NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

High-sensitivity troponin tests for the early rule out of NSTEMI

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 3 June 2020

Theme: Assay equivalency

Comment number	Name and organisation	Section number	Comment	NICE response
1	Abbott Laboratories, Abbott Diagnostics Division	Pages 3-9, section 1.5 – 2.3	"Re "1.5 There is currently not enough diagnostic accuracy evidence to recommend Alinity and Dimension EXL high-sensitivity troponin tests." The ARCHITECT and Alinity hsTroponin I assays are CE-marked and FDA approved as equivalent and hence both the ARCHITECT hsTroponin I assay and the Alinity hsTroponin I assay should be recommended by NICE. For another manufacturer (see 2.13 of the draft document) multiple analysers using the same reagent have already been recommended by NICE, based on that manufacturer stating "that performance is the same when used on these analysers." In like manner, the performance of the Abbott hsTroponin I assay is the same on ARCHITECT and Alinity and both should be recommended. Details are: [A] As stated in the Alinity hsTroponin pack insert: (1) "The Alinity I analyzer and the ARCHITECT I System utilize the same reagents and sample/reagent ratios." (2) "EXPECTED VALUES This study was performed on the ARCHITECT I System." The same male/female and overall 99th percentile data apply to both the ARCHITECT and Alinity assays. (3) "Analytical Specificity. This study was performed on the ARCHITECT I System." This data is the same for ARCHITECT and Alinity. (4) "Interference Potentially Interfering Endogenous Substances and Potentially Interfering Drugs. These studies were performed on the ARCHITECT I System." This data applies to ARCHITECT and Alinity. (5)	Thank you for your comment which the committee considered. The committee noted that the Alinity and the ARCHITECT high sensitivity troponin I assays were based on the same methods and principles and used the same reagents. It noted that the Alinity was a newer version of the ARCHITECT assay and that the diagnostic accuracy should be comparable between the two. It concluded that it was the responsibility of individual laboratories to assess the equivalency of the new test in practice, and to validate the diagnostic performance against their current system. The committee's discussion of this topic is summarised in section 4.10 of the diagnostics guidance document. The committee decided to recommend the Alinity assay for use in the NHS; see section 1.1 of the diagnostics guidance document.

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			"Potentially Interfering Other [HAMA,RF] Conditions. This study was performed on the ARCHITECT I System." And applies to Alinity. (6) "Method Comparison – Alinity I STAT High Sensitive Troponin-I vs ARCHITECT STAT High Sensitive Troponin-I": Correlation 1.00 ;(units pg/mL) Slope 1.00 Intercept 1.39 Analytical Range of comparison 10.5 to 47,065.9 pg/mL." Very close agreement in results and perfect correlation (r=1.00) between Alinity and ARCHITECT. (7) "Clinical Performance. This study was performed on the ARCHITECT I System." This data includes the sensitivity, specificity, NPV and PPV data of the sample types (serum, LiHep, EDTA), timings and deltas and all apply to both ARCHITECT and Alinity. Note that as per section 2.13 NICE has accepted for another manufacturer that "The company says that performance is the same when used on these analysers.", this company has 4 different models of analyser. Likewise, Abbott ARCHITECT and Alinity hsTroponin I assays are using the same Abbott reagents, calibrators and standardisation, with the same clinical performance, and both should be recommended by NICE to align with the way that NICE has responded to at least one other manufacturer. [B] An independent evaluation of the Alinity vs ARCHITECT hsTroponin I assay has been published and concluded that the two assays were equivalent: " The STAT hs-cTnI assay on the recently launched Abbott Alinity ci series analyzer offers comparable analytical performance to the existing Abbott ARCHITECT hs-cTnI assay in routine use in 5 independent clinical laboratories." And "In addition to excellent analytical comparability, this study showed very good concordance between the assays on the 2	

