EUnetHTA JA3 WP4 - Other technologies, OTCA22
Comments by external experts and fact check by manufacturers of the 2nd draft rapid assessment on POINT OF CARE TESTS: D-DIMER AND TROPONIN

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Summary					
AS	11		Warfarin is not usually prescribed in Austria - much wider use of Acenocoumarol or Phenprocoumon.	2	As suggested, we have reviewed the websites of the HVB but couldn't find relevant data on prescription of acenocoumarol or Phenprocoumon. This remains a limiation of our report!
AS	15		I don't understand why it was not possible to find out which POCT are in use in Austria. It should be possible to inquire with GPs and emergency departments, shouldn't it?	2	We received data from the HVB (German: Abrechnungsdaten). There are no information on which of these POCTs are currently in use. If we ask some EDs or GPs, the generalisability may significantly suffer. As a result, we have decided to keep the broad scope of the assessment (all POCTs)
AS			You should use consistently POCT instead of POC.	3	We used POC as point of care and POCT as point of care test(s). We checked throughout the document as to whether POCT was used instead of POC incorrectly (or vice versa).

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AS	28		What is the "Geneva <2 Model"?	2	Geneva ≤2 refers to the cut-off when using the Geneva score.
AS	29		What is "gestalt"?	3	Physician's unstructured estimate ("gestalt"). We have added a footnote to clarify this.
AS	31		The evidence from studies?	2	We changed to: "The identified evidence updating the overview of reviews (...)".
Scope					
AS	34	Table 1-1	Why did you choose this time restriction? Maybe you should provide the reason.	2	Change to: "Publications published from 2009 onwards will be included (to identify recently published systematic reviews)".
AS	37	Table 1-2	Why did you choose this time restriction? Maybe you should provide the reason.	2	Change to: "Studies published from 2009 onwards will be included (to identify recently published studies/systematic reviews)."
Methods and evidence included					
AS	39	283	May I suggest to check Dynamed as well as it usually provides more "up-to-date" information than UpToDate.	2	We do not have access to Dynamed.
AS	40	296	Did you apply limits to time and languages?	2	Yes we did, but not within the search strategy (at a later stage). We clarified this in the report.
AS	45	376	Why 2009?		We used a time filter of 2009 because we were interested in recent publications on the topic. In addition, it is common practice to

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					filter publications RE time. Afterwards, we updated/extended scope of the results of identified SRs.
AS	50	419	What does NR stand for?	3	Not reported: we inserted this.
Description and technical characteristics of the technology					
Abbott	33	799	Please correct the test name from "i-STAT CtnI CARTRIDGE (Abbott Diagnostics)" To "i-STAT cTnI (Abbott Point of Care)"	1	Changed accordingly.
Roche	33	Table 331	Roche CARDIAC Troponin T, **cobas h** 232		Changed accordingly.
Abbott	33	799	The Minicare I-20 Troponin I is not on the market anymore and Philips had divested the product.		The website is still live[1] It appears that there may be more tests that may not be on the market anymore. Hence, we have left it as it is and discussed this point in the discussion (= that there may be tests that are not on the market anymore).
Abbott	34	824	Please correct the test name from "i-STAT CtnI CARTRIDGE (Abbott	1	Changed accordingly

[1] See https://www.philips.com.bh/healthcare/product/HCNOCTN496/minicarei20enablingnearpatientbloodtestingintheacutecaresetting

