Appropriateness of colonoscopy in Europe (EPAGE II)
Chronic diarrhea and known inflammatory bowel disease

Authors   S. Schusselé Filliettaz[1], P. Juillerat[2], B. Burnand[1], C. Arditi[1], A. Windsor[3], C. Beglinger[4], R. W. Dubois[5], I. Peytremann-Bridevaux[1], V. Pittet[1], J.-J. Gonvers[2], F. Froehlich[2,4], J.-P. Vader[1] and the EPAGE II Study Group[6]

Institutions   Institutions are listed at the end of article.

Corresponding author
J.-P. Vader, MD MPH
Institute of Social and
Preventive Medicine
Rue du Bugnon 17
CH-1005 Lausanne
Switzerland
Fax: +41-21-3144954
john-paul.vader@chuv.ch

Background and study aims: To summarize the published literature on assessment of appropriateness of colonoscopy for investigation of chronic diarrhea, management of patients with known inflammatory bowel disease (IBD), and for colorectal cancer (CRC) surveillance in such patients, and to report report appropriateness criteria developed by an expert panel, the 2008 European Panel on the Appropriateness of Gastrointestinal Endoscopy, EPAGE II.

Methods: A systematic search of guidelines, systematic reviews, and primary studies regarding the evaluation of chronic diarrhea, the management of IBD, and colorectal cancer surveillance in IBD was performed. The RAND/UCLA Appropriateness Method was applied to develop appropriateness criteria for colonoscopy for these conditions.

Results: According to the literature, colonoscopic evaluation may be justified for patients aged > 50 years with recent-onset chronic diarrhea or with alarm symptoms. Surveillance colonoscopy for CRC should be offered to all patients with exten-

sive ulcerative colitis or colonic Crohn's disease of 8 years' duration, and to all patients with less extensive disease of 15 years' duration. Intervals for surveillance colonoscopy depend on duration of evolution, initial diagnosis, and histological findings. The EPAGE II criteria also confirmed the appropriateness of diagnostic colonoscopy for diarrhea of > 4 weeks' duration. They also suggest that, in addition to assessing extent of IBD by colonoscopy, further colonoscopic examination is appropriate in the face of persistent or worsening symptoms. Surveillance colonoscopy in IBD patients was generally appropriate after a lapse of 2 years. In the presence of dysplasia at previous colonoscopy, it was not only appropriate but necessary.

Conclusions: Despite or perhaps because of the limitations of the available published studies, the panel-based EPAGE II (http://www.epage.ch) criteria can help guide appropriate colonoscopy use in the absence of strong evidence from the literature.

Introduction
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Chronic diarrhea

Chronic diarrhea is defined by a duration of > 4 weeks and > 3 loose stools/day [1]. Chronic diarrhea can have organic as well as functional causes. The most frequent organic origins identified in these patients include inflammatory bowel disease (IBD) (7 % – 14 %), infectious causes (11 % – 15 %), malabsorption (3 % – 5 %), and drug use (4 % – 10 %) [2 – 4].

Known inflammatory bowel disease

Ulcerative colitis is characterized by diffuse continuous mucosal inflammation limited to the colon. The main symptom of ulcerative colitis is bloody diarrhea [5,6]. Based upon clinical and endoscopic findings, ulcerative colitis is character-

ized as to its severity and extent [5 – 8]. Symptoms of Crohn's disease are heterogeneous, commonly including diarrhea [5,9]. Crohn's disease encompasses a spectrum of clinical and pathological patterns manifested by inflammation affecting various sites in the gastrointestinal tract with the potential for systemic and extraintestinal complications [5,10]. Crohn's disease may be defined by location, by pattern of disease, by disease activity, by response to therapy, and by immunological features (see the Vienna and Montreal classifications) [9,11 – 16].

Diagnosis of IBD mainly relies on symptoms and is then confirmed by clinical evaluation and a combination of investigations, including endoscopy [6,9,10,17,18]. Until recently, complications of bowel ulceration prompted treatment and/or surgery, thus inducing temporary clinical remission.

New biological treatments now aim at halting the progression of the disease and at attaining complete mucosal healing as well as clinical remission. Therapeutic approaches to IBD are presented in a companion article [19].

