NICE advice

FebriDx for C-reactive protein and myxovirus resistance protein A testing

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is FebriDx. It is a rapid dual marker immunoassay test. The test detects raised levels of C-reactive protein (CRP) and myxovirus resistance protein A (MxA) in peripheral whole blood. The test is done at the point of care and gives results in 10 minutes.
- The **innovative aspects** are that the FebriDx test measures MxA, a marker for viral infection, as well as CRP. This helps clinicians to differentiate between bacterial and viral respiratory tract infections.
- The intended **place in therapy** would be in primary or secondary care, to help guide the appropriate use of antibiotics for people with acute febrile respiratory tract infections. It could also help with early detection of viral infections, such as COVID-19.

- The **main points from the evidence** summarised in this briefing are from 43 diagnostic accuracy studies (2 in COVID-19), 4 feasibility studies and 1 clinical evaluation (including 1,133 people in total). The evidence suggests that FebriDx is effective, meaning it has high sensitivity (over 80%) and specificity (over 90%) when identifying bacterial and viral infections in adults. It could also help with diagnosis in children. The emerging evidence of the test for people with viral infections, such as COVID-19, suggests it could have benefits as an early triage tool.
- **Key uncertainties** around the evidence are that there is currently only 1 published study exclusively in children and 1 published study for people with suspected COVID-19. There is limited follow-up evidence looking at the effect of the test on antibiotic use. Most of the evidence was on a previous format of the technology; the new integrated format is identical in performance to the earlier device.
- The **cost** of FebriDx is £12.75 (excluding VAT), which would be in addition to standard care. There is published evidence suggesting that FebriDx could save costs by reducing antibiotic use and avoiding complications associated with this.

The technology

The FebriDx test (Lumos Diagnostics) is a single-use, portable, in vitro diagnostic test. It is intended to give 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, which can be raised when there is bacterial infection. MxA is a protein marker that is raised in the blood when there is 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. This can then guide appropriate use of antibiotics. Tests that improve clinical decision making in antibiotic prescription at the point of care could support antimicrobial stewardship.

FebriDx is a self-contained, portable, all-in-one test device, which both collects and analyses the blood sample. It consists of a single strip test card, a buffer solution activated by an integrated push button, lancet and collection tube. No extra equipment is needed.

The FebriDx test card has a single lateral-flow test strip with monoclonal anti-MxA and

anti-CRP antibodies. The lancet punctures the skin and the first drop of blood is discarded. After this, a 5 microlitre blood sample is collected at a 45-degree angle using the blood collection tube. The blood is transferred into the blood transfer zone when the collection tube is full, and the buffer solution is applied by fully depressing the buffer release button. The test is left to develop for 10 minutes on a flat surface before the results are analysed and displayed in the result window.

Innovations

Point-of-care CRP tests could change current practice by helping clinicians to make decisions about 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. It is claimed that FebriDx eliminates the 'grey zone' of 20 mg to 100 mg per millilitre CRP by accurately differentiating viral from bacterial infection. This means that rapid and accurate antibiotic prescribing decisions can be made (if a diagnosis is unclear, antibiotic prescribing should be based on a point-of-care CRP test level of more than 100 mg per litre. Prescribing antibiotics should be delayed at levels between 20 mg and 100 mg per litre). It could also help identify and isolate people with suspected COVID-19, by differentiating viral and bacterial respiratory infections when they enter a healthcare setting.

Current care pathway

Respiratory infections (mainly consisting of otitis media, sore throat, sinusitis, pharyngitis, acute bronchitis and pneumonia) are one of the most common reasons for oral antibiotic prescriptions in the NHS (Del Mar 2016). Bacterial and viral respiratory tract infections clinically present similarly and are frequently misdiagnosed. The decision to prescribe antibiotics for a suspected respiratory bacterial infection in primary care is generally made by a GP or nurse practitioner. This decision is based on medical history, clinical examination and assessment of risk. The 2018 English surveillance programme for antimicrobial utilisation and resistance (ESPAUR), reported that 81% of all antibiotics prescribed in England in 2017 were from a primary care setting. This was equal to about 654 prescriptions for every 1,000 people. A recent study on antibiotic prescribing in English primary care suggested that approximately 9% to 23% of antibiotics used in secondary care were inappropriate (Smieszek et al. 2018).

