Accuracy and cost of diagnostic strategies for patients with suspected Crohn's disease

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KEYWORDS
Crohn's disease; Diagnostic strategy; Ultrasound; Magnetic resonance imaging; Ileocolonoscopy; Video capsule endoscopy

Abstract

Objective: To evaluate accuracy and cost of non-invasive diagnostic strategies including magnetic resonance imaging, intestinal ultrasonography, ileocolonoscopy and video-capsule endoscopy in suspected Crohn's disease.

Methods: A decision-analytic model was used to assess the costs in low (25%), intermediate (50%) or high (75%) pre-test probability of Crohn's disease. Based on the published accuracy of diagnostic modalities and Bayes' rule, we calculated post-test probability of Crohn's disease using different strategies, starting from ileocolonoscopy, ultrasonography or magnetic resonance. Each strategy was considered successful when post-test probability was $\geq 95\%$ or $\leq 5\%$.

Results: With low pre-test probability, only ileocolonoscopy as the first investigation could exclude or confirm Crohn's disease while a normal ultrasonography may exclude Crohn's disease. With high pre-test probability, ileocolonoscopy or ultrasonography as the first test may confirm Crohn's disease, but at least 3 negative tests are required to exclude Crohn's disease.

The cost to diagnose one patient was cheapest utilising an ultrasonography-based strategy both in low (ultrasonography €1076; ileocolonoscopy €2005; magnetic resonance €4515) and high pre-test probability of Crohn's disease (ultrasonography €321; ileocolonoscopy €712; magnetic resonance €1412).

Conclusion: The accuracy and cost of these strategies depend on pre-test probability of Crohn's disease and vary according to the first test used. Ileocolonoscopy plus ultrasonography is the most accurate and less expensive initial diagnostic strategy.

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1. Introduction

Crohn’s disease (CD) is a life-long inflammatory disease of unknown aetiology. Typically, the disease has its onset in the second and third decades of life with a heterogeneous clinical presentation. Symptoms in CD are non-specific and may include abdominal pain, diarrhoea, nausea and vomiting. Clinically it is often difficult to differentiate these symptoms from other gastrointestinal disorders, particularly irritable bowel syndrome (IBS) whose prevalence is reported to 10 to 50 times more frequently than CD.1–3 However, the incidence of inflammatory bowel diseases (IBD), in particular CD, is increasing around the world.4 This may be due to the increased awareness of IBD by physicians and the public, greater access to colonoscopy, and the advancements in diagnostic methods, especially the radiological and endoscopic advancements in the investigation of the small bowel. Nevertheless, a single gold standard for the diagnosis of CD is still not available. Ileocolonoscopy with biopsies has been adopted by many physicians as the first line procedure of choice, but it may not be preferred as an initial investigation in some cases (e.g. paediatric patients) and may be limited by the rate of technical failures (5–15%) in intubating the ileum.5,6 Irrespective of the findings at ileocolonoscopy, guidelines recommend further assessment of the gastrointestinal tract to completely examine the entire small bowel and the stomach7,8 in order to diagnose and fully stage CD. Significant radiological advancements such as high resolution intestinal ultrasonography (IUS), computed tomography (CT)- and magnetic resonance imaging (MRI)-enteroclysis now allow for complete assessment of the small bowel. Additional endoscopic techniques such as video capsule endoscopy (VCE) and double balloon enteroscopy (DBE) are also used to image parts of the bowel that are not traditionally accessible with standard endoscopic techniques.

A definitive diagnosis of CD using invasive diagnostic procedures is essential to confirm the clinical suspicion of IBD, even in patients with high pre-test probability of organic disease prior to initiation of treatment. However, with increasing rates of IBD, combined with availability of new non-invasive diagnostic methods for assessment of the small bowel, there may be a paradoxical increase in the utilisation of new diagnostic modalities, even in patients with low pre-test probability of IBD. This has the potential to have unexpected economic consequences in the form of increased healthcare costs to both the individual and the healthcare system.