Long-standing ulcerative colitis and Crohn's disease are associated with development of colorectal dysplasia and cancer, but the exact magnitude of the risk is not clearly defined [20–32] (see also Results section *Surveillance colonoscopy in known IBD*). Recent studies suggest that colorectal cancer (CRC) in IBD may be less frequent than was previously believed. This could partly be due to effective therapy and prevention strategies [33,34]. The main established risk factors for CRC in IBD include prolonged disease duration [23,35], extensive colonic involvement [36], and family history of CRC [37]. The macroscopic features of intraepithelial neoplasia are heterogeneous, ranging from flat to plaque-like and mass or polypoid lesions ("dysplasia-associated lesion or mass [DALM]") to strictures. Overall, 60%–70% of these lesions are visible during conventional colonoscopy. The evolution of low-grade dysplasia is still unclear [31,41–44]. Although colonoscopic surveillance programs are available, ulcerative colitis or Crohn's colitis are situations in which the optimal method of prevention of cancer-related mortality is still unclear [45,46].

In April 2008, a multidisciplinary European expert panel convened in Montreux, Switzerland, to discuss and develop criteria for the appropriate use of colonoscopy. This article presents the literature review, on the use of colonoscopy, in chronic diarrhea, known IBD, and surveillance for CRC in IBD patients, that was provided to the panelists before the panel meeting to support their ratings of appropriateness of use of colonoscopy in such circumstances, which are also reported here. It is an update of a previous literature review and appropriateness criteria published in 1999 [47,48].

In the first topic of this article, uncomplicated chronic diarrhea will be considered. In this context, "uncomplicated" is taken to mean that an infectious or malabsorption origin or laxative abuse has been excluded. The patients considered for colonoscopic evaluation in this context would also have no risk factor for CRC, except for age, and none of the following so-called alarm or "red flag" symptoms: hematochezia; positive fecal occult blood test (FOBT); anemia; personal/family history of colon cancer; personal/family history of inflammatory bowel disease; weight loss of ≥ 5 kg; fever; abdominal mass; or HIV/AIDS [49]. In the second topic treated in this article, the use of colonoscopy for management and follow-up of known IBD (i.e., ulcerative colitis and Crohn's disease), as well as the evaluation of strictures and CRC surveillance in ulcerative colitis and Crohn's disease, will be reviewed. Initial diagnosis of IBD will not specifically be addressed: patients presenting symptoms suggestive of IBD but not yet diagnosed are dealt with under the previous topic of chronic diarrhea.

Methods
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The literature review process included a systematic search of websites issuing guidelines and of Medline (1997–February 2008) to select published guidelines, systematic reviews, and primary studies assessing the use of colonoscopy in patients with chronic diarrhea and in known IBD. With the exception of certain relevant articles, the literature published before 1997 is presented in the previous literature review [47,48].

The application of the RAND/UCLA Appropriateness Method is described in a companion article in this issue [50]. Briefly, the RAND process is a formal explicit expert panel method that allows classification of each indication into one of the following categories of appropriateness: inappropriate, uncertain, appropriate, and both appropriate and necessary (i.e. the indication mandates colonoscopy). To simplify the graphical presentation of the appropriateness results, these four categories were consolidated into two clusters: "Appropriate" (comprising the two categories appropriate and appropriate and necessary) and "Not appropriate" (comprising categories inappropriate and uncertain). In addition to simplification and enhanced clarity of presentation, the rationale for this choice was that in many instances in the case of a nonappropriate scenario, whether it be uncertain or inappropriate, the decision for not proposing the colonoscopy should be specifically discussed and shared with the patient. All clinical indications and their ratings are available on the EPAGE website (www.epage.ch).

Results: Literature review
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Chronic diarrhea
A total of 18 primary studies investigating the diagnostic yield of colonoscopy in patients presenting chronic diarrhea and published between 1997 and February 2008 were identified. Nine guidelines published over the same period and giving recommendations on the use of colonoscopy for diagnostic purposes in these patients were retrieved.

