QuikRead go for C-reactive protein testing in primary care

Medtech innovation briefing

Published: 14 September 2016

www.nice.org.uk/guidance/mib78

Summary

- The **technology** described in this briefing is the QuikRead go C-reactive protein (CRP) point-of-care test. It is used to quantify CRP in blood, serum or plasma using the QuikRead go instrument.

- The **innovative aspects** are that QuikRead go CRP has the potential to provide rapid results by point-of-care testing of a 20 microlitre blood sample, with a reading time of 2 minutes.

- The intended **place in therapy** would be in primary care, where it would be used by GPs or nurse practitioners to help guide appropriate prescribing of antibiotics for people with lower respiratory tract infection.

- The **key points from the evidence** summarised in this briefing are from 2 randomised controlled trials, a retrospective diagnostic case-control study and a prognostic study (n=4,874). These studies reported reduced antibiotic prescribing rates compared with standard care, and that the technology performed with a similar accuracy as a standard laboratory CRP test in detecting pneumonia. The diagnostic case-control study reported sensitivity as 52% and 20% for low (20 mg/litre) and high (100 mg/litre) thresholds respectively for the detection of radiographic pneumonia, and specificity as 72% and 99%.

- **Key uncertainties** around the evidence are the use of the predecessor version of the technology in the randomised controlled trials. However, the core technology is the same for the predecessor version of QuikRead go and the clinical outcomes reported are likely to be applicable to both systems.

- The QuikRead go instrument **costs** £1,050 and the QuikRead go CRP test kits cost £215 for 50 single-use tests (excluding VAT). These would represent an additional acquisition cost to standard care, along with costs associated with maintenance and quality assurance. Using this technology could contribute to fulfilling antibiotic stewardship programmes.

- NICE has also published a medtech innovation briefing on the Alere Afinion CRP for CRP testing in primary care.

The technology

C-reactive protein (CRP) is a non-specific marker released into the blood in response to various infectious and inflammatory triggers. Measuring CRP in people presenting with suspected lower respiratory tract infection helps to differentiate viral and self-limiting infections from more serious bacterial infections that need antibiotics. Several clinical studies have evaluated point-of-care CRP testing in adults to guide antibiotic prescribing in respiratory tract infections when used along with clinical assessment (Aabenhus et al. 2014).

The QuikRead go system consists of the QuikRead go instrument and a range of QuikRead go CRP test kits. The QuikRead go CRP test is an in vitro diagnostic test intended to determine the amount of CRP in the blood of people who present with symptoms of infection. A QuikRead go CRP+Hb test is also available and provides additional haemoglobin concentration measurements from the same sample (see table 1).

Table 1. CRP assays for use in the QuikRead go device

Assay name	Analyte(s)	Detection range
QuikRead go CRP	C-reactive protein	CRP: 5–200 mg/litre
QuikRead go CRP+Hb	C-reactive protein and haemoglobin	CRP: 5–200 mg/litre Hb: 50–245 g/litre

The QuikRead go instrument is a photometer that is calibrated for both photometric and turbidimetric measurement. To do the test, a finger-prick blood sample is collected using a 20 microlitre capillary tube and is dispensed into a cuvette. Venous blood, plasma or serum can also be tested. The cuvette is inserted into the QuikRead go instrument. The QuikRead go CRP assay uses nanoparticles coated with anti-human CRP fragments, which react with the CRP in the sample. The instrument measures the resultant change in the turbidity of the solution within the cuvette and converts this value into a concentration value on the basis of pre-set test calibration data encoded on each cuvette label.

Results are shown within 2 minutes, in units of mg/litre CRP. The cuvette automatically rises up from the machine to be discarded in a sharps bin.

The results are automatically stored in the instrument's internal memory, along with user and patient identification. The instrument also has uni-directional (LIS01-A2) and bi-directional connectivity (POCT01-A2) to hospital and laboratory information systems, as well as compatible computer systems.

Full information of the QuikRead go CRP test procedure, quality control process and accuracy and precision data can be found in the manufacturer's instructions for use.

The manufacturer also supplies assays for detecting *Streptococcus* type A and an immunochemical faecal occult blood test that can be run on the QuikRead go instrument, but these are beyond the scope of this briefing.

The innovation

Point-of-care CRP tests have the potential to change current practice by informing the clinical decision to prescribe antibiotics for people with symptoms of respiratory tract

infections during a primary care consultation. Tests that improve clinical decision-making in antibiotic prescribing may support antimicrobial stewardship.

Testing for CRP is conventionally done by collecting a venous blood sample, which is then sent for laboratory analysis, with the results being available 1 to 2 days later. Because of this delay, CRP testing is not typically used to assess acute infections in primary care and is more commonly used when investigating chronic conditions.

