled estimates of

Comment number	Name and organisation	Section number	Comment	NICE Response
				length of stay by modified Rankin scale (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) The EAG considered that there may be barriers to implementing the point-of-care tests, but if implemented, then point-of-care test results should be available within 24 hours. Based on the SSNAP length-of-stay figures, on average patients should be able to receive their point-of-care test result prior to discharge, although there may be some TIA patients who are discharged sooner. For the laboratory-based tests, all TIA/minor stroke patients are likely to be discharged prior to receiving the lab-test result, as assumed in the EAG model. Most of the non-minor stroke will be discharged after 7 days when lab-test results are available. In the external assessment report the EAG conducted a scenario in which all non-minor stroke patients initiated clopidogrel immediately (Scenario 7), and required switching to alternative treatment at a later time when lab-results are available. This resulted in only a very small decrease in net monetary benefit in the non-minor stroke population. The committee noted that the tests were still cost effective

Comment number	Name and organisation	Section number	Comment	NICE Response
				when the timing of treatment was varied (see section 3.13 of the updated guidance).
50	ICSWP	3.1	Various factors related to consent to testing are noted. It is also noted that location could impact on uptake rates (e.g. if post-discharge, the patient is unable to drive to the location of testing). However, differing uptake rates for the testing do not seem to have been accounted for in the modelling. As a result the modelling may be overestimating the cost savings and QALY gains at a population level, especially if uptake were associated with risk status.	Thank you for your comments which the committee considered. The EAG model includes a scenario where only a proportion of patients receive an alternative antiplatelet treatment, which could be for a variety of reasons including low uptake of testing. In this scenario 69.9% of patients switched treatment, based on the findings of a recent study by Swen et al. 2023. In response to stakeholder comments, the EAG also added a threshold analysis (Scenario 16) to further explore the impact of low uptake of alternative treatments. This scenario estimated the level of adherence to the test results that was needed in order for testing to be cost effective. In the non-minor stroke population, testing was cost effective when adherence was below around 49%. In the minor stroke/TIA population testing was cost effective when adherence was below 7% to 14% depending on the method of testing. Full results of this threshold analysis are in section 5.2.8 of the addendum. The EAG commented that it did not model a relationship between uptake of testing and risk status, as there was no evidence on which to base this.
51	Inagene Diagnostics	2.11	The company states that the test takes 1 hour to run for each cartridge. It might be helpful to have a range of times that account for different conditions (i.e., multiple tests at once, time to troubleshoot common errors). We don't just want idealized	Thank you for your comments which the committee considered. In the external assessment report, the EAG identified 13 studies that reported time to results for the point-of-care tests. These ranged from around 1 to 2 hours and so in

Comment number	Name and organisation	Section number	Comment	NICE Response
			conditions because this doesn't necessarily reflect real-world conditions.	the economic model, the EAG assumed that there would be no delay (results available within 24 hours) in patients receiving targeted therapy for the point-of-care test strategy (see sections 4.6.1 and 5.2.5 of the external assessment report).

THEME: Point-of-care tests

Comment number	Name and organisation	Section number	Comment	NICE Response
52	NHS England	Less common loss-of-function alleles – 3.8 Laboratory testing versus point-of-care testing – 3.13	We acknowledge the improved accuracy and interpretation associated with laboratory testing, in comparison to point of care testing (POCT) which will require development and significant education and training, but it will be challenging for laboratory testing results to be immediately available for the patients starting clopidogrel within 24-48 hours. As the model and ultimate recommendation was one against the other, it is unclear how this subset of patients should be managed within proposed recommendations. It is important to consider POCT in context of sub-pathways (where short turnaround time is required) and review whether a mixed model of POCT and laboratory testing would be required with the POCT delivery being linked to the genomic laboratories for quality purposes and to ensure that the less common loss of function alleles are correctly interpreted and for example, if confirmatory laboratory testing would be expected after POCT, etc.	Thank you for your comments which the committee considered. The EAG's model included starting initial clopidogrel treatment and changing to an alternative antiplatelet treatment later if genotype testing indicated a loss-of-function allele was present. In the base case analysis, the EAG's cost effectiveness estimates are based on the assumption that laboratory-based test results are available after 1 week. This was extended to 4 weeks in a scenario analysis, resulting in only a very small decrease in net monetary benefit. The committee agreed that this was appropriate, and that starting antiplatelet treatment should not be delayed while waiting for test results. For clarification, an information box has now been added below the recommendations in the updated guidance. This states that this guidance does not replace existing guidance on the use of antiplatelet therapy when genotype testing is not available. Starting

Comment number	Name and organisation	Section number	Comment	NICE Response
				antiplatelet treatment should not be delayed while waiting for test results. The committee stated a preference for laboratory-based testing to be adopted 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. However, the committee also stated that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in section 3.16 of the updated guidance.
53	NHS England	Differences between point-of-care tests – 3.12	Ideally the recommendation for POCT devices should be generic, allowing for development of systems to address market need (such as increased relevant variants that can be tested). In addition, as devices change, future iterations will require reviews to redetermine/confirm accuracy and historic data from previous versions may not be applicable. Future recommendations and a device agnostic approach may be preferable alongside clear minimum requirements for suitable devices that manufacturers must actively demonstrate before use. Recommendations for implementation may require further testing on accuracy and performance for any named devices, based on pre-determined parameters.	Thank you for your comments which the committee considered. Although the assessment did not assess the point-of-care tests together as a generic class, the committee noted that evidence included in the external assessment report provided an indication of test performance (accuracy and failure rate) and costs, at which point-of-care tests are considered to be cost effective. This provides an indication of the minimum requirements that new technologies would need to meet.
54	UCLH/UCL Clinical Pharmacology and General	General Comments	4.***CYP2C19 genotype tests other than Genomadix Cube and GeneDriver.*** *CYP2C19* genotype tests from other manufacturers were not assessed in the review. It is not made	Thank you for your comments which the committee considered. Following the scoping phase of the assessment, including a scoping workshop with stakeholders, only the

Comment number	Name and organisation	Section number	Comment	NICE Response
	Medicine Firm		clear why tests manufactured by other companies were not in scope. This needs an explanation in the interests of transparency.	Genomadix Cube CYP2C19 system and the Genedrive CYP2C19 ID Kit were identified as being (or soon to be) available and licensed for use in the UK. The Genedrive CYP2C19 ID kit received its UKCA mark in September 2023 before the second committee meeting. Laboratory-based testing was considered as a group of tests rather than individual laboratory-based tests being assessed. As outlined in the final scope, there are several technologies already in place in diagnostic genetic laboratories that could be used to implement this testing into routine service. These include both targeted variant detection and DNA sequencing-based approaches. The EAG said that there was too much heterogeneity in methods, costs, and capacity between regions and testing centres to evaluate each lab-test independently. It aimed to model the result of the 'typical lab test' in England and Wales, but noted there was uncertainty in these estimates.
55	Genedrive		Genedrive anticipates UKCA marking in September with final product performance data submitted at this point and we request that this is scheduled for consideration and inclusion prior to finalisation of the report. Failure to do so would make the NICE report outdated at the time of release.	Thank you for your comments which the committee considered.
56	Genedrive	1.3 and 1.4	Can points 1.3 and 1.4 be combined into 1 point to state something along the lines ‘Recommend the Genedrive CYP2C19 ID Kit and further evidence will be required.’ Further evidence is scheduled to be provided to NICE prior to final publication, with a view to updating this statement prior to final publication in October. As per plan and timelines provided to NICE on 05 May 2023.	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
57	Genedrive	1.3	At the time the recommendation is due to be published the test will be UKCA approved, therefore this statement will be considered as not appropriate/not helpful.	Thank you for your comments which the committee considered.
58	Genedrive	1.1	In the report the POC tests are scrutinised on an individual product basis, whereas 'lab-based testing' is a broad term used in the report for any product, regardless of each test's accuracy, test fail rate or regulatory status. Why is this?	Thank you for your comments which the committee considered. As outlined in the final scope, there are several technologies already in place in diagnostic genetic laboratories that could be used to implement this testing into routine service. The availability of specific genomic testing platforms available at a local level would also impact on what approach could be used, which can differ between the NHS genomic laboratory hub (GLH) network. The EAG said that there was too much heterogeneity in methods, costs, and capacity between regions and testing centres to evaluate each lab-test independently. It aimed to model the result of the 'typical lab test' in England and Wales, but noted there was uncertainty in these estimates. The committee noted the differences between the point of care tests assessed (described in section 3.15 of the updated guidance) and considered that it was appropriate to consider each separately.
59	Genedrive	Attachment 1 Introduction	**Attachment 1 Introduction** **Please accept the comments below as commercial in confidence and redact in any public reporting.** [redacted]	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			[redacted]	

Comment number	Name and organisation	Section number	Comment	NICE Response
			[redacted]	
60	Genedrive	Attachment 2 Final Specifications for Genedrive® CYP2C19 ID	[redacted]	Thank you for your comments which the committee considered.

