# Can the Clinical History Distinguish Between Organic and Functional Dyspepsia?

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**Context** Upper gastrointestinal symptoms occur in 40% of the population. An accurate diagnosis would help rationalize investigation and treatment.

**Objective** To systematically review the literature of the accuracy of primary care physicians, gastroenterologists, or computer models in diagnosing organic dyspepsia.

**Data Sources** A search of Cochrane Controlled Trials Register (December 2003), MEDLINE (1966-December 2003), EMBASE (1988-December 2003), and CINAHL (1982-December 2003) for studies that reported on cohorts of patients attending for endoscopy that had symptoms, clinical opinion, or both recorded before investigation.

**Study Selection** Studies that prospectively compared the diagnosis reached by a clinician, computer model, or both with results of upper gastrointestinal endoscopy in adult patients with upper gastrointestinal symptoms.

**Data Extraction** Two authors independently assessed studies (n = 79) for eligibility and abstracted data for estimating likelihood ratios (LRs) of clinical opinion, computer models, or both in diagnosing an organic cause for dyspepsia.

**Data Synthesis** Fifteen studies were identified that evaluated 11 366 patients, with 4817 patients (42%) classified as having organic dyspepsia. The computer models performed similarly to the clinician; therefore, the 2 approaches were combined. The diagnosis reached by the clinician or computer model suggesting organic dyspepsia had an LR of 1.6 (95% confidence interval [CI], 1.4-1.8), and a negative result decreased the likelihood of organic dyspepsia (LR, 0.46; 95% CI, 0.38-0.55). A diagnosis of peptic ulcer disease performed similarly with an LR of 2.2 (95% CI, 1.9-2.6), but an evaluation that suggested the absence of peptic ulcer disease had an LR of 0.45 (95% CI, 0.38-0.53). A clinical history suggesting esophagitis had an LR of 2.4 (95% CI, 1.9-3.0) vs a negative history that had an LR of 0.50 (95% CI, 0.42-0.60).

**Conclusion** Neither clinical impression nor computer models that incorporated patient demographics, risk factors, history items, and symptoms adequately distinguished between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia.

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## CLINICAL SCENARIO

A 40-year-old woman presents with a 6-month history of intermittent upper gastrointestinal symptoms. She describes an epigastric and retrosternal burning sensation but finds it difficult to decide in which of these areas symptoms are predominant. She occasionally notices regurgitation and feels nauseated. Eating, swallowing, postural change, or exercise do not influence her symptoms. Antacids provide some relief. Her weight remains constant. She is not taking any prescribed or over-the-counter medications and has no significant past medical history. She smokes 20 cigarettes per day and drinks 10 glasses of wine per week. There is no family history of malignancy but her mother was diagnosed as having a hiatal hernia and her father died of a myocardial infarction at the age of 65 years. The physical examination is unremarkable apart from epigastric tenderness on palpation.

## WHY IS THE CLINICAL EXAMINATION IMPORTANT?

Upper gastrointestinal symptoms are common in the community, with approximately 40% of the population describing these symptoms in a given 6-month period.[1] The 2 most common upper gastrointestinal symptoms are epigastric pain or discomfort and heartburn (a burning sensation, often starting in the epigastric region and radiating retrosternally) and these frequently coexist.[2] These symptoms are associated with a reduced quality of life similar to that experienced by patients with moderate angina.[3] Upper gastrointestinal symptoms therefore represent a significant problem in the community; they account for 5% of all primary care physician referrals and

**See also Patient Page.**

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50% of a gastroenterologist's workload,[4] with more than $2 billion spent in the United States each year on acid-suppressing drugs.[5]

Patients are often referred for esophagogastroduodenoscopy (EGD) to investigate the cause of their upper gastrointestinal symptoms or rationalize the use of antisecretory therapy.[6] Endoscopy is the accepted reference standard test for diagnosing gastric and duodenal ulcers, esophagitis, and esophageal and gastric malignancy, with a sensitivity and specificity of more than 95%.[7] Because 40% of the population has upper gastrointestinal symptoms, it is not possible to investigate everyone with dyspepsia. Indeed, it is estimated that only 1% of the population has an EGD each year,[8] which suggests that the clinical examination is being implicitly used to reduce endoscopy workload. The US and British national guidelines[9-11] propose that the clinical examination is an important part of evaluating patients with dyspepsia, with 1 guideline suggesting, "For most patients under the age of 55, invasive investigation is not necessary before a working diagnosis of functional dyspepsia can be made."[11] *Functional dyspepsia* is defined as pain or discomfort centered in the epigastrium with a normal endoscopy.[12] International consensus groups suggest that the clinical examination is important in assessing upper gastrointestinal symptoms. The Rome II Committee, for example, suggests that gastroesophageal reflux disease (GERD) can be confidently diagnosed when heartburn is the dominant symptom.[12]

The use of the clinical examination in distinguishing between organic and functional dyspepsia is controversial. Some studies[13,14] suggest that a history and examination in patients with upper gastrointestinal symptoms facilitates diagnosis, while other studies have found that the clinical evaluation lacks effectiveness.[15] There have also been doubts expressed about the accuracy of heartburn in the diagnosis of GERD.[16] We have therefore conducted a systematic review to evaluate the accuracy of the clinical examination in making a diagnosis of organic dyspepsia. Our focus was on symptoms and the physician's clinical diagnosis, or the diagnosis suggested by computer models that included patient demographics, risk factors, history items, and symptoms.

