Coeliac Australia Medical Advisory Committee

Position Statement on:
Point of Care Testing for coeliac antibodies

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Recommendations regarding Point of Care Testing in coeliac disease

- Point of Care testing (PoCT) for coeliac antibodies provides a means of rapidly assessing the presence or absence of coeliac antibodies
- PoCT is accurate but inferior to laboratory based testing
- A positive test does not confer a diagnosis of coeliac disease
- A positive test should be followed up with laboratory based coeliac antibody testing and does not replace the need for a confirmatory diagnosis with small bowel biopsies obtained at the time of gastroscopy (endoscopy)
- A negative test does not exclude coeliac disease and if the clinical suspicion is high serological testing and specialist advice should be obtained
- The administration and interpretation of PoCT should be by trained practitioners
- The administration of PoCT testing by Community Clinics, General Practitioners and Pharmacies has not been studied
- PoC testing for coeliac disease does not evaluate the many other diseases that can cause gastrointestinal symptoms. If symptoms are an ongoing concern then specialist advice should be sought.

Background

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy caused by exposure to dietary gluten derived from wheat, rye, barley and oats in genetically susceptible individuals (1). CD is a serious medical condition affecting up to 1 in 70 Australians (2) and is an increasing public health problem with a myriad of extra-intestinal manifestations. Left untreated, it can lead to complications such as other autoimmune diseases, liver disease and cancer, as well as early onset osteoporosis (3-6). Four in five Australians with coeliac disease are unaware they have coeliac disease and up to 50% of people with coeliac disease are asymptomatic (2,7). The only treatment is a lifelong, strict gluten free diet (GFD).

As a minimum requirement, the diagnosis of coeliac disease requires the confirmation of characteristic findings on biopsies taken at the time of gastroscopy (endoscopy). A tissue diagnosis is required because currently available antibody tests have established false positive and false negative rates, and there is considerable assay and measurement variability between laboratories.

Coeliac antibody testing

Most Australian laboratories provide antibody testing for coeliac disease. Traditional testing with whole anti-gliadin antibodies (AGA) has become superseded by more accurate and less subjective antibody assays assessing either tissue transglutminase (tTG) antibodies or antibodies to deamidated gliadin peptides (DGP).

As 3-5% of patients with coeliac disease are IgA deficient, the accurate interpretation of coeliac antibodies requires the assessment of total IgA or the measurement of an IgG coeliac antibody. To account for this issue, many laboratories offer testing for tTG-IgA antibodies and DGP-IgG antibodies in order that false negatives are avoided (7).

The role of coeliac antibody testing in the diagnosis of coeliac disease

Although accurate, there are acknowledged false negative and false positive rates in coeliac disease that can be as high as 10% (8). Therefore, elevated serum antibodies should be followed up with confirmatory biopsies obtained via gastroscopy and negative antibodies by specialist opinion if the clinical suspicion is high or if gastrointestinal symptoms are a clinical concern.

As with all assessments for coeliac disease, the reliability of coeliac antibodies is contingent upon the patient following a gluten containing diet at the time of testing. Coeliac antibodies do not have a role in the assessment of coeliac disease in those following a gluten free diet.

Point of Care Testing in coeliac disease

Qualitative Point of Care Testing (PoCT) has developed considerably over recent years, particularly as a population based screening tool for patients with undiagnosed coeliac disease (9,10). Early cumbersome immunochromatographic assays have now been superseded by commercially available kits (11-13). PoCT provides a means of coeliac antibody testing in real time during a patient consultation. Results are available promptly (within 10 minutes) and the test is well tolerated, requiring only a finger prick blood sample or microliter serum sample. The available kits rely on a serum or blood being combined with a haemolysing buffer that releases the relevant antibody. Capillary action of the haemolysed sample through a conjugate pad results in appearance of a coloured line if coeliac antibodies are present (lateral flow immunochromatography). A positive test is indicated by the presence of a coloured line that in some kits can be compared to a control line.

The evidence base for PoCT in coeliac disease

Qualitative PoCT is relatively new to the field of CD diagnosis. When examined in serological studies in subjects with known coeliac disease and controls (i.e. where the study population prevalence of CD is high), the test performs well with inherent advantages of kits that examine both IgA and IgG antibodies (14). In the context of population screening, PoCT does not perform as well as serum antibodies but still performed adequately with sensitivities and specificities ranging from 79-93% and 95-96% respectively and a positive predictive value of 71% when compared to serum antibodies (9,10). In those attending for endoscopy (and thus with histological results), PoCT was inferior to standard serological tests in diagnosing coeliac disease (15). Nevertheless, PoCT has been demonstrated to reduce the time to biopsy which has implications for a condition where the diagnosis is often delayed (16).

There may also be a role for PoCT in monitoring of coeliac disease, however this has not been prospectively evaluated (17,18). The use of PoCT in CD follow-up will be limited by test accuracy as the antibody titres approach the reference range due to the colorimetric nature of the test (10).