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			[redacted]	
61		3 Genedrive CYP2C19 ID Kit performance	3 Genedrive CYP2C19 ID Kit performance Commercial in confidence The Genedrive CYP2C19 ID Kit performs automated detection of *CYP2C19* *1, *2, *3, *4, *8, *17 & *35 alleles, using one buccal cheek swab. The test is performed using ambient stable reagents provided and completes in approximately 1 hour on the associated instrument, the Genedrive System. [redacted]	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			[redacted]	

Comment number	Name and organisation	Section number	Comment	NICE Response
			[redacted]	

Comment number	Name and organisation	Section number	Comment	NICE Response
			[redacted]	
62	UK Clinical Pharmacy Association (UKCPA)	1.3	Genedrive CYP2C19 ID kit does not have regulatory approval. It is not clear who has approved the Genomadix device – is this the MHRA (Medical Devices), UKCA, CE authorisation or someone else? Understanding authorisation allows for reassurance of the level of scrutiny this device has been through.	Thank you for your comments which the committee considered. The company stated that its previous system (Spartan Cube CYP2C19 system) had a CE mark and that it is in the process of obtaining a UKCA mark.
63	UK Clinical Pharmacy Association (UKCPA))	2.10	We are concerned that the reagents need to be stored at -15 to -80°C; there is a 24h gap where the company say the DNA remains stable enough in the buffer (though not seen the evidence for that). Would hospital wards/GPs/community pharmacists etc have room to install an appropriate freezer?	Thank you for your comments which the committee considered. 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. See section 3.15 of the updated guidance.
64	UK Clinical Pharmacy Association (UKCPA)	3.4	The suggestion that testing using the Genomadix system could be conducted at home warrants further investigation as it raises several questions: (1) the sample needs to be into the reagent kit within 24h; the latter needs to be kept at below -15°, giving a logistical requirement to get the sample back to a test site with reagent storage freezers promptly, and have this processed near-immediately	Thank you for your comments which the committee considered. The population in the scope of this assessment is people who have had non-cardioembolic ischaemic stroke or transient ischaemic attack for whom clopidogrel treatment is being considered. Therefore, the assessment was focused on testing and prescribing for those patients in secondary care and specialist acute

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			(2) Who would conduct tests at a patient's home? A district nurse? Community pharmacies may be better placed to do this if they have a Genomadix machine (and freezer) onsite, however there will need to be considerable work done to ensure appropriate training and workload capacity (3) Test results need to flow seamlessly into NHS systems and be accessible across primary and secondary care i.e. follow the patient. As the Genomadix system does not interface with NHS systems, how will this occur? Will manual entry be necessary, and will community based practitioners have access to this?	stroke units. Section 3.4 of the updated guidance now states that the committee noted that home testing may not be appropriate if the sample must be added within 24 hours, to reagents that are stored in a freezer.
65	UK Clinical Pharmacy Association (UKCPA)	5	We are concerned that the reagents need to be stored at -15 to -80°C; there is a 24h gap where the company say the DNA remains stable enough in the buffer, but would wards/GPs/community pharmacists etc have room to install an appropriate freezer and would this be approrpiate for home testing? An alternative is siting the test machine in the laboratory where freezers are available, but this provides additional work for the laboratory staff which may be hard to schedule; in this case full laboratory mass array-type genotyping, that could be run in batches, may be preferred when these wider issues are considered. We agree that investment in existing infrastructure should be prioritised, though if this causes undue delays in implementation then non-laboratory testing could be appropriate, potentially as a short-term measure.	Thank you for your comments which the committee considered.
66	UK Clinical Pharmacy Association (UKCPA)	3.13	Cost for genomadix quoted at £197, but this is the cost of the test kit only, and does not appear to include purchase of the machine, or QA reagents, additional facilites (i.e. freezer), or	Thank you for your comments which the committee considered. The EAG explained that these costs include the

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			staff time as examples.	purchase of the machine, reagents and staff time (see table 38 in section 5.2.5 of the external assessment report). It further noted that that the cost of the machine is divided by the number of tests over the lifetime of the machine to obtain a per test cost, and hence this cost is small. A limitation was that the estimate did not include freezer costs, but again this cost would be divided by the number of tests over the freezers lifetime, and so would form a very small proportion of the per test cost.
67	UK Clinical Pharmacy Association (UKCPA)	2.11	Objective 4 of the Expert review refers to 3 versions of the Genomadix test; which of these were used to generate the registration data/evidence, and does the current system match up with the sensitivity and specificity estimates quoted (100%/100%)?	Thank you for your comments which the committee considered. The company stated that Genomadix Inc. acquired Spartan Bioscience in September 2021. The Spartan Cube *CYP2C19* System (device) naming convention is being updated to the Genomadix Cube *CYP2C19* System. The EAG stated that data in the external assessment report pertained to the previous versions of the test, as this was the only data available.
68	UK Clinical Pharmacy Association (UKCPA)	2.12	The test result is reported with a diplotype displayed; is there any decision support for prescribing provided, beyond the international CPIC guidance which required interpretation of diplotype to phenotype? Should this be included in the product literature for the system? Arguably some guidance should be provided, but this may alter regulatory status of the product. No consideration for guidance in this context has been explicitly made.	Thank you for your comments which the committee considered. The Genedrive *CYP2C19* ID Kit test results are presented as diplotype identified and a description of the metaboliser status as outlined by the Clinical Pharmacogenetics Implementation Consortium (CPIC). The Genomadix Cube test results display the detected diplotype or an inconclusive result. The Instructions for use document includes information on the interpretation of results and background information on how the results relate to metaboliser status.

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				Both companies state that the necessary training materials are provided.
69	Inagene Diagnostics	3.11	This is because it is likely that multiple machines would be needed in each centre to handle the volume of testing or as backup in case of failure. Delays, costs associated with troubleshooting malfunctioning and maintenance activities should be included in estimates. Did the supplier provide figures related to this items to use as inputs?	Thank you for your comments which the committee considered. A full breakdown of the costs of the point-of-care tests is provided in table 38 in section 5.2.5 of the external assessment report. The committee concluded that there is considerable uncertainty about the cost per test. But it acknowledged that when compared with no testing, costs would have to be much higher (around £1,800 higher for the Genomadix Cube and £1,900 for Genedrive) than those used in the EAG's model for testing not to be cost effective.
70	Web Comment	General	POCT tests have resource implications for cost and administration and operational testing which will have additional pressures on the acute pathway which haven't been fully clarified in the evidence presented	Thank you for your comments which the committee considered. A full breakdown of the costs of the point-of-care tests is provided in table 38 in section 5.2.5 of the external assessment report. In addition to the device and reagent related costs this also included 10 minutes of a band 5 nurse's staff time to administer the test.
71	Web Comment	2.12	Whilst the guidance states that the Genomadix Cube system test report will display the detected diplotype, it does not comment on the useability of this type of report in clinical practice. There is a need to accurately translate a reported diplotype into a phenotype and then determine the appropriate action according to evidence based clinical practice guidance. In the absence of any UK guidance on diplotype to phenotype to clinical actions, this may be an additional limitation of a point of care system vs laboratory testing via NHS genomics labs who could adapt a report to include phenotype.	Thank you for your comments which the committee considered. The Genomadix Cube test results display the detected diplotype or an inconclusive result. The Instructions for use document includes information on the interpretation of results and background information on how the results relate to metaboliser status. The company states that the necessary training

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				materials are provided.

THEME: Economic model results

Comment number	Name and organisation	Section number	Comment	NICE Response
72	ICSWP	Full incremental analysis	In this section, the ICSWP's health economics expert noted the statement that Genedrive dominated both laboratory-based testing and the Genomadix Cube, but if this is so, then why is lab-based testing selected as the first-line recommended strategy? Further, in the EAR report, all testing strategies dominate no testing (i.e. have lower costs and higher QALYs), but the cost savings and QALY gains are small in the context of the total values in the populations examined. The costs of the tests themselves largely drive the differences in total costs, and these are subject to significant estimation uncertainty against real world costs (see comments elsewhere). Such a situation can lead to erroneous interpretations of differences, something acknowledged by the committee when comparing the cost-effectiveness of the three testing strategies against each other. The interpretations are also at odds with the cost-effectiveness acceptability curves (pages 154-157 of EAR report) which seem to indicate that lab testing has a low probability of cost-effectiveness at usual willingness to pay thresholds.	Thank you for your comments which the committee considered. The committee stated a preference for laboratory-based tests over point-of-care tests. It noted that there was very little difference in the quality-adjusted life years (QALYs) generated in the EAG's model by the different methods of testing. The committee had previously concluded that tests that detected fewer loss-of-function alleles would likely disproportionately affect certain ethnic groups. While Genedrive detects more alleles than Genomadix, laboratory-based testing has the potential to detect an even broader range. Also, if needed, laboratory testing 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. These aspects are not included in the model, so are not reflected in model outputs (including the cost-effectiveness acceptability curves). These considerations are in section 3.16 of the updated

Comment number	Name and organisation	Section number	Comment	NICE Response
				guidance.
73	ICSWP	Health State costs	The ICSWP's health economics expert noted that this section in the overview document (and similarly described in the EAR report) suggests that only social care costs were allocated to people with no recurrent stroke. In the SSNAP economic report, which is the source document for health state costs, it is clear that ongoing NHS costs up to 5 years after stroke are significant (i.e. rehab does not happen in social care as appears to have been assumed) so it is unclear why such an assumption would be made to exclude NHS costs. Based on such an assumption, we could infer that in the treatment arms with a lower stroke recurrence rate (i.e. the genetic testing arms), health state costs would tend to be underestimated. It is noted that the cost-effectiveness is principally driven by estimates of the cost of recurrent stroke, so these would need to be reliable if there is to be confidence in the conclusions.	Thank you for your comments which the committee considered. The EAG clarified that in the model, all patients are assumed to have had an initial ischaemic stroke or TIA, and so the NHS costs to treat the index event would be the same for all patients, and so "cancel out". Therefore it only included costs subsequent to the initial event costs in the model. The EAG further explained that for patients with no recurrent stroke, the only additional costs would be those related to care subsequent to the initial treatment costs. The NHS costs from SSNAP include the costs for the initial event, and will also include costs for subsequent events. For this reason, the EAG considered that they will be a substantial over-estimate of the NHS costs a patient incurs that are subsequent to their initial event and prior to any further events (represented by the no recurrent stroke state in the model). The EAG acknowledged that the NHS costs for recurrent stroke state won't be zero, but said that they will be much closer to zero than the value reported in SSNAP. The EAG also considered that the social care costs from SSNAP will also be an over-estimate for the non-recurrent state in the model as they will include costs for subsequent events, which are not represented by the non-recurrent stroke health-state. However, it considered that the social-care costs following the index event should be included in the model, as these will be incurred subsequent to the index event. This is why the EAG included social care costs, but not the NHS costs

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				from SSNAP. For the other recurrent stroke states all costs would be incurred, and so the EAG included both NHS and social care costs. The EAG considered that including the social care costs (which is likely an over-estimate) and excluding the NHS costs for the no recurrent stroke state (which will be a small under-estimate) was a reasonable assumption to use in the base-case.