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			instruments at the early rule-out cutoff currently in use in our Trust." Reference: Hayley Sharrod-Cole and Clare Ford Multicenter Evaluation of a High-Sensitivity Troponin I Assay and Verification of an Early Rule-Out Algorithm The Journal of Applied Laboratory Medicine, Volume 4, Issue 1, 1 July 2019, Pages 95–100, https://doi.org/10.1373/jalm.2018.027466 Postscript added by NICE: Prior to the second committee meeting, Abbott requested a correction to this comment which stated that they wished to withdraw the comment that the Alinity assay had FDA approval. The Alinity assay does not yet have FDA approval. This request was made to NICE before the meeting and the committee were made aware of the clarification.	
2	Roche Diagnostics Ltd	1.2	The recommendation for the Elecsys assay should be worded "Elecsys Troponin T-high sensitive assay and Elecsys Troponin T-high sensitive STAT (**S**hort **T**urn **A**round **T**ime) " as the evidence applies for both versions.Therefore please include x2 bullets to reflect this. The STAT version of the assay is exactly the same in terms of technical specification and performance but has a faster turnaround time of 9 mins in comparison to 18 mins.	Thank you for your comment which the committee considered. The committee noted that the Elecsys TroponinT-high sensitive STAT test was the same in terms of technical specification and performance as the Elecsys troponin T-high sensitive test, as is run on the same analysers. The committee concluded that the diagnostic accuracy of these different versions of the tests should be comparable. The committee further concluded that it was the responsibility of individual laboratories to assess the equivalency of the new test in practice and to validate the

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				diagnostic performance against their current system. The committee's discussion of this topic is summarised in section 4.10 of the diagnostics guidance document. The committee decided to recommend the Elecsys STAT assay for use in the NHS; see section 1.1 of the diagnostics guidance document.
3	Siemens Healthineers	3.37 Table 1	Dimension VISTA LOCI immunoassay has exactly the same reagents as the Dimension EXL method, the only difference being that the VISTA has an additional analytical unit ie a nephelometer for plasma protein measurement. Siemens internal data supports the Method Correlation vs VISTA y=1.0123x + 0.6335 R2=0.9924 over the range 3 to 350ng/L demonstrating equivalence.	Thank you for your comment which the committee considered. The committee noted that the Dimension EXL High-Sensitivity Cardiac Troponin I assay and the VISTA assay were based on the same methods and principles and used the same reagents. It noted that the Dimension EXL assay was a different version of the VISTA assay, but they were all run on different analysers. It concluded that the diagnostic accuracy should be comparable between the two. The committee further concluded that it was the responsibility of individual laboratories to assess the equivalency of the new test in practice and to validate the diagnostic performance against their current system. The committee's discussion of this topic

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				is summarised in section 4.10 of the diagnostics guidance document. The committee decided to recommend the Dimension EXL assay for use in the NHS ;see section 1.1 of the diagnostics guidance document.
4	UK NEQAS/ Birmingham Quality	1.5	I would be concerned if a new method is not recommended just because of its 'newness'. All Abbott users will be being transitioned from Architect to Alinity and all new Abbott users will be offered only Alinity. Laboratory users will be undertaking their own evaluations. It will become a major method (it already has over 30 users for TSH which is an indicator of uptake) and while I wouldn't want it to be recommend it without seeing data, similarly I wouldn't want to single it out as not having enough evidence, as data on this method will be being accumulated all the time. It may become more difficult to accumulate evidence on any method that is not being recommended as an unintentional self-fulfilling prophecy. The Siemens Dimension EXL is less of an issue, as I think in the UK the Atellica and Centaur will be the predominant Siemens methods. Ongoing method scrutiny though a challenging EQA program should be enough to gauge the analytical performance all methods over time as even those methods that are currently being recommended may exhibit a decline in performance. Updating with the clinical performance is obviously still necessary.	Thank you for your comment which the committee considered. The committee heard that the Alinity High Sensitive Troponin I assay was a newer version of the ARCHITECT assay and that the Dimension EXL High-Sensitivity Cardiac Troponin I assay was a different version of the VISTA assay, but the tests were all run on different analysers. The committee noted that these tests were based on the same methods and principles and used the same reagents as other tests that were included in the modelling. The committee concluded that the diagnostic accuracy of these different versions of the tests should be comparable. It concluded further that it was the responsibility of individual laboratories to assess the equivalency of these tests in practice and to validate the diagnostic

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				performance against their current system. It noted that external quality assessment schemes had an important role to play in this process. The committee's discussion of this topic is summarised in section 4.10 of the diagnostics guidance document. The committee decided to recommend the Alinity assay and the Dimension EXL assay for use in the NHS; see 1.1 of the diagnostics guidance document.