## Anatomical and Physiological Origins of Dyspepsia

Peptic ulcer disease and GERD most commonly cause organic upper gastrointestinal symptoms. Peptic ulcer disease refers to duodenal or gastric ulceration and the main causes are *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs).[17] *H pylori* is also strongly associated with distal gastric adenocarcinoma.[18] GERD is caused by the reflux of stomach contents into the esophagus.[19] This can lead to esophageal inflammation observed during endoscopy (esophagitis). Frequently, reflux of stomach contents causes symptoms despite the absence of an inflammatory response (nonerosive reflux disease).[20] Nonerosive reflux disease can be diagnosed by 24-hour esophageal pH monitoring, although the accuracy of this test is not ideal and some patients with GERD may be missed.[21]

Barrett esophagus and gastric and esophageal cancers are less common but important diagnoses. Chronic GERD is important in the development of Barrett esophagus, which is observed as a metaplastic change of the esophageal mucosal lining from squamous to columnar mucosa. Barrett esophagus increases the risk of esophageal adenocarcinoma, with 0.5% of patients developing this complication annually.[22]

Cross-sectional surveys of patients having an EGD[23] suggest that approximately 20% of patients with upper gastrointestinal symptoms have esophagitis, 20% have endoscopy-negative reflux disease, 10% have peptic ulcer disease, 2% develop Barrett esophagus, and 1% have malignancy. Minor abnormalities at EGD include gastric erosions, duodenitis, and hiatal hernia. Duodenitis, gastritis, and gastric erosions do not correlate with dyspepsia symptoms and a hiatal hernia is usually asymptomatic, although this abnormality does predispose to GERD.[24] Therefore, almost 50% of patients who are investigated have an essentially normal endoscopy and are labeled as having functional dyspepsia. The causes of functional dyspepsia are uncertain and are likely to be multifactorial.[25]

## How to Elicit Symptoms and Signs

Upper gastrointestinal symptoms are common (about 40% of the population has dyspepsia); however, only half of patients who are affected tell their physician.[4] Of those patients who report symptoms, only approximately 5% are referred for endoscopy in a given year. When asked, patients describe various reasons for consulting, such as the severity of symptoms, fear of cancer, or concern about heart disease.[26] Clinicians should always inquire about the patient's underlying concerns related to dyspepsia. The clinical history helps establish the upper gastrointestinal tract as the source of the symptoms rather than other causes, such as ischemic heart disease or irritable bowel syndrome. Demographic information is important because, in the United States, upper gastrointestinal cancer is rare in patients younger than 55 years, and men are more than twice as likely to have upper gastrointestinal cancer as women at any given age. A family history of GERD, peptic ulcer disease, or upper gastrointestinal malignancy is also important. Risk factors for peptic ulceration include smoking and NSAIDs, including over-the-counter NSAIDs and low-dose aspirin. Risk factors for GERD include smoking, alcohol, calcium antagonists, nitrates, and theophyllines. A number of drugs including the bisphosphonates (alendronate and risedronate), some oral antibiotics such as erythromycin, the antiobesity agent orlistat, digitalis, potassium supplements, and the antidiabetic agent acarbose clinically seem to produce dyspepsia. However, apart from NSAIDs,[1] there is little to support the role of these drugs in the

**Box 1. Eligibility Criteria**

Adult patients (aged >16 years)

Cross-sectional design (not case-control)

Patients not specially selected*

Upper gastrointestinal symptoms recorded†

Symptoms and diagnosis recorded prospectively

Patients have upper gastrointestinal endoscopy diagnosis recorded‡

Symptoms and endoscopy diagnosis compared

≥100 Patients evaluated

*Patients could be selected by age or by primary care physician's referral but not other criteria (eg, all patients with positive *Helicobacter pylori* or all patients with gastric atrophy).
†This included scores generated from symptom questionnaires, computer-aided diagnoses, and clinically assessed diagnoses.
‡A small minority (<10%) could have the diagnosis made by barium meal as an alternative.

**Box 2. Method Used for Assigning Quality of Evidence**

**Level 1 (Highest)**

Independent blind comparisons of test with a valid criterion standard in a large number (≥200) of consecutive patients.

**Level 2**

Independent blind comparisons of test with a valid criterion standard in a small number (<200) of consecutive patients. Studies that had separate researchers performing test and criterion standard but did not explicitly state that these were masked included in this category.

**Level 3**

Independent, blind comparison of test with a valid criterion standard in patients who were not enrolled consecutively. Studies that did not have separate researchers performing test and criterion standard.

**Level 4**

Nonindependent comparison of a test with a valid criterion standard among a "convenience" sample of patients believed to have the condition in question.

**Level 5**

Nonindependent comparison of a test with a standard of uncertain validity; this standard may incorporate the test result into the criterion standard.

etiology of dyspepsia in large population, cross-sectional studies.[27,28]

The characteristics of upper gastrointestinal symptoms are thought to be important.[29] Predominant heartburn, heartburn relieved by an antacid, and heartburn exacerbated by stooping or lying flat is thought to be important in the diagnosis of GERD. Regurgitation is a symptom associated with GERD. Predominant epigastric pain or discomfort that is periodic (present for some months of the year and absent for other months), relieved with food, or causes nocturnal waking is thought to be important in the diagnosis of peptic ulcer disease. Alarming features, such as progressive dysphagia, weight loss, gastrointestinal bleeding, anemia, or persistent vomiting, may indicate underlying upper gastrointestinal malignancy. In addition, a history of gastric malignancy increases in pernicious anemia and after partial gastrectomy.

The physical examination has generally been considered less important in the assessment of dyspepsia, although the examination itself can reassure the patient. Epigastric tenderness on palpation is of little value[30] (sensitivity of 64% and specificity of 30% for diagnosing upper gastrointestinal pathology) but a palpable epigastric mass or an enlarged supraclavicular (Virchow) node raises the concern of gastric malignancy.