Current NHS 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 prescribing could be postponed until a later time if symptoms have not resolved (delayed).

NICE's guideline on the diagnosis and management of pneumonia in adults recommends that point-of-care CRP testing should be considered for people with symptoms of lower respiratory tract infection in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the result. 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. It is not recommended for CRP levels less than 20 mg/litre.

NICE's quality standard on infection prevention and control states that in order to help prevent the development of antibiotic resistance in bacteria, it is important to prescribe antibiotics according to the principles of antimicrobial stewardship. These include prescribing antibiotics only when needed (and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats) and reviewing the continued need for them.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function as the QuikRead go system:

- Afinion AS 100 analyser (Alere)

- AQT90 Flex (Radiometer Medical ApS)

- iChroma (Boditech Med)

- NycoCard Reader II(Alere)

- Smart analyser (Eurolyser Diagnostica)

NICE has also published a medtech innovation briefing on the Alere Afinion CRP test for use in primary care.

Population, setting and intended user

The QuikRead go CRP test would be done at the point of care in primary care for people with suspected bacterial lower respiratory tract infection. It would be done by primary care clinicians during a consultation. The QuikRead go CRP test would only be used in conjunction with a clinical examination and clinical judgement to help inform the decision to prescribe antibiotics.

The Medicines and Healthcare products Regulatory Agency guideline on management and use of in vitro point-of-care test devices provides advice and guidance for point-of-care testing services in primary and secondary care. This guidance addresses key issues including 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

Device costs

Table 2. Current costs of QuikRead go system components

Description	Cost (£, excluding VAT)	Additional information
QuikRead go instrument	1,050	Reusable
UK mains cable	5	Reusable

QuikRead go CRP test kits	215	Includes 50 single-use tests
QuikRead go CRP+Hb test kits	250	Includes 50 single-use tests
CRP control	25	1 millitre, concentration 30 mg/litre, ready to use
CRP control high	25	1 millitre, concentration 85 mg/litre, ready to use
Haemoglobin control	25	1 millitre

Each test kit includes 50 CRP reagent caps, 50 cuvettes (1 millitre) prefilled with buffer, 50 capillary tubes (20 microlitres), 50 plungers and instructions for use.

There would be additional costs associated with training, maintenance, and quality assurance.

Costs of standard care

Standard care for people presenting to primary care with symptoms of a lower respiratory tract infection would be a consultation with a primary care clinician without the use of a CRP point-of-care test to aid the diagnosis and the clinical decision to prescribe antibiotics. The unit cost of a GP consultation, excluding costs of antibiotic prescription, ranges from £33 to £65, depending on duration (Personal Social Services Research Unit 2015). The average cost of a course of amoxicillin is approximately £1.49; a course of erythromycin costs approximately £3.05.

The QuikRead go CRP test would be an adjunctive test to a primary care consultation, and so represents additional acquisition, consumable and staff time costs.

Resource consequences

The QuikRead go CRP test will incur both capital and consumable costs, and there will be costs associated with maintenance and quality assurance. However, it may reduce costs by avoiding unnecessary antibiotic prescribing. Antimicrobial stewardship is an important issue in healthcare and several 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 testing. The use of CRP point-of-care testing was associated with an incremental cost of £18.92 compared with standard care, and an incremental quality-adjusted life year gain of 0.0012. The use of a CRP point-of-care test was judged to be cost effective, at an incremental cost-effectiveness ratio of £15,763.

Regulatory information

The QuikRead go CRP test was CE-marked as an in vitro diagnostic medical device in September 2010. The QuikRead go CRP+Hb test was CE-marked in November 2012.

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 promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing 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 QuikRead go CRP in primary care.

Clinical and technical evidence

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

search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies are summarised in this briefing. Two randomised controlled trials investigated the potential of the predecessor QuikRead 101 CRP system to improve antibiotic stewardship in patients with respiratory tract infections. Little et al. (2013) carried out a multinational, cluster randomised controlled trial which prospectively enrolled 4,264 patients with lower or upper respiratory tract infections from 246 primary care practices. A study by Cals et al. (2010) randomised 258 patients with lower respiratory tract infections or rhinosinusitis into C-reactive protein (CRP)-assisted care (intervention; n=129) or standard care, (control; n=129).

Miravitlles et al. (2013) used the QuikRead 101 system to retrospectively analyse CRP levels in blood samples taken from patients with chronic obstructive pulmonary disease (COPD) who had been recruited into the placebo arm of a randomised controlled trial (n=152).