We developed a decision analytic model in order to estimate the accuracy of the most common non-invasive diagnostic strategies including MRI and transabdominal IUS, ileocolonoscopy and VCE and their combination, in order to diagnose CD. We also estimated the cost associated with each diagnostic strategy in patients at low, intermediate and high pre-test probabilities of CD.

2. Methods

2.1. Model design

A decision-analytic model, utilising the current guidelines of the European Crohn’s and Colitis Organization,9,10 was used to assess the accuracy and costs of obtaining a definite diagnosis of CD based on the clinical scenario of a patient undergoing evaluation of symptoms that suggest the presence of CD. Given the prevalence of CD is unknown in patients who present with clinical symptoms suggestive of the disease, we hypothesised 3 clinical scenarios: 1. A patient with low pre-test probability of CD, estimated to be no more than 25%. 2. A patient with an intermediate pre-test probability of CD, estimated to be 50%. 3. A patient with high pre-test probability, estimated to be at least 75%, according to previously published data.10,11 The first scenario may be characterised by isolated or episodic diarrhoea and abdominal pain with normal or absent biochemical and faecal tests. The second may include a patient with abdominal pain and episodic diarrhoea and a first degree relative with known IBD, but normal or absent biochemical and faecal tests. The final scenario may be characterised a patient with chronic symptoms such as diarrhoea, abdominal pain, weight loss and positive biochemical tests (positive C-reactive protein or faecal calprotectin) along with negative stool cultures. These levels of pre-test probability were arbitrarily chosen. Although the use of non-invasive faecal markers of inflammation (e.g. faecal calprotectin) can set pre-test probabilities less that <10% and >90%12 there are significant rates of false negative results, especially for isolated small bowel CD, therefore they cannot be relied upon alone for a definitive diagnosis. We have deliberately excluded clinical scenarios suggestive of acute illness including infectious gastroenteritis, appendicitis and diverticulitis.

The investigations were analysed exclusively for their accuracy and costs to make a diagnosis of CD. In ileocolonoscopy it is the presence of ulcers or erosions, combined with nodular and hyperaemia and friability that confirm a diagnosis of CD. In MRI and IUS, diagnostic criteria of CD include increased bowel wall thickening, associated with creeping fat or changes in bowel pattern and vascularity. Assessment of disease extent, site of disease and abdominal complications (e.g. strictures, fistulae or abscesses) were therefore not considered.

The impact of biochemical diagnostic tests (e.g., C-reactive protein, blood cell count and faecal calprotectin) was not considered in the diagnostic strategies, but it was generically considered within the definition of pre-test probability of CD. Since the aim of this study was to suggest a cost-effective strategy to make a correct initial diagnosis in patients with suspected CD, not to determine the gold standard, we assessed conditional probabilities for a three-test sequence based on 3 different algorithms (Fig. 1). The first algorithm used ileocolonoscopy as the first examination, followed by bowel IUS or MRI then VCE. The second algorithm used IUS followed by ileocolonoscopy or MRI then VCE, the third algorithm used MRI followed by ileocolonoscopy or IUS. The conditional probabilities were calculated based on VCE always utilised as a final modality. This is due to the fact that VCE, depending on the individual centre and country, may be a very expensive investigation and not always available. However, the European Crohn’s and Colitis Organization (ECCO) consensus guidelines have stated that in patients with suspected Crohn’s disease and negative ileocolonoscopy, VCE may be the initial diagnostic modality for the evaluation of the small bowel.13 Likewise, the International Conference on Capsule Endoscopy (ICCE) recommended that patients with suspected Crohn’s disease should be selected to undergo VCE in high pre-test or moderate pre-test probability of CD, in particular if they present with typical symptoms plus either extraintestinal manifestations,
inflammatory markers or abnormal small bowel imaging. Therefore, we have also assessed the usefulness of VCE as a second examination after a negative ileocolonoscopy in high and intermediate pre-test probabilities of CD.