## METHODS

### Search Strategy and Quality of Review

The systematic review was performed according to the Cochrane Methods Group on Screening and Diagnostic Tests guidelines.[31] A search of the medical literature was conducted using the Cochrane Controlled Trials Register (December 2003), MEDLINE (1966-December 2003), EMBASE (1988-December 2003), and CINAHL (1982-December 2003). Studies on upper gastrointestinal disease were identified with the terms *peptic ulcer*, *duodenal ulcer*, *gastric ulcer*, *gastroesophageal reflux*, *esophagitis*, *stomach neoplasms*, *esophageal neoplasms* (all Medical Subject Heading [MeSH] heading and free text terms), *gastric* adj5 *cancer*, *gastric* adj5 *adenocarcinoma*, *(o)esophageal* adj5 *adenocarcinoma*, *(o)esophageal* adj5 *cancer*, *(o)esophageal* adj5 *squamous carcinoma* (all free text terms). These studies were combined using the set operator AND, with studies evaluating symptoms using the terms *dyspepsia* (MeSH and free text terms), *indigestion*, *epigas$* adj5 *pain* (all free text terms). These studies were further combined with the set operator AND with studies that assessed diagnosis using the terms *diagnosis*, *endoscopy* (MeSH and free text terms), *diagnos$* adj5 *test$*, and *(o)esophagogastroduodenoscopy* (all free text terms). A recursive search of the literature was performed from the bibliography of identified studies. Articles were then independently assessed by 2 researchers (P.M. and N.V.) according to prospectively defined eligibility criteria (BOX 1). Any disagreement be-

tween investigators was resolved by consensus. We defined *dyspepsia* as any upper gastrointestinal symptom[9] rather than using the Rome II definition,[12] which describes dyspepsia as predominant epigastric pain and discomfort. This reflects the reality of dyspepsia presentation in primary care in which patients often find it difficult to describe the most predominant symptom.[9]

The quality of the studies was assessed using a meta-analysis, which identified factors that influenced the outcome of diagnostic studies.[32] Studies were evaluated according to whether assessors were blinded, cases were consecutive, and whether the sample size was adequate (BOX 2). Data were extracted on predefined forms and checked by a second reviewer (N.V.).

## Statistical Analyses

The sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR=positive LR/negative LR) were calculated for each study and then pooled using the DerSimonian-Laird method.[33] The DOR cannot be applied to an individual patient for decision making. However, as a global measure of test accuracy, the DOR can be useful in identifying the "best test" when this is not apparent from the performance measured by LRs (higher DORs indicate higher accuracy).[16,34,35]

Diagnoses established by a primary care physician, specialist, or computer models were analyzed separately and in combination. The results were combined when all studies gave similar conclusions. In the case of studies that gave multiple cutoff points for computer models, the score that gave the maximum overall accuracy was chosen. The primary goal was to describe the performance of the clinical examination in evaluating organic vs functional dyspepsia. *Organic dyspepsia* was defined as esophagitis, peptic ulcer disease, benign esophageal stricture, Barrett esophagus, or upper gastrointestinal malignancy. All other findings at endoscopy were classed as *functional dyspepsia*. The performance of the clinical examination in determining peptic ulcer disease and esophagitis was also addressed.

Sensitivity, specificity, and positive and negative LRs were calculated using a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp,

**Table 1.** Characteristics of Included Studies That Reported the Accuracy of Primary Care Physicians and Gastroenterologists in Diagnosing Organic Dyspepsia

| Source | Country | No. of Patients | Type of Patient | Setting | Exclusion Criteria | Assessors Blinded | Quality Level* |
|---|---|---|---|---|---|---|---|
| Heikkinen et al,[45] 1995 | Finland | 400 | All presenting to PCP with dyspepsia whether or not referral for investigation | 4 Primary care health centers; all referred to the gastroenterology unit of single teaching hospital | Consecutive unselected patients with dyspepsia presenting to primary care | Yes | 1 |
| Hansen et al,[44] 1998 | Denmark | 612 | PCPs were asked to refer all patients with dyspepsia regardless of severity of symptoms; 56 of 668 eligible patients did not attend for endoscopy | 66 PCPs referring to 1 teaching hospital open-access endoscopy unit | All patients >18 y with dyspepsia except upper GI bleeding, jaundice, acute abdomen, previous upper GI surgery, pregnancy, or endoscopy contraindicated | Unclear | 2 |
| Lance et al,[36] 1985 | England | 100 | Consecutive patients attending general practice with dyspepsia; referred to hospital regardless of seeking specialist opinion | Single general practice referring to single teaching hospital | Consecutive patients with upper abdominal pain related to eating; patients requiring emergency referral excluded | Unclear | 2 |
| Danish Dyspepsia Study Group,[37] 2001 | Denmark | 347 | Patients with dyspepsia for more than 2 weeks referred by PCP | 73 PCPs referring to 7 endoscopy centers | Consecutive patients with dyspepsia >18 y, excluding patients with signs and symptoms of serious disease, pregnancy, or need for an interpreter | Yes | 1 |
| Numans and de Wit,[49] 2003† | The Netherlands | 515 | Presenting to PCP with new-onset upper abdominal symptoms | 76 PCPs referring to single district open-access endoscopy unit | Consecutive patients excluding acute upper GI bleed, alarm symptoms, proton pump inhibitor use during last 30 d | Yes | 1 |
| Bytzer et al,[41] 1996 | Denmark | 1233 | 1026 With dyspepsia referred by PCP for open-access endoscopy; 207 with dyspepsia referred by PCP to participate in an RCT of prompt endoscopy | Open-access endoscopy unit, 2 teaching hospitals | All consecutive patients except those with acute GI bleeding or previous gastric surgery | Yes | 1 |
| Fjosne et al,[48] 1986 | Norway | 1526 | All referred for upper GI endoscopy; unclear who referred; one third were inpatient referrals | Single teaching hospital endoscopy unit | All patients referred for upper GI endoscopy (263 were examined twice) | No | 3 |
| Barenys et al,[40] 2000† | Spain | 501 | With dyspepsia referred to outpatient clinic; unclear who referred | Gastroenterology outpatient clinic and endoscopy unit, single district hospital | All consecutive patients aged 18-85 y | Yes | 1 |

Abbreviations: GI, gastrointestinal; PCP, primary care physician; RCT, randomized controlled trial.
*See "Box 2" for definition.
†These studies were also included in the computer model for diagnosing organic dyspepsia.

Redmond, Wash) and checked using StatsDirect version 2.4.4 (StatsDirect Ltd, Cheshire, England). StatsDirect was used to generate forest plots of positive and negative LRs and specificities. All DORs were calculated using Stata version 8 (StataCorp LP, College Station, Tex) and the receiver operating characteristic curve and area under the curve were constructed using Prism version 4 (GraphPad Software Inc, San Diego, Calif). $P<.05$ was considered statistically significant.

