Cost effectiveness of mass screening for coeliac disease is determined by time-delay to diagnosis and quality of life on a gluten-free diet

T. HERSHCOCICI*, M. LESHNO†,‡, E. GOLDIN*, R. SHAMIR†,§ & E. ISRAELI*

SUMMARY

Background
Coeliac disease is frequently diagnosed after a long delay resulting in increased morbidity and mortality.

Aims
To define the parameters which have the highest impact on the cost-effectiveness of mass screening for coeliac disease.

Methods
A Markov model examined a coeliac disease screening programme of the healthy young-adult general population compared with a no-screening strategy. The main outcome measures were quality adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER). Effects of variables were examined using sensitivity analyses.

Results
The screening strategy resulted in a gain of 0.0027 QALYs. The ICER of screening vs. no-screening strategy was US$48 960/QALYs. The variables with the largest impact on cost effectiveness were: the time delay from symptom onset to diagnosis, the utility of adherence to a gluten-free diet (GFD) and the prevalence of coeliac disease. Screening would be cost-effective if the time delay to diagnosis is longer than 6 years and utility of GFD adherence is greater than 0.978.

Conclusions
Our model suggests that mass screening for coeliac disease of the young-adult general population is associated with improved QALYs and is a cost effectiveness strategy. Shortening of the time-delay to diagnosis by heightened awareness of health-care professionals may be a valid alternative to screening.
INTRODUCTION
Coeliac disease (CD) is a gluten-sensitive enteropathy with large negative health consequences. CD can appear at any age, and has lately emerged as a worldwide public health problem. The disease is triggered by ingestion of the gluten proteins contained in wheat, barley, and rye, and symptoms range from minor complaints to severe symptomatic presentation. An overall increased morbidity and mortality have been reported in adults with CD. Gluten-free diet (GFD), the only treatment currently available for CD, involves lifelong elimination of the causative prolamines from the diet.

A majority of CD patients are now initially diagnosed by highly sensitive and specific serological tests, followed by readily performed endoscopic biopsy. Consequently, many more patients with only mild clinical symptoms are diagnosed, making the classical scenario of diarrhoea/steatorrhoea and weight loss a comparative rarity.

Theoretically, there are many points favouring mass screening in CD: it is a common disorder that causes significant health problems with an effective treatment available, which results in symptomatic relief and also prevents the complications of the disease. To consider whether mass screening is justified, its impact on quality of life and its cost-effectiveness (CE) must be considered. An NIH consensus statement published in 2005, as well as a recent debate in this subject referred to the paucity of data on the CE of screening.

The robustness of a CE analysis can be measured in sensitivity analyses where some or all of the parameters are varied within a plausible range. The aim of the present study was to define the parameters which have the highest impact on the CE of mass screening of the young adult population for CD. We calculated the cut-off values of these parameters that would allow maintaining the CE of the screening strategy.

METHODS
We developed a state transition Markov model to study the effect of different parameters on the CE of screening (Figure 1). The target population is young adults from the entire general population at the age of 18 years. The time horizon of this analysis is the lifetime. All patients were followed up until death. As the model uses values that can vary between studies and countries, the effect of establishing a certain value on the model was examined using sensitivity analysis.

Persons were placed into one of the following health states in each cycle of the model:
(i) No CD;
(ii) CD undiagnosed but with symptoms: Irritable Bowel Syndrome(ibs)-like symptoms, iron-deficiency anaemia (ida) or other symptoms;
(iii) CD undiagnosed without symptoms;
(iv) CD diagnosed and adherence to a GFD;
(v) CD diagnosed without adherence to a GFD;
(vi) Death.

In our model, with its cycle length of 1 year, we evaluated the following screening strategy: determination of human IgA anti tissue transglutaminase antibodies (IgA anti-tTG). In subjects with a positive serology, confirmation of the diagnosis was done by intestinal biopsy. In IgA-deficient patients, human IgG anti-tTG was used. We compared the screening strategy to a ‘no-screening’ strategy (in which coeliac disease is diagnosed based on symptoms of the subjects).

As guidelines on economic analyses suggest that QALYs are the most appropriate unit for a CE analysis, we measured the efficacy by this parameter. We calculated the incremental cost effectiveness ratio (ICER) between the screening and the ‘no-screening’ strategy. Sensitivity analyses were performed to assess the stability of the results over plausible ranges of uncertain parameters. Future costs and life years were discounted at an annual rate of 3%. The model was programmed in DATA (Pro 2008 Suit, TreeAge Software, Inc., Williamstown, MA, USA).