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Theme: Point of care testing

Comment number	Name and organisation	Section number	Comment	NICE response
5	Quidel	1.1	TriageTrue High Sensitivity Troponin Assay should be included in the recommended test section with the caveat “EDTA plasma samples only”	Thank you for your comment which the committee considered. The committee concluded that the diagnostic accuracy evidence for the TriageTrue High Sensitivity Troponin I test did not reflect how it would be used in clinical practice at the point of care, as defined in the scope. Applications of a test outside of scope cannot be considered. It concluded that further evidence on the diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice (see section 4.9 of the diagnostic guidance document). The committee recommended that there should be further research on the diagnostic performance of the TriageTrue High Sensitivity Troponin I test using samples at point of care (see section 5.1 of the diagnostics guidance document).
6	Quidel	1.4	Revised comment: Since the APACE study referenced in Section 3.19 was performed with EDTA plasma samples, sites that plan to implement the TriageTrue test using EDTA whole blood samples should perform an appropriate plasma/whole blood bias study to validate performance of the	Thank you for your comment which the committee considered.

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			test for this purpose. Data from these validations can be consolidated to support the further research recommended in Sections 5.1 and 6.0.	The committee concluded that the diagnostic accuracy evidence for the TriageTrue High Sensitivity Troponin I test did not reflect how it would be used in clinical practice at the point of care. It concluded that further evidence on the diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice (see section 4.9 of the diagnostics guidance document).
7	Quidel	Explanations to 1	Based on the above comments, the explanation section should cover the TriageTrue test as follows: “Evidence shows that, of the high-sensitivity troponin tests, 9 are similarly effective in terms of diagnostic performance. […] Although the TriageTrue test has the potential to be even more cost effective at the point-of-care, outcome studies to demonstrate this have not yet been performed. Therefore, only the use of plasma EDTA samples has been included in the analysis and recommendations so far.” Additionally, the system was specifically designed to accommodate whole blood. The impact of using whole blood in the system has been extensively studied and understood and therefore the product is both calibrated and released using both whole blood and plasma. In addition to being designed for both matrices, the product has a “matrix select” feature in the meter firmware that ensures that the calibration curve of the correct matrix is applied.	Thank you for your comment which the committee considered. The committee concluded that the diagnostic accuracy evidence for the TriageTrue High Sensitivity Troponin I test did not reflect how it would be used in clinical practice at the point of care. It concluded that further evidence on the diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice (see section 4.9 of the diagnostics guidance document).

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8	Quidel	4.9	The APACE data clearly demonstrates TriageTrue clinical diagnostic accuracy in plasma samples (Boeddinghaus 2020 Ref 173 in DAP 49 Committee Papers) therefore validating its use with plasma samples in clinical practice. Therefore, the sentence 'before the test can safely be used in clinical practice' is misleading - please remove or restructure. To support the recommendation that sites implementing testing with whole blood EDTA samples perform validation testing, we enclose additional data on the whole blood / plasma bias of the TriageTrue test. Also, in our recent experience implementing PlGF testing for pre-eclampsia under a similar NICE program we have noted that most of the early adopter sites will perform validation testing for key aspects of the assay anyway so we do not see this as an significant additional burden.	Thank you for your comment which the committee considered. The committee concluded that the diagnostic accuracy evidence for the TriageTrue High Sensitivity Troponin I test did not reflect how it would be used in clinical practice at the point of care. It concluded that further evidence on the diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice (see section 4.9 of the diagnostics guidance document).
9	Quidel	5.1 & 6.0	The report recommends further research into the TriageTrue test at point of care and declares an intention to support this research through a range of promotional activities. This is of interest, and we would like to discuss in more detail as soon as possible. Please note that two major sites in the UK Addenbrookes Cambridge and John Radcliffe Oxford, have performed initial studies of the Triage TRUE assay using whole blood EDTA at the POC. This data is not published and therefore we cannot share it. However, both sites are willing to provide this data for reference purposes.	Thank you for your comment which the committee considered. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations into its guidance research recommendations database and highlight these recommendations to public research bodies.

