NICE National Institute for Health and Care Excellence

High-sensitivity troponin for the early rule out of acute myocardial infarction

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BioMérieux	1			BioMérieux is fine with the document and won't provide comments to it	No response required.
British Cardiovascular Society (endorsed by RCP)	2			No comments	No response required.
Quidel	3			The study with Quidel Triage True has been published along with an editorial commentary	The reference for this study will be up-dated before publication of our report.
Siemens Healthineers	4	312	Appendix 4 details of excluded studies with rationale	Reference standard is quoted as the 3rd Universal Definition which was replaced by the 4th Universal Definition in Sept 2018. Why was this new standard not used in the assessment report?	This was an error in reporting. The reference standard definition was carried forward from the previous assessment. However, in practice, studies which used either the 3rd or 4th universal definitions were included, because the time period covered by this up-date systematic review spans September 2018 (2013 to September 2019). Corrected text has been provided.
Siemens Healthineers	5	20	Results Clinical Effectiveness	Siemens Dimension EXL method has been excluded as it is lacking evidence in the literature. However, it has exactly the same assay architecture, antibodies and assay protocol as that of the Dimension VISTA, which has been included. Dimension EXL assay performance is part of the HIGH US study protocol (detailed below) and is pending publication. Kavsak has also published an analytical	The Siemens Dimension EXL assay was not excluded from our systematic review. However, as stated in our report, "We did not identify any studies of Abbott Alinity hs-cTnI, or Siemens Healthineers Dimension EXL hs-cTnI, which met the inclusion criteria for this review."

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				performance assessment of the Dimension EXL high sensitivity Troponin I assay (detailed below). 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. Christenson RH et al. Trial design for assessing analytical and clinical performance of high sensitivity cardiac troponin I assays in the United States: The HIGH US study, *Contemporary Clinical Trials Communications* (2019) Kavsak PA et al. Analytical characterization of the Siemens Dimension EXL high-sensitivity cardiac troponin I assay. *Clinical Biochemistry* 2019, (69): 52-56 Kavsak PA et al. Four Different High-Sensitivity Cardiac Troponin Assays With Important Analytical Performance Differences. *Canadian Journal of Cardiology* 2019, (35): 796.e17 - 796.e18 Apple FS et al. Sex-Specific 99th Percentile Upper Reference Limits for High Sensitivity Cardiac Troponin Assays Derived Using a Universal Sample Bank. *Clinical Chemistry* 2020, (66):3, 434–444	The detailed studies do not meet the pre-specified inclusion criteria for this assessment (see Table 2 of our report).

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				Apple et al Sex-Specific 99th Percentile Upper Reference Limits for High Sensitivity Cardiac Troponin Assays Derived Using a Universal Sample Bank is a recent publication supporting the 99th percentile for Dimension VISTA and therefore applicable to Dimension EXL.	
Siemens Healthineers	6	169	References	References 127 and 128 are abstracts related to a paper which is now published: Novak RM et al. Performance of Novel High-Sensitivity Cardiac Troponin I Assays for 0/1-Hour and 0/2- to 3-Hour Evaluations for Acute Myocardial Infarction: Results From the HIGH-US Study. *Annals of Emergency Medicine* 2019 This article supports the use of the ESC 0/1.0/2 and 0/3hr protocols using the Atellica IM and ADVIA Centaur platforms.	The Nowak 2019 article meets the inclusion criteria for this assessment. It is, potentially, of particular interest, as it provides diagnostic performance data for ESC 0/1 and 0/3 hour pathways using the Siemens Atellica hs-cTnI assay, which indicate that these test strategies would probably have met the criteria for inclusion in our cost-effectiveness analyses, had these data been available. Unfortunately, the publication of this article post-dates our searches and, although the company's response to the request for information NICE included the general statement (in relation to the High-US study) that 'further publications are expected over the next 12 months,' no specific details were provided and no pre-publication AiC copy of the article was provided; consequently this article has not been included in the assessment and cannot be added to the report at this stage.