Sensitivity analyses
We performed a multivariable sensitivity analysis (Tornado analysis) to test the influence of all variables on the model results and to rank order the most influential variables. We then performed 1-way sensitivity analyses on the most influential variables. In addition, we conducted a second order Monte-Carlo simulation under the assumption of accordant beta distribution in chance nodes and accordant triangular distribution for cost outcomes. We evaluated 10 000 trials via this simulation and report the distribution of ICER between the screening and no-screening strategies.

Clinical data and parameter estimation
We performed a systematic search of the MEDLINE database, the Cochrane library and the Web of Science database to identify English language publications from
January 1996 to December 2008 using the following key words in our search: CD, prevalence, mortality rate, screening, sensitivity, specificity, serological test, IBS, IDA, osteoporosis, cost-benefit analysis, cost-effectiveness analysis and cost per QALY ratio. The base-case values and ranges used in the sensitivity analysis are presented in Table 1. Variable estimates were based only on published data on cohorts of patients. As described below, we systematically biased our analysis in favour of the ‘no-screening’ strategy. The study was performed according to criteria validated by Spiegel et al. as predictors of high-quality health economic analyses.10

**Screening of asymptomatic subjects.** We studied the prevalence of CD in asymptomatic young adults (aged 17–18 years) and found a prevalence of 0.9%.11 This prevalence, which is in concordance with that estimated in the medical literature (0.63% to 1%), was used in the base-case analysis.12, 13 However, a recent study from Finland reports an almost doubling of CD prevalence in the last two decades to 1.99%,14 and recent publications from Sweden suggest a threefold increase in the prevalence of CD during the years of ‘coeliac epidemic’.15 We used in the sensitivity analysis a range between 0.25% and 2%.

**Assumptions regarding the standardized mortality ratio.** Assumptions regarding the standardized mortality ratio (SMR) based on data from the literature4, 16, 17 were previously discussed.18 Corrao et al.4 found an
SMR of 2.0, which was even higher in patients who were diagnosed with CD at the ages of 18–49 compared to patients who were diagnosed at the age of 50 years or more. West et al.\textsuperscript{17} found that the overall hazard ratio for mortality in CD was 1.3; however, the hazard ratio for mortality in the first year after diagnosis was 2.09. All these studies demonstrated an increased SMR in non-treated coeliac patients. In the present study, to favour the no-screening strategy, we used in the base-case an SMR of 1.6 for untreated CD patients and an SMR of 1.1 for with CD patients on a GFD. In the sensitivity analysis, we used an SMR ranging from 1.1 to 2.5, acknowledging the fact that the SMR of 5.8 found by Cottone et al.\textsuperscript{16} is exceptionally high.

Assumptions regarding adherence to a GFD and the utility of CD patients on a GFD. Compliance to GFD varies significantly between different CD patient groups (childhood vs. adult-diagnosed CD, symptomatic vs. asymptomatic patients).\textsuperscript{2, 19–22} (See Supplementary material for details). Compliance to GFD was measured by dietary history (self-report and diet interview by a trained nutritionist). Although current serological tests have very high sensitivities and specificities for the diagnosis of CD, they cannot replace trained nutritionist evaluation in the assessment of adherence to GFD as recently shown in a systematic analysis.\textsuperscript{23} According to meta-analysis, rates for strict adherence range from 42\% to 91\% depending on definition and method of assessment.\textsuperscript{24} To favour the no-screening arm, we estimated the average compliance to GFD as 60\% after 10 years from diagnosis in asymptomatic subjects and 80\% in symptomatic CD patients. In the sensitivity analysis, we used for compliance on a GFD at 10 years a range between 90 and 35\% for asymptomatic patients and between 90 and 10\% for symptomatic patients.

There are remarkably few data in the literature with regard to utility of adherence to a GFD. Even after several years of a GFD, many patients with CD regard

