EUnetHTA JA3 WP4 - Other technologies, OTCA12: C-reactive protein point-of-care testing (CRP POCT) to guide antibiotic prescribing in primary care settings for acute respiratory tract infections (RTIs)

Comments form for manufacturers – Fact Check

Comment from ***Insert your company's name***	**Page number**	**Line or section number**	**Description of factual inaccuracy and proposed amendment** ***Please insert each new comment in a new row.***	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** ***Please indicate your choice by writing the according number in this field, e.g. for major choose "1".***	**Authors' reply**
Abbott	15	row 6	The overall time taken for the test to be performed was an important factor with times ranging from just over three minutes (QuikRead) to over 13 mins (AQT90 Flex), but it is unclear from the literature what time period would be considered acceptable in the primary care setting. **Change to:** The overall time taken for the test to be performed was an important factor with times ranging from just over three minutes (Afinion 2, QuikRead) to over 13 mins (AQT90 Flex), but it is unclear from the literature what time period would be considered acceptable in the primary care setting.		These data relate only to the findings of systematic review 3. No data were identified for the Afinion 2 device in this review.

RPS Diagnostics	16	Upcoming evidence	Please be advised of the following planned trial for FebriDx® The protocol of the trial listed on clinicaltrials.gov (Study Identifier:NCT02018198) is currently being updated to reflect the details below. Study Identifier:NCT02018198 Trial Name: DIStinguish Respiratory Underlying Pathogen associaTed host response in Upper Respiratory Infection: An Evaluation of FebriDx POC Test (FebriDx ®DISRUPT URI Trial) Estimated start date : 04/2019 Study type: Prospective observational study Number of patients: 1,225 Intervention: FebriDx ® Comparator: Expert clinical reviewers' evaluation in conjunction with the results of clinical standardised microbiologic and laboratory testing (Clinical reference algorithm) Patient population: Patients (one year and older) presenting with reported fever and acute respiratory symptoms to primary care and urgent care outpatient offices and emergency departments Endpoints: The primary analysis will determine performance characteristics of FebriDx test by assessing negative and positive agreement of FebriDx results in determining the presence of a bacterial associated systemic host immune response or viral associated systemic host immune response compared with a Clinical Reference Algorithm (comparator method) that is supervised by clinical experts.		Thank you. Now included in the upcoming evidence and in Table
Abbott	38	Table 7 column 5 (Afinion)	Manufacturer: Abbott GmbH Change to: Abbott Diagnostic Technologies AS		Changed as suggested.

Abbott	38	Table 7 column 5 (Afinion)	Reference codes: **Alere Afinion™ CRP:** 1116526, 1116522, 1116524, 1116058 (15 tests) and **Afinion™ AS100 Analyser:** 1116049 or **Alere Afinion™ 2 Analyser:** 1116556 **Alere Afinion™ CRP control:** 1116057 Change to **Alere Afinion™ CRP:** 1116526, 1116522, 1116524, 1116023 (15 tests) and **Afinion™ AS100 Analyser:** 1116049 or **Afinion™ 2 Analyser:** 1116679, 1116680, 1116681 **Alere Afinion™ CRP Control:** 1116057		Changed as suggested.
Abbott	38	Table 7 column (NycoCard)	Manufacturer: Abbott GmbH Change to: Abbott Diagnostic Technologies AS		Changed as suggested.
Abbott	38	Table 7 column (NycoCard)	Software updates: Not reported Change to: Not possible		Changed as suggested.
Abbott	39	Table 7 column 5 (Afinion)	**Analyser warm-up** **Time:** 4 min Change to Afinion AS100: 3 minutes Afinion 2 Analyzer: 1 min 30 seconds		Changed as suggested.
Abbott	39	Table 7 column 5 (Afinion)	Performance time for pre- and actual analysis:4.25 min (= 30 s + 3.75 min) **Change to:** For Afinion AS100 4.25 min (= 30 s + 3.75 min) For Afinion 2: 3.30 min (=30 s + 3.00 min)		Changed as suggested.

