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Published diagnostic models safely excluded colorectal cancer in an independent primary care validation study

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Abstract

Objective: To validate published diagnostic models for their ability to safely reduce unnecessary endoscopy referrals in primary care patients suspected of significant colorectal disease.

Study Design and Setting: Following a systematic literature search, we independently validated the identified diagnostic models in a cross-sectional study of 810 Dutch primary care patients with persistent lower abdominal complaints referred for endoscopy. We estimated diagnostic accuracy measures for colorectal cancer ($N = 37$) and significant colorectal disease ($N = 141$; including colorectal cancer, inflammatory bowel disease, diverticulitis, or >1-cm adenomas).

Results: We evaluated 18 models—12 specific for colorectal cancer—, of which most were able to safely rule out colorectal cancer: the best model (National Institute for Health and Care Excellence−1) prevented 59% of referrals (95% confidence interval [CI]: 56−63%), with 96% sensitivity (95% CI: 83−100%), 100% negative predictive value (NPV; 95% CI: 99−100%), and an area under the receiver operating characteristics curve (AUC) of 0.86 (95% CI: 0.80−0.92). The models performed less for significant colorectal disease: the best model (Brazer) prevented 23% of referrals (95% CI: 20−26%), with 95% sensitivity (95% CI: 90−98%), 96% NPV (95% CI: 92−98%), and an AUC of 0.73 (95% CI: 0.69−0.78).

Conclusion: Most models safely excluded colorectal cancer in many primary care patients with lower gastrointestinal complaints referred for endoscopy. Models performed less well for significant colorectal disease.

Keywords: Systematic review; Validation; Primary care; Colorectal cancer; Significant colorectal disease; Diagnosis

1. Introduction

The symptoms and signs of significant colorectal disease—including colorectal cancer, inflammatory bowel disease, adenomas, and diverticulitis—and functional disorders as irritable bowel syndrome overlap substantially. Excluding significant colorectal disease is therefore challenging in primary care, where patients with lower abdominal complaints are common. As primary care physicians aim to not miss or delay a significant colorectal disease diagnosis, the implicit threshold for endoscopy—necessary for diagnosing significant colorectal disease [1,2]—is low. Consequently, many patients are currently referred, whereas only about one-fifth to one-third actually have significant colorectal disease [3–6]. As endoscopy units have increasingly limited capacity and as endoscopy is a relatively costly procedure with a (small) risk of serious complications, increasing the number of primary care patients in whom significant colorectal disease can safely be excluded without referral would be very valuable.

Tools to help primary care physicians better identify patients in whom endoscopy can safely be omitted are therefore

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What is new?

Key findings

- We identified and externally validated 18 published diagnostic models and found that most models could safely exclude colorectal cancer in primary care patients with lower gastrointestinal complaints.
- Models performed less well for excluding significant colorectal disease.

What this adds to what was known?

- This is the first systematic review and external validation study of colorectal cancer and significant colorectal disease diagnostic models in primary care.

What is the implication and what should change now?

- These models may act as a decision support tool in primary care, making the diagnostic work-up more efficient.

needed. Individual symptoms and signs cannot accomplish this [7–10], and many diagnostic models for colorectal cancer and significant colorectal disease considering multiple variables together have therefore been developed over the years (e.g., [11–14]). Such models can help exclude significant colorectal disease and prevent unnecessary endoscopy referrals from primary care, but few have been validated and none have led to widespread implementation.

External validation—that is, in patients not included in model development—is essential before implementation of diagnostic models [15]. We therefore aimed to identify—by a systematic literature search—and externally validate diagnostic models that can help exclude significant colorectal disease/colorectal cancer in primary care and thus prevent unnecessary endoscopy referrals. For external validation, we used the large prospective Cost-Effectiveness of a Decision rule for Abdominal complaints in primary caRe (CEDAR) study [16]. The CEDAR study represents primary care patients at intermediate significant colorectal disease suspicion—that is, too high to not refer but not high enough for urgent referral—where diagnosis is most challenging and a diagnostic tool will be most relevant.

2. Methods

2.1. Systematic literature search

We searched MEDLINE for diagnostic models for significant colorectal disease, colorectal cancer, inflammatory bowel disease, or irritable bowel syndrome through July 31, 2015. We focused on studies from the Western World (i.e., Europe, North America, or Australia) as these best reflect the target population and setting of our clinical research question. A modified Ingui filter [17,18] was used to identify diagnostic models, including scoring systems or diagnostic criteria, with $\geq$ 3 predictors (see Supplementary Methods for search query). Two reviewers (L.K. and S.G.E.) independently appraised all title and abstracts, and models were selected after full-text screening if regression coefficients or odds ratios were provided, or if any kind of decision rule was presented (all named "models" in this article). When in doubt, a third reviewer (K.G.M.M.) was consulted. Models containing variables that were not available in CEDAR were excluded. We only included cross-sectional studies, excluding those predicting future colorectal cancer or significant colorectal disease (e.g., [19–21]). We evaluated the most recent model if multiple versions were published, but only if this version did not limit the generalizability by focusing on a particular population such as an ethnic minority (e.g., for Adelstein we evaluated the 2011 instead of the 2010 publication [22,23], and for the CAPER model, we evaluated the 2011 instead of the 2005 or 2009 version [8,14,24]).

2.2. The CEDAR study

The CEDAR study is a prospective cross-sectional diagnostic primary care study. The University Medical Center Utrecht ethics committee approved the study (protocol 08-462E). Briefly, significant colorectal disease suspected patients referred to three large endoscopy centers by one of 266 participating Dutch primary care practices were eligible. Inclusion criteria were lower abdominal complaints for at least 2 weeks in combination with rectal bleeding, change in bowel habit, abdominal pain, fever, diarrhea, weight loss, a sudden onset in the elderly, and/or physical examination findings suggestive of significant colorectal disease. Trained research nurses evaluated a pre-endoscopy fecal sample using a point-of-care fecal immunochemical test (Clearview iFOBT one-step fecal occult blood test device, Alere Health). All participants signed informed consent following recruitment at the primary care practice (19%) or directly following endoscopy scheduling (81%). Following recruitment, a blood sample was drawn and patients and primary care physicians filled in questionnaires about signs and symptoms (going back up to 6 months). We approached every *n*th referred patient if referral volume exceeded study resources to maintain a representative study population. Gender and age distribution of participating and nonparticipating patients were comparable, and baseline characteristics reflect primary care patients at intermediate suspicion of significant colorectal disease (for more details: [16]).

The reference standard consisted of colonoscopy (94%) or sigmoidoscopy (4%) performed by experienced gastroenterologists, or abdominal ultrasound or barium enema