A nested case-control study (Minnaard et al. 2015) aimed to determine the diagnostic accuracy of 5 point-of-care CRP tests, including the QuikRead go and QuikRead 101 systems, and whether they added diagnostic value in predicting radiographic-diagnosed pneumonia in adults presenting with acute cough in primary care (n=200).

Two studies assessed the analytical performance of the QuikRead go system (Brouwer and van Pelt, 2015 and Minnaard et al. 2013).

Table 3 summarises the clinical evidence as well as its strengths and weaknesses.

Table 3. Summary of the selected studies

Study	Details of intervention and comparator(s)	Outcomes	Strengths and limitations

Little et al. 2013 n=4,264 Cluster randomised factorial controlled trial Multinational (246 practices from 6 countries) Belgium, Spain, Wales, England, Poland, Netherlands	CRP testing using QuikRead 101 (n=1,062), enhanced-communication training (n=1,170), CRP testing in combination with enhanced-communication training (n=1,162) compared with standard care (n=870).	The antibiotic prescribing rate was lower with CRP training than without and with enhanced-communication training than without (33% compared with 48%, adjusted risk ratio 0.54, 95% confidence interval 0.42 to 0.69). The combined intervention was associated with the greatest reduction in prescribing rate. There was a higher admission rate in the CRP group compared with the non-CRP group, but this was of borderline statistical significance when controlled for all potential confounders. The symptom severities in the CRP group were similar to those in the non-CRP group. Rates of new or worsening symptoms did not differ significantly.	This was a large trial on the QuikRead 101 CRP system, powered to detect a 10% reduction in antibiotic prescribing. Several practices were excluded before and after randomisation because of recruitment issues.

Cals et al. 2010 n=258 Randomised controlled trial Multicentre (11 centres) Netherlands	CRP-assisted prescribing strategy (QuikRead 101 analyser intervention, n=129) compared with standard care (non-CRP-assisted prescribing strategy, control, n=129).	Patients in the CRP-assisted group used fewer antibiotics than those in the control group after the index consultation and during 28-day follow-up. There were fewer delayed prescriptions in the CRP-assisted group. Of those with delayed prescriptions, fewer prescriptions were filled in the CRP-assisted group than in the control group. Recovery was similar across both groups and patient satisfaction with care was higher in the CRP-assisted group.	The study was not powered to detect differences between the 2 groups. Patients were individually randomised and allocation concealment was done, reducing selection bias. The authors did a sensitivity analysis and accounted for variation at physician level.

Miravitlles et al. 2013 n=152 Prognostic study Patients with COPD from placebo arm of randomised controlled trial Spain	QuikRead 101 analyser with QuikRead CRP assay compared with Anthonisen criteria.	The only factors significantly associated with an increased risk of clinical failure (defined as incomplete resolution, persistence, or worsening of symptoms that needed a new course of antibiotics, oral corticosteroids, or hospitalisation) without antibiotics were the increase in sputum purulence (included in the Anthonisen criteria) and a CRP concentration $\geq$ 40mg/litre. The use of a point-of-care CRP test statistically significantly increased the predictive accuracy of clinical failure.	Only study to evaluate clinical outcomes associated with CRP $\geq$ 40mg/litre (cut-off determined on the basis of previous analysis). Authors could not rule out some placebo effect because the criteria for success were based on clinical evaluation.

Minnaard et al. 2015 n=200 Retrospective diagnostic case-control study Multinational (16 primary care research networks across 12 European countries) Belgium, Finland, Germany, Hungary, Italy, Netherlands, Norway, Poland, Spain, Slovakia, Sweden, UK	5 point-of-care devices including QuikRead go and QuikRead 101, compared against a laboratory reference standard (Vitros 5.1 FS, Ortho Diagnostics; Dimension Vista Systems, Siemens). Diagnostic accuracy outcomes were determined from 200 patient blood samples (100 with pneumonia, 100 without pneumonia). A clinical algorithm was used to determine the incremental predictive power of each CRP test to predict pneumonia.	The sensitivity and specificity of QuikRead go in predicting pneumonia was consistent with other point-of-care systems and a laboratory reference test. In all cases the discriminatory power of the tests to predict pneumonia were reduced when a higher threshold of CRP (>100mg/litre) was used. Sensitivity was 52% and 20% for low (20 mg/litre) and high (100 mg/litre) thresholds respectively for the detection of radiographic pneumonia, and specificity was 72% and 99%.	Retrospective case-control design subject to inherent bias (likely to overestimate effect). Radiographs were used as the reference standard. Samples were analysed retrospectively at a central laboratory. A diagnostic model was used to evaluate the incremental predictive power of CRP when added to symptoms and signs. This may not completely represent clinical judgement in real life.