Primary studies [51–68] investigating the diagnostic yield of lower gastrointestinal endoscopy in chronic diarrhea (**Table e1**) show wide variation in rates, with findings ranging from 15% up to 70% of the cases. Microscopic colitis [64,69] (both collagenous colitis and lymphocytic colitis) was diagnosed in 10%–14% of patients investigated endoscopically for chronic diarrhea. Guidelines [1,2,70–74] (**Table e2**) offer no clear consensus on the appropriateness of endoscopic procedures in chronic diarrhea. If an endoscopic procedure is performed, it is not clear whether the initial procedure should be sigmoidoscopy or colonoscopy, although some guidelines clearly recommend colonoscopy at > 50 years of age [70]. In the event of an endoscopic investigation, multiple biopsies should be taken – including in the ileum, except when the latter is macroscopically normal – but there is no clear consensus on their exact location and on the number of biopsies to be taken. There seems to be a trend towards the taking of multiple biopsies, ideally in the descending colon, especially when looking for microscopic colitis [69,75].

Practitioners might consider performing colonoscopy in the presence of chronic diarrhea mainly with the aim of excluding CRC. In the retrieved primary studies [76–78] (**Table e3**), chronic diarrhea does not appear to constitute an indicator or a risk factor for colonic neoplasia. Some CRC screening/surveillance guidelines [70,71,74] do cite diarrhea as a possible symptom which might indicate CRC, while the majority of the retrieved screening/surveillance guidelines do not even mention diarrhea[79–88] . Only the French guidelines from ANAES (Agence Nationale d'Accréditation et d'Evaluation en Santé) [70] recommend that, for patients with diarrhea of recent onset and unresponsive to treatment, a total colonoscopy be performed to identify a potential colonic neoplasm if symptoms appear in an individual > 50 years of age, or if symptoms appear at younger than < 50 years of age and if symptomatic treatment is not effective.

Table 8   Definitions related to chronic diarrhea, evaluation of known ulcerative colitis or Crohn's disease, and to surveillance for colorectal cancer in inflammatory bowel disease.

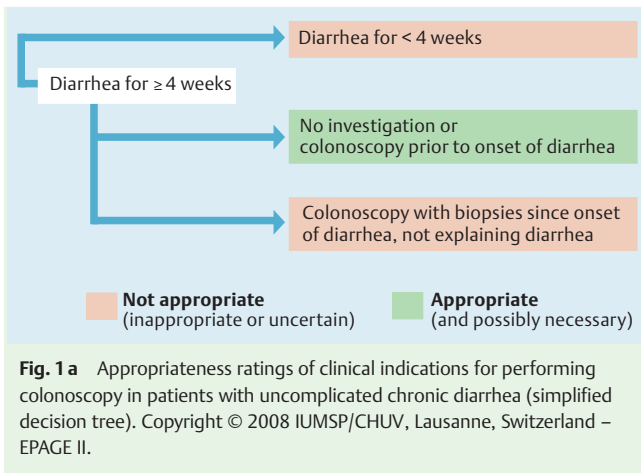|	Term	Definition
Chronic diarrhea	Uncomplicated diarrhea	Diarrhea with one or more of the following: > 3 loose stools/day, infectious or malabsorption origin excluded, without known IBD, no anemia, no bleeding, no risk factors for CRC, no HIV/AIDS, chronic diarrhea ≥ 4 weeks' duration
	Infection work-up	Stool culture for enteric pathogens and examination for ova and parasites, immunoassay for *Clostridium difficile* toxin if patient was taking antibiotics within 2 weeks prior to onset of diarrhea
	Lower gastrointestinal investigations	Sigmoidoscopy or barium enema since onset of lower abdominal pain or within past 5 years
	Barium enema	Double-contrast technique (in some countries barium enema may still be used widely, in particular in patients with nonspecific abdominal symptoms)
	Sigmoidoscopy	Flexible tube (60cm)
Known ulcerative colitis	Ulcerative colitis	Documented by one or more of the following: endoscopic appearance, mucosal biopsy, operative report with pathology AND infectious cause excluded
	Extension of ulcerative colitis	Evaluation of the extension of the disease (proctitis, pancolitis, left-sided colitis) with no previous colonoscopy done
	Previous investigation	Sigmoidoscopy performed within the last 3 months and since symptoms began, recurred or worsened.
	Sigmoidoscopy	Flexible tube (60 cm)
	Current therapy	Daily treatment for at least 14 days with one or more of the following: 5-aminosalicylic acid (5-ASA; enema, suppositories or oral), sulfasalazine, topical steroids OR daily prednisone for at least 2 weeks OR daily treatment with one of the following for at least 60 days: azathioprine, cyclosporin, 6-mercaptopurine (6-MP), methotrexate, tacrolimus, infliximab.
Known Crohn's disease	Crohn's disease	Documented by one or more of the following: endoscopic appearance, mucosal biopsy, radiography, operative report with pathology AND infectious cause excluded
	Extension of Crohn's disease	Evaluation of the extension of the disease with no previous colonoscopy done.
	Previous investigation	Small-bowel follow-through (SBFT) or entero-CT/MRI (computed tomography/magnetic resonance imaging) performed within the last 3 months and since symptoms began, recurred or worsened
	Current therapy	Daily treatment for at least 14 days with one or more of the following: 5-ASA (enema, suppositories or oral), sulfasalazine, or topical steroids OR daily prednisone or budesonide for at least 2 weeks OR daily treatment with one of the following for at least 60 days: azathioprine, cyclosporine, 6-MP, tacrolimus, methotrexate, anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, certolizumab).
Surveillance for colorectal cancer (CRC) in inflammatory bowel disease (IBD)	Ulcerative colitis	Documented by one or more of the following: endoscopic appearance, mucosal biopsy, operative report with pathology AND infectious cause excluded
	Crohn's disease	Documented by one or more of the following: endoscopic appearance, mucosal biopsy, radiography, operative report with pathology AND infectious cause excluded
	Low-grade dysplasia	Low degree of a combination of architectural and cytological alterations such as gross distortion, hyperchromasia, enlarged nuclei, large nucleoli, loss of cellular polarity confined within the basement membrane of the glands in which it arose
	High-grade dysplasia	High degree of architectural and cytological alterations