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					If NICE wish to include a copy of the article in the information for discussion at the DAC, we would be happy to provide comment separately.
Siemens Healthineers	7	81	3.2.10 Diagnostic accuracy of the Siemens ADVIA Centaur hs-cTnI assay	Body R et al. Single test rule-out of acute myocardial infarction using the limit of detection of a new high-sensitivity troponin I assay. *Clinical Biochemistry* 2020 Additional literature publication published Feb 2020. The Siemens ADVIA Centaur hs-cTnI assay has high sensitivity and NPV to rule out AMI with a single blood test in the ED. At the LoQ cut-off a sensitivity >99% can be achieved. At a 5 ng/L cut-off it may be possible to rule out AMI for over 50% patients.	This article also meets the inclusion criteria for this assessment. Please see response to comment 6, regarding search dates and provision of pre-publictaion AiC information. If NICE wish to include a copy of the article in the information for discussion at the DAC, we would be happy to provide comment separately. Please also note that the lead author of this article is a Specialist Committee Member for this topic.
Siemens Healthineers	8	31	2.2.11 Dimension Vista high-sensitivity troponin I assay (Siemens Healthineers)	The assay has a recommended 99th centile cut-off of 58.9 ng/L for lithium heparin samples and 57.9% for serum samples. Should read The assay has a recommended 99th centile cut-off of 58.9 ng/L for lithium heparin samples and 57.9ng/L for serum samples.	Corrected text has been provided.
Beckman Coulter	9	20	EXECUTIVE SUMMARY - Assessment of clinical effectiveness	The statement that two studies reported accuracy data for Beckman Coulter Access hsTnI does not account for the publication by Greenslade J, et al. Clin Chem 2018;64(5):820-829.	This article was identified by our searches, but did not meet the criteria for inclusion in this assessment, in respect of the study participants. The article reports a study using stored frozen samples from two clinical studies. One of these

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					studies included an appropriate population "Eligible patients were recruited if they were ≥18 years of age, had ≥5 min of chest pain consistent with ACS, were undergoing investigation for potential ACS and had provided informed consent." However, the second study only included "those for whom the clinician was comfortable with accelerated testing."
Beckman Coulter	10	20	EXECUTIVE SUMMARY - Assessment of clinical effectiveness	The statement that only the Siemens Atellica and Siemens ADVIA Centaur hs-cTnI assays were evaluated using a single presentation sample rule-out strategy is not accurate. Beckman Coulter evaluated using a single presentation rule-out strategy in 2018 (see Greenslade J, et al. Clin Chem 2018;64(5):820-829)	Please see response to comment 9.
Beckman Coulter	11	22	EXECUTIVE SUMMARY - Assessment of cost-effectiveness; *Secondary analysis*	The following sentence: Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) was the most effective testing strategy (11.4725 QALYs) at higher costs (£38,077) does not match the information in table 32 as the QALYs refers to 18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	Corrected text has been provided. "Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h))" has been replaced by "Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))"
Beckman Coulter	12	28	2.2 Subsection 2.2.3	In the 2.2 section introduction it indicates "The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals. This information is provided in each subsection for some assays listed.	This information has been added to section 2.2.3 (correction provided)

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				This is also true for Beckman Coulter hsTnI and is supported by the product labelling in the instructions for use and several peer-reviewed publications (e.g. Lippi G et al. Clin Chem Lab Med. 2017;56(1):157-161 and Pretorius et al. Clin Biochem. 2018 May;55:49-55) however this statement is missing from the description of Beckman Coulter's assay in section 2.2.3	
Beckman Coulter	13	28	2.2.3	In this section it indicates "the turnaround time of the assay is to be confirmed by the company" Beckman Coulter confirms the turnaround time of the assay is 17 minutes. This information is already displayed in Table 1 on page 32 of the document.	Corrected text has been provided.
Beckman Coulter	14	32	Table 1	Please update the table with Access hsTnI info from our OUS IFU claims: **99th centile (ng/L)** Female: 11.6; Male: 19.8; Overall: 17.5 **CV at 99th centile (%)** Female: 4.2; Male: 3.6; Overall: 3.7 **LoD (ng/L)** 2.3 **LoQ (ng/L)** 2.3	Up-dated text has been provided.
Beckman Coulter	15	45	3.2.1	Two studies reported accuracy data for Beckman Coulter ACCESS hs-cTnI; 58 is cited as the reference, it should be 60 & 171	This is not a referencing error; as noted at the start of section 3.2.1. Studies are cited using the primary reference (in this case for the APACE study), unless the citation accompanies specific data which have been taken from another publication.