Although this technology would be appropriate for applications such as targeted or population screening, at the time of writing there is no data on the cost effectiveness of PoCT in this context. In acknowledgement of this issue, the British NICE guidelines suggest PoCT awaits further evaluation and should not be used in the place of laboratory testing {NICE:ul}. Recommendations from this guideline predated some of the more recent publications but further studies are needed.

Who should administer PoCTs for coeliac disease?
To date, all studies have evaluated trained clinicians (nursing and medical) interpreting the PoCT results. The ESPGHAN guidelines note that adequate training of those interpreting the PoCT is a core component of PoCT administration and governance (19).

Advantages of PoCT
PoCT is comparatively inexpensive (approximately AU$30-60 per test), well tolerated and easy to administer. Results are generally easy to interpret after appropriate education and inter-observer agreement has been found to be very good to excellent (10,20). In the paediatric population, PoCT has a particular advantage in avoiding venepuncture.

Disadvantages of PoCT

1. Interpretation
   Although a visual cue for interpretation of PoCT is an attractive technology, there is an inherently subjective nature to the reporting of a positive or negative result. The degree of antibody binding to the conjugate pad will affect the intensity of colour on the test lines. Thus, whether a faint positive result represents a positive, negative or equivocal antibody result has not been clarified. To overcome this issue, investigators have suggested a colorimetric scale to define positivity of the PoCT. Although a Rann scale cut-off of 2 accurately separated diseases from controls, the technique may prove a cumbersome barrier to the implementation of an otherwise easy to use technology (10).

2. Qualitative testing
   PoCT provides a qualitative result. To enable accurate basis for further investigation and to provide a baseline comparator to guide follow-up, quantitative laboratory based ELISA assays are crucial.

3. Accuracy
   False positive results have been reported in up to 10% of kits and similarly false negatives in 15-20% (15). For reasons that are unclear, false positives are more common in type 1 diabetes (9). PoCT is therefore inferior to standard serological tests and it is critical that a positive test is followed up with formal serological ELISA based assays. Equally, if the clinical suspicion is high, laboratory testing should follow a negative test, and consideration should be given to seeking specialist advice.

4. Reporting
   There is no accepted nomenclature for reporting of PoCT results and this is an inherent issue of this subjective technology. As alluded to above, reporting 'Positive' and 'Negative' may be overly simplistic but it is unclear how a 'Faint Positive' result should be communicated. A key component of interpretation and accurate reporting will be familiarity with the relevant kit in order that true positives are not missed. As results are not recorded in an ISO compliant electronic laboratory record, tracking lost or misfiled results cannot be readily undertaken.

Conclusions
PoCT is an attractive technology but more evidence is required to support its role in clinical practice. Interpretation of test results requires training and sound clinical governance is required in test administration given the significant medical implications of both a positive and negative test. Protocols which establish regular internal and external control procedures are important to ensure robust performance. Further studies are awaited before PoCT can be adopted into routine clinical practice.

Table 1: Currently available PoCT for coeliac disease

Test Kit	Antibody	Substrate	Control Line	References
Biocard*	tTG IgA	Whole blood	Yes	17,21,22
Stick-CD1**	tTG IgA and IgG	Serum	No	23
Stick CD-2**	tTG IgA and AGA	Serum	No	-
Simple CD1WB**	tTG IgA, IgG and IgM	Whole Blood	Yes	-
Simple CD2WB**	tTG IgA and AGA	Whole blood	Yes	-
Coeliac Quick Testψ	tTG IgA, IgG and IgM	Whole blood	Yes	-
CoeliacScreen Pro (or Xeliac test)^	tTG IgA and IgG	Whole blood	Yes	-
Simtomax∞	DGP IgA and IgG, Total IgA	Whole blood, serum, heparinised and EDTA plasma	Yes	9,10

* Ani Biotech Oy, Vantaa, Finland
** Operon Immuno and Molecular Diagnostics, Zaragoza, Spain
ψ Biohit Healhcare, Cheshire, United Kingdom
^ Personal Diagnostics, United Kingdom
∞ Augurix SA, Monthey, Switzerland

Table 2: Summary of evidence for PoCT in coeliac disease

Ref	Comparator	PoCT	Population	Clinical context	Sensitivity / Specificity
21	Serology/Histology	Biocard	Positive serology	Retrospective serum samples (n=334: new CD, controls and CD follow-up)	96.7 / 93.5
22	Histology	Biocard	Children	Population Screening (n=2690)	78% / 100%
15	Histology	Biocard	Adults	Endoscopy (n=576)	70.1 / 96.6
20	Serology	Eu-tTG Quick, Eurospital	Children/adults	CD follow-up (n=350)	84 / 98.5
9	Serology	Simtomax	Children	High risk population (n=250)	93.1 / 95
10	Serology/Histology	Simtomax	Children/adults	Known CD (n=112)	78.9 / 95.7

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