THEME: Evidence base

Comment number	Name and organisation	Section number	Comment	NICE Response
74	Intercollegiate Stroke Working Party (ICSWP)	1.1	Members of the Intercollegiate Stroke Working Party (ICSWP) were not reassured that all possible causes of apparent clopidogrel resistance had been considered by the committee – for example, non-compliance with prescribed medication. There appears to be an underlying assumption that any lack of efficacy of clopidogrel arises solely from the presence of the loss-of-function mutation, when other causes should be appropriately considered by clinicians.	Thank you for your comments which the committee considered. The EAG commented that whilst there are other causes of clopidogrel resistance these would not be identified via *CYP2C19* genotype testing. It further highlighted that non-compliance will be an issue in those with and without loss-of-function alleles and so will be captured for both groups in trials. The EAG also commented that inputs to the model come from sources that will include non-compliance and other issues whilst taking clopidogrel, and so this is captured in the model outputs. The impact of loss-of-function

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				alleles comes from studies that control for other differences between patient groups, and so represents purely the increased event rates as a result of a loss-of-function allele when taking clopidogrel.
75	UCLH/UCL Clinical Pharmacology and General Medicine Firm	General Comments	**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE** **DIAGNOSTICS ASSESSMENT PROGRAMME** **Draft guidance** **Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack** **Invitation for comments from registered stakeholders, healthcare professionals and public**. NICE has produced the following key draft recommendation: 'Offer laboratory-based clopidogrel genotype testing, or the Genomadix Cube point-of-care test if laboratory testing is not possible, to people who have had an ischaemic stroke or transient ischaemic attack if treatment with clopidogrel is being considered.' We question this recommendation on the basis that not all the relevant evidence has been considered, and that the clinical and cost-effective summaries are not a reasonable interpretation of the available evidence. On that basis we consider the recommendations are not a sound and suitable basis for guidance to the NHS. Here are 10 reasons.	Thank you for your comments which the committee considered. Responses to the individual points are provided in the following rows. The EAG provided responses to the points raised (described below), which were considered by committee alongside the comments. The committee ultimately concluded that the model results provided by the EAG, and how available data were used in the model, were suitable for decision-making. It did not therefore change its recommendation on the use of testing.
76	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**1.Evidence on other factors influencing clopidogrel metabolism**. *CYP2C19* genotype accounted for 12% of the variance in clopidogrel metabolism in a detailed study (Shuldiner et al., 2009), i.e., genotype does not equate to metaboliser phenotype. The drug undergoes both extracellular and intracellular metabolism, processes that involve several enzymes and transporter proteins. These include CYP1A2, CYP2B6, CYP2C9, CYP3A4/5, CES1, PON1, and ABCB1, which are coded for by genes with known (and potentially	The EAG noted that its review showed evidence of improved outcomes for patients with *CYP2C19* loss of function alleles treated with alternative antiplatelets in objective 2 (that is, studies that assessed whether people who have loss of function alleles have a reduced risk of secondary vascular occlusive events if treated with an alternative antiplatelet drug to clopidogrel), and worse outcomes for patients with loss of function alleles

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			unknown) variants (Schilling et al., 2020). These considerations alone make it very unlikely that *CYP2C19* genotype testing by itself will be usefully predictive of adverse thrombotic outcomes or bleeding after during clopidogrel treatment. Evidence on other influences on clopidogrel metabolism, including variants in other genes, has not been considered in the development of this guidance.	when compared with those without (objective 3), despite all other potential causes of clopidogrel resistance, which are indirectly evaluated in the trials.
77	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**2.Evidence on the proportion of the population with the relevant genotype**. There seems to be no detailed estimate in the draft guidance of the proportion of the UK population who have the different *CYP2C19* genotypes (not alleles) associated with normal or fast, intermediate, and slow metaboliser status, but this is important – see point 5. The frequency of test-positive status and disease incidence/prevalence are required for the proper evaluation of the performance and cost-effectiveness of a diagnostic or predictive test in clinical practice. Using reported information on the frequency of *CYP2C19* genotypes in different ancestral groups from 2.2 million consumer genetic research participants (Ionova et al., 2020), we estimate that 2% of individuals of European ancestry, 12% of East or South Asian ancestry, and 3% of African descent individuals carry two copies of a reduced function *CYP2C19* allele and might in consequence be designated poor metabolisers. Taking this information together with ancestry data from the 2011 UK population census (as reported in the Our Future Health protocol – see reference list), and using the simplifying assumption that stroke risk does not differ substantially between people of different ancestry resident in the UK, we estimate that around 3% of the UK population overall could be categorised as poor metabolisers, or rather that 97% (the vast majority) of the UK population would be designated rapid, normal, or intermediate metabolisers of clopidogrel.	The EAG commented that it described in its report how estimates of the proportion with *CYP2C19* loss-of-function in an ischaemic stroke / TIA population were derived, in section 5.2.5 of the assesment report (subsection on Prevalence of *CYP2C19* loss-of-function). It said that it included people who are either intermediate or poor metabolisers in its definition of loss-of-function, and formed a weighted average based on the ethnicity distribution in a UK stroke population (which is different to that in the general population). The prevalence estimates by ethnicity come from the same source as mentioned in the comment, that is Ionova et al.(2020). Efficacy estimates of the different treatments were also derived from similar study populations, that is, people with 1 or 2 loss-of-function alleles.

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78	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**3. Evidence from previous evaluations in acute coronary syndrome**. Evidence on the effect of *CYP2C19* genotype and metaboliser status on thrombotic and bleeding outcomes in patients with acute coronary syndrome was not considered. If *CYP2C19* genotype status has a meaningful effect on these outcomes in patients prescribed clopidogrel for TIA or stroke, it should also be observed in the setting of acute coronary syndrome, but it was not. Holmes et al. previously conducted a systematic review and meta-analysis of the association of one or more *CYP2C19* *2–*8 alleles with cardiovascular disease (CVD) events and bleeding using *1 or *17 alleles as the reference group (Holmes et al., 2011). The analysis included 32 studies reporting 3545 CVD and 1413 bleeding events. Importantly, the analysis compared the findings from non-randomised 'treatment only' observational studies (where all participants receive clopidogrel and outcomes are assessed according to *CYP2C19* genotype) with the optimal study design which involves evaluation of 'genotype by treatment effect modification' in a randomised clinical trial (where the treatment effect is estimated from the randomised design and then formally compared between genotype categories by an interaction test). In the non-randomised treatment-only studies, they found nominal evidence of a slightly higher rate of CVD events (RR 1.18; 95% CI 1.09-1.28) but with strong evidence of small study bias (Harbord test P=0.001) with substantially larger effects reported in studies with fewer than 99 events (RR 1.83; 95% CI 1.50-2.23) than in studies with 200 or more events (RR 0.97; 95% CI 0.86-1.09). Moreover, in 'genotype by treatment effect modification' analyses using data from randomised clinical trials of clopidogrel there was no evidence of that *CYP2C19* genotype altered the treatment effect in terms of either CVD or bleeding events (Table 1). The same type of evidence is available in the setting of stroke and is completely consistent with the findings in acute	The EAG commented that whilst data from other conditions may provide some relevant information, it considered that the most reliable information to inform the research question is obtained from studies conducted in the population of interest (that is people who have had non-cardioembolic ischaemic stroke or transient ischaemic attack for whom clopidogrel treatment is being considered).

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			coronary syndrome. Indeed, the relevant papers were included as part of the evidence review, but the data was not analysed in this way. We provide additional details on this in point 10 and the Figure at the end of this document.	