## RESULTS

The search strategy identified 1209 studies, of which 79 were possibly relevant to the systematic review and retrieved. There was good agreement between reviewers (94% agreement, κ statistic=0.87; 95% confidence interval [CI], 0.71-0.94) when eligibility criteria were assessed and 39 studies were eligible. Three studies[36-38] reported on the precision of the clinical examination in evaluating organic vs functional dyspepsia. Eighteen studies[13-15,36,37,39-51] gave data on the accuracy of symptoms and signs that were extractable, and the majority of the remaining articles did not adequately separate organic from functional dyspepsia (TABLE 1 and TABLE 2 and FIGURE 1).

**Table 2.** Characteristics of Included Studies That Reported the Accuracy of the Computer Model in Diagnosing Organic Dyspepsia

| Source | Country | No. of Patients | Type of Patient | Setting | Exclusion Criteria | Assessors Blinded | Quality Level* |
|---|---|---|---|---|---|---|---|
| Talley et al,[47] 1993 | United States | 820 | Outpatients referred for upper GI endoscopy | Endoscopy unit from single teaching hospital | Consecutive sample excluding patients with previous gastric surgery and those referred for esophageal dilatation | Yes | 1 |
| Adang et al,[39] 1996 | The Netherlands | 1147 | With dyspepsia referred by PCP or hospital specialist | Unrestricted open-access endoscopy unit, single teaching hospital | Patients not completing questionnaire; having repeat or therapeutic endoscopy excluded | Unclear | 2 |
| Bytzer et al,[15] 1992 | Denmark | 878 | With dyspepsia referred by PCP | Open-access endoscopy unit, single teaching hospital | All consecutive patients except those with acute GI bleeding or previous gastric surgery | Yes | 1 |
| Johannessen et al,[46] 1990 | Norway | 930 | All outpatients referred for upper GI endoscopy; most referred by PCP | Single teaching hospital gastroenterology unit | All patients referred for endoscopy except upper GI bleeding, jaundice, acute abdomen, previous upper GI surgery, endoscopy in last 6 mo | Unclear | 2 |
| Mann et al,[13] 1983 | England | 235 | Referred directly from PCP | Single district hospital | Unclear whether consecutive patients recruited or whether any exclusion criteria | Unclear | 3 |
| Holdstock et al,[14] 1986 | England | 1279 | 439 Referred by PCP to open-access endoscopy service; 840 hospital outpatients | Endoscopy unit from single district hospital | Mixed group of patients referred from primary and secondary care; unclear whether consecutive; patients with gastric surgery or previous endoscopy excluded | Unclear | 2 |
| Hammer et al,[43] 2004 | Australia | 321 | Primarily referred by PCP but also by surgeons and internists | Single specialist gastroenterology practice | Consecutive patients included but 92 excluded because of missing data | Yes | 1 |
| Grace,[42] 2004 | Canada | 1037 | Consecutive patients with dyspepsia referred by PCP | 49 PCP practices referring to 39 gastroenterology units | 131 of 1171 patients refused or did not have endoscopy; exclusion criteria included documented upper GI pathology, previous GI surgery, previous endoscopy, *Helicobacter pylori* eradication in last 6 mo, severe concurrent disease, or use of proton pump inhibitor during last 30 d | Yes | 1 |
| Numans et al,[50] 1994 | The Netherlands | 861 | With dyspepsia referred for open-access endoscopy | 191 PCPs referring to single district open-access endoscopy unit | Consecutive patients excluding repeat endoscopy | Yes | 1 |
| Locke et al,[51] 2003 | United States | 1009 | Outpatients referred for endoscopy; described as primary, secondary, and tertiary care | Single teaching hospital endoscopy unit | 1009 of 1633 eligible patients included | Yes | 1 |

Abbreviations: GI, gastrointestinal; PCP, primary care physician.
*See "Box 2" for definition.

### Precision of Symptoms and Signs

The study by Heading et al[38] assessed the accuracy of clinicians in assessing upper gastrointestinal symptoms. A mock female patient was trained to consistently give 3 scenarios—an ulcer, reflux, and functional dyspepsia history. She randomly gave these histories to 27 primary care physicians; the κ statistic between the history the actor was meant to portray and the history recorded by the primary care physician was 0.57, indicating only modest agreement. The agreement between symptoms provided by the actor and recorded by the primary care physician was 78% for heartburn and 50% for epigastric pain. Two studies[36,37] reported the overall diagnoses reached by primary care physicians and gastroenterologists on the same group of patients with dyspepsia, although they did not report the data in terms of κ values or agreement on individual symptoms. One study[36] involving 100 patients (37% with organic disease) reported that the sensitivity for diagnosing organic disease was 95% for primary care physicians and 71% for the specialist. Conversely, the specificity was 23% for primary care physicians and 62% for the gastroenterologist. A second study[37] involving 347 patients (29% with organic disease) reported that sensitivity for diagnosing organic disease was 76% for primary care physicians and 72% for gastroenterologists, with a specificity of 37% and 59%, respectively.

### Accuracy of Symptoms and Signs

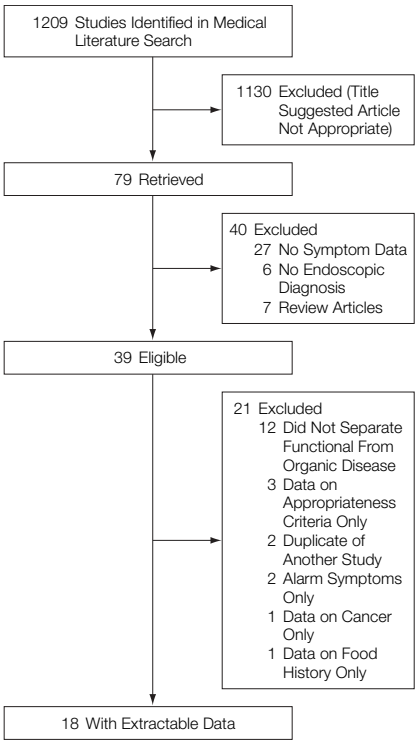
**Organic vs Functional Dyspepsia.** Fifteen studies[13-15,36,37,39-48] reported the accuracy of symptoms in distinguishing between organic and functional dyspepsia. A total of 11 366 patients were assessed, with 4817 patients (42%) classified as having organic dyspepsia.

