NICE advice

MR-proADM test for use with clinical deterioration scores in cases of suspected infection

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the MR-proADM test. It measures levels of mid-regional proadrenomedullin (MR-proADM), a precursor of adrenomedullin, levels of which can be increased in severe infections. The MR-proADM test is used alongside tools such as the National Early Warning Score (NEWS and NEWS2) to detect clinical deterioration in cases of suspected infection.
- The **innovative aspect** is that the test measures a unique biomarker (MR-proADM) that allows more accurate prediction of deterioration.
- The intended **place in therapy** would be with NEWS, NEWS2 and other tests and observations in people with suspected infection.
- The **main points from the evidence** summarised in this briefing are from 5 observational studies of 3,217 people with suspected infections in hospital. They show that MR-proADM can improve accuracy of infection diagnosis and can predict

the infection's severity.

- **Key uncertainties** around the evidence or technology are that there are only 2 studies that evaluate MR-proADM used with the NEWS.
- The **cost** of MR-proADM is approximately £10 to £20 per test. The **resource impact** could be less than standard of care because of reduced need for further tests and procedures. However, there is a lack of prospective studies showing how MR-proADM results influence clinical decisions.

The technology

The MR-proADM test (ThermoFisher Scientific) is an automated immunofluorescent assay that measures the blood-based biomarker, mid-regional proadrenomedullin (MR-proADM) in human ethylenediaminetetraacetic acid (EDTA) plasma. MR-proADM is a precursor for adrenomedullin, a vasodilator that has a role in microcirculation endothelial function. Adrenomedullin is widely expressed and has roles in vasodilation, immune modulation and metabolic regulation. Adrenomedullin may be differentially increased in many disease states, such as heart failure, sepsis, hypertension, and cardiovascular disease. However, adrenomedullin is not a suitable biomarker because it is unstable and cannot be easily measured. The company states that MR-proADM is an amino acid sequence that splits from the proADM molecule in 1:1 ratio with adrenomedullin, and proportionally represents the levels and activity of adrenomedullin. This briefing focuses on the use of the test in people with suspected infection.

The company states that MR-proADM levels are not influenced by food or water intake and there are no significant gender-related differences. It reports that the biomarker is stable, with no degradation seen up to 72 hours at room temperature.

The assay performance has been established in accordance with Clinical and Laboratory Standards Institute Guidelines. The test is for use with other clinical scores, such as the National Early Warning Score (NEWS) or NEWS2 for people with suspected infection or sepsis.

Innovations

The company claims that the technology is innovative because it is the first assay available that measures MR-proADM and that this biomarker has been shown to improve

existing scoring algorithms for infection.

The company states that the test can predict outcomes and determine risk in patients with conditions such as lower respiratory tract infections, urinary tract infections and kidney disease and sepsis. The company also states that the test can predict outcomes and risk in heart failure. This briefing only considers MR-proADM for suspected infections.

Current care pathway

NICE's guideline on sepsis: recognition, diagnosis and early management recommends that an early warning score (such as NEWS2, which has been endorsed by NHS England) should be considered to help assess people with suspected infection or sepsis in acute hospital settings. NEWS2 is a tool developed by the Royal College of Physicians. It improves the detection and response to clinical deterioration in adult patients by categorising the severity of their illness, and is a key element of patient safety and improving patient outcomes (NHS England). NEWS2 is based on a simple aggregate scoring system, which allocates a score to physiological measurements, and 6 parameters for the basis of the system: respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion and temperature.

Population, setting and intended user

MR-proADM is for use in secondary care and emergency care settings. It will be used in addition to standard care (NEWS2) to assess risk in patients with suspected infection.

A specialist commentator stated that MR-proADM might be used in 150,000 to 200,000 patients per year in the UK. Another specialist stated that it would probably be used in patients with NEWS of 2 to 5, which in their experience would include 80% of patients with suspected infection in hospital.

Costs

Technology costs

The company states that cost per test will depend on the total number of tests being done. For example, at a hospital running over 200 tests a month, the cost of the test would

be between £10 and £20 per patient.

