

FebriDx for C-reactive protein and Myxovirus resistance protein A testing in primary care

Medtech innovation briefing

Published: 31 July 2017

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Summary

- The technology described in this briefing is FebriDx. It is a rapid point-of-care immunoassay test that detects raised levels of C-reactive protein (CRP) and Myxovirus resistance protein A (MxA) in peripheral whole blood, with results in 10 to 15 minutes.
- The innovative aspects are that the FebriDx test measures MxA, a marker for viral infection, as well as CRP, helping clinicians to differentiate between bacterial and viral respiratory tract infections.
- The intended place in therapy would be in primary care, where it would be used by GPs or nurse practitioners to help guide the appropriate prescription of antibiotics to people with acute febrile respiratory tract infections.
- The main points from the evidence summarised in this briefing are from 2 feasibility studies and 1 clinical evaluation (n=569 people in total). One study reported FebriDx to have an accuracy of 80% and 70% for identifying bacterial and viral infections respectively. One study reported FebriDx to have sensitivities of 80% and 87%, and specificities of 94% and 83% for detecting bacterial and viral infections, respectively.
- Key uncertainties around the evidence are that it is limited to 1 peer-reviewed study and 2 conference posters, which were all designed and funded by the company, and done in the US. Also, the CRP test threshold (65 mg/litre) for offering treatment differs from that recommended in the NICE guideline on the [diagnosis and management of pneumonia in adults](#) (100 mg/litre).

- The cost of FebriDx is \$14.00 to \$16.00 per unit (£11.25 to £12.75 using exchange rate at June 2017), depending on volume (exclusive of VAT). This would represent additional acquisition costs to standard care which might be offset if unnecessary antibiotic prescriptions were avoided.

The technology

The FebriDx test (Rapid Pathogen Screening) is a single-use, portable in vitro diagnostic test intended to provide point-of-care semi-quantitative measurement of C-reactive protein (CRP) and qualitative measurement of Myxovirus resistance protein A (MxA) in human peripheral whole blood.

CRP is a non-specific indicator for the presence of acute inflammation and can be raised in the presence of bacterial infection. MxA is a non-specific protein marker that is raised in the blood in the presence of acute viral infection. Simultaneous measurement of MxA and CRP in people with acute febrile respiratory infections is designed to help differentiate between viral and bacterial infections, and therefore guide appropriate prescription of antibiotics. Tests that improve clinical decision-making in antibiotic prescription at the point of care have the potential to support antimicrobial stewardship.

FebriDx consists of a test card, a buffer solution, and an accessory kit which includes a lancet and 2 pipettes. The tests are available in boxes of 20, with 2 spare accessory kits and buffer solutions included. No extra equipment is needed.

The FebriDx test card has 2 lateral-flow test strips with monoclonal anti-MxA and anti-CRP antibodies. One lateral-flow strip detects MxA and low levels of CRP, while the other detects high levels of CRP. The lancet is used to puncture the skin to collect 2 5-microlitre blood samples in the pipettes. The blood is transferred onto the 2 test strips on the test card and the buffer solution is applied through an activation window. The test is left to develop for 15 minutes before the results are analysed. Most results develop in 10 to 12 minutes, but determination of a negative result needs 15 minutes.

If MxA and CRP are present in the blood above their level of detection, then a positive test line is visible on the relevant test strip. If the serum MxA level is 40 ng/ml or more, a positive line will appear on the test strip for 'MxA'. If the serum CRP level is 20 mg/l or more, a positive line will appear on the test strip for 'Low CRP'. If the serum CRP level is 65 mg/l or more, a positive line will appear on the test strip for 'Low CRP' and 'High CRP'. The test results are displayed on the test card as a multiplexed pattern of results (see table 1).

Table 1 Interpretation of immunoassay results

Control line	MxA	Low CRP	High CRP	Test prediction
+	+			Viral infection
+	+	+		Viral infection
+	+	+	+	Viral infection ¹
+		+		Bacterial infection ²
+		+	+	Bacterial infection ³
+				Negative ⁴
				Invalid

'+' denotes a positive test line

¹Cannot preclude co-infection

²Mild inflammation or infection – management may include monitoring and delayed antibiotic therapy

³More severe inflammation or infection – management may include immediate antibiotic therapy

⁴Microbiologically unconfirmed respiratory illness

The manufacturer's [package insert](#) includes information on the test procedure, quality control, accuracy and precision data, limitations and storage for FebriDx.