2.2. Measures of diagnostic accuracy

\( \theta_L \) and \( \theta_H \) respectively denote the low pre-test probability and high pre-test probability of CD; sensitivity is defined as the proportion of patients with CD who have a positive test; specificity is defined as the proportion of patients without CD who have a negative test. For the purpose of this study, we utilised the previously published sensitivity (SE) and specificity (SP) of IUS, MRI and VCE. However, regarding ileocolonoscopy, there is no published data documenting sensitivity and specificity of ileocolonoscopy in CD. In order to calculate the overall sensitivity of ileocolonoscopy for the initial diagnosis of CD at 0.887 based on the following formula:

\[
SE_{IC} = \frac{SE_{Ileal} \times PID + SE_{Colon} \times CID}{100}
\]

where \( SE_{Ileal} \) is the sensitivity for ileal CD (0.74); \( PID \) is the Pure Ileal (and/or jejunal) Crohn's disease at diagnosis (43.4%); \( SE_{Colon} \) is assumed to be equal to one; \( CID \) is the localization of colonic or ileocolonic (with or without jejunal localisation) at diagnosis, estimated to be 56.6%. The data on the tests' accuracy are reported in Table 1.

Since these investigations were not independent measures of CD, we calculated diagnostic accuracy of the second and third investigations by using Bayes' rule. This allows us to measure each investigation's accuracy conditionally on the results of the preceding tests by utilising the following formula:

\[
P_{Post} = \frac{SE \times \theta}{(SE \times \theta) + (1-SP) \times (1-\theta)}
\]

where \( SE \) and \( SP \) are the sensitivity and the specificity, respectively, of the test, and \( \theta \) is the pre-test probability.
Therefore we calculated the post-test probability of disease after the different diagnostic strategies, using ileocolonoscopy, IUS or MRI as initial investigation.

In absence of data on conditional probability among these tests, we assumed independence among these alternatives, despite their similarities as imaging techniques.

Each diagnostic strategy was halted when the probability of CD was \( \geq 95\% \) (confirmation of CD) or \(< 5\% \) (exclusion of the disease) and then the whole cost of the strategy was estimated. Using these probabilities, we assumed that the patients could be accurately diagnosed with CD (true positive) or with another GI disorder (true negative), inaccurately diagnosed with CD (false positive) or inaccurately diagnosed with another disease (false negative).

### 2.3. Costs

To calculate the overall cost of each test, we have combined the direct cost of each diagnostic test as well as the ancillary costs related to each test such as bowel preparation and blood tests. These have been derived from the 2012 Health Medicare Reimbursement of FASDAC (Federazione Fondo di Assistenza Sanitaria dei Dirigenti di Aziende Commerciali), and are reported in Table 2.\(^{19}\) In this analysis, we have not included other expenses relating to the overall care of the patient such as hospitalisation, surgery, medication and additional blood tests and investigations. We have also not included the income losses to patients due to time off work to undergo each investigation. All costs are shown in Euros.

### 3. Results

#### 3.1. Accuracy of the diagnostic strategies

We based our study on the assumption that the aim of the cost effectiveness analysis was to achieve a post-test probability greater than 95% to confirm or less than 5%, to exclude CD, starting from three clinical scenarios: high pre-test probability (75%), intermediate (50%) and low pre-test probability of CD (25%).

#### 3.2. Low pre-test probability of Crohn’s disease

Independently of the CD pre-test probability, ileocolonoscopy with biopsy is 100% specific for CD whenever a positive finding occurs. A negative result of ileocolonoscopy or IUS, may practically exclude the presence of CD (post-test probability 4.85% with US, 3.63% with ileocolonoscopy) only in case of low pre-test probability (Fig. 1).

A positive IUS result is suggestive of CD (post test probability 93.4%), but not enough to definitively confirm CD (requires post-test probability of \( \geq 95\% \)), while MRI was not helpful to either confirm (post-test probability 63.4%) or to exclude CD (post-test probability 7.9%), when used as a single test.

The use of VCE, after a positive IUS or MRI, but negative ileocolonoscopy, was not helpful to confirm CD (post-test probability ranging from 59.1% to 92.2%). On the other hand, a negative VCE was effective in excluding CD in patients with previous positive MRI (post-test probability: 0.89%), but not in patients with previously positive US (post-test probability: 6.86%) (Fig. 1).