Costs of standard care

Wong et al. (2017) measured the time taken for nursing staff to capture the parameters and manually calculate the early warning score was 3 minutes and 35 seconds. The cost of a band 2 nurse per working hour is £22 (Personal Social Services Research Unit, 2017). Assuming a time of 3 minutes and 35 seconds for a band 2 nurse to manually capture and record the 6 physiological parameters on the chart and calculate the NEWS2, an estimated cost of £1.31 per patient, per observation set, is produced (assuming a negligible cost of printing a NEWS2 chart).

Resource consequences

The MR-proADM test has recently been made available for the NHS and is being used in a few centres.

The company notes that the MR-proADM test costs more than current standard of care because it is an additional test. However, it expects the test to be resource releasing because it can improve the accuracy of identifying patient deterioration and reduce the need for further investigation procedures and treatments.

The test is run on the Kryptor analyser, laboratory staff already trained to use this analyser will not need further training. For those who have never used the analyser training takes around 1.5 to 2 days.

Regulatory information

MR-proADM is a CE-marked in vitro diagnostic device.

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 identified.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating 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

There are 5 studies summarised in this briefing, including 3,217 patients.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

The studies show that the MR-proADM test is effective at predicting outcomes for infection, when used with clinical scoring systems. The studies also show that the test could triage patients and predict the type of treatment they will need.

There are no studies that show the MR-proADM test used alongside the National Early Warning Score 2 (NEWS2). Although the studies are recent, they were done before NEWS2 was published. Three studies in the table used the test alongside the earlier NEWS. NEWS differs from NEWS2 because it does not consider oxygen saturation or confusion, and has less advice on serious sepsis and infection.

Further evidence showing how MR-proADM can improve clinical outcomes when used with NEWS/NEWS2 would provide evidence to support clinical adoption. This could be used to evaluate the resource impact of using MR-proADM.

One study was done in the NHS and another included an NHS centre. The studies done outside the UK using different clinical scoring systems may be less relevant to the NHS.

Table 1 Summary of selected studies

Graziadio et al. 2019	
Study size, design and location	300 people (with NEWS 2 to 5) in a prospective observational study. Location: UK.
Intervention and comparator(s)	MR-proADM. NEWS.
Key outcomes	NEWS and MR-proADM together predicted an increase of at least 2 in the NEWS (acuity increase) more accurately than NEWS alone. This increased the AUC to 0.61 (95% CI 0.54 to 0.69) from 0.55 (95% CI 0.48 to 0.62). When the confounding effects of chronic obstructive pulmonary disease or heart failure and interaction with MR-proADM were included, the prognostic accuracy further increased the area under the curve to 0.69 (95% CI 0.63 to 0.76).
Strengths and limitations	This study was done in an NHS setting. MR-proADM was used with NEWS (the standard scoring system in the NHS). This study was done in 2015 before the development of NEWS2. The authors state that the prognostic accuracy of MR-proADM might have been higher if more severely ill patients had been included. However, the aim of the study was to evaluate the usefulness of the test in less ill patients. The study was funded by the company.
Eckart et al. 2019	
Study size, design and location	1,303 adults seeking emergency department care in a secondary analysis of a multinational, observational study. Location: France, Switzerland and USA.
Intervention and comparator(s)	MR-proADM, white cell count and procalcitonin. NEWS.

Graziadio et al. 2019	
Key outcomes	The NEWS alone showed prognostic accuracy for 30-day mortality (AUC 0.73), with a multivariate adjusted odds ratio of 1.26 (95% CI 1.13 to 1.40, p<0.001). The AUCs for the prediction of mortality using MR-proADM, white cell count and procalcitonin were 0.78, 0.64 and 0.71, respectively. Combining NEWS with all 3 blood markers or only with MR-proADM improved discrimination with an AUC of 0.82 (p=0.002). Combining the 3 inflammatory markers with NEWS improved prediction of intensive care admission compared with NEWS alone (AUC 0.70 versus 0.65, p=0.006).
Strengths and limitations	This study is a secondary analysis of an observational study, so the results of MR-proADM and other biomarkers were not used in clinical decision making. NEWS was calculated retrospectively and so the mortality rates may not reflect clinical practice when NEWS informs clinical decisions. The authors excluded patients who did not have complete data, which may have led to a selection bias. The study was funded by the company.
Saeed et al. (2019)	
Study size, design and location	1,175 people presenting to the emergency department with suspected infection in an observational cohort study. Location: UK, France, Italy, Sweden, Spain.
Intervention and comparator(s)	MR-proADM. Also used: biomarkers (procalcitonin, lactate and C-reactive protein) and clinical scores (SOFA, qSOFA, NEWS hazard ratio).

