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Diagnostic Technology: Point-of-care testing for coeliac disease

Clinical Questions:
(1) In patients presenting to primary care with suspected coeliac disease (CD), what is the diagnostic accuracy, impact and cost-effectiveness of point-of-care testing for coeliac disease compared to standard practice?
(2) In the general population, what are the diagnostic accuracy, impact and cost-effectiveness of point-of-care testing for screening coeliac disease?

Existing technology and standard of diagnostic care:
The current gold standard for coeliac disease diagnosis is small-bowel biopsy. However, duodenal biopsy is expensive, invasive and carries a small risk of adverse events such as infection, bowel perforation, bleeding and anaesthetic reaction. Hence, biopsies are not a first line test for diagnosis of coeliac disease nor are they useful for screening.

Serological tests for coeliac disease have been an area of research interest since the 1970s as a means of non-invasive screening for coeliac disease. Serological tests for IgA anti-tissue transglutaminase antibody (tTGA), and anti-endomysial antibody (EMA) tests have high sensitivity and specificity for coeliac disease (1, 2) and are currently the first step in evaluating patients. Anti-gliadin antibodies are no longer considered sensitive enough or specific enough to be used for detecting coeliac disease, except in children younger than 18 months of age (2). In patients with IgA deficiency the IgG class of the tTGA and EMA tests are recommended (2).

Advantages over Existing Technology:
Conventional serological tests for coeliac disease are performed in central laboratories and results often take several days. By contrast, the point-of-care test (POCT) can be performed in ambulatory care settings or at home, and the price for a single test unit ranges from £17-£20. The Biocard test has been reported to be suitable for home use by patients (3, 4). Both the POCT and conventional serological tests require patients to be on a normal gluten-containing diet at the time of testing, since IgA-tTG antibody titres diminish when people with coeliac disease consume a gluten-free diet. Both tests are also of limited use in young children (<5 years) and patients with IgA deficiency.

Details of Technology:
Two POCT devices available in the market were studied:

1. *Biocard Coeliac Test Kit, Ani Biotech Oy, Finland; UK Distributor: BHR Pharmaceuticals Ltd. CE marked.*

There are two versions of the test, a home test and a professional test; the only difference is a 'total IgA measuring system' included in the professional kit. The home test is available from high street chemist shops and online (5). The Biocard requires a drop of whole blood, obtained via finger-prick and provides results within 10 minutes.

The Biocard test uses immunochromatography to detect anti-tTG IgA antibodies in whole blood samples. The test strip has control and test regions, which respond to the concentration of transglutaminase IgA antibodies in the blood. Anti-tTG IgA antibodies in the sample bind to gold-labelled antibodies in the test strip to form a visible, red line. A positive test result is two red lines; one in the control (C) field and another in the test field

(T). The test is negative if one red line appears in the C field. If there is no line in either the C or T region, IgA deficiency should be suspected.

2. *Stick CD1 and CD2, Operon S.A., Spain. CE marking unknown*

The Stick CD test kits are not readily available in the UK; but can be ordered through the Spanish company Operon (www.operon.es). These are one-step tests that use the same immunochromatography principle as the Biocard kit (7). Both detect antibodies against human tTG, and CD2 also detects anti-gliadin antibodies. There are two important differences: (a) the Stick CD kits detect a wide range of antibodies, including IgA, IgG and IgM antibodies against human tTG and (b) the Stick CD use serum instead of blood samples. This limits their applicability to ambulatory settings as serum must obtained through venous puncture (7). Results of the Stick CD test are available within 10 minutes.

Patient Group and Use:

- Patients attending primary care in whom coeliac disease is suspected because of signs or symptoms (chronic or intermittent diarrhoea, failure to thrive [children], persistent or unexplained GI symptoms such as nausea and vomiting, prolonged fatigue, recurrent abdominal pain, cramping or distension, sudden/unexpected weight loss, unexplained iron-deficiency anaemia) (2)
- Patients with risk factors for coeliac disease such as autoimmune thyroid diseases, dermatitis herpetiformis, irritable bowel syndrome, type 1 diabetes, or first-degree relatives with coeliac disease (2)
- Monitoring effect and compliance with gluten-free diet in patients with confirmed coeliac disease
- The Biocard test is not suitable for children <5 years of age in whom IgA levels are too low for accurate detection

Importance:

The prevalence of coeliac disease in the UK is estimated to be 0.8-1.9% of the general population, and between 4.5-12% amongst first-degree relatives (2). Most cases are undiagnosed; these cases may be latent, silent or misdiagnosed and several studies suggest that the diagnosis is made, on average, over 10 years after symptom onset (3, 5). Undiagnosed, coeliac disease can lead to chronic illness including anaemia and osteoporosis (with resulting increased risk of fractures) (2). In children, undiagnosed CD can result in growth failure, delayed puberty and dental problems. Diagnosis is important since a gluten-free diet can effectively eliminate symptoms, reverse the underlying pathology and prevent long-term complications. Dietary intervention has also been shown to have a significant impact on quality of life (5).

Previous Research:

Accuracy compared to existing technology:

There are six studies that have evaluated the accuracy of the Biocard test in coeliac disease (6-11) and two (7, 15) which evaluated the Stick CD1 test. Studies looking at earlier non-commercial versions of the technology are not considered here.

We identified four diagnostic case control studies applying the Biocard test to a population of biopsy-confirmed coeliac disease patients and laboratory controls (7-10). The same research group performed three of these studies; it is unclear to what extent the participants overlap, further limiting the generalisability of the results.

The earliest study was based on samples from 121 consecutive biopsy confirmed coeliac disease patients and 107 non-coeliac biopsied controls (8). Control patients comprised those who were biopsied for gastrointestional symptoms but had normal villous morphology on pathology. Patients were drawn from tertiary clinics in Hungary and Finland. Biocard and laboratory serum tests (EMA and tTGA) were compared to the

gold standard of duodenal biopsy. The Biocard test gave a sensitivity of 97% and a specificity of 94%, a positive likelihood ratio (LR+) of 14.9 and a negative likelihood ration (LR-) of 0.35. By comparison, laboratory serum EMA and tTGA tests had a sensitivity of 97% and 99%, respectively with both showing a specificity of 100%.

A subsequent study by the same authors (9) on a different set of patients compared a non-commercial POCT developed "in-house" (12) with the Biocard test using duodenal biopsy as the gold standard for comparison. The Biocard test was evaluated in 24 untreated coeliac disease patients and 19 controls. The sensitivity of the Biocard test was found to be 92% and the specificity was 79%. A third study by the same group (10) investigated the Biocard test in 150 consecutive untreated CD patients and 107 controls; all had undergone biopsy. However 15 blood samples were damaged, hence the Biocard test was applied to 139 CD patients and 103 controls; sensitivity and specificity were 93% and 94% respectively for the Biocard test compared with duodenal biopsy. None of the patients in the above studies were IgA deficient.

An Italian Study (7) investigated both the Stick CD1 serum-based test and the Biocard blood-based test. The Stick CD1 arm examined samples from 114 biopsy-confirmed coeliacs and 143 controls (120 healthy blood donors, 20 first degree relatives and 3 non-coeliac biopsied controls). The sensitivity of the Stick CD1 test was 100% (including 4 IgA deficient CD patients) and the specificity was 94.9%. The Biocard test was investigated on a smaller sub-population of the study sample, as the Biocard test became available eight months into the study. Within the Biocard arm there were 51 biopsy-confirmed coeliacs and 100 controls, and it reported a sensitivity of 90% and specificity of 100%. If one excludes the 3 patients who tested negative for IgA deficiency, the sensitivity of the Biocard test increases to 96% (46/48).

One prospective multicentre study in 4 paediatric gastroenterology units in Spain evaluated the accuracy of Stick CD1 and CD2 test on serum samples obtained from 113 CD-confirmed paediatric patients (15). For CD1 Stick test, sensitivity was 96.5% and specificity was 98.6%. CD2 displayed a sensitivity of 94.5% and a specificity of 98.6% for tTG antibodies and a sensitivity of 63.1% and a specificity of 95.2% for gliadin antibodies.

The diagnostic accuracy of the Biocard test was also assessed in cross-sectional studies in a clinical setting. Raivio et al. 2006 (8) applied the Biocard test prospectively to 150 patients from a tertiary clinic with suspected but unconfirmed coeliac disease. The Biocard results were compared with serological EMA and tTGA tests and found to be concordant in 145 of 150 patients. The sensitivity and specificity of the Biocard test relative to both EMA and tTGA serological tests were 97.1% and 95.7 respectively.