### 3.3. Intermediate pre-test probability of Crohn disease

In this setting, a positive ileocolonoscopy or positive IUS is sufficient to confirm CD, but negative results of all investigations require additional diagnostic tests to exclude CD. This is also valid for negative ileocolonoscopy, which requires a negative IUS or a negative MRI to exclude CD. Interestingly, if

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**Table 1** Sensitivity and specificity of the diagnostic investigations.\(^{15-17}\)

<table>
<thead>
<tr>
<th>Diagnostic investigation</th>
<th>Sensitivity</th>
<th>Sensitivity CI 95%</th>
<th>Specificity</th>
<th>Specificity CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic resonance imaging(^{15})</td>
<td>0.78</td>
<td>0.67–0.84</td>
<td>0.85</td>
<td>0.76–0.90</td>
</tr>
<tr>
<td>Intestinal ultrasound(^{16})</td>
<td>0.85</td>
<td>0.83–0.87</td>
<td>0.98</td>
<td>0.95–0.99</td>
</tr>
<tr>
<td>Ileocolonoscopy with biopsies(^{17})</td>
<td>0.89</td>
<td>0.80–0.99</td>
<td>1.00</td>
<td>0.87–0.99</td>
</tr>
<tr>
<td>Video capsule endoscopy(^{16})</td>
<td>0.96</td>
<td>0.80–0.99</td>
<td>0.87</td>
<td>0.80–0.99</td>
</tr>
</tbody>
</table>

CI 95%: confidence interval of 95%.

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**Table 2** Cost of each diagnostic test considered in the study.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Loss of work</th>
<th>Costs in € (FASDAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocolonoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel preparation</td>
<td>From 1 to 1-1/2 days</td>
<td>15.00</td>
</tr>
<tr>
<td>Ileocolonoscopy with multiple biopsies</td>
<td></td>
<td>280.00</td>
</tr>
<tr>
<td>Pathological examination of multiple biopsies</td>
<td></td>
<td>150.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>445.00</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Up to 4 h</td>
<td></td>
</tr>
<tr>
<td>Preliminary blood examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample</td>
<td></td>
<td>3.00</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
<td>3.50</td>
</tr>
<tr>
<td>Magnetic resonance imaging (with enteroclysis)</td>
<td></td>
<td>450.00</td>
</tr>
<tr>
<td>Contrast agent</td>
<td></td>
<td>90.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>546.50</td>
</tr>
<tr>
<td>Intestinal ultrasound</td>
<td>Up to 1 h</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>80.00</td>
</tr>
<tr>
<td>Wireless capsule endoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteroscopy (procedure)</td>
<td>1 day</td>
<td>350.00</td>
</tr>
<tr>
<td>Capsule</td>
<td></td>
<td>500.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>850.00</td>
</tr>
</tbody>
</table>

FASDAC: Federazione Fondo di Assistenza Sanitaria dei Dirigenti di Aziende Commerciali.\(^{16}\)
a MRI or IUS is positive as a second investigation after a negative ileocolonoscopy, the third test may still provide inconclusive results, in particular when MRI was used as the second investigation. On the contrary, the use of IUS as the first examination and IC in patients with negative IUS is able to correctly detect all CD patients, even if with a few false positive result (Fig. S1).

3.4. High pre-test probability of Crohn’s disease

In this scenario, a positive ileocolonoscopy or IUS confirmed CD, while a negative result did not exclude it. In this context, MRI performed as a single initial test was not helpful in confirming or excluding CD (Fig. 2).

In patients with high pre-test probability the negative results of two consecutive tests were not sufficient to exclude CD, except for patients who underwent IUS and then IC. With this strategy all patients reached a definite diagnosis with exclusion (~95%) or confirmation (~95%) of CD (Fig. 2). In patients with previous negative examinations, a positive VCE was not helpful in confirming the disease, but a negative result significantly lowered the probability of CD (post-test probability ~2%) (Fig. 2).