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			Diagnostics)" to "i-STAT cTnI (Abbott Point of Care)"		
Abbott	34	824	Correct Storage Requirements: Refrigerated at 2 to 8 ºC until expiration date. Up to 14 days at room temperature (20 to 25ºC). Individual cartridges may be used after standing five minutes at room temperature. All cartridges should be used immediately after opening pouch.	1	Corrected
Abbott	34	824	Connectivity: Wireless or wired data transfer (pending on i-STAT analyzer used) with flexible connectivity and interfacing software solutions, e.g. Abbott Info HQ.	1	Corrected
Abbott	34	824	Print Function: Yes, via separate i-STAT printer	1	Corrected
Abbott	34	824	Data storage on device: Up to 1,000 test records	1	Corrected
Radiometer Medical ApS	37	Table 3-3	Please correct for AQT90 FLEX cTnI the following:	2	Corrected
Radiometer Medical ApS	37	Table 3-3	Sample size: 2 mL whole blood (for up to 5 tests)	2	Corrected
Radiometer Medical	37	Table 3-3	Reportable range: 0.01-25 µg/L (ng/mL)	2	Corrected

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ApS					
Radiometer Medical ApS	37	Table 3-3	Coefficient of variation: 0.021 µg/L: CV = 12.9 % 0.035 µg/L: CV = 7.7 % 9.2 µg/L: CV = 4.4 %	2	Corrected
Radiometer Medical ApS	37	Table 3-3	Storage requirements: Whole blood: 2 hours at 18-25 °C Plasma: 2 hours at 18-25 °C Plasma: 24 hours at 2-8 °C Plasma: >24 hours at -18 °C	2	Corrected
Radiometer Medical ApS	37	Table 3-3	Cut-off: 99th percentile: 23 ng/L	2	Corrected
Radiometer Medical ApS	37	Table 3-3	Please correct for AQT90 FLEX cTnT: Cut-off: 99th percentile: 17 **ng/L**	2	Corrected
Radiometer Medical ApS	43	Line 898 Section A0021	Information on reimbursement in Europe: AQT90 FLEX analyzer technology is recommended for use in all European countries listed in the table. Countries marked with a "Y", provides reimbursement of the assays in question.	1	Corrected/ inserted the table. Many thanks for providing this information.

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<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Country</th><th>cTnI</th><th>cTnT</th><th>D-dimer</th></tr>
<tr><td>Austria</td><td></td><td></td><td></td></tr>
<tr><td>Italy</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Lithuania</td><td></td><td></td><td></td></tr>
<tr><td>Belgium</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Nederlands</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Czech Rep.</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Denmark</td><td></td><td></td><td></td></tr>
<tr><td>Germany</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Spain</td><td></td><td></td><td></td></tr>
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<tr><td>Hungary</td><td>Y</td><td>Y</td><td>Y</td></tr>
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<tr><td>Turkey</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>Finland</td><td></td><td></td><td></td></tr>
<tr><td>Norway</td><td></td><td></td><td></td></tr>
<tr><td>Sweden</td><td></td><td></td><td></td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Radiometer Medical ApS</td><td>43</td><td>Line 919-920 Section</td><td>It seems to be a misunderstanding that manufacturers in general use other matrices than blood for performance characteristics, however this is not the case for the AQT90 FLEX assays where imprecision data comes</td><td>1</td><td>To reduce misunderstandings, we have deleted the following sentence:</td></tr>
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		B0018	from native or antigen-spiked lithium-heparin plasma and whole blood pools. Reference to attached IFUs for AQT90 FLEX TnI and TnT.		"That is, manufacturers usually do not use patient specimens. Rather, different matrices are used instead"
Abbott	43	908	Consider to add Acute and/or Ambulatory Care Centers (Weihser & Giles, British Journal of Hospital Medicine, Sept 2018, Vol 79 (9), 520-523)	2	We decided to leave it as it was.
AS	65	605-608	Maybe the Gebietskrankenkasse or Hauptverband could comment on this question.	2	We received and inserted some information on this from the manufacturers.
Health problem and current use					
SR	47	1046	Marburg Herz Score: tests probability for CHD, not valid fpr ACS. Algorithm for PC for ACS: Degam Leitlinie Nr.15, Brustschmerz		OK, we deleted the sentence on the Marburg Heartscore completely!
SR	47	1055	Suspecting ACS: thorough cardiovascular examination neither possible nor useful in an outpatient setting (contradiction to first part of sentence		This was cited from the AHA guideline, which applies to the U.S. where care is organised in a different way. That is why we deleted the sentence because we realised this is not applicable for the European setting.
SR	48	1058	First line diagnostic tool is clinical assessment, in case of suspicion of ACS (which is an outcome of first assessement!) ECG is next step		We deleted the numbering of the paragraphs which might have been confusing and amended the text. The clinical assessment is the first step including the physical examination and obtaining the medical