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**Table 1. Base-Case values and ranges used in sensitivity analyses**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-case value</th>
<th>Range</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Clinical variables</td>
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<td></td>
<td></td>
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<tr>
<td>Prevalence of CD (%)</td>
<td>0.9</td>
<td>0.7–2</td>
<td>11–15</td>
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<tr>
<td>Prevalence of IBS-like symptoms (%)</td>
<td>30</td>
<td>24–36</td>
<td>28, 34–37</td>
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<tr>
<td>Prevalence of anaemia (%)</td>
<td>50</td>
<td>40–70</td>
<td>28, 34–37</td>
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<tr>
<td>Annual probability to develop symptoms in asymptomatic CD patient (%)</td>
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<td></td>
<td>12</td>
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<tr>
<td>Average time delay until CD diagnosis in asymptomatic patients (years)</td>
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<td>2–10</td>
<td>28–33</td>
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<td>Utility of IBS</td>
<td>0.76</td>
<td>0.7–0.95</td>
<td>45, 46</td>
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<tr>
<td>Utility of IDA</td>
<td>0.73</td>
<td>0.7–0.8</td>
<td>47</td>
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<td>Compliance and utility of GFD</td>
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<td>Compliance to GFD at 10 years-asymptomatic patients (%)</td>
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<td>90–10</td>
<td>2, 19–22, 24</td>
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<td>Compliance to GFD at 10 years-symptomatic patients (%)</td>
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<td>0.98</td>
<td>0.95–0.985</td>
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<td>SMR in CD on GFD</td>
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<td>SMR in CD with symptoms</td>
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<td>Sensitivity/Specificity of serological tests</td>
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<td>Sensitivity of IgA-tTg (%)</td>
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<td>Sensitivity of IgG-tTg (%)</td>
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<td>Specificity IgG-tTg (%)</td>
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<tr>
<td>Cost of IgA-tTg or IgG-tTg (US$)</td>
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<td>60–120</td>
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it as a substantial burden, with a quarter of screen-detected patients reporting regret at being diagnosed. Hallert et al. showed that adult CD patients failed to attain the same degree of subjective health as the general population after 10 years on a GFD. Using the provided SF-36 scores and a previously published regression equation, we calculated that the utility of treated CD is 0.98 on a scale from 0 to 1. In the sensitivity analysis, we used a range between 0.95 and 0.985.

Assumptions regarding the time to CD diagnosis in the nonscreened group. The diagnosis of CD is frequently delayed because of the atypical presentation of the disease in adult patients and lack of awareness. A retrospective German study published in 1996 determined a lag-time of 10.1 years between the onset of symptoms and diagnosis of CD. Nonetheless, in the last 2 years of the study, this period was shortened to an average of 6.9 years.

In a national survey performed in the US during 1996–1997, the mean duration of symptoms before diagnosis was 11 years. An additional single university-hospital study from England demonstrated a lag-time of 4.9 years.

We assumed in the base-case analysis that the average time delay in diagnosing CD is 6 years and in the sensitivity analysis, we used a range between 2 and 10 years. These values were used only for symptomatic CD presenting as IBS-like symptoms and IDA. To bias the model in favour of the no-screening strategy, we did not incorporate a time delay to diagnosis for all other clinical presentations of CD.

Assumptions regarding symptoms in CD. The classical symptoms of CD (e.g. diarrhoea and malabsorption) seem to account for a diminishing fraction of cases. More subtle presentations are common in adults, including IBS-like symptoms, and IDA. On the basis of a systematic search of the literature (see supporting information for details), we used a base-case value for the prevalence of IBS-like symptoms among CD patients of 30% (range 24–36%) and for the prevalence of IDA of 50% (range 40–70%).

Serological testing can diagnose asymptomatic CD. It is estimated that 18% of symptomatic subjects with a positive serology will become symptomatic during an observation period of 7 years, yielding an annual probability of 2.8%. We used this value in the base-case analysis and a range between 2% and 5% in the sensitivity analysis.

Assumptions regarding the sensitivity and specificity of serological testing. Of the serological tests that are available for diagnosing CD, the IgA anti-endo-mysial antibodies (EMA) and IgA anti-tTG are reported to have high sensitivity and specificity. However, IgA anti-tTG has been recommended as the first step in coeliac screening because it is less costly than EMA. New serological tests are available for CD diagnosis (for example, antibodies to deamidated gliadin peptides); however, their additional diagnostic value over IgA anti-tTG was not fully validated in large populations of CD patients. In a recent meta-analysis, it was demonstrated that the IgA anti-tTG antibody test outperforms the deamidated gliadin peptide antibody test and remains the preferred serological test for the diagnosis and/or exclusion of CD.

The sensitivity and specificity of IgA anti-tTG (measured by ELISA with human-recombinant or red-cell derived tTG as substrate) range between 91.8% and 98.1% and between 97.1% and 99.6% respectively. We selected the mean values from these ranges and adopted for IgA anti-tTG antibodies a sensitivity of 95% and specificity of 98% as the base-case estimates and in the sensitivity analysis, a range between 90% and 99% was used.

Selective IgA deficiency is 10–15 times more common in patients with CD than in the general population (1.7–3%). Nonetheless, the sensitivity and the specificity of IgG anti-tTG are 98.7% and 98.6% respectively in IgA-deficient CD. We selected these values as base-case values and in the sensitivity analysis, we used a range between 90% and 99%.

