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Horizon Scanning Technology Prioritising Summary

Point of care testing for Coeliac disease

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This Horizon scanning prioritising summary was prepared by Adrian Purins, Linda Mundy, and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, Mail Drop 545, University of Adelaide, Adelaide, SA, 5005.

PRIORITISING SUMMARY

REGISTER ID: 000359
NAME OF TECHNOLOGY: POINT OF CARE TESTING FOR COELIAC DISEASE
PURPOSE AND TARGET GROUP: COELIAC DISEASE PATIENTS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|--|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input type="checkbox"/> No | |
| <input checked="" type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Finland	✓		
Hungary	✓		
Italy	✓		

IMPACT SUMMARY:

Point of care testing for coeliac disease (CD) would be provided in general practice clinics and other community based health care settings. This could diagnose the estimated 80 to 90 per cent of CD sufferers who aren't aware of their condition. Diagnosis of CD is important as an effective lifestyle modification, that is following a gluten free diet, can completely abrogate the symptoms and underlying physiological changes of the disease.

BACKGROUND

Coeliac disease is an immune mediated disease caused by inflammation of the gut due to an inappropriate immune reaction against gluten, a protein in many cereals. The gut is subsequently damaged leading to a wide array of symptoms such as fatigue, anaemia, failure to thrive (in children), weight loss, flatulence, diarrhoea or constipation. There is a significant genetic link with CD shown by the propensity of

near relatives of CD sufferers to also have CD and the fact that CD is associated with specific human leukocyte antigen (HLA) classes (AGA 2001).

Due to the diverse manifestations of symptoms in each patient and the non-specific nature of these symptoms, diagnosis of CD is problematic and many sufferers can go undiagnosed for long periods. The definitive diagnosis of CD is based on investigation of duodenal biopsy samples which, in CD patients, show characteristic signs of damage such as flattening and atrophy of the gut villi. Other serum based tests show good efficacy for diagnosing CD. As many as seven in eight CD sufferers are not aware of their status and, given the treatable nature of the disease, the identification of these patients is considered imperative. The application of standard tests as broad screening tools is not viable due to costs and the time required, and with biopsy the risk of adverse effects is too great when considering population screening (AGA 2001). New point-of-care tests, if effective, may allow the efficient screening of target populations and the identification and subsequent treatment of CD patients. One such point-of-care test is the Biocard™ Celiac Disease Stick. This uses a lateral flow immunochromatographic strip that has a positive control indicating the test is functioning properly and also a test region which responds to the presence of anti-transglutaminase IgA antibodies in the subject's blood. If a test is negative a line at only the control region will appear. If the test is positive then two lines will appear, both at the control region and the test region. Other combinations indicate an invalid result. Blood for the test is obtained from a finger prick and the result is readable after five minutes.

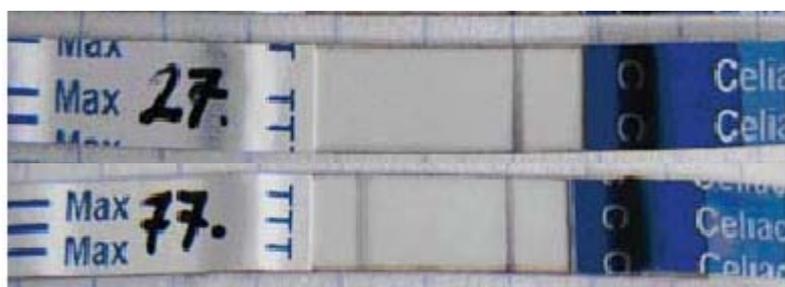


Figure 1 Biocard™ Celiac Disease Stick (Nemec et al 2006)

Top strip: A negative result showing just the positive control band

Bottom strip: A positive result showing both the test positive band and positive control band

CLINICAL NEED AND BURDEN OF DISEASE

There is a lack of data for the prevalence of CD in Australia. This is due to the estimated large proportion of CD affected individuals who are unaware of their status and thus harbour the disease latently. The Coeliac society of Australia estimates that 1 in 100 Australians have CD and 4 in 5 of these are undiagnosed (CSoA 2008).

DIFFUSION

No evidence was found during the preparation of this prioritising summary that indicated the entry of this technology into the Australian health system.