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					history. The ECG is the next step. Biomarkers complement the initial clinical assessment and the ECG.
SR	50	1124	nT POCT testing cannot rule out ACS (UA), only MI if symptoms persist for 12 hours – so rarely spares admission. It can in case of positive result help decide on where to send the patient and by what kind of transport (PCI via helicopter e.g.)		We value the critique and will try to make it more transparent throughout the report that Tn-POCT cannot rule out ACS. We specified that Tn-POCT can spare the referral of MI patients to an inpatient unit in cases where there are no ischemic ECG changes, if there is clinical ambiguity, and if symptoms last for more than 12 hours (this is cited from the DEGAM guideline).
SR	52	1234	Cinically ruling out DVT/PE hardly possible – once suspicion arose (on clinical grounds).		We changed to: 1. "Measurement of the **D-dimer** level in the blood has a role in the exclusion of DVT in oligosymptomatic patients as a negative D-dimer assay implies that thrombosis is not occurring. On the other hand, a positive test can indicate not only thrombosis but also other causes, such as liver diseases, inflammation, malignancy, pregnancy, trauma, and recent surgery. With the change of the

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					three-level scoring to the two-level scoring, the patients in the unlikely group can be more safely ruled out when the pre-test probability is combined with D-dimer testing [85]."
Clinical effectiveness					
SR	68	1781	If it is used according to rules it must have an influence on subsequent interventions: it is apt to rule out DVT/PE together with e.g. Wells (under preconditions described in the text) and thus reduce further testing/hospitalisation in case testing is not available in outpatient care. Suppose this aspect lacks research, since in many countries testing is routinely used in PC settings.		How exactly should we change this? We suggest the following change (in red): **[D0026] – How does the technology modify the effectiveness of subsequent interventions?** ***Morbidity*** Answer: There is no evidence that the D-dimer test has an influence on subsequent interventions for venous thromboembolism. However, subsequent interventions (e.g., imaging) are likely to be influenced.

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SR	68	1799	Same. Saving further investigations including their associated risks is patient relevant.		No change. In line 1799 solely the data on diagnostic accuracy are presented.
SR	72	1968	Not quite: D-Dimer an Tn are being used, but no quantification possible because the costs are not refunded – so no data available.		We changed it in text: "For the use of Tn-POCT in general practice, one expert states GPs who perform acute medicine or emergency medicine or so-called "Gemeinde- und Sprengelärzte" may have access to troponin testing if they are far away from hospitals or centres. However, it is highlighted that Tn testing must not be interpreted without at least clinical history, presentation and ECG reading. Another clinical expert reflected on the Austrian system that is quite hospital-based, meaning that the patients are usually referred to the hospital quickly where no Tn-POCT is done. The ED would usually have access to CL testing. Another expert mentions that no quantification on the use of Tn-POCT is possible because it is not refunded. For the use of troponin as a diagnostics in

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					the context of ACS, one clinical expert specifically mentions that the current ESC guideline is to be followed [14]. For D-dimer POCT, one expert did not specifically reflect on the use of D-dimer POCT in general practice or ED and another expert mentioned that D-Dimer is being used, but no quantification possible because the costs are not refunded. One further expert did not know if the D-dimer test is used currently in office-based practices in Austria. ". AND in the appendix Answer to Q1: 1. "In General practices (randomly – not refunded everywhere: either patient or doctor pays testing), hospital outpatient units (emergency rooms). D-Dimer and Tn are being used, but no quantification possible