Innovations

Point-of-care CRP tests have the potential to change current practice by helping clinicians to make the decision as to whether to prescribe antibiotics for people with symptoms of respiratory tract infections during a primary care consultation. The addition of the MxA biomarker in the FebriDx test is designed to increase specificity compared with CRP alone to help differentiate viral and bacterial infections.

Current NHS pathway or current care pathway

The decision to prescribe antibiotics for a suspected respiratory infection in primary care is generally made by a GP or nurse practitioner, and is based on medical history, clinical examination and assessment of risk.

Antibiotics can be prescribed at the time of the patient's first clinical examination (immediate), or postponed until a later time if the symptoms persist (delayed) as recommended in the NICE guideline on [the prescription of antibiotics for respiratory tract infections](#).

Point-of-care CRP tests are not yet widely used in primary care. Standard laboratory analysis for CRP followed by MxA is typically only done by collecting a venous blood sample. This is sent off for laboratory analysis, with the results available 1 to 2 days later. Because of this delay, CRP and MxA testing are not typically used to assess acute respiratory infections in primary care.

NICE's guideline on the [diagnosis and management of pneumonia in adults](#) recommends that point-of-care CRP tests should be considered for people with symptoms of respiratory tract infection in primary care, if a diagnosis is unclear after clinical assessment and that antibiotic prescribing should be based on the results. Immediate antibiotic treatment should be offered if the CRP level is more than 100 mg/litre and a delayed prescription should be considered at levels between 20 and 100 mg/litre. The FebriDx 'high CRP' reading suggests CRP levels of 65 mg/l or more, which is lower than the 100 mg/litre level recommended in the guideline. Antibiotics are not recommended for CRP levels less than 20 mg/litre.

NICE's quality standard on [infection prevention and control](#) states that to help stop bacteria becoming resistant to antibiotics, it is important to prescribe antibiotics in accordance with the principles of antimicrobial stewardship. These include only prescribing them when needed (and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats) and to review the continued need for them.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to FebriDx (although none include a viral biomarker and all need bench-top analysers):

- [AQT90 Flex](#) (Radiometer Medical ApS)
- [iChroma CRP](#) and [AFIAS CRP](#) (Boditech Med)
- [NycoCard CRP](#) and [Afinion CRP](#) (Alere)

- [QuikRead go CRP and CRP+Hb](#) (Orion Diagnostica)
- [Eurolyser CRP](#) (Eurolyser Diagnostica).

NICE has published medtech innovation briefings on the [Alere Afinion system](#) and the [QuikRead Go system](#).

Population, setting and intended user

The FebriDx test would usually be used for people with suspected acute febrile respiratory tract infections presenting in primary care. It could also be used in community care and in out-of-hours facilities. It would be done as a point-of-care test by clinicians during a consultation. The FebriDx test would only be used together with a clinical examination and clinical judgement, to help clinicians to make the decision to prescribe antibiotics, because a negative result would not preclude a respiratory tract infection.

The Medicines and Healthcare products Regulatory Agency guideline on [management and use of IVD point-of-care test devices](#) provides advice and guidance for point-of-care test services in primary and secondary care. This guidance addresses important issues which include arrangements for training, management, quality assurance and quality control, assessment by an external accreditation body, and consideration of available evidence for the performance of the test.

Costs

Technology costs

The cost of each single-use FebriDx test is \$14.00 to \$16.00 (£11.25 to £12.75 using the exchange rate at June 2017) per test (excluding VAT), depending on the volume purchased. This includes the test cards, accessory packs and buffer solution. These are available in packs of 20 with 2 spare accessory packs and buffer solutions included. No extra equipment is needed.

The company, through its UK distributor, provides training to NHS users.