	Cases, No/Total No.		
	Clopidogrel	**Placebo**	**RR (95% CI)**
Original RCT	2210/19 585	2593/ 19 625	0.84 (0.79-0.89)
Genetic sub study	>495/>5518	>602/ >5494	0.80 (0.72-0.89)
***2 or *3**	>135/>1511	>149/ >1520	0.87 (0.70-1.09)
***1 or *17**	>360/>4007	>453/ >3974	

Table 1. Data are from Figure 5 in Holmes et al., JAMA 2011 Analysis of *CYP2C19* Genotype on Composite Cardiovascular End Points and Major Bleeding in Randomized Trials Where Both Clopidogrel and Placebo Groups Were Genotyped: “Effect-

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			Modification" Analysis. Four clinical trials were evaluated: ACTIVE-A, CURE, CHARISMA and CLARITY-TIMI 28.	
79	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**Clinical and cost-effective summaries are not a reasonable interpretation of the available evidence** **5.Potentially misleading terminology.** The draft guidance refers to 'clopidogrel genotype'. Clopidogrel is a drug not a gene. Clinical and cost-effectiveness summaries refer to 'loss of function' variants and 'clopidogrel resistance'. However, even individuals with two copies of variants that reduce CYP2C19 activity generate the active form of clopidogrel and manifest an effect on platelet reactivity. For example, as shown by Hulot et al. 2006, or Shuldiner et al., 2009, and by studies summarised in Holmes et al., 2011, there is a marked overlap in achieved clopidogrel active metabolite concentration or measures of platelet reactivity among those with and without reduced function alleles (for a potential explanation see point 1). Therefore, the use of the terms 'loss of function' and 'clopidogrel resistance' might mislead clinicians or patients into thinking the effects are all or nothing.	The term 'clopidogrel genotyping' has been replaced with *CYP2C19* genotype testing in the updated guidance.
80	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**6. Relationship of *CYP2C19* genotype to metaboliser status.** The Technology Assessment Report supposes that it is possible to predict how a person will respond to clopidogrel based on genetic tests of the *CYP2C19* gene. It considers individuals with one or two copies of a reduced function *CYP2C19* allele to be equally impaired. However, clopidogrel-induced inhibition of platelet aggregation is not clearly separated between those with two normal genes and those with a single copy of a *CYP2C19* variant associated with reduced metabolism of clopidogrel (and who are 'intermediate metabolisers') as shown by Schilling et al., 2020, Hulot et al., 2006, and Shuldiner et al., 2009.	The EAG commented that an additional analysis stratifying by intermediate and poor metaboliser would have been beneficial, and was something it considered, but very few papers, with very few events presented data this way, so there were insufficient data to draw conclusions in these subgroups. The EAG also said that in practice, it is likely that patients would be treated the same whether they had 1 or 2 copies of a loss-of-function allele. Because the efficacy estimates of the different treatments were derived from a study population with 1 or 2 loss-of-

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				function alleles the inputs to the economic model represent an average of the costs and benefits over intermediate and poor metabolisers.
81	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**7. Potential for small study bias in 'treatment only' studies.** 'Treatment only studies' in the context of TIA and stroke were identified to address objective 3 'Do people who have LOF alleles associated with clopidogrel resistance have an increased risk of secondary vascular occlusive events when treated with clopidogrel compared to patients without LOF alleles who are treated with clopidogrel?'. Unlike Holmes et al. (see point 3) the Technology Assessment Report did not find formal evidence of small study bias among the included studies. However, the summary effect estimate reported in Figure 13 of the Technology Appraisal report for these studies (HR 1.72; 95% CI 1.48 – 2.03) is much closer to effect estimates found in small studies of <99 CVD events by Holmes et al. (RR 1.83; 95% CI 1.50-2.23) than in the large studies of >200 events (RR 0.97; 95% CI 0.86-1.09). The Forest plot in Figure 13 does not show the number of participants/CVD events but our rapid scan of these studies indicates the majority had fewer than 100 incident CVD events and several had fewer than 50. Many of the studies included in the Technology Assessment Report for this objective overlap with those included in a meta-analysis by Liu et al., 2020, in which the number of events per study was reported. The median number of events was 23 (range 6–121). Small study bias will be difficult to ascertain formally when there are no large studies for comparison, but this does not preclude its presence, and it clearly should be suspected from the previous work in acute coronary syndrome. The findings from this group of studies are also inconsistent with the findings from 'genotype by treatment effect modification' studies as we discuss in point	The EAG commented that studies included in the meta-analysis ranged in size from 42 to 2,933 participants, with number of events ranging from 6 to 229. It stated that there was no association between study size and effect estimates and that the fixed effect meta-analysis (which gives relatively more weight to larger studies) produced an identical summary estimate to the pooled results from random effects analysis. Despite most studies being relatively small, the EAG stated that it would expect to see some association between study size and effect estimate in this range if publication bias were present.

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			10.	
82	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**8. Metrics used to gauge the performance of *CYP2C19* carrier status as a predictive or diagnostic test.** Throughout the Technology Assessment Report, the performance of *CYP2C19* carrier status is reported in terms of relative risk measures (relative risk, hazard ratio or odds ratio). However, the performance of *CYP2C19* genotyping to guide treatment decisions requires metrics that have been established for evaluation of the performance of a predictive or diagnostic test. These are the detection and false positive rate and odds of being affected given a positive result (which is the positive predictive value in its odds form). Table 2 shows data extracted from Table 3 of the study of Wang et al, 2016., as reported in the meta-analysis of Liu et al., 2020 (both studies were included in the evidence review). The Wang study reports the outcome among participants treated with clopidogrel according to *CYP2C19* carrier status. We show it as an example here as it is one of the larger studies analysed in this way.	The EAG said that it used diagnostic accuracy measures in Objective 4 (see section 4.5 in the external assessment report), which evaluated the diagnostic performance of the tests (that is, the ability to distinguish between people with and people without a target condition). The EAG stated that it considered the question asked by objective 3 (to which this comment relates) to be aetiological rather than relating to diagnostic accuracy. However, these are just alternative approaches to looking at the same data and should lead to similar conclusions. For example: • odds of a subsequent stroke given a positive *CYP2C19* carrier status test = 80:774 = 1:10 • odds of a subsequent stroke given a negative *CYP2C19* carrier status test = 41:568 = 1:14 • Therefore diagnostic odds ratio (DOR) = 14/10 = 1.4 • (Or, more precisely, the DOR = (80*568)/(41*774) = 1.43) The EAG commented that the HR included in its report for this study (Wang 2016a) was 1.39, which is very similar to this. It further noted that the use of hazard ratios also has the advantage of allowing for varying follow up time across study arms.

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	Subsequent event	No subsequent event	Total
***CYP2C19* *2 or*3 (test positive)**	80	774	854
***CYP2C19* *1 (test positive)**	41	568	609
	121	1342	1463

Table 2. Subsequent events among participants treated with clopidogrel according to *CYP2C19* carrier status from Wang et al., 2016, as reported in the meta-analysis of Liu et al., 2020.

The odds ratio is (80/774) / (41/568) = 1.43

- The detection rate for *CYP2C19* carrier status as a predictive test is 80/121 = 66%
- The false positive rate of *CYP2C19* carrier status as a predictive test is 774/1342 = 58%
- The odds of a subsequent stroke regardless of *CYP2C19* carrier status is 121:1342 = 1:11
- The odds of a subsequent stroke given a positive *CYP2C19* carrier status test is 80:774 = 1:10

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			These are not the performance characteristics of a useful test.	
83	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**9. 'Genotype only studies' used to address objective 2**. Two studies whose findings are reported in Figures 7–11 were used to address objective 2: 'Do people who have loss of function (LOF) alleles associated with clopidogrel resistance have a reduced risk of secondary vascular occlusive events if treated with alternative interventions compared to treatment with clopidogrel?' Most of the information comes from the CHANCE-2 study, in which carriers of *CYP2C19* alleles associated with reduced function were randomised to receive ticagrelor or clopidogrel. Those randomised to ticagrelor were found to have a reduced rate of vascular events and a higher rate of bleeding than those randomised to clopidogrel. However, the inferences drawn from this study in the guideline are compromised for reasons of study design and external validity. The study design of CHANCE-2 precludes conclusions on whether the difference between treatment groups can be attributed to *CYP2C19* genotype since the treatment difference between the two agents was not assessed among individuals who do not carry *CYP2C19* reduced function alleles (i.e., this was not a 'genotype by treatment effect modification design'). Without this, it is impossible to differentiate two possibilities: (1) ticagrelor confers an advantage over clopidogrel in *CYP2C19* variant carriers and (2) ticagrelor is simply a more effective antiplatelet agent than clopidogrel regardless of *CYP2C19* genotype. In fact, the findings of Wang et al., 2019 (discussed in detail in point 10) confirm that ticagrelor is simply a more effective antiplatelet agent than clopidogrel regardless of *CYP2C19* genotype. The external validity of the CHANCE-2 study for the UK population is also questionable. CHANCE-2 was study 'among Chinese patients with minor ischemic stroke or TIA who were carriers of *CYP2C19* loss-of-function alleles.' The authors' own conclusion from this study was: 'Our results are not generalizable to non-	The EAG commented that it considered that the ideal study design to investigate the benefits of introducing genetic testing to identify *CYP2C19* loss-of-function alleles are RCTs that evaluate a "test and treat strategy", and this was evaluated in Objective 1 in the EAG's report. Objective 2 and 3, indirectly address the same aim. The EAG considered that if there is evidence showing: 1. Patients with loss-of-function alleles have worse outcomes than patients without them when treated with the standard regimen (objective 3); and 2. Patients with loss-of-function alleles have better outcomes if treated with an alternative antiplatelet regimen, then it can be concluded that testing and treating accordingly will result in better outcomes for patients with loss-of-function alleles than the standard regimen, even if the improved outcomes are due to the alternative regimen being more effective than the current standard including clopidogrel. The EAG further explained that it investigated both ethnicity and country of study as potential sources of heterogeneity for objective 3. It found no differences in impact of loss-of-function alleles on outcomes based on these variables (see table 11 of the EAG's report). There were insufficient data to stratify analyses for objective 2. The EAG further commented that the POINT study does not provide results according to loss-of-function status, and the proportion of patients who are poor or intermediate metabolisers is likely to be much lower compared with the CHANCE study. The EAG therefore expected that clinical outcomes that are affected by loss-

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			Han patients, because Han patients made up 98.0% of those enrolled.' Notably, the findings from CHANCE-1, also among Chinese patients were not reproduced in the POINT trial which had the same design but was conducted in 10 countries outside China (largely N. America and Europe).	of-function status may differ between the studies. There were also other differences between the studies including different regimens of dual antiplatelet therapy.