Assumptions regarding utilities. Data on quality of life in IBS, IDA and treated CD are available, including studies that use SF-36 and permit utility calculation by using a regression equation. This equation and published SF-36 scores have been used previously to perform cost-utility analyses of screening for CD in patients with IBS symptoms. The utility of the IBS was calculated from published SF-36 data for IBS patients in the USA, yielding a value of 0.76. This value was used in the base-case analysis and a range between 0.7 and 0.95 in the sensitivity analysis. The utility of IDA was calculated from published SF-36 data for young anaemic patients.
in Japan yielding a value of 0.73. We used this value in the base-case analysis and a range between 0.7 and 0.8 in the sensitivity analysis. To bias our model in favour of the no-screening strategy, we considered the utility of all the other clinical presentations of coeliac disease as 1 (perfect health).

Assumptions regarding costs. Costs were the basis for inputs in the model and were derived from published literature and from Medicare data. We considered only direct health care costs, representing the average payments for each coded procedure based on the 2004 Medicare Fee Schedule (http://www.hsga.com/professionals/feebd-2004.shtml).

The cost of upper endoscopy with biopsy and the associated risks of major complications or death were estimated from the published data at US$1105 (with range between US$300 and 1405).

The base-case cost for standard IBS care was extracted from a recent study on IBS costs in a health maintenance organization (US$450/patient-year after the index year updated to year 2003 dollars). For reasons of lack of data regarding the cost of care of IDA and to bias the model against the screening strategy, we assumed a base-case cost of 0 for this condition.

The cost of evaluating a patient suspected of having CD includes two office visits (each visit costing US$40), routine blood tests (US$15), a serological test (US$70 for IgA anti tTG) and endoscopy (US$1105, including biopsies and their interpretation). Finally, the costs attributable to ongoing care for those diagnosed with CD were estimated to be US$130 annually. The follow-up care included a general medicine office visit, a serological test (for assessment of compliance to GFD diet) and routine blood tests.

RESULTS

Given the conditions used in the base-case analysis, at an annual discount rate of 3%, the screening strategy resulted in life year savings related to CD and a gain of 0.00274 QALYs. The ICER of screening vs. no-screening strategy was US$48 960 per QALYs (Table 2).

Sensitivity analyses

The multivariable sensitivity analysis demonstrated that the variables that had the largest impact on the cost-effectiveness in descending order were: the time delay from onset of symptoms to CD diagnosis, the utility of treated CD and the prevalence of CD (as shown in the Tornado diagram—Figure S1 in the supporting information).

The sensitivity analysis on the time delay from symptoms onset to diagnosis of CD in a symptomatic patient is presented in Figure 2. For a time delay of 6 years, the ICER is US$48 960 per QALYs; however, when the time delay is shortened, the ICER increased progressively. Thus, for a time delay to diagnosis of CD of less than 5.9 years, mass-screening would not be cost-effective.

Another determinant of the ICER is the utility of treated CD. Screening is cost-effective for a utility of treated CD greater than 0.978, while for a utility between 0.95 and 0.978, the screening is not cost-effective. For an estimated utility of less than 0.95, the no-screening strategy became dominant.

The ICER of the screening remained cost-effective for a wide range of CD prevalence (0.875–2%), but it increased significantly if the prevalence decreased below 0.875%.

Parameters that had no significant influence on the ICER are: the probability to develop symptoms in

<table>
<thead>
<tr>
<th>Table 2: Results of base-case analysis</th>
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<tbody>
<tr>
<td>Strategy</td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>No Screening</td>
</tr>
<tr>
<td>Screening</td>
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<tr>
<td></td>
</tr>
<tr>
<td>ICER (US$ per QALYs)</td>
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</table>

Figure 2. Sensitivity analysis: decremented cost-effectiveness ratio (ICER/QALY) as a function of the reduction in time delay to diagnosis of coeliac disease.
asymptomatic CD patients, the probability to suffer from IDA or IBS-like symptoms, the utility of these states, the compliance to a GFD and the costs of endoscopy with biopsy and of the serological testing. Additionally, an SMR between 1.5 and 2.5 for symptomatic CD patients had no major effect on the ICER.

Based on the uncertainties included in the simulation, for a willingness to pay of US$50,000, the probability that CD screening is cost-effective is 60% (as shown in the acceptability curve – Figure 3).

**DISCUSSION**

Screening for CD is advocated by current guidelines only in high-risk groups with conditions associated with an increase in CD prevalence.29 CE of targeted screening for high-risk groups has been shown in subjects with IBS43, 44 and with Down’s syndrome.50

We developed a state transition Markov model to evaluate the effect of different parameters on the CE of screening vs. no-screening strategy for CD of the young adult general population.