Costs of standard care

Standard care for people who present to primary care with symptoms of a respiratory tract infection would be a consultation with a primary care clinician without the use of point-of-care tests to help the diagnosis and the clinical decision to prescribe antibiotics. The unit cost of a GP consultation, with the exclusion of antibiotic prescriptions, ranges from £27 to £36, for an average

consultation time of 9.22 minutes, dependent on the inclusion or exclusion of qualification and direct care staff costs ([Personal Social Services Research Unit 2016](#)). The average cost of a course of amoxicillin is about £1.49; a course of erythromycin costs about £3.05.

Resource consequences

The FebriDx test would be an extra cost compared with a standard primary care consultation, adding test cost and staff time. These extra costs may be offset if it reduces repeat appointments, helps to avoid unnecessary antibiotic prescribing and reduces adverse events associated with this.

Antimicrobial stewardship is an important issue in healthcare and a number of guidelines have been published in relation to this ([NICE \[2015\]](#), [Public Health England \[2015\]](#), [Royal College of General Practitioners](#) and [NHS England \[2015\]](#)).

The NICE guideline on [pneumonia in adults: diagnosis and management](#) included a cost-utility analysis of generic CRP point-of-care tests. The use of CRP point-of-care tests was associated with an incremental cost of £18.92 compared with standard care, and judged to be cost effective at an incremental cost-effectiveness ratio of £15,763. However, this was based on point-of-care analysers for CRP testing, which were associated with recurrent costs of £13.50 per test. This is slightly more expensive than the disposable FebriDx test kits which are £11.25 to £12.75 per test and do not need an analyser.

Regulatory information

FebriDx was CE-marked as an in vitro diagnostic device in September 2014.

A search of the [Medicines and Healthcare products Regulatory Agency](#) website revealed that no manufacturer field safety notices or medical device alerts have been issued for this technology.

Equality considerations

NICE is committed to the promotion of equality, elimination of unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In the production of guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No equality issues have been identified for the use of the FebriDx test in primary care.

Clinical and technical evidence

A literature search was done for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence which relates to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

The literature search identified 1 study published in full that reported on the use of the FebriDx test. This was a prospective, single-centre, feasibility study to assess diagnostic accuracy ([Sambursky and Shapiro 2015a](#)). A further 3 conference posters were identified; a clinical evaluation study ([Shapiro et al. 2015](#)), a multicentre feasibility study ([Sambursky and Shapiro 2015b](#)) and a single-centre feasibility study ([Sambursky et al. 2014](#)). The latter, single-centre feasibility study was not included for review because it included data which was duplicated in the fully published peer-reviewed study ([Sambursky and Shapiro 2015a](#)).

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

Overall, there was very limited evidence in terms of quantity and quality to assess the FebriDx test. Of the 3 studies identified, only 1 was reported in a peer-reviewed journal article. All studies were designed and funded by RPS, who designed the FebriDx test, introducing the potential of sponsor bias. All studies were done in US medical centres and therefore results may not be generalisable to the UK population.

All 3 studies were described as being blinded, which may have reduced the risk of performance bias, but 1 paper (Shapiro 2015) did not provide details of the blinding methods used. Two studies did not report patient selection methods (Sambursky and Shapiro 2015a, Shapiro et al. 2015), which may introduce the possibility of sampling bias.

Table 2 Summary of the selected studies

Sambursky and Shapiro (2015a)