Abbott	39	Table 7 column 5 (Afinion)	Practical aspects of tests: Auto-self check with integrated error detection. Error codes possible due to small sample volume that quickly dries out). Analyser cannot be moved if on. Change to Auto-self check with integrated error detection. Error codes possible due to small sample volume that may dry out after the 1 minute limit instructed in the package insert. Analyser cannot be moved if on.		Changed as suggested.
RPS Diagnostics	43	Table 7 Reference Codes (FebriDx)	**Description of factual inaccuracy**: Reference Codes entered as ‚Not Provided' **Proposed Amendment**: FebriDx BP0036 (25 CRP test kit)	2	Changed as suggested.
RPS Diagnostics	43	Table 7 Class/GMDN Code (FebriDx)	**Description of factual inaccuracy:** CE Mark approval. Updated CE, mark for submission in July 2018.No information on class or GMDN. **Proposed Amendment:** CE Mark updated in October 2018. Please delete current info and replace with the following "*Declaration of conformity with directive 98/79/EC for IVD medical devices*". GMDN: 64042	2	Changed as suggested.
RPS Diagnostics	44	Table 7 Analytical Range (FebriDx)	**Description of factual inaccuracy:** CRP ≥ ~ 20 mg/L and ≥ ~ 65mg/L; MxA ≥ ~40 **Proposed Amendment:** qualitative thresholds: CRP ≥ ~ 20 mg/L; MxA ≥ ~40ng/ml	2	Changed as suggested.
RPS Diagnostics	44	Table 7 Performance time for pre- and actual Analysis (FebriDx)	**Description of factual inaccuracy:** 11 min (= 1 min + 10 min*) (*analysis time to confirm positive result; negative result confirmation should be less than 15 min) **Proposed Amendment:** The entire test takes 10 minutes from start to finish, we prefer not separate performance and time to result (performance + time to result = 10 minutes). Analysis time should not exceed 3 hours of results being displayed.	2	Changed to: 10 min (= performance + time to result). Analysis time should not exceed 3 hours of the results being displayed.
RPS Diagnostics	44	Table 7 Practical aspects of the test (FebriDx)	**Description of factual inaccuracy:** Semi-quantitative test. FebriDx does not require any additional ancillary equipment. FebriDx "high CRP" reading suggests 65mg/L or more which is <100 mg/L. Can involve considerable time to result. **Proposed Amendment:** ~~Semi-quantitative test.~~ FebriDx does not require any additional ancillary equipment. FebriDx "high CRP" reading suggests 20 mg/L or more. ~~which is <100 mg/L. Can involve considerable time to result.~~ Please remove struck text. Time to result is approximately 10 minutes and thus 'can take considerable time to result' is not factually accurate.	1	Changed as suggested.

RPS Diagnostics	44	Table 7 Size & Weight (FebriDx)	**Description of factual inaccuracy:** blank **Proposed Amendment:** Please add, light weight, hand held device (0.073 kg; 29cm x 20cm x 14cm)	2	Amended to N/A as reflect analyser size and weight. No analyser required for semi-quantitative devices
biosurfit	44		Change analytical range to 2-180 mg/L. Current test presented in the market uses this range.	2	Changed as suggested.
biosurfit	44		Change haematocrit auto-correction to NO.	2	Changed as suggested.
biosurfit	44		Change performance time to 5 min. (= 1min + 4min), to be comparable to what is written in other comparators. As it is written (including waiting time only on spinit), will give the perception that spinit system needs more time. Other comparators produtcs also have to wait some minutes to reach room temperature.	2	5 min (= 1 min* + 4 min) (*however wait-time of at least 3 mins after fridge removal before opening pouch)
biosurfit	45		Add data storage information: YES	2	Changed as suggested.
RPS Diagnostics	45	Table 7 Data storage on device (FebriDx)	**Description of factual inaccuracy:** blank **Proposed Amendment:** Please add, Results display for 3 hours	2	Changed as suggested.
RPS Diagnostics	45	Table 7 Quality Checks (FebriDx)	**Description of factual inaccuracy:** blank **Proposed Amendment:** Please add, External controls are available.	2	Changed as suggested.
RPS Diagnostics	45	Table 7 Training & Support (FebriDx)	**Description of factual inaccuracy:** Training provided through UK distributor (NICE MIB July 2017) **Proposed Amendment:** Please add, Training provided through UK distributor as well as RPS Detectors.com or FebriDx.com (NICE MIB July 2017)	2	Changed as requested.
RPS Diagnostics	45	Table 7 Data storage on device (FebriDx)	**Description of factual inaccuracy:** blank **Proposed Amendment:** Please add, Results display for 3 hours	2	Changed as suggested.
RPS Diagnostics	45	Table 7 Quality Checks (FebriDx)	**Description of factual inaccuracy:** blank **Proposed Amendment:** Please add, External controls are available.	2	Changed as suggested..

<table>
<tr>
<td>RPS Diagnostics</td>
<td>94, 97 or 98</td>
<td>Omission of FebriDx Diagnostic Accuracy data</td>
<td>
<u>Description of factual inaccuracy:</u> Authors indicate that the FebriDx data did not meet the inclusion criteria for the setting (specifically in reference to LRTI). Although this is partially true (where stated in the document), since FebriDx is mentioned as a CRP POC device (with MxA), we would proopose the addition of FebriDx's diagnostic accuracy in the two studies reference (160, 161) for completeness. Since the diagnostic accuracy tables (14, 17, 18, 19) are categorized by clinical diagnosis (sinusitis, pharyngitis, LRTI) it is difficult to report FebriDx study (160, 161) diagnostic accuracy findings since the studies were a composite of these clinical diagnosis (i.e. Acute bronchitis, pharyngitis, sinusitis were defined as acute upper respiratory tract infection). Nevertheless, readers should be informed of the FebriDx test performance in comparison to the other CRP POC devoices

<u>Proposed Amendment:</u> RPS would request the addition of the diagnostic accuracy findings as described in the included references, 160, 161 to the discussion in either of the following sections: (pg. 94: Determining the optimal threshold in combination with signs and symptoms or pgs. 97/98 [D1002] - How does the test compare to other optional tests in terms of accuracy measures?).