*Primary Care Physicians.* Four studies[36,37,44,45] evaluating 1459 patients reported the accuracy of the primary care physician in diagnosing organic dyspepsia. The primary care physician and endoscopist made the diagnosis independently in 2 studies[37,45] and in 2 other studies[36,44] blinding was unclear, although all reported on consecutive patients. The overall number of patients with organic dyspepsia was 579 (40%); the sensitivity of the primary care physician varied between 67% and 95%, and the specificity between 25% and 52%. The summary positive LR was 1.3 (95% CI, 1.2-1.4; $P=.39$ for homogeneity) and the summary negative LR was 0.66 (95% CI, 0.55-0.79; $P=.23$ for homogeneity) (FIGURE 2). The study that reported a negative LR of 0.21 classified 82% patients as having organic dyspepsia, which resulted in a 95% sensitivity but a specificity of only 23%.[36] The clinical use of this assessment is unlikely to be helpful as the primary care physicians in this study classified most patients as having organic disease.

*Specialists.* Five studies[36,37,40,41,48] reported the accuracy of the specialist in diagnosing organic dyspepsia; 3707 patients were assessed, with 42% having organic dyspepsia overall. The clinician and endoscopist made blind evaluations in 3 studies[37,40,41]; in 1 study,[36] masking was unclear; and in 1 study,[48] the same clinician made both assessments and was therefore not masked. All studies enrolled consecutive patients. The sensitivity of the specialist in diagnosing organic dyspepsia varied between 59% and 86%, with a specificity of between 63% and 71%. The summary positive LR was 1.9 (95% CI, 1.5-2.5; $P<.001$ for homogeneity) and the summary negative LR was 0.40 (95% CI, 0.24-0.66; $P<.001$ for homogeneity) (Figure 2). The study that reported an LR of 0.24 was the only study in which the specialist made the clinical assessment and also performed the endoscopy.[48] The chance of bias in this study is increased and may explain the more accurate results.

*Computer Models.* Nine studies[13-15,39,40,42,43,46,47] reported the accuracy of computer models using data from questionnaires in diagnosing organic dyspepsia; 7148 patients were evaluated, with 43% having organic dyspepsia. The questionnaires were completed by a researcher or were self-administered. The endoscopist was blind to the results of the computer model and questionnaire data in 5 studies[15,40,42,43,47] and in 4 studies masking was unclear.[13,14,39,46] Six studies[15,40,42,43,46,47] enrolled consecutive patients. The models identified demographic factors, history of peptic ulcer disease, and various symptoms that were predictive of organic disease. One study[15] prospectively tested the model reported in a previous study.[14] The sensitivity of the models was between 60% and 99% and the specificity was between 17% and 80% (Table 1 and Table 2). The study that reported 99% sensitivity had only a 17% specificity.[43] The model allocating nearly all patients as having organic dyspepsia achieved the highest sensitivity and consequently gave a very low specificity and was of little clinical use. The summary positive LR for computer models was 1.6 (95% CI, 1.4-1.9; $P<.001$ for homogeneity) and the summary negative LR was 0.45 (95% CI, 0.37-0.55; $P<.001$ for homogeneity) (Figure 2).

**Figure 1.** Flow Diagram of the Studies Identified in the Systematic Review



*Comparison Between Approaches.* Despite statistical heterogeneity between primary care physicians, specialists, and computer models ($P<.001$ for the positive and negative LR), all methods gave clinically similar results; therefore, data were combined. In studies that reported the accuracy of more than 1 method, the most accurate assessment was selected. When the primary care physician, specialist, or computer assessed the patient as having organic dyspepsia, the summary LR was 1.6 (95% CI, 1.4-1.8). When the primary care physician, specialist, or computer assessed the patient as having functional dyspepsia, the summary LR was 0.46 (95% CI, 0.38-0.55). The pooled DOR was 4.0 (95% CI, 2.8-5.7; heterogeneity $\chi^2_{14}=190$; $P<.001$).

**Peptic Ulcer Disease.** Eleven studies* reported the accuracy of clinical examination in 8802 patients, with 1502 patients (17%) having peptic ulcer disease.