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84	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**10.Failure to analyse at least three relevant studies as genotype by treatment effect modification design studies**. At least three of the studies considered in the evidence review were designed and reported by their authors as 'genotype by treatment effect modification studies'. This is the optimal study design to address whether *CYP2C19* genotype affects the response to clopidogrel because the treatment effect is evaluated in the context of a randomised trial and effect modification by genotype can be evaluated using a test of genotype by treatment interaction. However, perhaps because of the way in which the objectives of the review were framed, none of the three studies was analysed as such. Two of the relevant studies are Wang et al., 2016 and Meschia et al., 2020, both of which addressed the question of treatment modification by genotype within a randomised controlled trial comparing the effect of clopidogrel plus aspirin vs clopidogrel alone in the prevention of subsequent events in patients presenting with a TIA or stroke. The third relevant study is that of Wang et al., 2019 which investigated whether *CYP2C19* carrier status modified the treatment effect in a randomised trial comparing ticagrelor plus aspirin vs clopidogrel plus aspirin. We have pasted figures from the relevant publications into Figure 1 and set them alongside the corresponding analyses in the setting of acute coronary syndrome from the systematic review and meta-analysis of Holmes et al., 2011. All four analyses are consistent in showing no treatment effect modification by *CYP2C19* genotype. Three of the four studies (Meschia et al., 2020 see their Figure 1; Wang et al., 2019 see their Figure 3 and Holmes et al., 2011 see their Figure 5) properly evaluated treatment modification by genotype using an interaction test. Wang et al., 2016 (see their Figure 1) reported p-values for treatment effects within genotype groups, which is an inappropriate analysis. However, scrutiny of the Forest plot in the paper indicates it is not materially different from the corresponding plots in the other	The EAG said that it considered the optimal study design to answer the research question is a test and treat design, as specified in objective 1 for its review. However, there were very few studies for this objective. The review included 5 studies that compared standard antiplatelet regimens (clopidogrel with or without aspirin) with alternative antiplatelet regimens (aspirin, ticagrelor plus aspirin, or trifusal) in loss-of-function allele carriers and non-carriers (Yi 2018, Wang 2016a, Chen 2019, Han 2017 and Meschia 2022). These were not analysed as genotype by treatment effect modification studies due to the way the objectives were framed, but all contributed data to both objectives 2 and 3. Only Meschia 2020 and Chen 2019 included results for formal interaction tests, so the EAG performed unadjusted interaction tests for ischaemic stroke in all for comparison. The EAG said that this analysis shows evidence for interaction in 1 study (Wang 2016). This is the study with the biggest patient sample and the highest number of events, showing a benefit for clopidogrel plus aspirin compared with aspirin monotherapy in non-carriers, but not in carriers. It also shows aspirin monotherapy confers a very similar effect in both carriers and non-carriers as expected.

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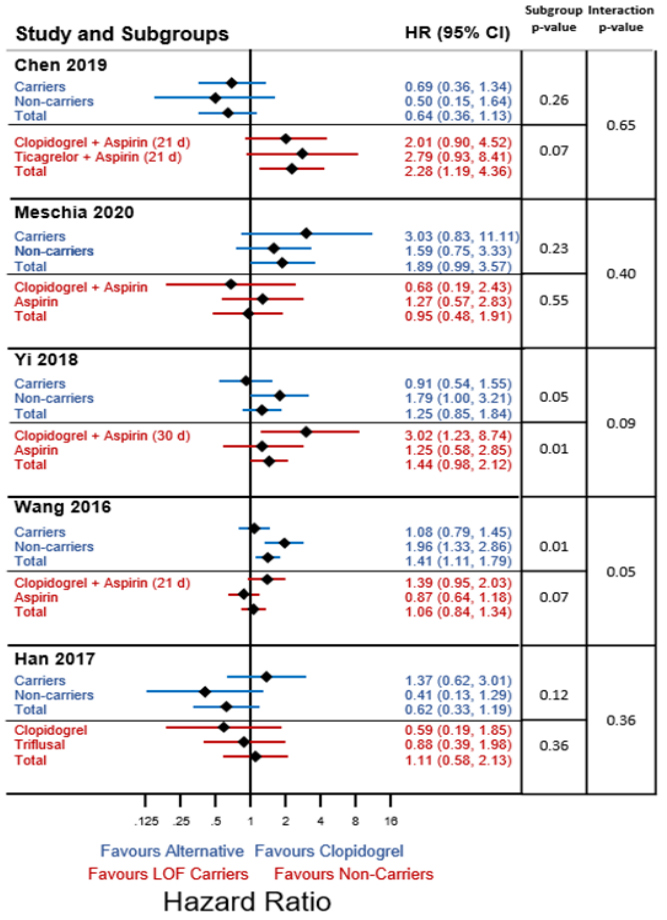
			three papers.	

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				The EAG further commented that Yi 2018 and Meschia 2020 did not find evidence for interaction, however it noted that both gave aspirin to the clopidogrel group for extended periods. In its review, the EAG found that when a loading dose of clopidogrel was used and when clopidogrel was given in combination with aspirin, the difference in effect between carriers and non-carriers decreased. Additionally, the authors in Meshia 2020 report their study is not powered to detect a difference in effect because of the low number of participants and the low rate of events. Han 2017 compared clopidogrel with triflusal and doesn't show evidence of a difference in effect between treatments. Chen 2019 did not find evidence for interaction, however, they emphasize clinical outcomes were not their primary outcome, and the study is not adequately powered to find a difference in effect between genotypes and treatments. Additionally, they found an unexpected difference in the effect of ticagrelor plus aspirin between carriers and non-carriers annulling the interaction effect and suggesting results should be interpreted with caution. The EAG said that authors found some evidence of improvement in outcomes in general (both for carriers and non-carriers individually and together) when comparing ticagrelor plus aspirin with clopidogrel plus aspirin (objective 2). The EAG found some evidence of increased risk of secondary occlusive events for loss-of-function carriers compared with non-carriers when treated with clopidogrel (objective 3). However, against what would be expected, the subgroup treated with ticagrelor behaved similarly, annulling any interaction effect.

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				In response to stakeholder comments the EAG also provided an alternative network meta-analysis to inform the economic model. The economic model uses relative effects for each treatment and loss-of-function status combinations relative to a reference, which the EAG took to be clopidogrel with no loss-of-function. This analysis includes the CHANCE, CHANCE-2, POINT (Meschia 2020), PRoFESS, PRINCE (Wang 2019), and THALES studies in a combined analysis. Results from this additional analysis were considered by the committee in its decision making. Further details on the methods and results are provided in the EAG's addendum.
85	UCLH/UCL Clinical		**Summary** In summary, we find no reason to recommend *CYP2C19* genetic	Thank you for your comments which the committee considered.

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	Pharmacology and General Medicine Firm		testing (whether laboratory-based or point of care) if treatment with clopidogrel is being considered for people who have had an ischaemic stroke or transient ischaemic attack, or for any other indication. [redacted] and [redacted] on behalf of the UCL Hospitals Clinical Pharmacology Firm. Declaration of interest [redacted] was a co-author of the paper by Holmes et al., cited here.	
86	UCLH/UCL Clinical Pharmacology and General Medicine Firm		**References** Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. *CYP2C19* genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA. 2011 Dec 28;306(24):2704-14. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, Aiach M, Lechat P, Gaussem P. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006 Oct 1;108(7):2244-7. 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. Clin Transl Sci. 2020 Nov;13(6):1298-1306. Liu G, Yang S, Chen S. The correlation between recurrent risk and *CYP2C19* gene polymorphisms in patients with ischemic stroke treated with clopidogrel for prevention. Medicine (Baltimore). 2020 Mar;99(11):e19143. Meschia JF, Walton RL, Farrugia LP, Ross OA, Elm JJ, Farrant M, Meurer WJ, Lindblad AS, Barsan W, Ching M, Gentile N, Ross M, Nahab F, Easton JD, Kim AS, Zurita KG, Cucchiara B,	Please see responses to comments 75 to 85 above. Please note that the figures in the original comment have been removed and replaced with links to the relevant journal articles.

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			Johnston SC. Efficacy of Clopidogrel for Prevention of Stroke Based on *CYP2C19* Allele Status in the POINT Trial. Stroke. 2020 Jul;51(7):2058-2065. doi: 10.1161/STROKEAHA.119.028713. Our Future Health. https://ourfuturehealth.org.uk/ (Accessed June 7th, 2023) Schilling U, Dingemanse J, Ufer M. Pharmacokinetics and Pharmacodynamics of Approved and Investigational P2Y12 Receptor Antagonists. Clin Pharmacokinet. 2020 May;59(5):545-566 Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009 Aug 26;302(8):849-57. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009 Aug 26;302(8):849-57. Wang Y, Chen W, Lin Y, Meng X, Chen G, Wang Z, Wu J, Wang D, Li J, Cao Y, Xu Y, Zhang G, Li X, Pan Y, Li H, Zhao X, Liu L, Lin J, Dong K, Jing J, Johnston SC, Wang D, Wang Y; PRINCE Protocol Steering Group. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. BMJ. 2019 Jun	

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			6;365:l2211. Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, Li H, Bath PM, Dong Q, Xu A, Jing J, Lin J, Niu S, Wang Y, Zhao X, Li Z, Jiang Y, Li W, Liu L, Xu J, Chang L, Wang L, Zhuang X, Zhao J, Feng Y, Man H, Li G, Wang B; CHANCE-2 Investigators. Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. N Engl J Med. 2021 Dec 30;385(27):2520-2530. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, Liu L, Wang D, Wang C, Meng X, Xu J, Wang Y; CHANCE investigators. Association Between *CYP2C19* Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. JAMA. 2016 Jul 5;316(1):70-8. (a) Wang et al. JAMA 2016, figure 1 (b) Meschia et al. Stroke 2020, figure 1 (c) Wang et al. BMJ 2019, figure 3 (d) Holmes et al. JAMA 2011, figure 5A **Figure.** Effect of *CYP2C19* carrier status on response to clopidogrel treatment in three randomised controlled trials in patients with stroke (a-c: Wang et al., JAMA 2016; Meschia et al., Stroke 2020; and Wang et al., 2019) and a meta-analysis of randomised controlled trials in the setting of acute coronary syndrome (d: Holmes et al., 2011)	
87	Inagene Diagnostics	3.6	The committee recalled that clinical experts had said during scoping that dipyridamole with aspirin was the most likely alternative antiplatelet that would be used in the NHS. But no data was found on the impact on people with loss-of-function alleles if treated with clopidogrel compared with dipyridamole plus aspirin.	Thank you for your comments which the committee considered.