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10	Quidel	7.0	If the research advocated in comment 3 is forthcoming, would this qualify as 'significant new evidence' and as such trigger an update to the guidance?	Thank you for your comment which the committee considered. NICE may review and update the guidance at any time if significant new evidence becomes available. The interim addendum on reviews is available here: https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-diagnostics-guidance

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Theme: Test strategies

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11	Roche Diagnostics Ltd	1.2	Our interpretation of these draft guidelines is that strategies that include a single measurement only are recommended. Our understanding is that this is not in line with clinical practice across the UK. If this is not the intention of the committee then we recommend the wording is changed to clarify that strategies based on a single hs-troponin test only are not included. Additional comments in this table reflect our belief that the intention of the committee was to include single sample only strategies in the recommendations.	Thank you for your comment which the committee considered. The committee reaffirmed that single sample strategies should be recommended and commented that these strategies can be useful for ruling out NSTEMI early in emergency departments and for this purpose, specificity is not a priority. This consideration is described in section 4.4 of the diagnostics guidance document.
12	Roche Diagnostics Ltd	General	Although similar cost-effectiveness estimates are produced by the single-sample only strategies we do not think it is helpful to recommend these in practice. In support of this, the evidence review shows that the sensitivity of the Roche and Abbot assays in the ESC pathway is the same as the single sample version of these assays with marked increased in specificity.	Thank you for your comment which the committee considered. The committee reaffirmed that single sample strategies should be recommended and commented that single sample strategies can be useful for ruling out NSTEMI early in emergency departments and for this purpose, specificity is not a priority. This consideration is described in section 4.4 of the diagnostics guidance document.
13	Roche Diagnostics Ltd	4.5	We do not agree that it is unreasonable to make comparisons of specificity between single and multiple sample strategies; particularly those strategies for which there is a large weight of evidence. Prevalence	Thank you for your comment which the committee considered.

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			varies in the underlying studies but there were no concerns highlighted around significant patient heterogeneity or problems with small sample sizes. The relatively low prevalence in the studies meant that there were a large number of TNs in most of the studies from which to calculate reliable specificity estimates.	The committee noted that there was limited evidence comparing the diagnostic performance of 1 test with another. This meant that although there may be differences in performance between the tests, it is difficult to estimate these differences with any certainty (see section 4.3 of the diagnostics guidance document).
14	Roche Diagnostics Ltd	1.2	The evidence underpinning this recommendation relates to algorithms that include measurements at 0 and 1, 2 or 3 hours. The use of “typically include” may be misleading.	Thank you for your comment which the committee considered. The committee concluded that recommending a range of early rule-out strategies would enable hospitals to use strategies that worked with the set-up of their emergency department (see section 4.16 of the diagnostics guidance document).
15	Roche Diagnostics Ltd	1.2	We suggest that only strategies that include a rule-out hs-troponin measurement on admission, followed by a second hs-troponin test for those that are not ruled out by the first test should be recommended. This is in line with ESC guidelines and maximises efficiency in the emergency department with no loss in sensitivity.	Thank you for your comment which the committee considered. The committee noted that all strategies assessed were cost effective compared with a standard troponin test strategy. The committee concluded that recommending a range of early rule-out strategies would enable hospitals to use strategies that worked with the set-up of their

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				emergency department (see section 4.16 of the diagnostics guidance document). The committee decided to clarify recommendation 1.2 in the diagnostics guidance document to state that a single sample on presentation using a threshold at or near the limit of detection should not be used to rule-in NSTEMI if positive.

