Citation: Clinical and Translational Gastroenterology (2015) 6, e116; doi:10.1038/ctg.2015.41

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GUT INSTINCTS: MY PERSPECTIVE

Use of Biomarkers in Irritable Bowel Syndrome: To Predict the Future, Look at the Past

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Clinical and Translational Gastroenterology (2015) **6,** e116; doi:10.1038/ctg.2015.41; published online 8 October 2015

As clinicians, we are trained to make a positive diagnosis of irritable bowel syndrome (IBS), by using a combination of the most pertinent parts of the patient history, physical examination findings, and a limited panel of blood tests. However, in routine practice, it is not uncommon for a diagnosis of IBS to be made by exclusion, following extensive and negative investigations.[1] One possible reason for this is the lack of a non-invasive diagnostic test for IBS. The current gold standard is symptom-based diagnostic criteria, developed in the 1970s,[2] and modified over time. The latest of these, the Rome III criteria (Table 1), were published in 2006.[3] However, symptom-based criteria perform only modestly in predicting a diagnosis of IBS.[4,5]

Partly as a result of this unsatisfactory situation, research has focused on developing novel biomarkers (physiological mechanisms, genes, proteins, or metabolites) to aid in the diagnosis of IBS. A non-invasive biomarker that accurately predicts a diagnosis of IBS would be a significant advance, but are we any closer to developing one? A recent systematic review and meta-analysis summarized the various approaches to diagnosing IBS,[6] using pooled likelihood ratios (LRs) to assess the diagnostic accuracy of available methods. As a rule of thumb for readers of this article, a positive LR >10 is useful for ruling in disease, whereas a negative LR <0.1 is useful for ruling out disease. A serum-based 10 biomarker panel (including interleukin-1ß and anti-tissue transglutaminase), assessed in two separate studies,[7,8] demonstrated pooled positive and negative LRs of 3.03 (95% confidence interval (CI): 1.49–6.17) and 0.52 (95% CI: 0.43–0.64), respectively. In the later study,[8] an additional 24 biomarkers were added to the original 10 biomarker panel. However, the 34 biomarker panel did not perform any better, with positive and negative LRs of 2.28 (95% CI: 1.71–3.17) and 0.30 (95% CI: 0.21–0.42), respectively.

In a more recent study,[9] the accuracy of two serum biomarkers, antibodies to cytolethal distending toxin B (CdtB), a bacterial toxin commonly produced by *Campylobacter jejuni*, and vinculin, a host cell adhesion protein with which CdtB is known to cross-react, were assessed in terms of their ability to differentiate between diarrhea-predominant IBS, inflammatory bowel disease, celiac disease, and health. The biomarkers performed best in differentiating diarrhea-predominant IBS from inflammatory bowel disease. Using a cutoff level of anti-CdtB antibodies ≥ 2.80, positive and negative LRs were 5.2 and 0.6, respectively. Using a cutoff level ≥ 1.68 for anti-vinculin antibodies, positive and negative LRs were 2.0 and 0.8, respectively. Fecal biomarkers, in the form of volatile organic metabolites, chemicals released in feces, which can undergo change in the presence of organic disease, have also been evaluated in one small study in differentiating diarrhea-predominant IBS from active inflammatory bowel disease.[10] Positive and negative LRs were 4.83 (95% CI: 3.36–7.14) and 0.04 (95% CI: 0.01–0.21), respectively.[6]

What is noticeable in these studies is that individual biomarkers appear to perform only moderately well in differentiating IBS from organic disease and, at present, are probably no better, and may be considerably more expensive, than symptom-based criteria, which cost nothing to implement in the clinic. The Rome III criteria had a positive and negative LR of 3.39 (95% CI: 2.96–3.88) and 0.47 (95% CI: 0.41–0.53), respectively.[5] One possible reason why individual biomarkers perform sub-optimally is that IBS is a complex heterogeneous disorder, with a multifactorial etiology, and it is therefore unlikely that a single biomarker will be able to differentiate IBS from organic disease with the degree of accuracy required from a diagnostic test.

If an accurate individual biomarker eludes us, are there any other ways that biomarkers could be used? The Kruis statistical model,[11] described >30 years ago, is a scoring system that incorporates the clinical history, physical examination findings, and biomarkers in the form of blood tests, including hemoglobin level, erythrocyte sedimentation rate, and leukocyte count. In the studies that have evaluated this model, which have been summarized in a previous meta-analysis,[4] the pooled positive and negative LRs were 8.63 (95% CI: 2.89–25.8) and 0.26 (95% CI: 0.17–0.41), respectively, approaching the LRs required for a diagnostic test to be useful, and more accurate than any of the individual biomarkers assessed to date. Another study published in 2002 used a combination of the Rome I criteria, fecal calprotectin levels of <10 mg/l, and a small intestinal permeability test,[12] and was able to differentiate IBS from organic disease with a positive LR of 26.4 (95% CI: 11.4–61.9) and a negative LR of 0.51 (95% CI: 0.45–0.56).[6]

Combining symptoms and signs with biomarkers seems more intuitive, in that it takes into account the probable

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Table 1 Rome III diagnostic criteria for irritable bowel syndrome

Recurrent abdominal pain or discomfort[a] *for at least 3 days per month, in the last 3 months, and associated with two or more of the following:*
a. Improvement with defecation
b. Onset associated with a change in stool frequency
c. Onset associated with a change in stool form or appearance
The Rome III criteria are fulfilled when symptoms are present for the last 3 months, with symptom onset at least 6 months prior to diagnosis