Point-of-care testing should be considered in primary care for people with suspected

lower respiratory tract infections. 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. Antibiotic prescribing should be based on the results. Immediate antibiotic treatment should be offered if the CRP level is more than 100 mg per litre and a delayed prescription should be considered at levels between 20 mg and 100 mg per litre.

Antibiotics can be prescribed at the time of the patient's first clinical examination, or postponed until a later date if the symptoms continue.

Point-of-care CRP tests are not yet widely used in primary care. Standard laboratory analysis for CRP and MxA is typically only done by collecting a venous blood sample. These are 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. FebriDx uses 2 biomarkers with MxA used to confirm a negative test for CRP.

To help stop bacteria becoming resistant to antibiotics, it is important to prescribe antibiotics in line 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 have some of the functions that FebriDx has, but none include a viral biomarker and all need bench-top analysers:

- AQT90 Flex (Radiometer Medical ApS)
- ichroma CRP (Boditech Med)
- NycoCard CRP and Afinion CRP (Alere)
- QuikRead go CRP and CRP+Hb (Aidian)
- Eurolyser CRP (Eurolyser Diagnostica)
- ImmunoXpert (MeMed).

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use
- NICE's COVID-19 rapid guideline on managing suspected or confirmed pneumonia in adults in the community
- NICE guideline on the prescription of antibiotics for respiratory tract infections
- NICE's quality standard on infection prevention and control

Population, setting and intended user

The FebriDx test would usually be used for people with suspected acute febrile respiratory tract infections presenting in primary or secondary 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. It would be used together with a clinical examination and clinical judgement, to help clinicians to make the decision to prescribe antibiotics. This is because a negative result would not preclude a respiratory tract infection.

During the COVID-19 pandemic or pandemics of a similar nature, the technology could also be a way to initially test, triage and isolate individuals presenting to hospital with symptoms associated with the pandemic.

Costs

Technology costs

The cost of each single-use FebriDx test is £12.75 per test (excluding VAT). The company has advised that it offers volume discounts on this price. No extra equipment is needed.

The company, through its UK distributor, provides training to NHS users. This is included in the cost of the test and is free of charge.

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. This would not include point-of-care tests to help the diagnosis. The clinician would make the clinical decision

about whether to prescribe antibiotics. The unit cost of a GP consultation, excluding antibiotic prescriptions, ranges from £27 to £36, for an average consultation time of 9.22 minutes. This depends on the GP's 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. An economic evaluation by Schneider et al. (2020), using a UK NHS perspective, suggests that FebriDx could save the NHS £88 million every year. This is through avoiding unnecessary antibiotic prescription and related adverse events.

Antimicrobial stewardship is an important issue in healthcare and a number of guidelines have been published related to this:

- NICE's guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use
- Public Health England's guidance on antimicrobial stewardship: start smart – then focus
- Royal College of General Practitioners' TARGET antibiotic toolkit
- NHS England's introduction to the antibiotic Quality Premium.

Regulatory information

FebriDx was CE marked as an in vitro diagnostic device in September 2014. This was updated in October 2018.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination

and fostering good relations between people with particular protected characteristics and others.

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 6 studies published in full that reported on the FebriDx test. The most relevant study to the NHS was a single-centre retrospective chart review in a UK GP practice (Davidson et al. 2017), which assessed the effect of FebriDx test results on therapeutic decisions. Of the other published studies, 1 was a prospective, single-centre, feasibility study to assess diagnostic accuracy (Sambursky and Shapiro 2015a), and 1 was a study in children only (Onrubia et al. 2020), and 2 (Self et al. 2017 and Shapiro et al 2018) were prospective, cross-sectional, observational studies done in the US comparing FebriDx with a reference standard algorithm that a physician could override. Clark et al. 2020 was a peer-reviewed study in people with suspected COVID-19. A further 2 conference posters were identified; 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 were duplicated in the fully published peer-reviewed study (Sambursky and Shapiro 2015a). An additional unpublished and non-peer reviewed study was identified for COVID-19 (Karim et al. 2020).