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Theme: Economic analysis

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16	Roche Diagnostics Ltd	4.1	The patient expert highlighted that reducing waiting times in A&E is important. We suggest that this benefit, associated with higher specificity assays, has not been captured in the economic model and should have been factored into decision-making to discriminate between assays.	Thank you for your comment which the committee considered. The external assessment group commented that not all potential cost and benefits could be captured in the economic model and that the benefits could have been underestimated. However, this would have been unlikely to substantially change conclusions (see section 4.14 of the diagnostics guidance document).
17	Roche Diagnostics Ltd	Economic Model	The estimates on rule-out rate used in the consultation version of the economic model were not factored into the ED resource use (e.g. Parameters!B552). We believe this has led to higher specificity strategies looking less cost-effective.	Thank you for your comment which the committee considered. The external assessment group commented that not all potential cost and benefits could be captured in the economic model and that the benefits could have been underestimated. However, this would have been unlikely to substantially change conclusions (see section 4.14 of the diagnostics guidance document).
18	Roche Diagnostics Ltd	4.14	The clinical experts commented that ED stay would likely be 24 hours rather than 14. If these data were corrected, higher specificity strategies would look more cost-effective.	Thank you for your comment which the committee considered. The committee noted that the benefits of using early rule-out strategies may have been underestimated by assuming a hospital stay of 14 hours rather than

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				24 hours. The external assessment group commented that changing this assumption would be unlikely to affect the model results (see section 4.14 of the diagnostics guidance document).
19	Roche Diagnostics Ltd	Economic Model	The secondary analysis produces different numbers of “healthy” people in the Markov Trace between testing strategies where the primary analysis does not. We are concerned that this might be a calculation error. Although the absolute number of “healthy” people might be expected to be lower in the model structure for the secondary analysis, we are not sure that this should be relatively different between the strategies. The secondary analysis also reduces the number of people with UA and we are not sure why that would be the case. Perhaps some of them could be assumed to have moved into the previously unoccupied “suspect MI” state? There also appears to be a relationship between the number of people who die in the initial decision tree and the specificity of the test, which we do not think is intuitive. Overall, while we support the rationale for undertaking this sensitivity analysis we are not sure that it is achieving its aims. We would ask the EAG to consider removing it from decision-making consideration or highlighting its limitations to the DAC.	Thank you for your comment which the committee considered. The external assessment group commented that the true non-NSTEMI - Healthy (no acute coronary syndrome) are identical for the different strategies (i.e. =Y12+Z12+AA12+AB12 on the Markov trace worksheets). Clinical experts on the committee noted that it is now widely accepted that people with a negative standard troponin test and a positive high-sensitivity troponin test (classified as false positives in the analysis) have an increased risk of reinfarction and mortality compared with people who have a negative result from both tests. The committee concluded that the secondary analysis was most appropriate for decision making (see section 4.12).

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20	Roche Diagnostics Ltd	4.12	We understand that it is appropriate to accrue some benefits to people who have raised levels on hs-troponin where their standard troponin would be normal but we are concerned that this appears to re-order the cost-effectiveness of the assays. Given all the assays have fairly high numbers of FPs, it might be reasonable to assume that this benefit is the uniform across assays. We wondered whether assuming otherwise might advantage assays with a lower specificity?	Thank you for your comment which the committee considered. The external assessment group commented that not all potential cost and benefits could be captured in the economic model. Clinical experts on the committee noted that it is now widely accepted that people with a negative standard troponin test and a positive high-sensitivity troponin test (classified as false positives in the analysis) have an increased risk of reinfarction and mortality compared with people who have a negative result from both tests. The committee concluded that the secondary analysis was most appropriate for decision making (see section 4.12).
21	Quidel	4.17	Section 4.1 reports the comments of a patient expert who highlighted the important of reducing waiting times for patients and families. Point of care testing saves time and increases clinical efficiency. Remote testing is even more attractive at this unprecedented time. The committee expressed concern that these benefits may not have been 'fully captured in the economic model' **however there is no consideration of them at all.** This becomes clear in section 3.42 that factors in a 2-hour delay between sampling and result availability for all tests which is significantly reduced by the point-of-care approach of TriageTrue. Therefore, the diagnostic accuracy put into the model and	Thank you for your comment which the committee considered The external assessment group commented that not all potential cost and benefits could be captured in the economic model. The committee concluded that the diagnostic accuracy evidence for the TriageTrue High Sensitivity Troponin I test did not reflect how it would be used in clinical practice at the point of