3.5. Costs of the diagnostic strategies

3.5.1. Low pre-test probability of Crohn’s disease

When following the diagnostic algorithms, in patients with a low pre-test probability, the cheapest option to correctly confirm or exclude CD was to begin with IUS (range £221–£223). The most expensive option was to begin with MRE (£1023 to £1145), while starting with ileocolonoscopy costs £445 per patient.

If an algorithm was then applied in this clinical context (100 patients with suspected CD, but only 25% of whom actually have CD), the costs to correctly diagnose one CD patient was again cheapest starting with IUS (range £1076,22–£1139,18 per patient). However, this strategy had the highest overall false negative rate of 6.2%. MRI was again the most expensive (range £4514,50–£4979,28), but with a lower false negative rate of 3%, which was equal to the miss rate of ileocolonoscopy at 3%, but with a significantly lower cost of £2004,50 per patient (Table 3).

3.5.2. Intermediate pre-test probability of Crohn’s disease

In patients with an intermediate pre-test probability of CD, the use of IUS as the first examination seems to be the most cost-effective strategy, with the cost of correctly detecting one patient with CD being £663. Beginning with ileocolonoscopy costs £1072–£1791 per patient. Finally, MRI was the most expensive, costing £2065–£2474 per patient when used as first exam (Table S1).

3.5.3. High pre-test probability of Crohn’s disease

In patients with high pre-test probability IUS as first exam was again the cheapest strategy (£238,87 to correctly diagnose one patient), beginning with ileocolonoscopy cost £524,37 to £1072,67 per patient and MRI was again the most expensive (£1092,68 to £1502,47).

In this clinical context, the costs to correctly detect one CD patient were still cheapest beginning with IUS (£321,49, miss rate 0.7%). Employing the ileocolonoscopy strategy cost £711,75–£1372,67 per patient (miss rate 1.5–8.5%) and MRI was the most expensive (range £1412,45–£1923,34, miss rate 2.9–8.6%). However, given that a positive IUS result still required ileocolonoscopy for confirmation, the cost of IUS as first examination was actually similar to beginning with ileocolonoscopy (£706,59 per patient) (Table 4).

4. Discussion

We have developed a decision analytic model to estimate the accuracy and the costs of the common diagnostic strategies for patients with symptoms suggestive of CD. In particular, we have compared diagnostic models including MRI, transabdominal IUS, ileocolonoscopy and VCE in three different clinical scenarios, characterised by low, intermediate and high pre-test probabilities of CD.

Our findings suggest that the clinical scenarios and pre-test probability significantly affect the accuracy and the cost of the diagnostic strategies. In patients with low pre-test probability of CD, ileocolonoscopy alone accurately excludes or confirms CD, while IUS may exclude CD only if the result is negative. MRI is of limited value in confirming or excluding CD when used as a single initial test. These findings may have relevant clinical implications. In adult patients, colonoscopy may be recommended as the first and only test for detecting IBD, and is also useful as a screening test for colorectal cancer. On the other hand, in paediatric and young patients, ileocolonoscopy and MRI may not be preferred as initial tests, being invasive, complicated and needing deep sedation. Therefore, in children, IUS may be a preferable exam to exclude CD, in particular when other biochemical tests are negative. The benefit of IUS used for this clinical purpose has been already demonstrated prospectively, where an Italian group investigated 45 consecutive children with symptoms suggestive of IBD. They found that if faecal calprotectin, ASCA/pANCA and IUS, were all normal, this reduced the probability of having IBD to less than 0.69%, thus avoiding unnecessary invasive procedures and providing diagnostic certainty with a reassuring added value. The fact that a negative IUS, in a clinical context of low pre-test probability of CD, may be sufficient to exclude CD, is of striking relevance, especially for the paediatric and adolescent populations. In these patients, ileocolonoscopy is invasive and should not be preferred as the initial test. Furthermore, due to the low risk of intestinal malignancies and the limited negative impact of a short diagnostic delay of CD in false negative cases, IUS can be the preferable diagnostic exam, also due to its potential reassuring effect.