Graziadio et al. 2019	
Key outcomes	MR-proADM was associated with predicting 28-day mortality with significantly more accuracy compared with other biomarkers and scores, in a cohort of patients in the emergency unit (n=1,175, sensitivity 92%, 95% CI 80% to 97%; specificity 75%, 95% CI 72% to 78%). Patient subgroups with high MR-proADM concentrations (1.54 nmol/litre or higher) and low biomarker (procalcitonin below 0.25 ng/mlitre, lactate below 2.0 mmol/litre or C-reactive protein below 67 mg/litre) or clinical score (NEWS below 4 or CRB-65 score below 2) values were characterised by a significantly longer length of hospitalisation ($p<0.001$), rate of intensive care unit admission ($p<0.001$), elevated mortality risk (for example, NEWS hazard ratio, 32.6, 95%CI 9.4 to 113.6) and a greater number of disease progression events ($p<0.001$), compared with similar subgroups with low MR-proADM concentrations (below 1.54 nmol/litre).
Strengths and limitations	There were 2 patient cohorts considered, 1 consisted of prospective patients enrolled after presenting to the emergency department in 5 countries. This was compared with a subgroup of a cohort from a previous study done in the Netherlands. This second cohort was used to validate the results measured prospectively. This method of comparison is subject to bias because the 2 cohorts of data were collected under different conditions. The authors published further analysis in a letter to the journal indicating that delayed antibiotics for patients with low MR-proADM concentrations might result in fewer adverse effects, potentially allowing for a more detailed clinical assessment before any further treatment. Further studies in larger patient populations are needed to confirm these findings. The study was funded by the company.
Bellia et al. (2018)	
Study size, design and location	126 people in a consecutive case series. Location: Italy.
Intervention and comparator(s)	MR-proADM (measured on admission, T0 and after 24 hours, T24). Also used: APACHE II and SAPS II.

Graziadio et al. 2019	
Key outcomes	Multivariate analysis showed that T0 MR-proADM was a significant predictor of mortality (odds ratio: 1.27; 95% CI 1.03 to 1.55; p=0.022). Receiver operating characteristic curves analysis showed that MR-proADM on admission identified non-survivors with high accuracy and was less accurate than APACHE II and SAPS II scores (AUC 0.71; 95% CI 0.62 to 0.78; p=0.0002 for MR-proADM; AUC 0.71; 95% CI: 0.62 to 0.79; p<0.0001 for APACHE II; AUC 0.8; 95% CI 0.71 to 0.87; p<0.0001 for SAPS II).
Strengths and limitations	This study uses the technology alongside APACHE II and SAPS II clinical scoring systems, which are not standard of care in the NHS.
Stalenhoef et al. (2018)	
Study size, design and location	313 people with suspected febrile urinary tract infections in a consecutive case series. Location: Netherlands.
Intervention and comparator(s)	MR-proADM. Also used: procalcitonin, C-reactive protein, and a clinical score (PRACTICE).
Key outcomes	MR-proADM had the highest diagnostic accuracy for predicting a complicated febrile urinary tract infection (AUROC [95% CI] 0.86 [0.79 to 0.92]), followed by procalcitonin (AUROC [95% CI] 0.69 [0.58 to 0.80]). MR-proADM concentrations were unique in being significantly elevated in patients directly admitted and in outpatients who then needed hospitalisation, compared with those completing treatment at home. A virtual triage algorithm with an MR-proADM cut-off of 0.80 nmol/litre resulted in a hospitalisation rate of 66%, with only 2% secondary admissions.
Strengths and limitations	This study only considered MR-proADM in people with suspected febrile urinary tract infections. This study uses the PRACTICE clinical scoring system and other biomarkers, which may not be standard of care in the NHS. One of the authors is employed by the company.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUC, area under the curve; AUROC, area under receiver operating characteristic curve; CI, confidence interval; qSOFA, quick sequential organ failure assessment; NEWS, National Early Warning