The time delay from onset of symptoms to diagnosis of CD in the no-screening arm was found to be the most important independent determinant of the CE. Although this finding could have been intuitive, our model enabled us to calculate the cut-off values of this parameter and its interaction with other parameters on CE. Various investigators have noted a long duration of symptoms before the diagnosis of CD. In one retrospective study from Germany,30 the interval from onset of symptoms to the first visit to a physician was greatly surpassed by the interval from the first visit to a physician to diagnosis. Thus, the long duration of symptoms was mostly because of a physician delay in reaching the diagnosis rather than a patient delay in seeking medical attention. Although the total time to diagnosis of CD has decreased in the most recent studies,32, 33 it remains high. The findings of consultations with multiple physicians and a previous diagnosis of IBS in a substantial number of patients suggest that a similar situation exists in the United States.28 A plausible explanation would be that physicians regard adult CD as rare and fail to consider it in clinical situations other than the classical state of chronic diarrhoea and malabsorption.

The second parameter with a large impact on CE is the utility of treated CD. In our analysis, we used data from a study on Swedish CD patients adhering to a GFD.26 This was the only study found in the systematic literature review that directly measured the quality of life of treated CD. Although adult CD patients on long-term GFD experienced more gastrointestinal symptoms than the general population, the utility of treated CD in this study was relatively high.51 It is also reasonable to assume that there would be a strong cultural effect on the utility of adherence to a GFD.

Our base-case model calculated an ICER of 48,960 US$/QALYs. Although different third-party payers have different budgets, based on our results, mass-screening for CD may fall well within the limits of some third-party payers.52, 53 A recent published study demonstrates that comparative effectiveness and cost-effectiveness analyses can be used by national reimbursement agencies.54 Information on cost-effectiveness could be used to inform the payment level (or copayment) for a particular drug or medical strategy. In the end, however, in any health care system, coverage and pricing choices need to be made based on information beyond these two criteria.55 As Wilen-sky states: ‘payers will have to make difficult decisions, and different payers may make different decisions’.56

Our model takes into account the utility of the most common symptoms of CD in the adult population (IBS-like symptoms and IDA). We did not include in our analysis other disease manifestations for which insufficient data regarding their utility are available. For example, our model did not take into account the increased risk for osteoporosis in CD patients. Osteoporotic fractures and not osteoporosis *per se* are associated with a decreased quality of life.57 Despite
the clear, established association between CD and osteoporosis, data on the risk of fractures in CD are inconsistent.\textsuperscript{58–64} We also did not take into account the decrease in utility of CD complicated by lymphoma or other malignancies. In a recent study, it was demonstrated that there is no additional risk of overall malignancy among untreated adults with screening-identified evidence of CD in a follow-up of nearly twenty years.\textsuperscript{65} Thus, for the aforementioned disease states as well as others (e.g. infertility, congenital birth defects, and neurological symptoms) where conclusive data measuring utility are lacking, we favoured the no-screening arm.

Possible shortcomings of the present model should be noted. First, there are no studies that directly compare the impact of a GFD on the quality of life of asymptomatic CD patients. This question must be addressed by future clinical studies.

Second, we assumed the perspective of a third-party payer and used Medicare reimbursement costs. This approach is limited because it does not account for indirect societal costs including opportunity costs from missed work or out-of-pocket expenses for maintaining a GFD. Although indirect costs may impact the CE of mass screening, there are limited data regarding these costs, and in light of this shortcoming, we could not use a societal perspective without relying on conjectural cost estimates.

Finally, we estimated the utility of symptomatic CD based on its most common clinical manifestations. Measurement of utility of this health state would certainly be superior, but is not available at present.

Our model allowed us to identify the crucial parameters that play a role in the CE of mass screening. Not less important is defining which parameters do not significantly impact the model within a wide range of values used in the sensitivity analyses. Thus, policy makers can decide on mass screening for CD in a certain society or certain geographical area, on the basis of local values of these parameters. When the time to diagnosis from initiation of symptoms compatible with CD is less than 6 years, our model predicts lack of CE of mass-screening. Thus, education of health professionals to increased awareness for CD diagnosis in symptomatic individuals, (thereby decreasing the time delay to diagnosis) may be a valid alternative to screening. High-quality studies directly examining the utility of screening-diagnosed CD are needed to validate our base-case scenario.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Tornado diagram. The variables with the largest impact on the cost-effectiveness in descending order are: the time delay from onset of symptoms to CD diagnosis, the utility of treated CD and the prevalence of CD.

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