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			It may be worth noting that CYP2C19 is not a recognized metabolic pathway of dipyridamole nor aspirin. This is a theoretical point, but still holds some relevance.	
88	Inagene Diagnostics	3.9 Web Comment	The Clinical Pharmacogenetics Implementation Consortium states that it is reasonable to extrapolate its recommendations to paediatric patients if needed (the guidance was also based on data from studies in adults). Experts also said that the benefits from successfully preventing further clotting events by prescribing appropriate antiplatelet therapy would likely be larger for children and young people because of the longer expected remaining lifetime. Additionally: "CYP2C9, 2C19, 2D6, 3A4, as well as most of the UGTs have negligible activity at birth and reach adult activity within a few weeks (e.g., 2D6) to several years (until post-puberty for 2C9) after birth, so genotyping neonates and toddlers may not be meaningful [122]." Source: Zhao J, Bian J, Zhao Y, et al. Pharmacogenetic Aspects of Drug Metabolizing Enzymes and Transporters in Pediatric Medicine: Study Progress, Clinical Practice and Future Perspectives. Paediatr Drugs. 2023;25(3):301-319. doi:10.1007/s40272-023-00560-3	Thank you for your comments which the committee considered.
89	UK Clinical Pharmacy Association (UKCPA)	4.1	There is a lack of evidence on the likely outcomes of a mass switch from clopidogrel to dipyridamole +/- aspirin or ticagrelor; clinical outcomes and adverse event (bleeding) incidence should be followed and testing/prescribing practice reviewed if safety signals suggest harm in excess of benefit. Outcome data on patients with loss-of-function alleles treated with dipyridamole and aspirin (or ticagrelor) should be included	Thank you for your comments which the committee considered. The committee's research considerations are discussed in section 3.21 of the updated guidance.

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			as a research recommendation in absence of data. We support the four areas of research recommended in the Expert Review: (1) Accuracy and technical performance (e.g., test failure rate, cost, time to perform the test) of Genedrive) (2)Test failure rate of Genomadix Cube in an NHS setting (3) Value of testing additional LOF alleles beyond *2 and *3 (4) Appropriateness of treatment dichotomy based on LOF alleles used in our appraisal compared to a more complex approach to tailored treatment	
90	Web Comment	General	The issue of genotype testing to identify potential reduced benefit of clopidogrel with AIS and TIA is clinically important but the current evidence for introduction of testing in the UK population wholescale has limitations. There is clear data to indicate testing in the Han Chinese population but cost benefit in our population less clear and warrants further research and health economic evaluation of Number needed to genotype to get benefit	Thank you for your comments which the committee considered. The committee noted the limitations of the available evidence, but said there was strong evidence that people with loss-of-function *CYP2C19* alleles had worse outcomes when taking clopidogrel than people without loss-of-function alleles. The committee understood that the prevalence of *CYP2C19* loss-of-function alleles differed between ethnic groups and noted that most of the evidence in the external assessment report was from studies in Chinese populations. The EAG did a subgroup analysis but noted no statistically significant differences in loss-of-function effect by ethnicity (see section 4.4.2 in the external assessment report).
91	Web Comment		We agree that there are patients who we think could be resistant to clopidogrel. However, the cause for resistance vary ranging from dietary factors and true resistance in a subgroup of people	Thank you for your comments which the committee considered The EAG noted that other potential causes of clopidogrel

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			could be identified by testing for the *CYP2C19* variation (https://www.ahajournals.org/doi/full/10.1161/SVIN.122.000576).	resistance are indirectly evaluated in the trials evaluated in its report, and used to inform cost effectiveness estimates.
92	Web Comment	3.3	My practice has done such pharmacogenomic testing in primary care for patients with depression and who are on antidepressants. We are in the process of writing this up as the original research was in 2019, just prior to COvid-19 and I've just reviewed the 4 year data.	Thank you for your comments which the committee considered.

THEME: Further implementation issues

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93	BIASP	8	Training and education tools would be useful.	Thank you for your comments which the committee considered.
94	BIASP	8	Area of consent for genetic testing needs expanding. Question regarding testing of family members in those found to have the gene will also be raised – recommendation needed.	Thank you for your comments which the committee considered. The committee noted that consent is an important consideration if introducing testing. A patient expert highlighted that people who have had a stroke often have severe cognitive impairment, may have difficulty with their language or speech (aphasia) or may be unconscious. They also said that some people or communities may be less likely to give consent for genetic tests. The committee also noted that acceptability and consent for genetic testing may differ according to religious or philosophical beliefs, and that people may also have concerns about data security and privacy. It is important to consider how the genetic data will be stored, protected, shared, and if necessary deleted. More detail can be found in the Royal College of Physicians' guidance on consent and confidentiality in

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				genomic medicine. These considerations are in section 3.1 of the updated guidance. Clinical experts highlighted that *CYP2C19* loss-of-function variants are common, and their presence would only impact on decisions about which drugs should be used. So, they do not have health implications for the person outside of the context of drugs like clopidogrel. But the committee acknowledged that the *CYP2C19* genotype can be relevant for drugs other than clopidogrel, such as some antidepressants. Experts also commented that consent requirements are similar to other medical tests. These considerations are in section 3.3 of the updated guidance.
95	NHS England	General Comments	As highlighted by labs and the EAG, there are multiple steps to implementation required and significant changes needed in infrastructure, as well as adaptation of clinical pathways and potentially new models of provision that will require quality assurance to be taken into account especially associated with the interpretation of less common alleles. This is not well reflected and needs careful consideration and coordination with wider guidelines and may prompt review of other guidance.	Thank you for your comments which the committee considered. Experts highlighted a shortage of clinical scientists, which would impact on the possibility of increasing laboratory testing capacity. The committee acknowledged that implementing testing for everyone who has a stroke or TIA could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for

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				earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee recalled that, compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added below the recommendations to highlight these implementation considerations (See 'What this means in practice').
96	NHS England	General Comments	It should also be noted that the guidance may have implications for heart attack patients, although most cardiologists have moved away from clopidogrel to an alternative.	Thank you for your comments which the committee considered.
97	NHS England	Recommendation 1.1	Whilst we acknowledge the importance of tailoring preventative measures in line with individual patients' genetic susceptibility, we are concerned that there are significant practical implications for clinical teams. The proposed guidance would require a change in practice for all stroke units as most do not currently do	Thank you for your comments which the committee considered. The committee acknowledged that there are barriers to implementing laboratory-based testing. It said that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it,

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			any genetic testing and this must be taken account of in terms of providing genetic testing in a managed and equitable manner. Further supporting work is needed if these recommendations were to be implemented, considering in more detail many of the points below.	then point-of-care tests could be used. These considerations are in section 3.16 of the updated guidance. Experts highlighted a shortage of clinical scientists, which would impact on the possibility of increasing laboratory testing capacity. The committee acknowledged that implementing testing for everyone who has a stroke or TIA could be done in a stepwise process. This would involve a gradual increase in numbers tested while capacity was established. The committee suggested that the NHS may need to identify subgroups of the overall population to start offering testing to initially. If a group was to be prioritised for earlier roll out of testing, there would need to be capacity to test everyone in this group. The committee recalled that, compared to no testing, *CYP2C19* testing after a non-minor stroke generated more net monetary benefit than testing after a minor stroke or TIA. Estimates provided by the NICE resource impact team indicate that the non-minor stroke population equates to around 35,900 people per year (rather than about 110,000 people who have any stroke or a TIA). The committee concluded that to facilitate implementation, testing could potentially be started in the smaller non-minor stroke population before being expanded to the minor stroke and TIA population. The committee also agreed that point-of-care testing should be considered as an alternative if laboratory-based testing is not feasible at this scale, or for use while capacity for laboratory-based testing is increased. These considerations are in section 3.19 of the updated guidance. An information box has also been added