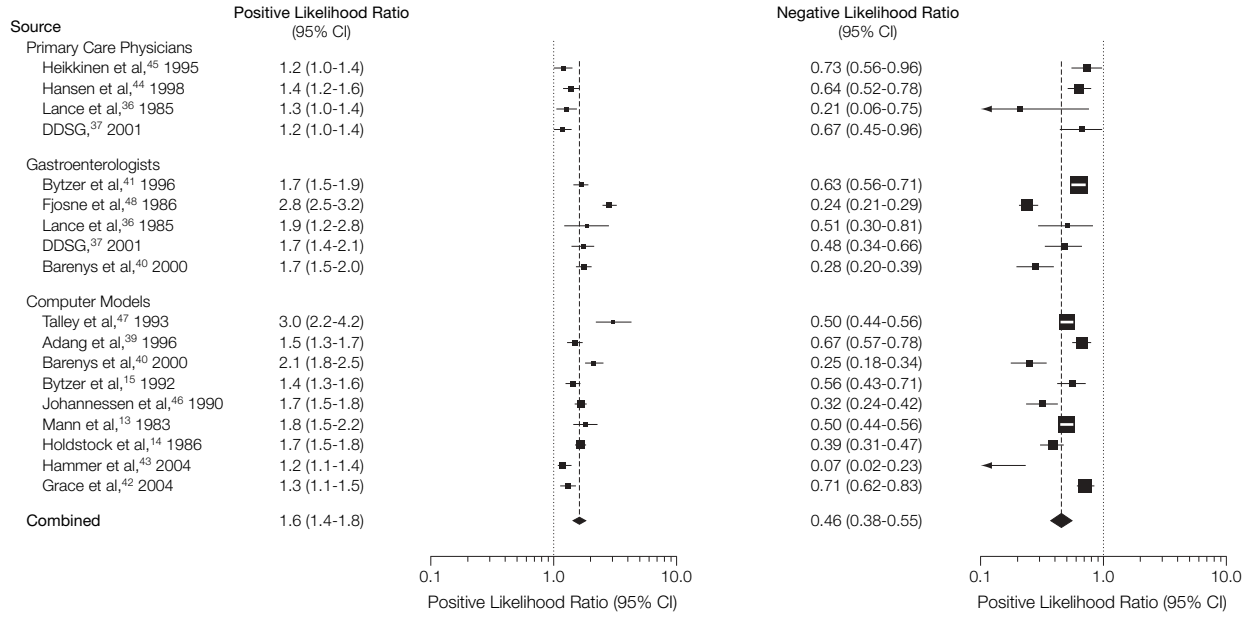
*Clinical Diagnosis.* Six studies[37,40,41,44,45,48] assessed the clinical diagnosis of peptic ulcer disease in 4619 patients, with 820 patients (18%) having peptic ulcer disease. All studies recruited consecutive patients, and clinical opinion and endoscopy assessment were made independently in 4 studies.[37,40,41,45] Three studies[40,41,48] reported the accuracy of a specialist opinion, 2 studies[44,45] gave the accuracy of the primary care physician, and 1 study[37] reported on both. The sensitivity of a clinical diagnosis was between 37% and 65%, and the specificity was between 37% and 84%. The positive LRs of specialist opinion (summary positive LR, 2.9; 95% CI, 2.1-4.0; $P<.001$ for homogeneity) appeared slightly better than primary care physician (summary positive LR, 2.2; 95% CI, 1.8-2.5; $P=.95$ for homogeneity) (FIGURE 3). The study reporting the most positive LR was the only study in which the clinician making the diagnosis was also the specialist performing the endoscopy.[48] Negative LRs of both primary care physicians and specialists were clinically similar (primary care physicians: summary negative LR, 0.63; 95% CI, 0.51-0.79; $P=.10$ for homogeneity; and specialists: summary negative LR, 0.48; 95% CI, 0.43-0.52; $P=.72$ for homogeneity) (Figure 3).

*Computer Models.* Six studies[13-15,40,46,50] with 4684 patients evaluated the diagnostic accuracy of computer models; 802 patients (17%) had peptic ulcer disease. Four studies[15,40,46,50] recruited consecutive patients, and a blinded assessment of the diagnosis was made in 3 studies.[15,40,50] The sensitivities of the models varied between 70% and 90%, with specificities between 47% and 74%. The summary positive LR was 1.9 (95% CI, 1.6-2.3; $P<.001$ for homogeneity) and the summary negative LR was 0.34 (95% CI, 0.25-0.47; $P<.001$ for homogeneity) (Figure 3). In the study with a negative LR of 0.19,[46] it was unclear whether the endoscopist was masked to the result of the model.

*Comparison Between Approaches.* Despite statistical heterogeneity between primary care physicians, specialists, and computer models, the approaches all gave clinically similarly results for peptic ulcer disease; therefore, data were combined. When the primary care phy-

*References 13-15, 37, 40, 41, 44-46, 48, 50.

**Figure 2.** Positive and Negative Likelihood Ratios of Different Approaches to Diagnosing an Organic Cause of Dyspepsia




CI indicates confidence interval; DDSG, Danish Dyspepsia Study Group. Each square represents an individual study. The size of the square is a measure of the size of the study and the horizontal line through the square indicates a graphical representation of the 95% CI of that study. For the combined analysis, the diamond and vertical dashed line indicate the pooled positive or negative likelihood ratio, with the left and right ends of the diamond indicating the pooled 95% CI.

sician, specialist, or computer model assessed the patient as having peptic ulcer disease, the summary LR was 2.2 (95% CI, 1.9-2.6), and when the primary care physician, specialist, or computer model assessed the patient as not having peptic ulcer disease, the summary LR was 0.45 (95% CI, 0.38-0.53). The pooled DOR was 5.2 (95% CI, 3.8-7.2; heterogeneity $\chi^2_{10}=56$; $P<.001$).

**Esophagitis.** Twelve studies† reported the accuracy of clinical examination in 9642 patients, of whom 1744 patients (18%) had esophagitis.

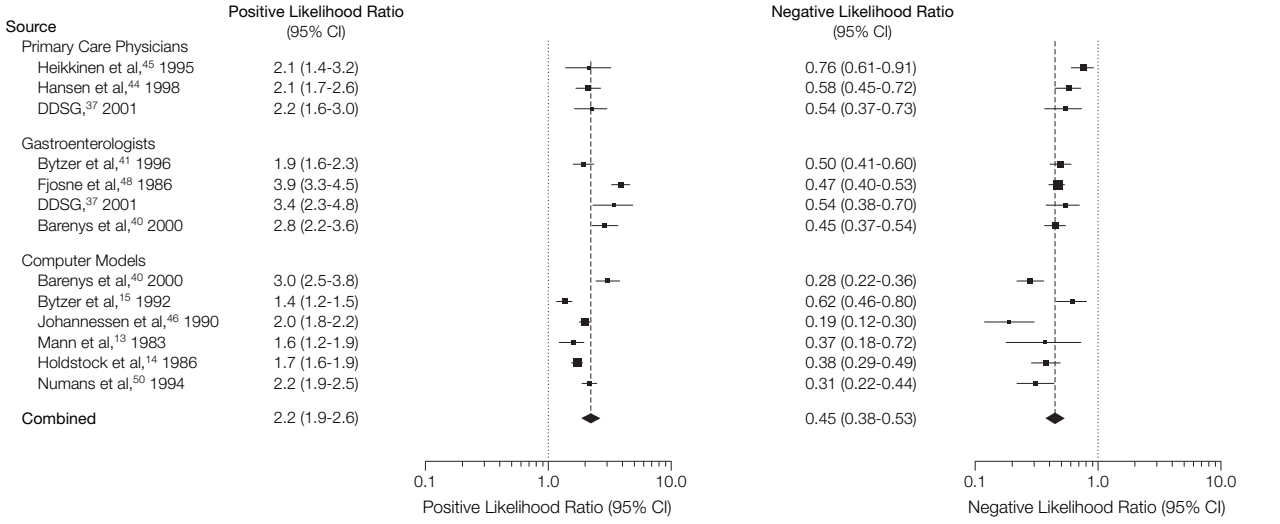
*Clinical Diagnosis.* Seven studies[37,40,41,44,45,48,49] assessed the accuracy of clinical opinion in diagnosing esophagitis. A total of 5134 patients were included, with 894 patients (17%) having esophagitis. Three studies[44,45,49] evaluated the accuracy of the primary care physician, 3 studies[40,41,48] evaluated the accuracy of the specialist, and 1 study[37] evaluated the accuracy of both in diagnosing esophagitis. All studies recruited consecutive patients; 5 studies[37,40,41,45,49] reported masking of the clinician and endoscopist; in 1 study,[44] it was not clear; and in 1 study,[48] the endoscopist also made the clinical diagnosis. The sensitivity of clinical opinion in diagnosing esophagitis varied between 30% and 76%, with specificity between 62% and 96%. Except for 1 study in which the clinician making the diagnosis also endoscoped the patient (FIGURE 4),[48] the positive LRs for a clinical diagnosis of esophagitis were similar for primary care physicians (summary positive LR, 2.3; 95% CI, 1.6-3.2; $P<.001$ for homogeneity) and gastroenterologists (summary positive LR, 4.5; 95% CI, 2.3-8.9). When the study that may have involved specialist's diagnostic suspicion bias was eliminated,[48] the summary positive LR for specialists was similar to that for primary care physicians (summary positive LR, 3.0; 95% CI, 2.6-3.5). A clinical diagnosis that esophagitis was absent had a similar range across physician type (primary care physicians: summary negative LR, 0.58; 95% CI, 0.43-0.79; and specialists: summary negative LR, 0.48; 95% CI, 0.35-0.65).

