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Commentary: Reaching a milestone in diagnosing coeliac disease

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Clinical prediction rules for diagnosis seek to optimise the sensitivity and specificity of our diagnostic approach to a given problem. In this issue of the *BMJ*, Hopper and colleagues report a rare accomplishment in this regard—a decision rule that achieved 100% sensitivity in disease detection, in this case for coeliac disease.[1] The rule is simple—a positive serological test for IgA antibody to tissue transglutaminase combined with being at "high risk" (having weight loss, diarrhoea, or anaemia). The rule identified every patient with the disease in a cohort of 2000 patients, all of whom underwent intestinal biopsy as the gold standard and the final diagnostic step. This is a welcome advance. As the authors emphasise, coeliac disease may affect up to one in a 100 people, only one case in seven is ever diagnosed, and an appreciable diagnostic delay of many years often occurs.[2 3]

This result will probably not change clinical practice, however, as current algorithms for coeliac disease already incorporate these factors. Rather, this study strongly validates this approach and allows us to estimate with some confidence the probabilities of success or failure at each step of the process. The results support the current practice of forgoing endoscopic biopsy in low risk patients with negative serology, as none of the 1170 patients meeting these criteria was found to have coeliac disease on biopsy. The study confirms that biopsy has an important role in high risk patients with positive serology. It has been suggested that this combination provides adequate evidence to diagnose coeliac disease without the need for biopsy, and a substantial proportion of patients given the diagnosis (up to 25% in one survey) have never been biopsied.[3] However, 40% of high risk patients with positive serology in Hopper and colleagues' study did not have coeliac disease when biopsied. Even acknowledging the possibility that coeliac disease can be missed on biopsy, we agree with the authors that biopsy is essential in this cohort, given the daunting prospect of lifelong adherence to a gluten-free diet.

The wisdom of biopsy in high risk patients who are tissue transglutaminase antibody negative is debateable. Although Hopper and colleagues recommend biopsy in this group, this approach identified only seven additional cases out of the 585 patients biopsied, and at least some of these cases could be predicted by testing for IgA deficiency.

This decision rule now needs to be tested in other settings,[4] and the rule may fare less well because:

- The population studied was a referral cohort; the base rate of disease will probably be lower in primary care cohorts
- Variability in assigning patients at high risk will increase if subsequent clinicians use their own definitions of weight loss, diarrhoea, or anaemia
- The results of tissue transglutaminase antibody testing will vary more as many different laboratories will be used
- The interpretation of biopsies will be less uniform, given the inherent variability between pathologists and differences in the quality of biopsy samples, which will come from multiple endoscopists.

The decision rule might be improved by incorporating a panel of serological markers. In particular, almost all patients with coeliac disease carry the HLA markers DQ2 or sometimes DQ8. The absence of DQ2 and DQ8 would therefore be reassuring in patients who are at high risk but are tissue transglutaminase antibody negative. Until a better rule is developed and validated, the decision rule of Hopper and colleagues seems to be the most cost effective and efficient way to assess coeliac disease.

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