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				below the recommendations to highlight these implementation considerations (see 'What this means in practice').
98	ICSWP	1.2	ICSWP members were struck by the impression that a blanket testing policy would render this second recommendation redundant. Why consider the background prevalence of the different genotypes when all patients are going to be tested in any event?	Thank you for your comments which the committee considered.
99	Inagene Diagnostics	1.2	To support implementation of the recommendations; Pre-emptive testing of high risk patient groups would reduce the risk of exclusion where there is variation between ethnic groups.	Thank you for your comments which the committee considered. Pre-emptive genetic testing is outside of the scope of this assessment.
100	Inagene Diagnostics	2.12	Has consideration been given to where and how the results of pharmacogenomic testing will be stored so they are readily accessible? The RCP and BPS report, "Personalised Prescribing: using pharmacogenomic information to improve patient outcomes" highlighted result and report storage and access as a barrier to implementing pharmacogenomic testing, and something to be considered. Laboratory testing could potentially overcome this issue more readily than point of care testing, since the GLH laboratories will have Laboratory IT systems linked to hospital patient records, enabling upload of reports to the electronic health records as part of the automated report issuing process. Uploading results / reports from a point of care device may not be so streamlined. and therefore laboratory testing may offer a further advantage in this respect.	Thank you for your comments which the committee considered. The committee concluded that laboratory-based testing was its preferred method. But the committee also acknowledged that there are barriers to implementing laboratory-based testing. If laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in section 3.16 of the updated guidance.
101	Inagene Diagnostics	2.15	Laboratory testing usually requires a blood sample.	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			Blood is usually required for more diagnostic genetic tests, but for simple genotyping technology such as MassArray, or even Sanger sequencing, a mouth swab will provide DNA of suitable quality. This may offer a simpler sampling solution for most patients.	
102	Inagene Diagnostics	3.1	Consent is an important consideration if introducing testing. A patient expert highlighted that people who have had a stroke often have severe cognitive impairment, may have difficulty with their language or speech (aphasia) or may be unconscious. Consideration could be given to using pre-emptive testing in high risk patients seen in primary care settings. Since pre-emptive testing doesn't require a high level of urgency, a multi-gene/drug panel could be used to help determine suitability of other potential therapies, helping to add additional value to the test. Of course, there will always be cases that cannot be pre-emptive, but it could reduce the burden of consent challenges (as mentioned) in the face of an acute event. Another consideration is the fact that those with baseline cognitive or learning disabilities might have difficulty understanding the intervention and providing informed consent whether pre-emptive or reactive pharmacogenomic testing is used. The advantage of pre-emptive testing is the fact that it would allow for the individual to discuss with family members or caretakers (or consult other resources) to better appreciate the nature of the test and what their consent entails. The urgency and subsequent duress of an acute event do not allow for this.	Thank you for your comments which the committee considered. Pre-emptive genetic testing is outside of the scope of this assessment. A patient expert highlighted that people who have had a stroke often have severe cognitive impairment, may have difficulty with their language or speech (aphasia) or may be unconscious. This raises issues with getting consent for testing. More detail on consent in this group can be found section 3.5.3 in the Royal College of Physicians' guidance on consent and confidentiality in genomic medicine. These considerations are described in section 3.1 of the updated guidance.
103	Web Comment	General	I believe there is a huge benefit in implementing genotyping for *CYP2C19* to identify if clopidogrel is suitable for patients after a ischaemic stroke or TIA.	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			The tests appear to be cost-effective, both for point-of-care and laboratory testing. Knowing the genotype will help personalise treatment and avoid administration of medications that will highly likely be ineffective, which for me, adds points to cost-effectiveness (less waste, more targeted). The way I see it, if this lowers adverse events such as further strokes, as well as decreases hospitalisation episodes, contributing to more savings. The testing is non-invasive, which is an advantage in itself. Sample collection is flexible and appears to be simple (cheek swabs only). Educating healthcare staff, I feel, should be included in this, even just to increase awareness and understanding of why this test is being done.	
104	Web Comment	3.1	If consent is done in a sensitive and informative way, in a way that patients can readily understand, then it can be done in various religious and minority ethnic groups, who are crucial for this genotypic testing. My practice (I am a GP) has done this testing in primary care in patients with depression and we have found it quite straightforward.	Thank you for your comments which the committee considered.
105	Web Comment	3.2	There is a role here therefore for primary care, to consent and review the treatment, as they would normally do post discharge of most newly developed chronic conditions.	Thank you for your comments which the committee considered.
106	Web Comment	3.4	Wholly agree, cheek swabs can be done in the GP surgery: GPs and wider team members like nurses or clinical pharmacists could do this. The latter would bring expertise in medicines management also.	Thank you for your comments which the committee considered.
107	UK Clinical Pharmacy	General	All comments are on behalf of UK Clinical Pharmacy Association:	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
	Association (UKCPA)		General comments: Please consider the comissioning pathway for this test. Will this test be added to the National Genomics Test Directory (for England)? Commissioning status should be made very clear, and if it is not centrally commissioned then there is a risk of introducing inequality/a 'postcode lottery'	This guidance is advisory and does not have a funding mandate. NHS England may decide to consider CYP2C19 genotype testing for inclusion in the National Genomics Test Directory.
108	UK Clinical Pharmacy Association (UKCPA)	3.1	Does consent include possibility of impact on family/cascade testing? Although this is unlikely to be needed in the acute phase of illness, if a patient's result shows loss of function, this should be communicated to their family to inform their personal decisions if they subsequently need to take clopidogrel. If a potentially affected family member is also on clopidogrel, should they be prioritised for testing (regardless of indication for the drug)?	Thank you for your comments which the committee considered. The committee noted that it is important to consider how the genetic data will be stored, protected, shared, and if necessary deleted. More detail can be found in the Royal College of Physicians' guidance on consent and confidentiality in genomic medicine.

Comment number	Name and organisation	Section number	Comment	NICE Response
109	UK Clinical Pharmacy Association (UKCPA)	3.3	There is no evidence of consideration of the ethical implications of having this information on file but prescribers/pharmacists being unaware, or not using it where it could impact other medicines (e.g. antidepressants, antifungals). Similarly, it is unclear where responsibility for communication of this result between healthcare settings would lie - including for alternative testing locations, such as community pharmacies.	Thank you for your comments which the committee considered. The committee acknowledged that the *CYP2C19* genotype can be relevant for drugs other than clopidogrel, such as some antidepressants. Section 3.3 of the updated guidance cites the Royal College of Physicians' and British Pharmacological Society's report on personalised prescribing which includes discussion on consent and ethics, genotyping and laboratory considerations, and clinical decision support for pharmacogenomic testing (see sections 5.4 to 5.6).
110	UK Clinical Pharmacy Association (UKCPA)	5	In the overview of the expert report (page 38-39), recording of *CYP2C19* genotype either well, or imperfectly, in patient notes raises an ethical question about what duty future prescribers/pharmacists have to take this status into account (with relevant *alleles) for other drugs that are metabolised via CYP2C19. In addition, should concurrent medication be reviewed at the time of the result, and whose responsibility would this be?	Thank you for your comments which the committee considered. The committee acknowledged that the *CYP2C19* genotype can be relevant for drugs other than clopidogrel, such as some antidepressants. Section 3.3 of the updated guidance cites the Royal College of Physicians' and British Pharmacological Society's report on personalised prescribing which includes discussion on consent and ethics, genotyping and laboratory considerations, and clinical decision support for pharmacogenomic testing (see sections 5.4 to 5.6).

THEME: Equality considerations

Comment number	Name and organisation	Section number	Comment	NICE Response

Comment number	Name and organisation	Section number	Comment	NICE Response
111	Inagene Diagnostics	Equality	Equality issues The recommendation: 'Offer laboratory-based clopidogrel genotype testing, or the Genomadix Cube point-of-care test if laboratory testing is not possible, to people who have had an ischaemic stroke or transient ischaemic attack if treatment with clopidogrel is being considered' needs to be supported with very specific guidance where a laboratory test is not available. This recommendation is commended as a huge improvement in care and should be implemented appropriately. However there may be a risk that in urgent situations the full implications of using the point of care test over a lab test may not be considered.	Thank you for your comments which the committee considered.
112	Inagene Diagnostics	General	Are the recommendations sound, and a suitable basis for guidance to the NHS? With respect to allele selection, it's really just that they test for the primary alleles, but they are missing ones that matter. For instance, using those tests, >10% of of subsaharan africans, >5% of african americans, and around 1% of europeans would be identified as normal metabolizers but are not. When they are talking about 40K tests per day in their proposal, this starts to amount to an alarming number of people who would not be receiving the standard of care that NICE thinks is warranted	Thank you for your comments which the committee considered. The committee noted that tests that only detect the most common loss-of-function alleles are likely to introduce inequalities. The committee concluded that laboratory-based testing was its preferred method 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. But it also acknowledged that there are barriers to implementing laboratory-based testing. Therefore, it said that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in sections 3.8 and 3.16 of the updated guidance.
113	Inagene Diagnostics	1.4	But, some less common loss-of-function *CYP2C19* variants occur at a higher rate in certain ethnic groups. This means that tests that only identify the most common variants may disproportionately misdiagnose people in these groups.	Thank you for your comments which the committee considered.