[a]Discomfort means an uncomfortable sensation not described as pain. In research and clinical trials, a discomfort frequency of at least 2 days a week during screening is required for subject eligibility.

composite structure of IBS, and appears to be more accurate than either symptoms or individual biomarkers alone. However, using this approach could result in an overly complex test not practical for use in a clinical setting. How can we overcome this complexity to produce an accurate and easily administrated diagnostic test in the clinic? Latent class analysis (LCA) is a statistical method that can be applied to multivariate categorical data to form sub-types of related cases (latent classes), by recognizing patterns within the data, when using a combination of patient-reported symptoms, clinical examination findings, and biochemical markers. This results in the identification of clinical indicators, which can then be incorporated in to a statistical model, and therefore the development of a diagnostic test that potentially discriminates between IBS and non-IBS profiles with the degree of accuracy needed.

To date, there are few examples of LCA being used in functional gastrointestinal disorders,[13] possibly because of a perceived view that utilizing LCA will also result in a test that is too unwieldy to use easily in routine practice. However, LCA has been used in many other diagnostic situations, and has been shown to be particularly valuable when, as is the case for IBS, an accurate and accepted gold standard test is lacking.[14–17] In the modern era of smartphones, an easy-to-use application (app) could be developed, into which clinical data are inputted by the patient, while sitting in the waiting room, with the results of physical examination and biomarker tests added by the physician. This would then compute a probability of an individual having IBS utilizing LCA methods, and could provide clinicians with a reliable and simple test that is suitable for use in real-time during a busy outpatient clinic.

The performance of the majority of biomarkers is not superior to current symptom-based criteria, and most are experimental at the time of writing. As LCA calculates the probability of having IBS, this means it may be possible to vary the discrimination threshold utilized in the model, using a combination of symptoms, examination findings, and biomarkers, in order to reduce the false positive test rate, minimizing the risk of missed organic disease, and therefore maximizing the clinical utility of the model. This would represent a significant advantage over either symptom-based diagnostic criteria or biomarkers alone. LCA may therefore herald a new and promising approach to diagnosing IBS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1. Shivaji UN, Ford AC. Beliefs about management of irritable bowel syndrome in primary care: cross-sectional survey in one locality. *Prim Health Care Res Dev* 2014: 1–7.
2. Manning AP, Thompson WG, Heaton KW *et al.* Towards positive diagnosis of the irritable bowel. *Br Med J* 1978; **2**: 653–654.
3. Longstreth GF, Thompson WG, Chey WD *et al.* Functional Bowel Disorders. *Gastroenterology* 2006; **130**: 1480–1491.
4. Ford AC, Talley NJ, Veldhuyzen van Zanten SJ *et al.* Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? *JAMA* 2008; **300**: 1793–1805.
5. Ford AC, Bercik P, Morgan DG *et al.* Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology* 2013; **145**: 1262–1270.
6. Sood R, Gracie DJ, Law GR *et al.* Systematic review with meta-analysis: the accuracy of diagnosing irritable bowel syndrome with symptoms, biomarkers and/or psychological markers. *Aliment Pharmacol Ther* 2015; **42**: 491–503.
7. Lembo AJ, Neri B, Tolley J *et al.* Use of serum biomarkers in a diagnostic test for irritable bowel syndrome. *Aliment Pharmacol Ther* 2009; **29**: 834–842.
8. Jones MP, Chey WD, Singh S *et al.* A biomarker panel and psychological morbidity differentiates the irritable bowel syndrome from health and provides novel pathophysiological leads. *Aliment Pharmacol Ther* 2014; **39**: 426–437.
9. Pimentel M, Morales W, Rezaie A *et al.* Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. *PLoS One* 2015; **10**: e0126438.
10. Ahmed I, Greenwood R, Costello Bde L *et al.* An investigation of fecal volatile organic metabolites in irritable bowel syndrome. *PLoS ONE [Electronic Resource]* 2013; **8**: e58204.
11. Kruis W, Thieme C, Weinzierl M *et al.* A diagnostic score for the irritable bowel syndrome. Its value in the exclusion of organic disease. *Gastroenterology* 1984; **87**: 1–7.
12. Tibble JA, Sigthorsson G, Foster R *et al.* Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. *Gastroenterology* 2002; **123**: 450–460.
13. Koloski NA, Jones M, Young M *et al.* Differentiation of functional constipation and constipation predominant irritable bowel syndrome based on Rome III criteria: a population-based study. *Alimentary Pharmacol Ther* 2015; **41**: 856–866.
14. Rindskopf D, Rindskopf W. The value of latent class analysis in medical diagnosis. *Stat Med* 1986; **5**: 21–27.
15. Christensen AH, Gjorup T, Hilden J *et al.* Observer homogeneity in the histologic diagnosis of Helicobacter pylori. Latent class analysis, kappa coefficient, and repeat frequency. *Scand J Gastroenterol* 1992; **27**: 933–939.
16. Ferraz MB, Walter SD, Heymann R *et al.* Sensitivity and specificity of different diagnostic criteria for Behcet's disease according to the latent class approach. *Br J Rheumatol* 1995; **34**: 932–935.
17. LaJoie AS, McCabe SJ, Thomas B *et al.* Determining the sensitivity and specificity of common diagnostic tests for carpal tunnel syndrome using latent class analysis. *Plast Reconstr Surg* 2005; **116**: 502–507.

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