*Computer Models.* Computer models were used to diagnose esophagitis in 7 studies[13,14,40,42,46,49,51] evaluating 5506 patients, with 1133 patients (21%) with esophagitis. Four studies[40,42,49,51] reported that the endoscopist was masked, in 3 studies[13,14,46] masking was unclear, and 5 studies[40,42,46,49,51] recruited consecutive patients. Sensitivities varied between 50% and 82%, with specificities between 50% and 75%. The summary positive LR was 1.7 (95% CI, 1.5-2.1) and appeared worse than that achieved by clinical opinion, although the negative LRs had a summary LR of 0.48 (95% CI, 0.36-0.63) that overlapped the negative LR for clinical opinions (Figure 4).

*Comparison Between Approaches.* As for organic dyspepsia and peptic ulcer disease, comparisons were statistically heterogeneous but clinically similar; therefore, data were combined. When the primary care physician, specialist, or computer model assessed the patient as having esophagitis, the summary LR was 2.4 (95% CI, 1.9-3.0), and when the primary care physician, specialist, or computer model assessed the patient as not having esophagitis, the summary LR was 0.50 (95% CI, 0.42-0.60). The DOR was pooled for clinical opinion alone, because this appeared to perform bet-

†References 13, 14, 37, 40-42, 44-46, 48, 49, 51.

**Figure 3.** Positive and Negative Likelihood Ratios of Different Approaches to Diagnosing Peptic Ulcer Disease




CI indicates confidence interval; DDSG, Danish Dyspepsia Study Group. Each square represents an individual study. The size of the square is a measure of the size of the study and the horizontal line through the square indicates a graphical representation of the 95% CI of that study. For the combined analysis, the diamond and vertical dashed line indicate the pooled positive or negative likelihood ratio, with the left and right ends of the diamond indicating the pooled 95% CI.

ter than computer models in diagnosing esophagitis. The pooled DOR was 6.7 (95% CI, 3.7-12.0; heterogeneity $\chi^2_6$=76; $P$<.001).

## SCENARIO RESOLUTION

Although the history presented few clues as to the nature of the patient's dyspepsia, the clinical history must be obtained to address the concerns that led her to consult her physician. For example, she may be concerned about ischemic heart disease because her father died of a myocardial infarction. The patient is young and has no alarm features; therefore, the risk of upper gastrointestinal malignancy is low and endoscopy is not appropriate at this stage.[9-11] If she remained symptomatic or had been older, endoscopy would be helpful given the limited value of the clinical examination.[10]

## THE BOTTOM LINE

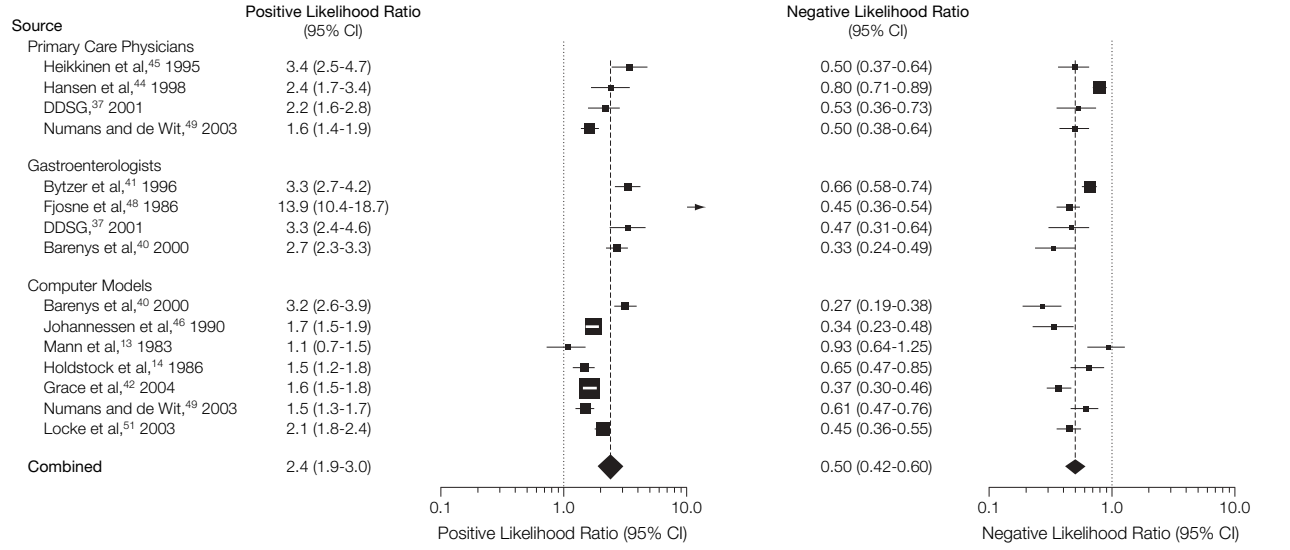
These data suggest that the diagnosis based on symptoms assessed by a primary care physician, specialist, or a computer model from patient questionnaires are of limited use in distinguishing between organic and functional dyspepsia. In most cases, the positive and negative LRs were statistically significantly different from unity; therefore, clinical opinion performs better than chance at diagnosing organic upper gastrointestinal disease. The computer models used patient demographics, risk factors, history items, and symptoms collected from patient questionnaires, but the models did not appear to perform any better than a clinician. There was a suggestion that the specialist had a greater diagnostic accuracy than the primary care physician because of improved positive LRs, but the difference was small and of doubtful clinical significance. Similar outcomes occurred for peptic ulcer disease and esophagitis.