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Overall, there is adequate evidence in terms of quantity and quality for the FebriDx test. Of

the 8 studies identified, 1 was an unpublished abstract, 6 were peer-reviewed journal articles, and 1 was an unpublished, non-peer reviewed study. In addition, a published economic study was identified, which is reported in the resource consequences section. Most of the studies had some involvement from the company either in design, financial or material support, introducing the potential for bias. Most studies were done outside the UK, predominantly in the US. However, there is clinical evidence in the UK, including for FebriDx's use in COVID-19 testing, and economic evidence from a UK NHS perspective. There is evidence for the benefit of FebriDx in both children and adults. Evidence was found for its use in a real-world setting in people suspected to have COVID-19 (Clark et al. 2020). Given the nature and timescale of the pandemic at the time of this review that evidence is understandably developing but limited. Karim et al. (2020) was identified in this area, this was unpublished and not peer reviewed, but is similarly supportive of the use of FebriDx in people with suspected COVID-19.

Clark et al. (2020)

Study size, design and location

Non-randomised, interventional pre- and post-implementation study of 251 results (248 valid results) from 266 adults with suspected COVID-19 presenting at hospitals in the UK between 20 March to 12 April 2020.

Intervention and comparator(s)

FebrixDx.

Reference standard: SARS-CoV-2 RNA detected by polymerase chain reaction (PCR) respiratory samples using QIAstat-Dx or laboratory PCR or both was considered as positive for COVID-19.

Key outcomes

Sensitivity for detecting viral infection 93% (95% confidence interval [CI] 87% to 97%), specificity 86% (95% CI 79% to 92%). Overall accuracy 90% (95% CI 86% to 93%), positive predictive value (PPV) assuming a 20% prevalence of viral infection, 63% (95% CI 52% to 72% and negative predictive value (NPV) 99% (95% CI 96% to 99%). A predictive multi-variate model involving data from 201 people found that the addition of patient and clinical characteristics did not add significantly to the diagnostic accuracy compared with using

the FebriDx MxA result alone.

Several patients with FebriDx viral positive results (negative by PCR) had radiological features of COVID-19. So, these results were likely to be true positives despite negative PCR results.

Strengths and limitations

This is a relatively large real-world study. The reference standard is likely to be suboptimal, and the results cannot be applied to people who are immune-compromised or to children.

Onrubia and Gonzalez (2020)

Study size, design and location

Prospective non-randomised pilot study of 20 children (2 to 12 years old) presenting at a private paediatric clinic in Switzerland with suspected (based on clinical assessment and symptoms) acute respiratory infection.

Intervention and comparator(s)

FebrixDx compared with standalone C-reactive protein (CRP) testing.

Key outcomes

All 20 children were considered to have a bacterial infection using clinical assessment alone, and had point-of-care CRP testing and FebriDx. Standalone quantitative CRP testing showed a CRP of 20 mg per litre or more in 50% (10/20) of patients, who were deemed to have a bacterial infection.

FebriDx found that 10% (2/20) of patients had a bacterial infection and further differentiated 85% of patients as having a viral infection (17/20). Microbiologically unconfirmed respiratory illness was found in 5% (1/20) of patients. Both patients found to have a positive CRP line on FebriDx without an associated elevated myxovirus resistance protein A (MxA), also showed a quantitative CRP of 20 mg per litre or more.

Strengths and limitations

The study shows that FebriDx could improve diagnosis certainty and reduce unnecessary antibiotic use in children compared with both clinical assessment and CRP testing. The study involves a small sample of children from a single site.

Karim et al. (2020)

Study size, design and location

Prospective observational cohort study of 48 patients presenting in a hospital emergency department in the UK with symptomatic acute respiratory infection suspected to be COVID-19.

Intervention and comparator(s)

FebriDx compared with nasal and pharyngeal swab for viral PCR testing and an assessment by 2 physicians to determine the clinical likelihood of COVID-19.