Our study also found that employing a diagnostic strategy including IUS as the first or secondary modality in patients with low pre-test probability of CD is cost-effective. This has the potential to provide significant cost savings to the health care system considering the high rate of functional symptoms in children and young patients. It has been shown that a considerable number of IBD patients experience co-existing IBS symptoms, in particular those with longer symptom duration before diagnosis of IBD. Considering the increased awareness among physicians and in the public of IBD and the availability of new diagnostic methods (e.g. MRI and VCE) for investigating the small bowel, one could expect an increased...
use of these diagnostic modalities, particularly in patients with functional symptoms and low pre-test probability of IBD. Epidemiological data regarding the exact prevalence of functional GI disorders in adults and children are lacking, but recent adult and paediatric data suggest it could be estimated that upwards of 10% of the population suffer from these conditions. Given that all of these patients require diagnostic investigations to make a correct diagnosis, employing IUS rather than an ileocolonoscopy, MRI or VCE based diagnostic algorithm could have a profoundly positive impact on healthcare expenditure.

In patients with high pre-test probability, a positive ileocolonoscopy or IUS may confirm CD, while negative results of any other investigation is not sufficient to exclude the presence of CD. Indeed, in this specific context – which excludes patients with acute symptoms suggestive of infectious enteritis or appendicitis and considers patients characterised by chronic symptoms and positive biochemical tests (e.g. positive C-reactive protein or faecal calprotectin) – at least 3 negative tests are necessary to exclude CD. However, it should be recognised that the diagnosis of CD should require the positivity of a direct endoscopic investigation (possibly with histological confirmation) in combination with radiological imaging. The latter is usually required not only to confirm the presence of the disease, but also to assess potential abdominal complications, extension and proximal localisation of CD.

Figure 2  Post-test probabilities (PTP) of Crohn’s disease in clinical context under high probability (75%) of the disease, using different diagnostic strategies. MRI: magnetic resonance imaging; VCE: video-capsule endoscopy.

Figure 2
contexts, an endoscopic confirmation is required. This is valid in any case, when a non-invasive test (including MRI) was selected as the first tool in the diagnostic strategy.

However, from an economic perspective, an MRI based first-line diagnostic strategy for CD should not be adopted. There are the significantly higher costs of MRI, especially compared to IUS. Furthermore, prospective comparative studies, systematic review and meta-analyses have demonstrated that IUS is comparable, if not superior to Magnetic Resonance Enterography (MRE) in detecting CD.\(^\text{15,24–27}\) Therefore we do not believe that there is a role for MRI as the first line of investigation.

It is recognised that the role of VCE is limited in the initial diagnosis of CD. Our study confirms that the utility of VCE is confined to patients with a high pre-test probability of CD and three previously negative investigations (ileocolonoscopy, IUS and MRI). In this clinical context VCE has been proved to be useful, as shown in previous cost-effective analyses.\(^\text{10}\) In particular, we have observed that in patients with intermediate or high pre-test probability of CD, but with a negative ileo-colonoscopy performed as the first examination, a negative VCE result is sufficient to exclude the presence of the disease. On the other hand, based on the previously published sensitivities and specificities of VCE in diagnosing CD, our model has demonstrated that a positive VCE result may not be sufficient to diagnose CD and further investigations (preferably IUS) are required to confirm the presence of CD (Fig. S2). However, in clinical practice, for patients with a high pre-test probability of CD, providing the limited differential diagnoses are excluded (ie: NSAID abuse, vasculitis and Behcet’s disease) and characteristic lesions seen on VCE, this modality is probably sufficient to diagnose CD without additional imaging modalities.\(^\text{11}\) In patients with high pre-test probability, the cost to correctly confirm or exclude CD is higher than in patients with low pre-test probability of CD. However, there was far less variability in the cost for the different strategies. Beginning with IUS is the cheapest option while starting with MRI is the most expensive. We also found that by assuming the definite absence or presence of CD when post-test probability of the disease was <5% and >95%, the diagnostic strategies showed a variable rate of missed and indeterminate diagnoses. These were more frequent in patients with high pre-test probability of CD, and when the diagnostic algorithm started with MRI, but lower if the algorithm started with IUS. All these issues should be taken into account in considering the diagnostic approach in patients presenting for investigation of symptoms suggesting the presence of CD.