Known inflammatory bowel disease (IBD)

Nine guidelines on the use of colonoscopy for clinical management of patients with known IBD and published between 1997 and February 2008 were identified. For the same period, 19 guidelines were retrieved on the use of colonoscopy for surveillance for CRC in these patients.

Colonoscopy in clinical management in known IBD. Guidelines [5, 6, 9, 10, 18, 89 – 92] issuing recommendations on the use of colonoscopy for clinical management purposes (surveillance excluded) in known ulcerative colitis and Crohn's disease are presented in **Table e4** and **Table e5**. In management of known ulcerative colitis, sigmoidoscopic rather than colonoscopic evaluation may be used to define disease activity or assess superimposed colitis. However, the appropriateness of this detection mode depends upon the evolution of the disease and on the potential con-

sequences in terms of therapeutic approach. A colonoscopy is useful in the elective preoperative phase. Management of known Crohn's disease does not systematically require colonoscopic procedures, either for evaluation of treatment, or after a new relapse. Colonoscopic procedures are useful for the examination or for the management of short accessible strictures and of bleeding; a colonoscopy is useful in the elective preoperative phase.

Surveillance colonoscopy in known IBD. According to the retrieved guidelines [5, 6, 9, 18, 21, 70, 73, 80, 81, 83, 88 – 91, 93 – 97] (**Table e6**), surveillance colonoscopy should be offered:

▶ to all patients with extensive ulcerative colitis or colonic Crohn's disease of 8 years' duration;

▶ to all patients with less extensive disease of 15 years' duration;

Fig. 1a Appropriateness ratings of clinical indications for performing colonoscopy in patients with uncomplicated chronic diarrhea (simplified decision tree). Copyright © 2008 IUMSP/CHUV, Lausanne, Switzerland – EPAGE II.

▶ to all patients with IBD-associated primary sclerosing cholangitis.

The literature appears to favor surveillance colonoscopy every 3 years for 10 years, every 2 years for 10 years, and then annually, depending on the decade of evolution. This procedure should include at least 4 biopsies taken randomly every 10 cm throughout the colon plus biopsy of any macroscopic lesion. Meta-analyses, reviews and studies on the association between IBD and CRC are shown in **Table e7**.

Results: EPAGE II panel
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Of the 463 indications examined by the EPAGE II panel, 6 concerned chronic diarrhea, 27 the evaluation of ulcerative colitis, 23 the evaluation of Crohn's disease, and 43 the use of colonoscopy for CRC surveillance in IBD. The number of scenarios (indications) considered inappropriate in each of these clinical categories was 2, 15, 9 and 15 respectively. Frank disagreement among the expert panelists was low (11% of scenarios). Indications considered necessary (mandating colonoscopy) were concentrated mainly in the group of CRC surveillance, especially when previous colonoscopy had revealed any grade of dysplasia or in presence of long-standing disease.