Approximately 50% of patients with GERD have endoscopically negative disease.[52] These patients may have been misclassified as having functional dyspepsia; therefore, the accuracy of clinical features in distinguishing between organic and functional dyspepsia may be slightly higher than estimated. Misclassification bias probably has a greater impact on the accuracy of symptoms in diagnosing GERD, although it should have no influence over the accuracy of peptic ulcer disease diagnosis. There is no criterion standard for measuring GERD, although response to proton pump inhibitors may be useful in primary care and 24-hour pH can improve accuracy in secondary care. One study[45] included 24-hour pH studies for patients with heartburn and a normal endoscopy; this did not show any improvement in sensitivity and specificity or LRs. Furthermore, the presence of esophagitis at endoscopy is highly specific for GERD and the sensitivities for clinical opinion were modest. This suggests the history has a relatively poor sensitivity in diagnosing GERD.

Whether minor mucosal pathology represents disease or functional dyspepsia remains controversial and has been inconsistently defined in most prior clinical studies of this disorder. Most patients with organic disease in the studies included in this systematic review had esophagitis, benign esophageal stricture, Barrett esophagus, peptic ulcer disease, or upper gastrointestinal malignancy.

The accuracy of computer models to diagnose peptic ulcer disease and

**Figure 4.** Positive and Negative Likelihood Ratios of Different Approaches to Diagnosing Esophagitis




CI indicates confidence interval; DDSG, Danish Dyspepsia Study Group. Each square represents an individual study. The size of the square is a measure of the size of the study and the horizontal line through the square indicates a graphical representation of the 95% CI of that study. For the combined analysis, the diamond and vertical dashed line indicate the pooled positive or negative likelihood ratio, with the left and right ends of the diamond indicating the pooled 95% CI.

esophagitis may be underestimated because these models were usually constructed to distinguish between functional and organic disease rather than peptic ulcer disease or esophagitis. However, given their accuracy in predicting functional dyspepsia, they are unlikely to perform better than clinical opinion.

Referring clinicians could be highly accurate at identifying patients without serious disease, selecting only the most diagnostically difficult patients for a gastroenterologist's evaluation. For example, primary care physicians might preferentially refer patients with a confusing history or whose symptoms do not respond to empirical treatment. The net effect of such a referral pattern ought to be a reduction in the diagnostic accuracy of the gastroenterologist. Most of the studies do indeed come from a referred population of patients. Fortunately, 3 studies[36,44,45] originate in a generalist's setting and attempted to include all patients presenting to their primary care physician with dyspepsia. These studies of consecutive patients with dyspepsia are the most relevant for primary care physicians and show positive and negative LR results that are not clinically different from the studies that included only patients referred to a gastroenterologist. This suggests that referral bias is unlikely to be the sole explanation of the poor performance of gastroenterologists in distinguishing organic from functional upper gastrointestinal disease.

A clinical history remains important in patients presenting with dyspepsia. The clinician needs to establish that the symptoms are arising from the upper gastrointestinal tract by determining the location of the epigastric pain or discomfort and establishing that the history does not suggest other disorders, such as angina or irritable bowel syndrome. Endoscopy is not required for all patients with dyspepsia. The reason for consultation also needs to be explored so that patient concerns about possible ischemic heart disease or cancer can be addressed. Nevertheless, these results point to the diagnostic difficulty of identifying functional dyspepsia, peptic ulcer disease, and esophagitis. How this relates to the management of dyspepsia is beyond the scope of this article. Most guidelines agree, however, that young patients with dyspepsia and no alarm features can be managed with empirical acid suppression therapy or testing, and treating *H pylori* and endoscopy is not indicated.[9-11] Future research should evaluate whether adding response to interventions, such as acid suppression to the clinical history, improves diagnostic accuracy across a broad spectrum of patients. Unfortunately, current data suggest that a patient's dyspeptic symptoms appear inefficient for diagnosing the presence or absence of disease, even when the symptoms are modeled in a computer analysis or assessed by a gastroenterologist.

**Author Contributions:** Dr Moayyedi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Moayyedi, Talley, Fennerty, Vakil.
*Acquisition of data:* Moayyedi.
*Analysis and interpretation of data:* Moayyedi, Talley, Fennerty, Vakil.
*Drafting of the manuscript:* Moayyedi, Fennerty, Vakil.
*Critical revision of the manuscript for important intellectual content:* Moayyedi, Talley, Fennerty, Vakil.
*Statistical analysis:* Moayyedi.
*Obtained funding:* Fennerty.
*Administrative, technical, or material support:* Moayyedi, Fennerty, Vakil.
*Study supervision:* Talley, Fennerty.
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In every work of genius we recognize our own rejected thoughts; they come back to us with a certain alienated majesty.
—Ralph Waldo Emerson (1803-1882)

 