Only one study assessed the Biocard test for screening (11). District nurses at primary care centres in Hungary tested 6-year old children (n=2676) with the Biocard and serological tests. They were offered biopsy if any result was positive and coeliac disease was confirmed in 32 children (1.2%); this corresponds with the estimated population prevalence of coeliac disease of 1%. The Biocard test was positive for 28 of the 2676 subjects (1.05%). From these positive patients, 3 refused biopsy; biopsies evaluated by assessors blinded to the rapid test results from the remaining 25 children confirmed coeliac disease in all. Seven children with a negative Biocard test but positive on other laboratory tests had abnormal biopsies. Thus, when compared to biopsy plus follow-up, Biocard test sensitivity was 78.1% and specificity was 99.8% (including the 3 refusals as non-coeliac patients). When compared with EMA and tTGA serology results (IgA and/or IgG) in the same population, the Biocard test had a sensitivity and specificity of 65.1% and 100% respectively. Conventional serology identified 15 subjects as being CD positive who were missed (tested negative) with the Biocard test.

Of the 43 patients identified as CD positive by serological screening, 32/38 who underwent biopsy were found to be coeliac disease positive.

In a Brazilian study (6), the Biocard test was applied to 299 consecutive patients from a tertiary clinic setting. The sample consisted of a mixed population of healthy controls, patients with suspicion of coeliac disease, patients with other GI problems and first-degree relatives of CD patients, the rationale of which is not clear. Of the 299 patients screened with the Biocard Test, 16 were positive and underwent further testing by EMA-IgA serology and biopsy. By EMA-IgA serology, 14 patients were positive and 2 negative. Of the 15 patients who agreed to biopsy, 14 were confirmed as coeliac disease positive. There was no verification (biopsy or follow-up) of the patients testing negative, thus preventing reliable estimation of the diagnostic accuracy.

Table 1. Summary of results of accuracy studies.

Test	Population	Comparator	Reference Standard	Accuracy result	Ref
Biocard	121 biopsy-confirmed coeliac disease patients	107 non-coeliac controls, biopsied for gastrointestinal complaints	Biopsy	Sensitivity 97%; Specificity 94%	8
	24 untreated coeliac disease patients	19 non-coeliac controls, biopsied for gastrointestinal complaints	Biopsy	Sensitivity 92%; Specificity 79%	9
	139 consecutive untreated coeliac disease patients	103 non-coeliac controls, biopsied for gastrointestinal complaints	Biopsy	Sensitivity 93%; Specificity 94%	10
	51 biopsy-confirmed coeliac disease patients	100 non-coeliac controls	Serological tTGA laboratory testing	Sensitivity 90%, Specificity 100%	7
	150 patients with suspected coeliac disease	None	Serological EMA and tTGA laboratory testing	Sensitivity: 97% Specificity 96%	8
	Screening of 2676 6-year-old children	None	Biopsy plus follow-up	Sensitivity 78% Specificity 99.8%	11
			Serological EMA and tTGA laboratory testing	Sensitivity 65% Specificity 100%	
Stick CD1	114 biopsy-confirmed coeliac disease patients	143 controls, biopsied for gastrointestinal complaints	Biopsy	Sensitivity: 100%; Specificity: 95%	7
	113 untreated coeliac disease paediatric patients <16 years	72 controls, biopsied for gastrointestinal complaints	Biopsy and laboratory serological testing	Sensitivity: 97%; Specificity: 99%	15
Stick CD2	113 untreated coeliac disease paediatric patients <16 years	72 controls, biopsied for gastrointestinal complaints	Biopsy and laboratory serological testing	tTGA: Sensitivity: 95%; Specificity: 99% Gliadin: Sensitivity 63% Specificity 95%	15

Refer to text for further details of the studies

Impact compared to existing technology

Both under-diagnosis and prolonged delay in the diagnosis of coeliac disease is significant in the UK. New

point-of-care tests have potential as a screening test in symptomatic individuals in place of conventional serological tests. The diagnostic accuracy of the Biocard rapid test appears to be high (sensitivity between 90-97% and specificity between 79-100%) in case-control studies or in populations at risk. It is important to note that given the design, these studies would overestimate the accuracy and are less generalizable due to the selective population. Sensitivity as a screening test in an asymptomatic population of children was significantly less (65-79%), which means that the ability to rule out CD in these children is reduced. There is limited evidence available for the Stick CD1 test which has a higher sensitivity than the Biocard test due to its ability to detect tTG antibodies in IgA deficient patients. However as a serum-based test its usability is restricted to health care settings.