The diagnostic accuracy of FebriDx® has been evaluated in both children and adults with observed or reported fever and acute uppper respiratory tract infection (URI) in the outpatient setting (160, 161). Two prospective, multi-center clinical trials enrolled patients age > 1 year, with a new fever ≥ 100.5ºF <u>reported</u> or <u>exhibited</u> within the past 3 days of visiting the emergency department, urgence care or primary care center, and new onset of cough or sore throat within the past 7 days. FebriDx® was compared to a Clinical Reference Algorithm which included (i) the identification of pathogen presence (via viral/bacterial PCR and bacterial culture) as well as measures of host-response (Procalcitonin, WBC, lyphocytosis, bandemia, EBV IgM) and was found to have better diagnostic accuracy than standalone CRP or PCT for identifying clinically significant viral and bacterial URI. Diagnostic performance sumarized below:

<table>
<tr><th>Device</th><th>Population</th><th>Sample Size</th><th>Confirmed Fever at Time of Testing (Hyperthermia)</th><th>Nonfebrile - Reported Fever Within Past 3 Days</th><th>Bacterial Sensitivity (95% CI)</th><th>Bacterial Specificity (95% CI)</th><th>Bacterial PPV (95% CI)</th><th>Bacterial NPV (95% CI)</th><th>Citation</th></tr>
<tr><td>FebriDx MxA + CRP</td><td>Outpatient/ER</td><td>205</td><td>13% (26)</td><td>87% (179)</td><td>80% (61-91)</td><td>93% (89-97)</td><td>62% (47-79)</td><td>97% (94-99)</td><td>160</td></tr>
<tr><td rowspan="2">FebriDx MxA + CRP</td><td>Outpatient/ER</td><td>220</td><td>55% (121)</td><td>45% (99)</td><td>85% (69-95)</td><td>93% (89-96)</td><td>69% (56-79)</td><td>97% (94-99)</td><td rowspan="2">161</td></tr>
<tr><td>Outpatient/ER</td><td>121</td><td>100% (121)</td><td>None</td><td>95% (77-100)</td><td>94% (88-98)</td><td>76% (59-87)</td><td>99% (93-100)</td></tr>
<tr><td>Standalone PCT 0.25 ng/ml</td><td>Outpatient</td><td>220</td><td>55% (121)</td><td>45% (99)</td><td>41%</td><td>94%</td><td>54%</td><td>90%</td><td>161</td></tr>
<tr><td>Standalone CRP 20mg/L</td><td>Outpatient</td><td>209</td><td>55% (115)</td><td>45% (94)</td><td>81%</td><td>51%</td><td>23%%</td><td>94%</td><td>161</td></tr>
</table>

Moreover, 38%-56% of viral infections were associated with a CRP ≥ 20 mg/L and the FebriDx test was found to have a 97-99% NPV to rule out a bacterial associated systemic host response (depending on the presence or absense of hyperthermia at the time of enrollment).
</td>
<td></td>
<td>Outside scope of factual accuracy check.

It is noted for this assessment element [D1002], that a comprehensive analysis of the performance of alternative tests was beyond the scope of this study. This section was therefore restricted to descriptions of test accuracy of alternate tests identified in clinical guidelines (A0024) (A0025) and in the studies included in this systematic review (Table 11).</td>
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biosurfit	226	Table A.13 in Appendix 2	Information missing from Table A.13 in Appendix 2 provided: Column 2: Portugal Column 5: spinit® is a fully automated Point-of-Care diagnostics solution designed to deliver quantitative measurement of blood parameters to physicians in minutes. The spinit® CRP disposable disc is used with the spinit®instrument as a quantitative assay for the measurement of C-reactive protein concentration in whole blood (venous and capillary), serum and plasma samples. This type of assay is used for the detection and evaluation of infection, tissue injuries, inflammatory responses and associated diseases. Column 6: Not available Column 8 Yes Column 9 – Not available		Changed as suggested.
Medix Biochemica	227	Line 4	Actim CRP is manufactured in Finland not in Denmark	1	Changed as suggested.

Please add extra rows as needed.

[1] a “major”: the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
b “minor”: the comment does not necessarily have to be answered in a detailed manner
c“linguistic“: grammar, wording, spelling or comprehensibility, only if they lead to inaccuracy.