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Beckman Coulter	16	45	3.2.1	One study on diagnostic accuracy of Beckman Coulter Access hsTnI is missing: Greenslade J, et al. Clin Chem 2018;64(5):820-829	Please see response to comment 9.
Beckman Coulter	17	48	Table 3	Update Beckman Coulter Access hsTnI section with Reference 60 and 2018 Greenslade LoD paper (Greenslade J, et al. Clin Chem 2018;64(5):820-829)	Please see response to comment 9. Reference 60 is included in Table 3 (under the APACE study).
Beckman Coulter	18	79	3.26	The statement that 'no single sample strategies were assessed' does not account for the publication by Greenslade J, et al. Clin Chem 2018;64(5):820-829)	Please see response to comment 9.
Beckman Coulter	19	79	3.2.6	In this study, 1/116 (0.9%) with NSTEMI were missed using the ESC 0/1 hour rule-out criteria.	The figure of 1/96 (1.04%) given in our report was calculated using the data for the validation cohort (figure 3b of reference 60) and is correct. The combined prevalence from the rule-in and observe categories gives a total number of TP of 95; this combined with 1 FN, gives the total number of NSTEMI of 96.
Beckman Coulter	20	89	3.2.13	"…only the Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays were evaluated in the same patient subgroup, reported in a single publication.59 For this reason, the comparison between Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays has been rated low risk of bias with respect to the flow and timing domain of QUADAS-2C, whilst the all tests comparison was rated high risk of bias (see Table 6, section 3.2.2)." This statement is not accurate. Roche Elecsys hsTnT, Abbott ARCHITECT hsTnI and Beckman Coulter Access	We acknowledge the point made, with respect to reference 60. Both references 59 and 60 relate to data from the APACE study. In order to avoid 'double counting' of participants, we have only extracted one data set per. study for each unique test strategy. In this instance data for the ESC 0/1 hour strategy and the APCAE study have been taken from reference 50 for the Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays and from reference 60 for the Beckman Coulter

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				hsTnI were also evaluated in the same patient subgroup from the APACE trial reported in a single publication. (REF 60) Beckman Coulter Access hsTnI should be rated low risk of bias using the same criteria stated above.	Access hsTnI assay. Hence, for the data included in this assessment it is correct to say that the comparison of all four studies is at high risk of bias, with respect to the flow and timing domain of QUADAS-2C. It is the 4-way comparison that is associated with the high risk rating, and not (as suggested by the comment) the Beckman Coulter Access hsTnI assay itself. This would be the case irrespective of which publication data were taken from, since no publication reports data for all four assays.
Beckman Coulter	21	119	Table 25	PPV for 17 Beckman Coulter ACCESS hs-cTnI (ESC pathway) is displayed as 0.00, this would appear incorrect.	Corrected text has been provided.
Beckman Coulter	22	127	4.4.1	Misspelling of Beckmann – should read Beckman	Corrected text has been provided.
Beckman Coulter	23	133	4.4.2	The following sentence: Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) was the most effective testing strategy (11.4725 QALYs) at higher costs (£38,077) does not match the information in table 32 as the QALYs refers to 18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	Corrected text has been provided. “Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h))” has been replaced by “Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))”
Beckman Coulter	24	139, 140	4.4.3	Misspelling of Beckmann x 6 – should read Beckman	Corrected text has been provided.