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			Many of these ethnic groups already suffer poorer outcomes, or are disadvantaged. Note that excluding some relevant variants may not only reduce health equity, but it can have an additive effect with pre-exisiting "non-genomic" structural factors/social determinants.	
114	Inagene Diagnostics	3.8	Other committee members felt that a wide range of alleles should be tested for to minimise potential inequalities. The range of alleles to test for should not discriminate against ethnic minorities. The Association of Molecular Pathology recommended tier 1 and tier 2 levels of alleles, where tier 1 alleles were recommended for testing, and tier 2 were optional alleles that could be tested. The criteria for falling into tier 1 were based on allele frequencies, clinical significance of the allele, and availability of reference material. These AMP recommendations have not been updated since 2018. The *35 allele in particular has a prevalence of up to 3% in sub-Saharan African backgrounds, and therefore should be included. Panel testing, where a number of alleles can be tested simultaneously, is a cost-effective and efficient method for testing. Since the cost difference of testing a larger panel compared with a limited panel is negligible, it would seem sensible to test all relevant alleles in a panel so that individuals of all ethnic backgrounds receive an optimal test. The AMP's requirement for reference materials in order to class an allele as a tier 1 allele, is not so essential in UK, since GenQA External Quality Assessment can provide quality assurance, and samples with the relevant alleles should now be readily available from biobanks where whole genome sequencing has been performed. Therefore laboratory testing could be recommended to include any clinically significant alleles with a frequency greater than 1/1000 in any	Thank you for your comments which the committee considered. The committee considered that tests that only detect the most common loss-of-function alleles are likely to introduce inequalities. The committee concluded that laboratory-based testing was its preferred method. These considerations are in sections 3.8 and 3.16 of the updated guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
			population, so as not to disadvantage any patients.	
115	Web Comment	2.6 2.10	The guidance only refers to the significance loss-of-function alleles but the tests considered also test for gain-of-function alleles (such as the *17 allele). It would be helpful to include information regarding the significance of testing for gain-of-function alleles.	Thank you for your comments which the committee considered. The EAG said that it is unclear how those with gain-of-function would be treated differently and noted that in the CPIC guidance standard treatment with clopidogrel is recommended for ultrarapid (2 increased function alleles), rapid (1 increased function alleles and 1 normal function allele) and normal metabolisers (2 normal function alleles).
116	UK Clinical Pharmacy Association (UKCPA))	2.10	The DAP report highlights that the Genomadix cube only tests for the most common alleles *2, *3 and *17, therefore missing patients with other alleles. Consideration of additional alleles (such as *4, *8 and *35) and others should be included to reduce inequalities based on ethnicity, as has been taken with other point of care tests (see Genedrive), which will ensure equity regardless of tests used. The report highlights the lack of testing in UK populations which differ from those in the studies reported. There is a risk of introducing further inequity by using the point of care test which is reporting on alleles most relevant in the EUR and East Asian population, whereas laboratory genotyping can be more tailored (in theory). The *17 allele is reported to confer increased function of CYP2C19 by CPIC and within the Expert review. it is unclear if the model characterises variation resulting in rapid-metabolism or ultra-rapid metabolism as requiring intervention in dosing or not (noting that CPIC guidelines do not recommend a dose	Thank you for your comments which the committee considered. The committee considered that tests that only detect the most common loss-of-function alleles are likely to introduce inequalities. Some clinical experts suggested that commissioners could consider the demographics in their local area when deciding how to do *CYP2C19* genotype testing. Other committee members felt that a wide range of alleles should be tested for to minimise potential inequalities. The committee concluded that laboratory-based testing was its preferred method, but also acknowledged that there are barriers to implementing laboratory-based testing. Therefore, it said that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in sections 3.8 and 3.16 of the updated guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
			change in these patients).	
117	UK Clinical Pharmacy Association (UKCPA)	3.8	We agree that the current available POC test is inequitable in that it does not serve patients of non-European ancestry as effectively as those from European populations; laboratory testing may theoretically provide a greater flexibility in adding alleles, but also may be a while away in terms of implementation. It is hugely complex to model ancestries from local populations as suggested, though it is possible with specialist databases, and we would require guidance as to what level this should be considered at. e.g. ICS level? Furthermore, the suggestion to offer alternative testing methodologies at a local level implies local/ICS-level prescribing guidance would be required, running a risk of duplication of effort. Central prescribing guidance should be provided.	Thank you for your comments which the committee considered. The committee concluded that laboratory-based testing was its preferred method, but also acknowledged that there are barriers to implementing laboratory-based testing. Therefore, it said that if laboratory-based testing is not possible or feasible, or it will take a long time to develop capacity to provide it, then point-of-care tests could be used. These considerations are in section 3.16 of the updated guidance.

THEME: Alternative laboratory-based tests and pharmacogenomic panels

Comment number	Name and organisation	Section number	Comment	NICE Response
118	Mantara Health	General	Overall, we believe that the testing for clopidogrel is a positive step however with an investment in cost per test of a similar magnitude then the Mantara test could provide more than a yes/no result for one drug without investment in expensive POCT The Mantara test provides the opportunity to increase testing availability, access to primary care and community (eg pharmacy) and direct to patient (at home).	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
			All data is GDPR compliant and there is potential to move testing (new lab) and also reporting The reporting is also a key element as validated recommendations are provided with Mantara Health which provides added clinical value.	
119	Mantara Health	2.7	The *CYP2C19* gene encodes the enzyme cytochrome P450-2C19 (CYP2C19) CYP2C19 is involved in the metabolism of up to 15% of all active ingredients this includes, e.g., the following drugs -anaesthetics phenobarbital -anticoagulants clopidogrel, ticlopidine -anticonvulsants diazepam, phenytoin -antidepressants amitriptyline, citalopram, moclobemide -beta blockers labetalol -cytostatics cyclophosphamide -muscle relaxants carisoprodol -proton pump inhibitors lansoprazole, omeprazole, pantoprazole -treatment of fungal infections voriconazole -and many others Effects of DNA variants on drug efficacy Around 50% of Europeans carry variants in the *CYP2C19* gene which may affect the efficacy of drugs For certain active ingredients, there are recommendations for adjusting the dose and/or prescribing an alternative therapy analyzing such variants may help to better adjust the medication We would argue that limiting the *CYP2C19* reporting to Clopidogel is not optimised for cost effective analysis and	Thank you for your comments which the committee considered. The population in the scope of this assessment is people who have had non-cardioembolic ischaemic stroke or transient ischaemic attack for whom clopidogrel treatment is being considered. The intervention is genetic testing of the *CYP2C19* gene. Testing of *CYP2C19* or other genes to guide use of drugs other than clopidogrel is therefore outside of the scope of this assessment. Experts 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 (see section 3.16 of the updated guidance).

Comment number	Name and organisation	Section number	Comment	NICE Response
			reporting and more benefit could be achieved for either broadening the *CYP2C19* reporting to include other drugs in the genotype or increase the genotype reporting to include other genotypes and increase the number of genotype and associated drugs. Using the Mantara PGx DNA test - we can achieve and critically report on both of these options. It is critical to provide a wide variant collection due to ethnicity which the Mantara test can support	
120	Mantara Health	2.9	2.9 The interventions review should be broadened to include laboratory testing with reporting that could be offered both direct to patient and through primary care eg GP, pharmacy etc. therefore improving patient access and at home testing. Mantara Health PGx DNA test is commercially available in the UK and is UKCA marked/Class 1 medical device and can test for genetic variants and the resulting effect on clopidogrel for common variants. Our test uses validated technology via the UPGx-PREPARE study and reported in the LANCET (04/02/2023) and currently tests for 12-genes rather than one. A test purely for clopidogrel would be beneficial as per the report however there are other validated options	Thank you for your comments which the committee considered.
121	Mantara Health	2.15	The Mantara PGx DNA test can test for both blood and saliva so is ideally placed to be used in the community and primary care especially if access and mobility is an issue. Mantara PGx DNA kit currently uses a lab based in Germany for both analysis (diagnosticum) and digital reporting (bio.logis) - both of which were involved in the UPGx - PREPARE study and named in the LANCET published report.	Thank you for your comments which the committee considered.

Comment number	Name and organisation	Section number	Comment	NICE Response
122	Inagene Diagnostics	General	Inagene Diagnostics would like to commend NICE and the companies mentioned for bringing this forward. It is a positive step for patients and translational medicine. Please note comments have been added from our Global and UK Scientific Directors along with our chief pharmacist. We hope that they add some value to the consultation. Thank you.	Thank you for your comments which the committee considered.
123	Inagene Diagnostics	General	Has all of the relevant evidence been taken into account? Two commercial point of care tests have been assessed. No specific commercially available laboratory genotyping assay has been assessed, such as the Agena-based assay offered by Inagene Diagnostics UK. This is a Pharmacogenomic genotyping panel test which tests a number of loci in addition to *CYP2C19* which are associated with drugs used to treat other conditions. Some of those additional conditions may be present as co-morbidities in patients suffering from stroke, for example mental health issues and pain. This may be outside scope for the current consultation, but suggesting consideration as it may impact the long term approach. Testing a large pharmacogenomic panel that includes medications for these co-morbidities may offer even better cost benefits than just testing for *CYP2C19*, since other medications could then be optimised as well using the data obtained from the panel test. This could avoid side-effects associated with these other medications, and reduce or avoid additional costs resulting from potential adverse drug reactions. Additionally, the results of testing a large pharmacogenomic panel will be available in the patient record for the long term future, meaning that medicine optimisation will be available for patients requiring new medicines for new medical problems arising in years to come. It should be borne in mind that testing a larger pharmacogenomic	Thank you for your comments which the committee considered. Testing of *CYP2C19* or other genes to guide use of drugs other than clopidogrel is outside of the scope of this assessment. Experts 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 (see section 3.16 of the updated guidance).

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			panel would not cost much more than a single *CYP2C19* test, and therefore the long term cost benefits could be even greater for the NHS.	
124	Inagene Diagnostics	3.14	The committee agreed that *CYP2C19* genotype testing was likely to be cost effective. Large pharmacogenomic panel tests are available that include CYP2C9 and numerous other genes which are associated with drugs used to treat other conditions. Some of those additional conditions may be present as co-morbidities in patients suffering from stroke, for example mental health issues and pain. Testing a large pharmacogenomic panel that includes medications for these co-morbidities may offer even better cost benefits than just testing for CYP2C9, since other medications could then be optimised as well using the data obtained from the panel test. This could avoid side-effects associated with these other medications, and reduce or avoid additional costs resulting from potential adverse drug reactions. Additionally, the results of testing a large pharmacogenomic panel will be available in the patient record for the long term future, meaning that medicine optimisation will be available for patients requiring new medicines for new medical problems arising in years to come. It should be borne in mind that testing a larger pharmacogenomic panel would not cost much more than the a single CYP2C9 test, and therefore the long term cost benefits could be even greater for the NHS.	Thank you for your comments which the committee considered.