Key outcomes

There were 35 patients who had a positive FebriDx test result, all of whom had either positive PCR for COVID-19 (30/35) or a clinical assessment suggesting COVID-19 (5/35). This gave a PPV of 100%. For the 13 patients with viral negative test results PCR was also negative. Including 1 lower respiratory tract infection in which it was not possible to determine the exact cause of infection, and a viral infection could not be excluded, the NPV was 12/13 (92%). This excluded the NPV of PCR at 71% (12/17). Sensitivity was calculated at 100% for COVID-19 (97% for viral infection) compared with 85.7% for PCR (COVID-19). The specificity of both FebriDx and PCR for COVID-19 was 100%.

Strengths and limitations

This study was a pre-print, which means it was not peer-reviewed or published. The study provides evidence of the technology's benefit in identifying COVID-19. The evidence is mostly from adults and from a single centre.

Shapiro et al. (2018)

Study size, design and location

Prospective, cross-sectional, observational cohort study in the US of 223 people in emergency department and urgent care settings reporting a history of fever in the previous 72 hours who presented with clinical signs and symptoms of an upper respiratory tract infection.

Intervention and comparator(s)

FebrixDx compared with a reference method algorithm with physician override that included bacterial cell culture, respiratory PCR panels for viral and atypical pathogens, procalcitonin, and white blood cell count.

Key outcomes

One patient had an invalid FebriDx test, 2 patients did not have adequate testing for the reference standard and were excluded from the analysis. Sensitivity 95% (95% CI 77% to 100%), specificity 94% (95% CI 88% to 98%), PPV 76% (95% CI 59% to 87%) and NPV 99% (95% CI 93% to 100%).

For viral detection in patients reporting fever in the last 72 hours, when classifying results as viral or not viral, overall agreement was 87% (95% CI 82% to 91%). FebriDx showed a sensitivity of 90% (95% CI 83% to 94%), specificity of 76% (95% CI 66% to 84%), PPV of 83% (95% CI 77% to 87%), and NPV of 85% (95% CI 77% to 90%).

Strengths and limitations

Multicentre prospective study. No follow up after the index test, so it is difficult to assess FebriDX effect on antibiotic prescribing decisions. How study participants and samples were selected is described as convenience sampling, meaning it was determined by the availability of staff and the constraints of shipping biological samples. This may have biased the results.

Davidson et al. (2017)

Study size, design and location

Retrospective chart review in a UK GP practice of 21 people.

Intervention and comparator(s)

FebriDx test results assessed to establish if they affected therapeutic decisions that would have been otherwise determined based solely on clinical exam findings. The patient's history and medical chart were followed up a month after the test to see if there were any subsequent medical consultations or hospital admissions.

Key outcomes

FebriDx altered clinical management in 48% (10/21) of patients and reduced antibiotic prescribing in 80% (8/10) of clinical cases of suspected bacterial infection.

Strengths and limitations

Study was done in a UK GP practice. The study used a small sample size. There was no inclusion or exclusion criteria reported.

Self et al. (2017)

Study size, design and location

Prospective, cross-sectional, observational study in the US of 371 people (206 people with suspected upper respiratory tract infection, 165 people who were part of an asymptomatic control group).

Intervention and comparator(s)

FebriDx compared with a reference standard for classifying upper respiratory track infection aetiology with an algorithm which could be overridden by 2 clinicians. There was also an asymptomatic control group (who did not have reference tests because the tests were presumed to be negative).

Key outcomes

All 206 people with suspected upper respiratory tract infection had a valid FebriDx test, but 1 person did not have adequate reference standard testing to enable a diagnosis, and so was excluded from the analysis. Two (1%) people from the asymptomatic control arm had invalid FebriDx tests.

FebriDx had overall agreement with the reference standard algorithm in 76.6% of cases. When classifying results as bacterial or not bacterial, overall agreement was 91.7%, sensitivity was 80%, specificity 93%, there was a PPV of 63% and an NPV of 97%. When classifying results as viral or not viral, overall agreement against the reference standard was 84%, sensitivity 87%, specificity 83%, there was a PPV of 64% and an NPV of 95%.