COMPARATORS

Intestinal biopsy via endoscopy followed by histology is the gold standard for CD diagnosis. Histological features commonly observed in CD patient biopsies are atrophy of the villi, crypt hyperplasia, inflammatory cell infiltrate. When these signs are mild there is difficulty in diagnosing CD. For a definitive diagnosis of CD a second subsequent biopsy should show marked improvement in the above signs after the patient has adhered to a strictly gluten free diet (AGA 2001).

Serological tests which test for antibodies against specific foreign (anti-gliadin) and self-antigens (anti-tissue transglutaminase and anti-endomysium) also exist for CD. Modern versions of these tests have high specificity and moderate to good sensitivity (Table 1). It is also recommended that total Immunoglobulin A (IgA) levels are measured due to the fact that a subset of coeliac patients have an IgA deficiency leading to false negative results. If a suspected CD patient has an IgA deficiency a biopsy would be performed (AGA 2001).

Table 1 Effectiveness of serum tests for diagnosing CD compared to gold standard (n=463)

	Sensitivity % (95% CI)	Specificity % (95% CI)
AGA ¹ IgA	50	98
Anti-EMA ²	81	99
ATA ³	81	99

¹ anti-gliadin antibody, ² endomysium antibody, ³ anti-tissue transglutaminase. Adapted from (Hadithi et al 2007)

SAFETY AND EFFECTIVENESS ISSUES

Several studies have investigated new point of care coeliac disease diagnostic kits for the purpose of either diagnosing or screening populations. The diagnostic use of the kits is intended for rapid diagnosis of patients whom may have a high risk of CD e.g. patients presenting with classic CD symptoms. The screening use of the kits is aimed at general population screening to identify as yet undiagnosed individuals with CD patients.

The assessment of the diagnostic accuracy of two rapid kits was performed in a population of 114 consecutive biopsy confirmed cases of CD, 120 healthy controls, 20 first degree relatives of CD cases, and 75 non-CD diseased controls (Nemec et al 2006)(level II diagnostic evidence). The two kits were: Stick CD1 (Operon S.A., Saragoza, Spain) which detects IgA-IgG anti-human-tissue transglutaminase antibodies in serum and; BiocardTM Celiac Disease Stick (Ani Biotech Oy, Vantaa, Finland) which detects IgA anti-human-tissue transglutaminase anti-bodies in whole blood. The Biocard test was only used on a subset of the patients due to its only recent availability. All tests were assessed blind to the status of the patient. Results are presented in Table 2.

Table 2 Performance of rapid test kits in a population with a known CD profile

	Sensitivity	Specificity
Stick CD1	100 % (114/114 positive)	94.9 % (11/215 negative)
Biocard	90.2 (46/51 positive)	100% (100/100 negative)
Biocard accounting for IgA deficiency ¹	95.8 (46/48 positive)	100% (100/100 negative)

¹ Three patients exhibited total IgA deficiency hence could never be positive for the Biocard test which is IgA based. When they are removed the Biocard test correctly identified 46 of the 48 biopsy confirmed CD cases.

The disadvantage of the Stick CD1 assay is that it requires serum and thus some sample preparation. The Biocard assay is designed to work on whole blood and is therefore better suited to point-of-care testing. The Biocard kit, being based only on IgA, is unable to diagnose CD in the eight per cent of CD patients who have a total IgA deficiency (Lenhardt et al 2004). This study reported the cost of the two methods to be approximately \$AUD 10.20 per test per patient.

A second study investigated point-of-care testing using the Biocard test in a clinical setting. The population consisted of 121 consecutively recruited confirmed CD patients and 107 non-coeliac controls. CD diagnosis was based on gold standard methods. Compared to the gold standard method 117/121 (96.7%) CD patients tested positive by the Biocard test giving a sensitivity of 96.7 per cent. Seven of 107 controls tested positive using the Biocard test, giving a specificity of 93.5 per cent. None of the patients were IgA deficient. Follow up of 15 patients was performed after a one year adherence to a gluten-free diet. All of the patients converted to negative status for the control test of anti-tissue transglutaminase. Of the patients tested at follow up with the biocard assay 13 converted to negative and two remained positive. This indicates that the Biocard test would be useful to monitor patient response to gluten free diet treatment (Raivio et al 2006) (level III-2 diagnostic evidence).