Self-testing by patients may be of concern for a number of reasons. Commercially available self-tests may lead to self-diagnosis and discourage people from seeking medical evaluation. Patients who self-diagnose using a commercially available rapid-test kit may begin gluten-free diets without confirmatory testing, appropriate nutritional advice or medical investigation for complications or co-morbid conditions associated with CD.

Furthermore the possibility of false negatives with the Biocard test amongst patients with IgA deficiency reduces the sensitivity of the rapid test making it a less ideal population screening measure given that 8% of CD patients are also IgA deficient. Patients with false negative tests may delay seeking medical attention.

Use of the Biocard test by professionals may be of value in situations where a regular blood sample is difficult, e.g. children and people in whom venepuncture has proven difficult in the past.

Guidelines and Recommendations
The 2009 NICE guideline CG 86 1.1.14 recommends that self-tests and/or point-of-care tests for coeliac disease should not be used as a substitute for laboratory-based tests, and that patients with positive self- or point-of-care tests be sent for further serological testing (2). NICE advises, based on an evaluation of one early POCT (13), that "limited evidence suggests that point-of-care tests and self tests may be accurate but require further evaluation" (2).

Cost-effectiveness and economic impact:
Early case identification through POCT has the potential to prevent gluten-related morbidity and reduce the costs incurred by unnecessary medical examinations, laboratory tests and hospital admissions. Despite a number of cost and cost-effectiveness studies outlined in a recent NICE clinical guideline (2), only one focussed on the cost-effectiveness of screening for CD in an adult population(14). This however was based on screening using a number of serological tests. Interestingly, although the results from the cost-effectiveness model indicated EMA to be the preferred option, the authors pointed out that this test is onerous for the laboratories because it is technically difficult to interpret, has large inter-observer variability and is time-consuming.

An Italian before and after study assessed the cost and cost-effectiveness of case-finding for CD in a primary care setting (4). Again, the case-finding approach was based on a serological test (based on testing for anti-tissue transglutaminase IgA antibodies) rather than any POCT and resulted in a cost of €923.25 per newly-diagnosed case.

A notable exclusion related to all the above studies was the lack of any QALY measures used in the analyses. Evidence of the likely impact on health-related quality of life of introducing a POCT for CD comes from a retrospective study of patients diagnosed with CD (4). Based on responses from 697 CD patients the authors

found that the quality of life of people with undiagnosed symptomatic disease is substantially reduced compared to the general population and increases markedly after diagnosis. Using quality of life valuations from the UK population tariff for the EQ-5D questionnaire, resulted in a mean value of 0.56 (where 0= death and 1= full health) prior to diagnosis and 0.84 post-diagnosis (at the time of the survey). A caveat to these findings is that they are based on a retrospective assessment of the quality of life prior to diagnosis.

In conclusion, no evidence currently exists on the cost-effectiveness of POCT to screen for CD in a primary care setting. Although given the evidence on the cost-effectiveness of serological testing and the likelihood that POCT will reduce the laboratory burden, it is likely that point-of-care testing would offer a cost-effective alternative to serological testing.

Research Questions:

1. What is the diagnostic accuracy of the Biocard test in a primary care population with signs and symptoms or risk factors for coeliac disease?
2. Could point-of care tests for coeliac disease replace serological tests and would this be cost-effective?
3. Will the introduction of point-of-care testing decrease the lag-time to diagnosis?
4. Is point-of care testing useful in assessing dietary compliance of newly diagnosed patients?

Suggested next steps:

1. Further studies of utility and diagnostic accuracy, particularly prospective studies in the primary care setting.
2. Cost-effectiveness analysis of Biocard point-of-care as a population screening measure for coeliac disease
3. Study of accuracy of rapid-test results when administered by patients in a primary care setting
4. Impact of introducing the test on diagnostic delay, improvement of patient outcomes

Expected outcomes:

Point-of care testing may be helpful in the diagnostic work-up of coeliac disease in primary care settings by increasing speed of results or access to testing in some settings, and may eventually replace conventional serological testing, but it cannot yet replace endoscopic duodenal biopsy for definitive diagnosis of coeliac disease.

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Comments:

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