Study size, design and location	n=60 (people with suspected pharyngitis=12, suspected LRTI=24, asymptomatic control group=24). Single-centre blinded clinical feasibility trial (hospital setting), US.
Intervention and comparator(s)	Intervention: CRP and MxA-guided therapy with the use of the FebriDx test. Reference standard: Clinical diagnostic algorithm with the use of microbiology and laboratory assessments (PCR panels, bacterial cell cultures, ELISA tests) and radiological assessment (chest X-ray).
Key outcomes	Two invalid tests occurred and 4 subjects were diagnostically indeterminate because of specimen leakage or rejection. The FebriDx test correctly identified 92% (22/24) of patients as negative for infection, 80% (16/20) as having confirmed bacterial infection and 70% (7/10) as having confirmed viral infection. The authors considered the FebriDx test to be a sensitive and specific method to differentiate acute febrile respiratory infections.
Strengths and limitations	Appropriate reference standards were used in the study. The cohort was small and limited to adults (aged over 17 years). Therefore results may not be generalisable to the younger population. No diagnostic accuracy outcomes (for example specificity and sensitivity) were reported. Control subjects were not clearly defined and were described as being primarily admitted with suspected acute febrile respiratory infection.
<u>Shapiro et al. (2015)</u>	
Study size, design and location	n=370 (acute febrile respiratory infection symptoms=205, asymptomatic controls=165). Prospective multicentre clinical evaluation (11 clinical emergency departments and urgent care centres), US.
Intervention and comparator(s)	Intervention: FebriDx Reference standard: Clinical microbiological and laboratory assessments (viral and atypical bacteria PCR tests and routine bacterial cell culture).

Key outcomes	<p>Of the 205 patients with respiratory infection symptoms, 78 had confirmed infection (53 viral, 25 bacterial) and 127 had microbiologically unconfirmed respiratory illness.</p> <p>For the detection of bacterial infection, the FebriDx test showed 80% sensitivity and 94% specificity with a PPV of 65% and NPV of 97%.</p> <p>For viral infection the FebriDx test showed 87% sensitivity and 83% specificity with a PPV of 64% and NPV of 95%.</p>
Strengths and limitations	<p>The multicentre methodology provides a more generalised population. Largest study population out of the 3 studies evaluated, with clearly defined asymptomatic controls.</p> <p>Patient characteristics were not reported. Many patients were considered to be microbiologically unconfirmed for infection.</p>
<u>Sambursky and Shapiro (2015b)</u>	
Study size, design and location	<p>n=139 (confirmed infections=56, microbiologically unconfirmed respiratory illness=81, excluded because of incomplete data collection=2).</p> <p>Prospective multicentre blinded clinical feasibility trial.</p> <p>(11 medical institutions), US.</p>
Intervention and comparator(s)	<p>Intervention: FebriDx.</p> <p>Reference standard: BioFire PCR respiratory panel, additional viral PCR tests, routine bacterial cell culture, procalcitonin, CRP, MxA, white blood cell count and Epstein-Barr virus IgM/IgG levels.</p>
Key outcomes	<p>In patients with confirmed bacterial infection, 95% (21/22) had CRP \geq 20mg/l. In patients with confirmed viral infection, 41% (14/34) had CRP \geq 20mg/l. Of these 14, the FebriDx test correctly identified 64% (9/14) of them as positive for viral infection.</p> <p>It was reported that the FebriDx test would have reduced the over-prescription of antibiotics in 26% (9/34) of confirmed cases of viral infection compared to the use of CRP alone.</p>
Strengths and limitations	<p>The multicentre methodology provides a more generalised population. Consecutive enrolment reduces the potential for selection bias.</p> <p>Patient characteristics were not reported. A relatively large cohort was enrolled, however FebriDx test results were only reported on patients with an infectious aetiology (41%, 56/137).</p>

Abbreviation: CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; LRTI, lower respiratory tract infection; MxA, Myxovirus resistance A; NPV, negative predictive value; PCR, polymerase chain reaction; POC, point of care; PPV, positive predictive value.

Recent and ongoing studies

- [Clinical Performance Study of FebriDx in Patients Being Evaluated for Acute Community Acquired Febrile Upper Respiratory Infection](#). ClinicalTrials.gov identifier: NCT02018198. Status: recruiting, Indication: acute respiratory infection. Devices: FebriDx
- [Validation of Promising Biomarker Assays to Assess Their Diagnostic Performance Characteristics](#). ClinicalTrials.gov identifier: NCT03047642. Status: Not yet recruiting. Indication: acute respiratory infection. Devices: FebriDx will be evaluated as part of this study.
- A single-centre retrospective study of the use of the FebriDx test in UK general practice was highlighted by the manufacturer. The study reports clinical outcomes in 21 patients with respiratory tract infection. This has been submitted to a peer-reviewed journal and is currently under review.