Moreover, we should also consider that CD is a life-long, but not lethal condition. Therefore, greater economic benefit could be obtained with diagnostic strategies that may accurately exclude the disease. In fact, false positive results may lead to both costly, invasive investigations and false positive diagnoses of CD, resulting in life-long, fruitless, costly and potentially harmful treatments. On the other hand, false negative results are often associated with the persistence of symptoms, which usually require short-term repeated investigations whose impact, in terms of clinical, economical and social costs, still has to be clarified. For these reasons, post-test probabilities of CD, even if arbitrarily set at >95% (confirmation of CD) and <5% (exclusion of the disease), could be less restrictive. It may be considered that, with a wider range of error (eg post-test probabilities set at >80% and <20%), the use of only ileocolonoscopy and IUS may be sufficient in patients with a low and intermediate pre-test probability to exclude CD. However, in the context of high pre-test probability of CD

### Table 3 Costs based on low pre-test probability scenario.

<table>
<thead>
<tr>
<th>1st test</th>
<th>2nd test</th>
<th>3rd test</th>
<th>Costs (£) (×1000 patients)</th>
<th>Detected/missed/undiagnosed (×1000 patients)</th>
<th>Cost (£) per patient correct diagnosis</th>
<th>Cost (£) to detect one patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC</td>
<td>IC</td>
<td>MRI</td>
<td>445,000</td>
<td>222/28/0</td>
<td>445,00</td>
<td>2004,50</td>
</tr>
<tr>
<td>US IC VCE</td>
<td>202,329</td>
<td>188/62/39</td>
<td>214,165</td>
<td>222/28/21</td>
<td>210,54</td>
<td>1,076,22</td>
</tr>
<tr>
<td>US IC US</td>
<td>1,002,220</td>
<td>222/28/21</td>
<td>1,105,400</td>
<td>222/28/35</td>
<td>1023,72</td>
<td>4514,50</td>
</tr>
<tr>
<td>MRI IC US</td>
<td>1,105,400</td>
<td>222/28/21</td>
<td>1,105,400</td>
<td>222/28/35</td>
<td>1145,49</td>
<td>4979,28</td>
</tr>
</tbody>
</table>

US: ultrasonography; IC: ileocolonoscopy; MRI: magnetic resonance imaging; VCE: video-capsule endoscopy.

### Table 4 Costs based on high pre-test probability scenario.

<table>
<thead>
<tr>
<th>1st test</th>
<th>2nd test</th>
<th>3rd test</th>
<th>Costs (£) (×1000 patients)</th>
<th>Detected/missed/undiagnosed (×1000 patients)</th>
<th>Cost (£) per patient correct diagnosis</th>
<th>Cost (£) to detect one patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC</td>
<td>US VCE</td>
<td>537,250</td>
<td>735/15/7</td>
<td>541,04</td>
<td>730,95</td>
<td>730,95</td>
</tr>
<tr>
<td>IC</td>
<td>US MRI</td>
<td>513,881</td>
<td>722/28/20</td>
<td>524,37</td>
<td>711,75</td>
<td>711,75</td>
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<tr>
<td>IC</td>
<td>MRI US</td>
<td>654,878</td>
<td>665/85/124</td>
<td>747,58</td>
<td>984,78</td>
<td>984,78</td>
</tr>
<tr>
<td>IC</td>
<td>MRI VCE</td>
<td>912,828</td>
<td>665/85/149</td>
<td>1072,65</td>
<td>1372,67</td>
<td>1372,67</td>
</tr>
<tr>
<td>US IC</td>
<td>238,865</td>
<td>743/7/0</td>
<td>238,865</td>
<td>238,87</td>
<td>321,49 b</td>
<td>321,49 b</td>
</tr>
<tr>
<td>MRI IC US</td>
<td>1,018,380</td>
<td>721/29/68</td>
<td>1,018,380</td>
<td>1092,68</td>
<td>1412,45</td>
<td>1412,45</td>
</tr>
<tr>
<td>MRI IC VCE</td>
<td>1,277,100</td>
<td>664/86/150</td>
<td>1,277,100</td>
<td>1502,47</td>
<td>1923,34</td>
<td>1923,34</td>
</tr>
</tbody>
</table>

US: ultrasonography; IC: ileocolonoscopy; MRI: magnetic resonance imaging; VCE: video-capsule endoscopy.