Score; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

Recent and ongoing studies

- MR-proADM and CT-proET-1 during intensive care unit treatment (MR-proADM). ClinicalTrials.gov identifier: NCT03651635. Status: recruiting. Indication: unknown. Devices: MR-proADM.
- Identifying patients with suspicion of infection in the emergency department who have low disease severity using MR-proADM - pilot study (IDEAL). ClinicalTrials.gov identifier: NCT03770533. Status: recruiting. Indication: unknown. Devices: MR-proADM.

Specialist commentator comments

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

All specialists were familiar with MR-proADM and 2 specialists had used it in a research setting.

Level of innovation

Two specialists noted that MR-proADM was a novel biomarker and they did not know of any other tests available to measure this. All specialists agreed that measuring mid-regional proadrenomedullin (MR-proADM) could better inform triaging of patients compared with National Early Warning Score (NEWS/NEWS2) alone. Two specialists mentioned that further validation of the test would be needed. Another specialist stated that the test results would need to be available at the point of care to deliver patient and system benefits.

Potential patient impact

One specialist stated that results from MR-proADM testing, when used alongside NEWS2,

would likely help clinicians make better decisions about care for people with suspected infection and sepsis. This could potentially avoid admissions and allow for earlier transfer to high dependency and intensive care units.

One specialist stated that the test may be useful as a rule-out test for suspected infection and sepsis, and could lead to quicker discharge for some patients. However, this specialist stated that this would need to be evaluated in a prospective study directly comparing decisions based on NEWS2 with decisions based on MR-proADM results alongside NEWS2. This specialist also noted that there was no evidence directly comparing NEWS2 with NEWS2 and MR-proADM.

One specialist noted that the test would probably be used in adults attending emergency departments and further testing was needed to evaluate the effectiveness in children and people with immunosuppression.

Potential system impact

One specialist stated that MR-proADM could allow safer discharge of patients and lower readmission rates, as well as earlier and more accurate triaging. This could improve clinical outcomes and cost savings. One specialist stated that the test could lead to earlier, safe, patient discharge.

One specialist stated that MR-proADM could help with 4-hour waiting time targets in emergency departments. However, they noted that there was limited evidence to support this. One specialist noted that the technology could be very helpful to emergency department staff who often have to make difficult decisions under pressure.

All specialists agreed that this technology would be an additional cost to current care. Further evidence would be needed to show that using the test would improve outcomes and result in cost savings.

Although running the test on the Kryptor analyser takes around 30 minutes, 1 specialist commentator noted that the test cannot be run immediately and that if sample transport, processing and reporting are considered it usually takes over an hour for results to be available. Two specialist commentators noted that a point-of-care test would be a better option to provide results as soon as possible. One specialist noted that results would need to be available within 1 hour for risk stratification. This is because patients at high risk must have antibiotics within 1 hour (medium risk within 3 hours and patients at low risk

may not need antibiotics).

One specialist commentator noted that the Kryptor platform is semi-automated (rather than fully automated) and does not fit with current workflows in most NHS labs that use high-throughput automated platforms. Two specialists stated that the Kryptor platform is not widely available in the NHS.

General comments

One specialist commentator noted that MR-proADM is a non-specific marker for infection and that it reflects disease severity for many conditions, including infection.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Kordo Saeed, consultant microbiologist and clinical lead for microbiology and honorary senior lecturer, University Hospital Southampton NHS Foundation Trust. Dr Saeed has received research grants from the company.
- Professor Enitan Carrol, professor of clinical infection, microbiology and immunology, University of Liverpool. Professor Carrol is doing research on MR-proADM, and a study on MR-proADM and a competitor test has been submitted.
- Professor Thomas Evans, professor of molecular microbiology (bacteriology), University of Glasgow. Did not declare any interests.

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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