Brouwer and van Pelt, 2015 Analytical performance study Netherlands	8 point-of-care devices including QuikRead go, compared with a comparative laboratory method (Synchron CRP). All blood samples were from GPs' patients, aged over 18 years, with CRP concentrations ranging from 5 to 200 mg/litre, determined with the Synchron analyser.	The linear regression equation of QuikRead go revealed an underestimation of CRP values compared with the laboratory method. The coefficient of variation of QuikRead go met the criteria of <10%. The correlation of the CRP tests to the reference standard varied considerably.	Patient blood samples were used with CRP values determined from an appropriate reference standard. Patient characteristics and diagnosis were not reported.

Minnaard et al. 2013 Analytical performance study Netherlands	5 point-of-care devices including QuikRead 101 and QuikRead go, compared with a laboratory method (Olympus AU2700). Residual stored material from routinely done laboratory blood tests was pooled to obtain lithium heparin plasma pools with CRP concentrations of approximately 10, 15, 20, 25, 50, 90, 100 and 110 mg/litre.	The within-day coefficient of variations for low and high CRP concentration samples were smaller for the QuikRead go compared with the QuikRead 101 and other point-of-care devices. The between-day coefficient of variations for high CRP concentration samples was also lowest with the QuikRead go CRP test. For high CRP values (>100mg/litre), agreement with the laboratory standard systematically decreased for all 5 point-of-care tests. The analytical performance and agreement of the CRP tests to the laboratory method varied considerably, but was considered adequate.	Lithium heparin plasma samples were used instead of blood obtained by finger prick. A separate plasma pool was created to evaluate the QuikRead 101 device.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.			

Strengths and limitations of the evidence

The diagnostic accuracy and analytical performance studies were done in a laboratory setting and may not be representative of the primary care setting the technology is intended for.

Although there is no evidence with clinical outcomes for the QuikRead go, the studies that compared the diagnostic accuracy and analytical performance of QuikRead 101 and QuikRead go showed that the systems were comparable. The antibiotic prescribing rates described in the 2 randomised controlled trials on the QuikRead 101 system and clinical outcomes in the prognostic study are therefore likely to be generalisable to the QuikRead go system.

Recent and ongoing studies

No ongoing or in-development trials were identified.

Specialist commentator comments

Three specialist commentators considered that the QuikRead go CRP point-of-care test would be done for patients presenting with symptoms of respiratory tract infections, because there is only evidence for the diagnosis of this indication in primary care. It may also be used for some inflammatory conditions, such as arthritis or polymyalgia rheumatica.

The main system benefit of point-of-care technology for C-reactive protein (CRP) testing may not be quantifiable in terms of cost savings due to reduced antibiotic usage. Instead, the benefits from using point-of-care tests would be in helping the safe and appropriate prescribing of antibiotics, and in improving clinical care.

One commentator noted that there is evidence to show that delayed antibiotic prescriptions reduce consultations. They felt that point-of-care CRP testing may similarly reduce future presentations with similar illnesses, but were unsure whether there is evidence for this. The QuikRead go CRP test could possibly prevent accident and emergency attendance by those patients who feel they need antibiotics and have not been given them by their primary care clinician. It could also improve sensitivity in diagnosing pneumonia in some vulnerable patients so that effective treatment can be given to avoid hospital admissions.

One commentator noted a range of factors, which may influence results and should be accounted for in any point-of-care test. For example, it is unclear whether testing whole blood, serum and plasma could give different results. The commentator also mentioned the hook effect, where beyond a critical concentration of CRP (the hook point), the signal level decreases as the CRP concentration increases. The manufacturer's instructions for use show that CRP concentrations less than 1000 mg/litre do not give falsely low results. However, the commentator was concerned that this may imply that CRP concentrations above 1000 mg/litre give falsely low results and it may be difficult to determine when this is the case. The commentator felt that there should be more technical awareness around these tests in users.

Specialist commentators

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

The following clinicians contributed to this briefing:

- Ann Marie Carroll, Pathology Point-of-Care Testing Manager, Nottingham University Hospitals Trust

- Professor Jonathan Cooke, Visiting Professor in the Infectious Diseases and Immunity Section, Imperial College London (has received consultancy, educational and research grants from Alere Ltd.)

- Dr Tha Han, Consultant in Public Health Medicine, Enfield Council

- Michael Moore, Professor of Primary Care Research, University of Southampton (co-author on several publications using C-reactive protein for management of lower respiratory tract infection in primary care and was on the NICE guidelines development group for the pneumonia guideline)

- Dr Simon Spooner, GP Partner, Linden Medical Centre (is working on the asthma – diagnosis and monitoring guideline and also on a primary care implementation feasibility project)

Development of this briefing

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

ISBN: 978-1-4731-1970-3