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					because the costs are not refunded"
Safety					
SR	71	2186	This is wrong. Both tests are meant to be used by doctors because indication (!!) and interpretation need specific clinical expertise. Austrian family doctors do have (must have) this expertise.		We will see what the other experts will say (maybe we misinterpreted it as a whole). If we did not misinterpret it, I would suggest to make the following change (this needs to be validated by all authors (RO+AT) yet: "In terms of the Austrian situation, some experts believed that D-dimer POCT could only have a limited role outside the hospital setting at present, because of the shortage in the training and expertise required to correctly interpret the results alongside the pretest probability. In addition a prerequisite for the use of the test is familiarity with and routine use of clinical decision rules, which may not be the case in ambulatory care settings in Austria, unlike other healthcare systems with a strong primary care sector. However, one of the consulted experts

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					believes that Austrian family doctors do have (must have) the needed expertise to use D-dimer POCT. This expert mentions that the goal is hereby to avoid unnecessary hospitalisations, and the test would be able to do that to a relevant extent. Furthermore the time element is not considered to be as crucial for D-dimer as there is less danger in the patient waiting to attend hospital and have further tests there."
SR	71	2191	Difficult to understand. D-Dimer is meant as a tool to avoid hospital admission, since it is understood to be apt to rule out DVT/PE in case of low pretest probability. PE/DVT are potentially dangerous conditions, and very often oligosymptomatic, thus very hard to be ruled clinically. Correct is: it is not confirmation of diagnosis, that is the aim of preclinical testing. This latter can indeed wait for inpatient care.		Redundant after changes (see above).
SR		1976			We added a further sentence from your expert summary for d-dimer: "However, one experts interprets the D-dimer test as highly valuable in general

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					practice according to own experience, while this expert had no experience with Tn-POCT in general practice, highlighting that no exclusion is possible with this test: D-dimer: yes (see above; (fear or symptoms of) DVT and PE rather frequent reasons for encounter: highly valuable in daily practice, Troponin: no – no exclusion possible, applicable after hours after symptom onset, so rather infrequent and good chance or expiring unused (no refund either)"
Discussion					
AS	97	1782	In my opinion the lower sensitivity of Tn-POCT compared to CL makes as clearly advice against the use, because it will lead to missing diagnoses.		OK. Thank you for the input. We think it is in line with our conclusion. A major limitation of our report is that we included several different tests. So narrowing the intervention to the ones with the best diagnostic accuracy may lead to a more definitive answer/conclusion for clinical utility to use these tests.

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AS	98	1811	What about the DEGAM Guideline which advises against the use of Tn-POCT. And one of the reviews found that due to low sensitivity Tn-POCT leads to a reduction in referral-rate at the cost of missing patients with ACS. I think this would be worth discussing here.	2	Thank you. We have inserted the recommendation from the DEGAM guideline in the discussionsection as well: "One guideline [15] recommends not to use qualitative troponin tests routinely in primary care to exclude an acute myocardial infarction"
AS	98	1841	This is only true in a low pre-test probability setting to rule out the small chance of DVT or PE. If there is a high pre-test probability (from the history, symptoms or physical findings), further evaluation and hospitalisation should not be delayed due to a negative D-Dimer-POCT.	2	We complemented the sentence. "Eight out of ten guidelines conclude that POCT can be used to exclude suspected PE or DVT in combination with low pre-test probability. "
AS	99	1854	In a low pre-test probability setting.	2	We complemented the sentence.
AS	99	1901	Sentence is not understandable.	2	We changed to: "In the context of diagnosis and treatment of acute coronary syndrome, for instance, there are different algorithms. Usually these are dependent on the sensitivity of the devices used to measure troponin and of when troponin is tested. "

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AS	162		this sentence is not understandable, please check grammatical structure	3	Typo. Of instead of if. We corrected it.

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