In the asymptomatic control group (163 people) specificity was 99%. FebriDx resulted in 2 false positive tests (1%); 1 false positive viral result and 1 false positive bacterial result.

Strengths and limitations

Multicentre prospective study. A convenience sample was used, which may have biased the results.

Sambursky and Shapiro (2015a)

Study size, design and location

Single-centre blinded clinical feasibility trial of 60 people in a hospital setting in the US. There were 12 people with suspected pharyngitis, 24 with suspected lower respiratory tract infection and an asymptomatic control group of 24 people.

Intervention and comparator(s)

Intervention: CRP and MxA-guided therapy with the FebriDx test.

Reference standard: clinical diagnostic algorithm with microbiology and laboratory assessments (PCR panels, bacterial cell cultures, enzyme-linked immunosorbent assay tests) and radiological assessment (chest X-ray).

Key outcomes

There were 2 invalid tests and 4 people 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 primarily admitted with suspected acute febrile respiratory infection.

Sambursky and Shapiro (2015b)

Study size, design and location

Prospective multicentre blinded clinical feasibility trial of 139 people in 11 medical institutions in the US. There were 56 people with confirmed infections, 81 with microbiologically unconfirmed respiratory illness and 2 people who were excluded because of incomplete data collection.

Intervention and comparator(s)

Intervention: FebriDx.

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 immunoglobulin M and immunoglobuin G levels.

Key outcomes

In patients with confirmed bacterial infection, 95% (21/22) had CRP of 20 mg per litre or more. In patients with confirmed viral infection, 41% (14/34) had CRP of 20 mg per litre or more. Of these 14, the FebriDx test correctly identified 64% (9/14) of them as positive for viral infection.

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 with tests of CRP levels alone.

Strengths and limitations

The multicentre method gives a more generalised population. Consecutive enrolment reduces the potential for selection bias. Patient characteristics were not reported. A relatively large number of people were enrolled, but FebriDx test results were only reported for people with an infectious aetiology (41%, 56/137).

Sustainability

The company has not submitted any sustainability claims.

Recent and ongoing studies

- FebriDx DISRUPT acute respiratory infection trial in acute respiratory infection: an evaluation of FebriDx point-of-care test. ClinicalTrials.gov identifier: NCT02018198. Status: recruiting, estimated study completion date: December 2020. Indication: acute respiratory tract infections. Devices: FebriDx.

Expert 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 expert had used the technology. The other 2 experts had not but were either familiar with the technology itself or the concept.

Level of innovation

All the experts considered the device to be innovative and novel.

Potential patient impact

All experts considered the potential patient benefits to be that the test was rapid and could avoid unnecessary antibiotic use. Two noted the benefits in COVID-19. They suggested that patients with suspected COVID-19 or acute respiratory illness could be quickly tested and symptoms treated accordingly.

Potential system impact

The potential system benefits identified by experts were avoiding unnecessary antibiotic use and its associated costs, and any resulting treatment costs. In COVID-19 it could be used to quickly and effectively to triage patients with suspected COVID-19. This could avoid unnecessary use of COVID-19 treatment resources and facilities. One expert noted that the technology was convenient because no other equipment is needed to use it, such as an analyser. The expert stated that this makes the technology easier to use in a primary care setting and potentially in the community.

General comments

One expert noted their experience in an emergency department, where most patients identified as having COVID-19 because of symptoms such as fever or cough were subsequently found not to have COVID-19. This expert noted the potential benefits the technology could provide in COVID-19 testing if used nationally. The same expert noted ongoing data collection and research they are involved in. They said that the technology can fail if insufficient blood travels down the sample collection tube. This can be hard to detect as the control line will still be present.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Tristan W Clark, associate professor and honorary consultant in infectious diseases, University of Southampton. Dr Clark has been involved in research on the technology.
- Dr Anthony Leung, GP, Badgerswood Surgery. Dr Leung did not declare any interests.
- Ms Nichola MacDuff, advanced clinical nurse specialist, New Cross Hospital Adult Cystic Fibrosis Service. Ms MacDuff has received honorarium from Roche Pharmaceuticals for participating in an online symposium.

Development of this briefing

This briefing was developed by NICE. 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.

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