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			the cost-effectiveness calculation are both based on the same clinical use in EDTA plasma samples for which evidence has been shown. The section should be rephrased as "Further diagnostic evidence is needed before TriageTrue can be recommended for routine clinical use in whole blood samples."	care. It concluded that further evidence on the diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice (see section 4.9 of the diagnostic guidance document).
22	Siemens Healthineers	3.37 Table 1	Sandoval, Y. et al. J Am Coll Cardiol. 2019;74(3):271–82. This paper clearly demonstrates the effectiveness of using a single optimised sample cut off of 5ng/L for both Atellica and ADVIA Centaur with over 46% of patients ruled out, yet the single sample cut off LOD <2ng/L (21% rule out) has been used for Atellica to assess cost effectiveness of a single sample rule out strategy. This data was available at the time of submission so we are unclear as to why this has been overlooked.	Thank you for your comment which the committee considered. The external assessment group commented that the Sandoval paper was identified and data from this study were included in the diagnostics assessment report but the 5ng/L threshold was not included in the model. The committee noted that only early rule-out strategies with a sensitivity of 97% or more were used in the cost-effectiveness modelling, based on expert opinion about the minimum sensitivity acceptable in clinical practice. The committee noted that this approach could mean that some potentially cost-effective strategies were excluded from the economic modelling. But overall it agreed that it was an acceptable approach (see section 4.11).

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Theme: Use of sex specific thresholds

Comment number	Name and organisation	Section number	Comment	NICE response
23	Roche Diagnostics Ltd	1.3	While we understand the aims of the committee in making this recommendation, we do not think there is enough evidence to recommend sex-specific cutoffs across all assays. While data on the 99th percentil is available across all assays, it is not clear that the 99th percentile is the cutoff that optimises sensitivity and specificity when stratified by sex across all assays. We do not support the recommendation for Sex specific cutoffs for the Elecsys® Troponin T-hs assay. Sex specific cut-offs are available for the Elecsys® Troponin T-hs test and are listed in the package insert however they have not been shown to deliver additional clinical benefit and add additional complexity for clinicians when interpreting test results. While evidence may exist for the Abbott assay (Shah et al 2015 High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study) this can not be extrapolated to other assays. For example, the ESC clinically validated one hour algorithm utilises the same cut-offs for both males and females the evidence for this algorithm was based on the TRAPID - AMI study. In this study, the NPV for males and females were 99.2% and 99.1% respectively. The main evidence base for other assays recommended by the committee only includes evidence from the APACE group and the use of single cut-offs for both male and female sex. Further reading in support of our position to not recommend the use of sex specific cutoffs: 1. Giannitsis E, Katus HA **Troponins: established and novel indications in the**	Thank you for your comment which the committee considered. Clinical experts on the committee reiterated that there was consistent evidence from reference range studies that the 99th percentile threshold differs between men and women. They also noted that there was no evidence that using sex-specific 99th percentile thresholds affected clinical outcomes. The committee noted that there was a wider equality issue because women with acute myocardial infarction are generally under-diagnosed and under-treated compared with men. It concluded that using sex-specific 99th percentile thresholds to help diagnose NSTEMI could be a step towards reducing this health inequality (see section 4.7 of the diagnostics guidance document). The committee decided to change the wording of recommendation 1.3