A Hungarian trial using the Biocard test was conducted in six year old children (n=2676). Testing was conducted by district nurses on site at primary care centres using the Biocard test. Blood was collected simultaneously for laboratory based reference tests (plasma IgA antibodies to endomysium and transglutaminase) . Children who were positive on either the laboratory or point-of-care tests were then offered a biopsy as a definitive diagnostic test. The Biocard test result was positive for 28 of 2676 subjects (1.05%). Of these positive subjects 25 were biopsied and CD was confirmed in all cases. Laboratory testing found 43 subjects to be CD positive, of these 38 underwent biopsy with 32 being confirmed as CD positive. Thus the Biocard test correctly identified 25/32 (78%) CD positive subjects. One of the 32 patients was IgA deficient and thus the Biocard negative was the expected result as the Biocard test only assesses IgA antibodies. Results are presented in Table 3 (Korponay-Szabo et al 2007) (level II diagnostic evidence).

Table 3 Performance of Biocard compared to laboratory testing and biopsy

	PPV	NPV
Biocard vs Total laboratory testing	100%	99.4%
Biocard vs positive laboratory testing	N/A	46.2%
Biocard vs biopsy	100%	N/A ¹

¹ biopsy was not performed on the subjects who tested negative with Biocard or laboratory testing. Thus NPV cannot be calculated.

In summary the rapid point-of-care tests provided fast and accurate diagnosis of diverse patient populations. The application of the Biocard test to a large population showed a high specificity. This allows the confident application of more invasive investigations as the subjects that test positive are very likely to have CD and therefore require further testing.

COST IMPACT

Nemec et al reported the cost of the two rapid point of care tests (Biocard and Stick CD1) at approximately \$AUD 10.20 per test per patient (Nemec et al 2006).

Korponay-Szabo reported the Biocard test to cost \$AUD17.00 from pharmacies in Hungary in 2005 (Korponay-Szabo et al 2007).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

The point-of-care tests, particularly the Biocard test, were rapid and easy to use and provided accurate results compared to the gold standards of CD diagnosis. They may fill several roles in the future including screening, diagnosis and CD monitoring in diagnosed populations. Additionally, the tests were relatively cheap and did not require any special infrastructure or training to use. Given that effective management of CD exists the identification of more CD patients is a worthwhile goal.

HEALTHPACT ACTION:

The point-of-care tests included in this summary appear to be an effective tool for the diagnosis of coeliac disease. These tests do not require approval from the TGA and may be used by general practitioners. Therefore HealthPACT recommend that the information contained within this summary is disseminated and that no further action is warranted.

NUMBER OF INCLUDED STUDIES

Total number of studies

Level II diagnostic evidence 2

Level III-2 diagnostic evidence 1

REFERENCES:

AGA (2001). 'American Gastroenterological Association medical position statement: Celiac Sprue', *Gastroenterology*, 120 (6), 1522-1525.

CSoA (2008). *Are you 1 in 100?* [Internet]. The Coeliac Society of Australia. Available from: <http://www.coeliac.org.au/> [Accessed 9th April].

Hadithi, M., von Blomberg, B. M. et al (2007). 'Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease', *Ann Intern Med*, 147 (5), 294-302.

Korponay-Szabo, I. R., Szabados, K. et al (2007). 'Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study', *BMJ*, 335 (7632), 1244-1247.

Lenhardt, A., Plebani, A. et al (2004). 'Role of human-tissue transglutaminase IgG and anti-gliadin IgG antibodies in the diagnosis of coeliac disease in patients with selective immunoglobulin A deficiency', *Dig Liver Dis*, 36 (11), 730-734.

Nemec, G., Ventura, A. et al (2006). 'Looking for celiac disease: diagnostic accuracy of two rapid commercial assays', *Am J Gastroenterol*, 101 (7), 1597-1600.

Raivio, T., Kaukinen, K. et al (2006). 'Self transglutaminase-based rapid coeliac disease antibody detection by a lateral flow method', *Aliment Pharmacol Ther*, 24 (1), 147-154.

SEARCH CRITERIA TO BE USED:

Mass Screening/economics/methods
Celiac Disease/ diagnosis/ diet therapy
Point-of-Care Systems
Prospective Studies
Reagent Kits, Diagnostic