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Beckman Coulter	25	145	5.1.1	The statement that only the Siemens Atellica and Siemens ADVIA Centaur hs-cTnI assays were evaluated using a single presentation sample rule-out strategy is not accurate. Beckman Coulter evaluated using a single presentation rule-out strategy back in 2018 (see Greenslade J, et al. Clin Chem 2018;64(5):820-829. doi: 10.1373/clinchem.2017.283887.)	Please see response to comment 9.
Roche Diagnostics	26	126	Sensitivity and scenario analyses	We would like to clarify that £6.05 is the list price for Elecsys TnT. This is not the typical price paid by the NHS. Because lab contracts are so variable; managed service models, discounts for both scale and scope, cost-per-reportable models etc. it is not possible for us to define an estimated average price. We suspect that some of the other prices provided in this list are not list prices. We therefore do not think that this sensitivity analysis is meaningful and would request that it is removed or that list prices are checked and used for all products. Overall, we support the assumption of equal test costs.	We acknowledge that the scenario analyses using test costs provided by manufacturers are only as good as the information provided, and different companies may have provided prices based on different assumptions. It is for this reason precisely that we opted to only reflect prices indicated by manufacturers in scenario analyses. We would, however, be reluctant to remove these scenarios altogether, as we have requested the information in a standardised manner and the scenarios may spark discussion. It is then up to the committee to decide whether these analyses are plausible and/or informative.
Roche Diagnostics	27	33	Overview of cardiac biomarkers	Proposal for changes to Elecsys LOQ We believe that other manufacturers have submitted LOQs that have been updated from their initial specification. Our initial specification used an LOQ of 13ng/l but there are additional data within our Package Insert which show the level that is achieved in practice across the different Cobas e instruments.	Up-dated text has been provided.

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				These data have been generated using the Clinical and Laboratory Standards Institute guidelines (CLSI) EP7 2A for the verification of our detection capability claims i.e. limit of Blank, Detection and Quantitation. In light of this we propose changing the LOQ from 13ng/l to "2.97-6.60ng/l achieved across the different cobas e platforms".	
Roche Diagnostics	28	148	Discussion	Although we understand that it is difficult to include data from the Chew 2019 RCT in the economic model, we believe it would be worthwhile including in the overall review and the DAP committee's considerations. This is because it provides RCT level evidence that the Elecsys rapid 0-1 hour rule-out algorithm enables faster discharge without being associated with poorer patient outcomes.	As noted in the discussion section (referenced in the comment), this study does not meet the inclusion criteria for this assessment. However, the points of interest were noted, and are included in the discussion section of our report.
Roche Diagnostics	29	79	Diagnostic test accuracy	Section on the DTA of Beckman-Coulter multiple test strategies. We feel it should be highlighted here that for Strategy 18, underpinned by study ref 64 that there are reasons to be suspicious of the data. The reported specificity of 0.83 appears implausibly high compared to the other 20 strategies and has been derived from a cohort with a prevalence of only 6.9%, which is much lower than the majority of the evidence base. We would note that this study comprised a derivation cohort, where the algorithm had a specificity of 0.64 and the validation cohort, which provide the DTA data used in the economic model. It make also be worth highlighting this in the conclusions as this strategy performs well in the PSA derived results.	It is certainly the case that the prevalence of NSTEMI varies widely across the studies included in our systematic review (see Appendix 2, Table 37). The estimated UK prevalence of NSTEMI, for the population specified in the inclusion criteria for this assessment, was 12.2% (see Discussion, section 5.1.1). The prevalence of NSTEMI (calculated from included studies) for the test strategies included in our cost-effectiveness analyses ranged from 6.9% for the Beckman ACCESS strategy 18 noted in the comment (please note that source data are from ref 171, not ref 64 as indicated in the comment) to 17.2%. The only other test strategy with an

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					associated NSTEMI prevalence <10% was the Roche Elecsys strategy 4 (ref 87), prevalence 8.1%. The variation of NSTEMI prevalence across included studies may be a topic for discussion by the committee.
Roche Diagnostics	30	125	4.3.1	It is not entirely clear how the secondary analysis works. If it is to be included (see our comment on the model comments form) we would ask that more detail is added here.	The secondary analysis is identical to the secondary analysis provided in the original DAR. The model file, including this analysis was circulated to relevant stakeholders for consideration of the technical implementation of this scenario.