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			management of cardiovascular disease Heart 2018;104:1714-1722. 2. Matthias Mueller-Hennessen, Bertil Lindahl, Evangelos Giannitsis, Moritz Biener, Mehrshad Vafaie, Christopher R. deFilippi, Michael Christ, Miguel Santalo-Bel, Mauro Panteghini, Mario Plebani, Franck Verschuren, Tomas Jernberg, John K. French, Robert H. Christenson, Richard Body, James McCord, Peter Dilba, Hugo A. Katus, Christian Mueller, **Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T — Sub-analysis from the TRAPID-AMI study**, International Journal of Cardiology, Volume 209, 2016, Pages 26-33, ISSN 0167-5273, https://doi.org/10.1016/j.ijcard.2016.01.213. (http://www.sciencedirect.com/science/article/pii/S0167527316301899) 3. Rubini Giménez M, Twerenbold R, Boeddinghaus J, et al. **Clinical Effect of Sex-Specific Cut-off Values of High-Sensitivity Cardiac Troponin T in Suspected Myocardial Infarction.** JAMA Cardiol. 2016;1(8):912–920. doi:10.1001/jamacardio.2016.2882 4. Kavsak, P. A., Worster, A., Shortt, C., Ma, J., Clayton, N., Sherbino, J., … Devereaux, P. (2018). **High-sensitivity cardiac troponin concentrations at emergency department presentation in females and males with an acute cardiac outcome**. Annals of Clinical Biochemistry, 55(5), 604–607. https://doi.org/10.1177/0004563217743997 5. Raphael Twerenbold, Jasper Boeddinghaus, Christian Mueller, **Update on high-**	to state that when NSTEMI is not ruled-out using early rule-out test strategies, use NICE's guideline on recent-onset chest pain of suspected cardiac origin to help make a diagnosis of myocardial infarction, and consider the use of sex-specific thresholds at the 99th percentile.

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Theme: Use of sex specific thresholds

Comment number	Name and organisation	Section number	Comment	NICE response
			sensitivity cardiac troponin in patients with suspected myocardial infarction, European Heart Journal Supplements, Volume 20, Issue suppl_G, August 2018, Pages G2–G10. https://doi.org/10.1093/eurheartj/suy020 6. Maria Rubini Gimenez, MD, Patrick Badertscher, MD, Raphael Twerenbold, MD, Jasper Boeddinghaus, MD, Thomas Nestelberger, MD, Desiree Wussler, MD, Òscar Miró, MD, F. Javier Martín-Sánchez, MD, Tobias Reichlin, MD, and Christian Mueller, MD **Impact of the US Food and Drug Administration–Approved Sex-Specific Cut-off Values for High-Sensitivity Cardiac Troponin T to Diagnose Myocardial Infarction**, Circulation. 2018;137:1867–1869. 7. Raphael Twerenbold, Jasper Boeddinghaus, Thomas Nestelberger, Karin Wildi, Maria Rubini Gimenez, Patrick Badertscher, Christian Mueller, **How to best use high-sensitivity cardiac troponin in patients with suspected myocardial infarction**,Clinical Biochemistry,Volume 53,2018,Pages 143-155, ISSN 0009-9120, https://doi.org/10.1016/j.clinbiochem.2017.12.006. (http://www.sciencedirect.com/science/article/pii/S0009912017310378) 8. **GENDER-SPECIFIC REFERENCE VALUES FOR HIGH-SENSITIVITY CARDIAC TROPONIN T AND I IN WELL-PHENOTYPED HEALTHY INDIVIDUALS AND VALIDITY OF HIGH-SENSITIVITY ASSAY DESIGNATION** Matthias Mueller-Hennessen, Evangelos Giannitsis, Tanja Zeller, Matthias Aurich, Moritz Biener, Mehrshad Vafaie, Anna-Sophie Schuebler, Marco Ochs, Johannes Riffel, Derliz Mereles, Stefan Blankenberg, Hugo Katus	

DIAGNOSTICS ASSESSMENT PROGRAMME

High-sensitivity troponin tests for the early rule out of NSTEMI

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 3 June 2020

Theme: Use of sex specific thresholds

Comment number	Name and organisation	Section number	Comment	NICE response
			Journal of the American College of Cardiology Mar 2019, 73 (9 Supplement 1) 175; DOI: 10.1016/S0735-1097(19)30783-1.	