Specialist commentator comments

Comments on this technology were invited from clinical experts who work in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

One of the 3 specialist commentators was familiar with the FebriDx technology; 2 were familiar with other point-of-care CRP tests.

Level of innovation

Two specialist commentators considered the innovative aspect of the FebriDx test is its ability to also identify viral infections. One considered that this is only a minor variation from existing CRP tests. Another commentator highlighted that the FebriDx test is simpler than bench-top analyser tests and can therefore be used by health care assistants with minimal training.

Potential patient impact

Specialist commentators considered the test to be suitable for all patients, especially immunocompromised patients, adults with pre-existing respiratory conditions, and patients with self-limiting infections but who demand antibiotics.

All 3 specialist commentators considered that FebriDx could reduce the unnecessary prescription of antibiotics. Two noted that this might contribute to antimicrobial stewardship and the Global Strategy of Antimicrobial Resistance. However, 1 commentator added that any reduction in prescribing would be dependent on baseline levels. One added that it could also provide reassurance to patients, reduce the number of patients needing GP appointments for side effects of antimicrobials, and reduce the need for chest X-rays.

Potential system impact

Two specialist commentators stated that point-of-care CRP tests are not routinely used in general practice in the NHS. Two commentators considered the test will be educational for both clinicians and patients to raise awareness of antimicrobial stewardship. One highlighted that it could be useful in geographical areas with high antibiotic use.

One commentator considered that, although CRP testing had already been shown to be beneficial in reducing antibacterial prescribing, advantages of additional viral testing using MxA would need to be determined.

All commentators suggested that FebriDx would cost more than the current standard of care. One commentator added that the increased cost could be offset elsewhere in the healthcare system through reduced antimicrobial prescription, reduced imaging, and reduced antimicrobial side effects. Two added that this could reduce re-attendance in primary and urgent care centres. One specialist commentator highlighted that the cost could be offset with rewards from the [NHS England 5th Quality Premium](#) for reducing inappropriate antibiotic prescribing in at risk groups and from reduction of hospital stay by timely antibiotic treatment of pneumonia in those with pre-existing conditions.

Commentators noted that the barriers to adoption would be from clinicians and commissioners who may be concerned about upfront costs and increased workload. One commentator estimated that during peak winter months, a practice with a list size of 10,000 could do 1 to 3 tests per day using this technology.

One commentator identified that FebriDx could considerably delay the patient pathway as point-of-care testing is generally done in 5 minutes. It would need an adjustment in the patient flow, as patients would have to wait while the results are processed and during this time another patient could be seen. They also noted that multiple concurrent tests could be done, without the need for queuing of equipment which is often needed for existing bench-top analyser tests.

Two specialist commentators considered that very little or no changes in facilities or infrastructure would be needed. One commentator highlighted that consideration should be given to different models of management if it were to be implemented in nurse-led community and pharmacy systems.

One commentator also highlighted that false positive results for the test could be substantial, and patients who do not need antibiotics may receive them. Therefore if the test was used without high clinical suspicion or for assurance it might not achieve a reduction in the unnecessary use of antibiotics.

General comments

Two specialist commentators highlighted that, although the test is simpler than existing bench-top technologies, FebriDx takes longer, needs a larger volume of blood than other systems and does not give quantitative results.

One specialist commentator highlighted that the cut off for high CRP in this technology is 65 mg/litre whereas NICE guidelines use a cut-off point of 100 mg/litre for existing CRP tests.

All 3 specialist commentators highlighted that more research would be needed to address uncertainties which should include a larger scale study in primary care in the UK. One added that there would need to be robust evidence of cost savings.

Specialist commentators

The following clinicians contributed to this briefing:

- Professor Jonathan Cooke, honorary professor, University of Manchester (Professor Cooke has worked as an advisor to Alere on point-of-care testing).
- Ms Liz Cross, advanced nurse practitioner, Attenborough Surgery (no conflicts of interest declared).

- Dr Tha Han, consultant in public health medicine, Enfield Council (no conflicts of interest declared).

All specialist commentators also advised on Alere Afinion MIB102, a similar product which assists the diagnosis of bacterial infection.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2617-6