\(^a\) The cost will increase up to €525,00 adding IC in patients with positive US.

\(^b\) The cost will increase up to €706,59 adding IC in patients with positive US.
(e.g. highly suggestive clinical context with positive C-reactive protein or faecal calprotectin), a single positive result is sufficient to confirm the diagnosis while a single negative result is not sufficient to exclude CD.

Our study has several limitations. The sensitivity and specificity of the diagnostic test used in our analysis were based on the most recent and highest quality available evidence, which included only patients with a high pre-test probability of CD and within small cohorts. In addition, these studies, despite being based on the most up-to-date publications, utilized MRI, IUS and endoscopic equipments that have now become obsolete. With the advent of 3 T MRI, MR-enteroclysis, contrast enhanced IUS (oral and intravenous) as well as high definition endoscopes with narrow band imaging, it is possible that the diagnostic accuracy of all modalities are much improved. To confirm our findings, these studies should be repeated in a prospective manner across a wider cohort of patients utilising current technologies. Another limitation includes the paucity of data regarding the accuracy of VCE in CD, therefore the strength of our assumptions regarding VCE can be questioned. Furthermore, there are no prospective data on the accuracy of ileocolonoscopy in diagnosing CD. Therefore, while we assumed that ileocolonoscopy has 100% specificity, multiple other diseases can have similar endoscopic features when compared to CD. Conditions such as autoimmune (vasculitis), ischaemic, infectious (Yersinia and Campylobacter infection) and iatrogenic (aspirin and non-steroidal anti-inflammatory induced) enterocolitides can mimic CD leading to false positive results. Furthermore, the sensitivity of ileocolonoscopy being based, to our knowledge, on a single study, we have also taken into account a hypothetical sensitivity for ileocolonoscopy of 90%, and using the same formula we assessed an overall sensitivity of ileocolonoscopy of 95.6%. Using this sensitivity we have found a higher number of correct diagnoses (an average of 14, 18 and 52 correct diagnoses in plus in low, intermediate and high pre-test probabilities, respectively) and an overall 10–15% reduction of cost to detect one CD patient, depending on the diagnostic strategy (Table S2).

It may also be suggested that another limitation is the calculation of costs. We considered only the cost of the diagnostic tests obtained from the 2012 Italian Health Medicare Reimbursement of FASDAC, and also assumed that these costs are similar throughout Europe.

We did not consider several other indirect costs such as: a) costs associated with different amounts time off work required for each procedure, b) costs associated with procedural complications, c) costs of incorrect diagnoses.

Apart from these economic aspects, the usefulness and advantage of IUS in detecting IBD should be considered together with some of its limitations, in particular the limited expertise and competence in many centres. However, many IBD units in Italy and Germany already include gastroenterologists who are competent in bowel ultrasound and the importance of this issue has rapidly increased in recent years as suggested by courses endorsed by the European Crohn’s and Colitis Organisation and training programmes of ultrasound in IBD.

In conclusion, the accuracy and cost of different diagnostic algorithms depend on the pre-test probability of the disease, namely the patient’s history and results of previous biochemical tests. Accuracy and cost of diagnostic strategies may also vary significantly according to the first diagnostic test used and there is no role for MRI as the first investigation. For the early detection of CD, in patients with a low, intermediate or high pre-test probability of CD, ileocolonoscopy combined with IUS seems to be the most accurate and the most effective strategy to confirm or to exclude CD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrohns.2014.08.005.

Conflict of interest

None.

References