DIAGNOSTICS ASSESSMENT PROGRAMME

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 3 June 2020

Theme: Clarity of recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
24	British Cardiovascular Society	Pages 2-3	As far as I can tell, all of the tests recommended in the document for measuring the plasma concentration of high sensitivity troponin are laboratory based tests. No point of care test is supported. I think it would be sensible for this to be clear from reading the recommendations alone, which is currently not the case.	Thank you for your comment which the committee considered.
25	Royal College of Physician		The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the BCS.	Thank you for your comment which the committee considered
26	Roche Diagnostics Ltd	1.4	Need to clearly state “Assay not recommended for use” Followed by the reasons for this decision as already stated in the draft	Thank you for your comment which the committee considered
27	Roche Diagnostics Ltd	1.5	Need to clearly state “Assay not recommended for use” Followed by the reasons for this decision as already stated in the draft	Thank you for your comment which the committee considered
28	Roche Diagnostics Ltd	General	While we understand the committee’s desire to give as much flexibility to the system as possible, we are concerned that this updated guidance is so permissive it will create delays to adoption of rapid algorithms as each trust will need to review and interpret all the evidence for each of the recommended assays to then decide at a local level what algorithm they will adopt. Previous experience shows that this leads to the slow adoption of algorithms that are not always evidence based and open to individual clinician interpretation. Greater weight should be given to diagnostic tests with more evidence, tighter confidence intervals around their diagnostic test accuracy point estimates and higher specificity with negligible reductions in sensitivity.	Thank you for your comment which the committee considered. The committee noted that all strategies assessed were cost effective compared with a standard troponin test strategy. The committee concluded that recommending a range of early rule-out strategies would enable hospitals to use strategies that worked with the set-up of their emergency department (see section 4.16 of the diagnostics guidance document).

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29	Roche Diagnostics Ltd	1.2	We feel that the wording "at or *near* the limit of detection" is ambiguous. It encourages unwarranted variation in care as it is open to local interpretation. We would recommend published assay-specific cutoffs.	Thank you for your comment which the committee considered. The committee had concerns about the consistency of different analysers to provide accurate results at low thresholds. However, clinical experts commented that samples with results close to these low thresholds would be from people considered very low risk and would have a good prognosis regardless of treatment (see section 4.4 of the diagnostics guidance document). Recommending thresholds at or near the limit of detection rather than assay-specific cut offs gives greater flexibility to NHS trusts and enables them to work with any local restrictions. It is the responsibility of individual laboratories to assess the diagnostic performance of the test at the chosen threshold. This would be achieved in part by participating in external quality assessment schemes.
30	Roche Diagnostics Ltd	General	With regards to rule-out on the first measurement of hs-troponin, its important that the guideline includes advice on timing of the sample being taken and time since onset of chest pain. For example LoDED strategy vs >3 hours post onset of chest pain as recommended in the ESC 1 hour algorithm	Thank you for your comment which the committee considered. The committee concluded that healthcare professionals should consider the likely time

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			(LoDED - https://heart.bmj.com/content/heartjnl/early/2020/05/04/heartjnl-2020-316692.full.pdf)	since the onset of symptoms when interpreting test results. This has been included in recommendation 1.2 of the diagnostics guidance document.

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 3 June 2020

Theme: General comments

Comment number	Name and organisation	Section number	Comment	NICE response
31	Roche Diagnostics Ltd	General	We think that it would be enormously helpful for clinical practice if a visual algorithm could be produced based on this guidance. It would also be helpful if, in time, this could be joined with the relevant clinical guideline. This should include the specific published/validated cutoffs for each of the recommended assays.	Thank you for your comment which the committee considered. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
32	Roche Diagnostics Ltd	General	It would be helpful for the healthcare system if a grading of the evidence for each assay was provided, highlighting where the assays are underpinned by a lower quality evidence base (single, small or ungeneralisable studies, for example).	Thank you for your comment which the committee considered.