⊙ **Table 8** shows the definitions used for the clinical categories.
⊙ **Fig. 1a**, **2a**, **3a**, and **4a** summarize appropriateness of colonoscopy consolidated into two categories: "Not appropriate" (comprising categories uncertain and inappropriate) versus "Appropriate" (including necessary).

As in the literature review, the EPAGE II panel criteria confirmed the appropriateness of diagnostic colonoscopy for diarrhea of at least 4 weeks' duration (⊙ **Fig. 1a**). They also recommend that in addition to assessment of the extent of IBD by colonoscopy, colonoscopic examination is appropriate in the face of persistent or worsening symptoms (⊙ **Figs. 2a** and **3a**), with some nuances for ulcerative colitis depending on the existence and nature of prior sigmoidoscopy findings. The indication for surveillance co-
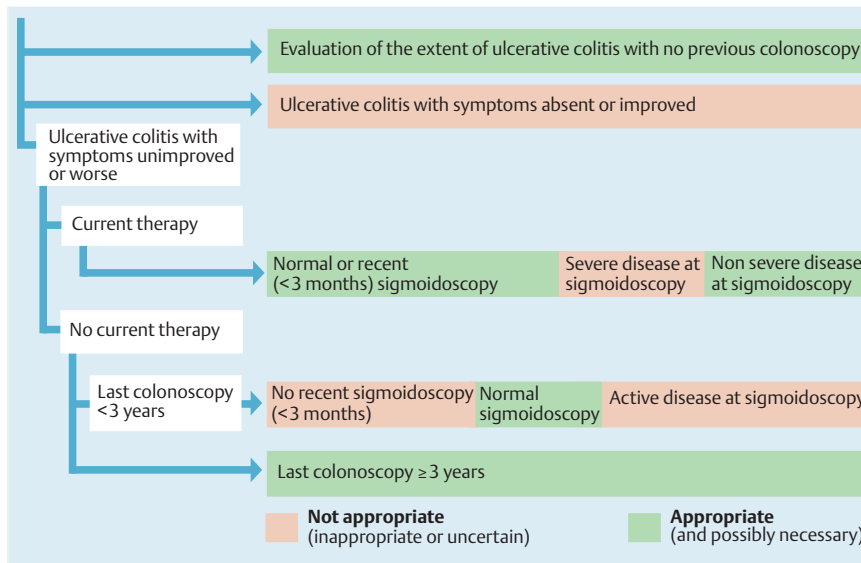

Fig. 2a Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known ulcerative colitis, excluding surveillance for colorectal cancer (simplified decision tree). Copyright © 2008 IUMSP/CHUV, Lausanne, Switzerland – EPAGE II.
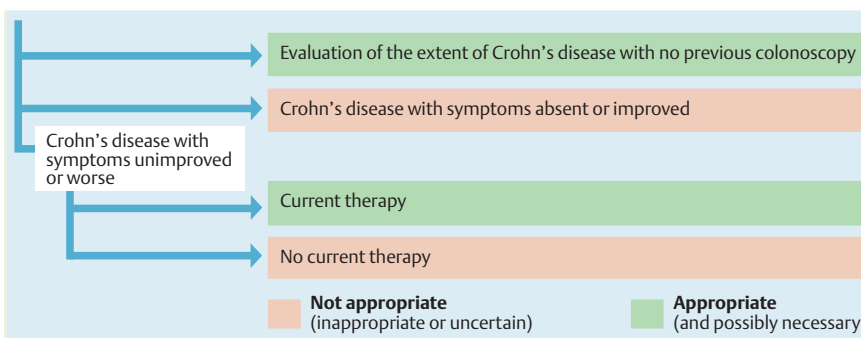

Fig. 3a Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known Crohn's disease, excluding surveillance for colorectal cancer (simplified decision tree). SBFT, small-bowel follow-through; CT/MRI, computed tomography/magnetic resonance imaging. Copyright © 2008 IUMSP/CHUV, Lausanne, Switzerland – EPAGE II.
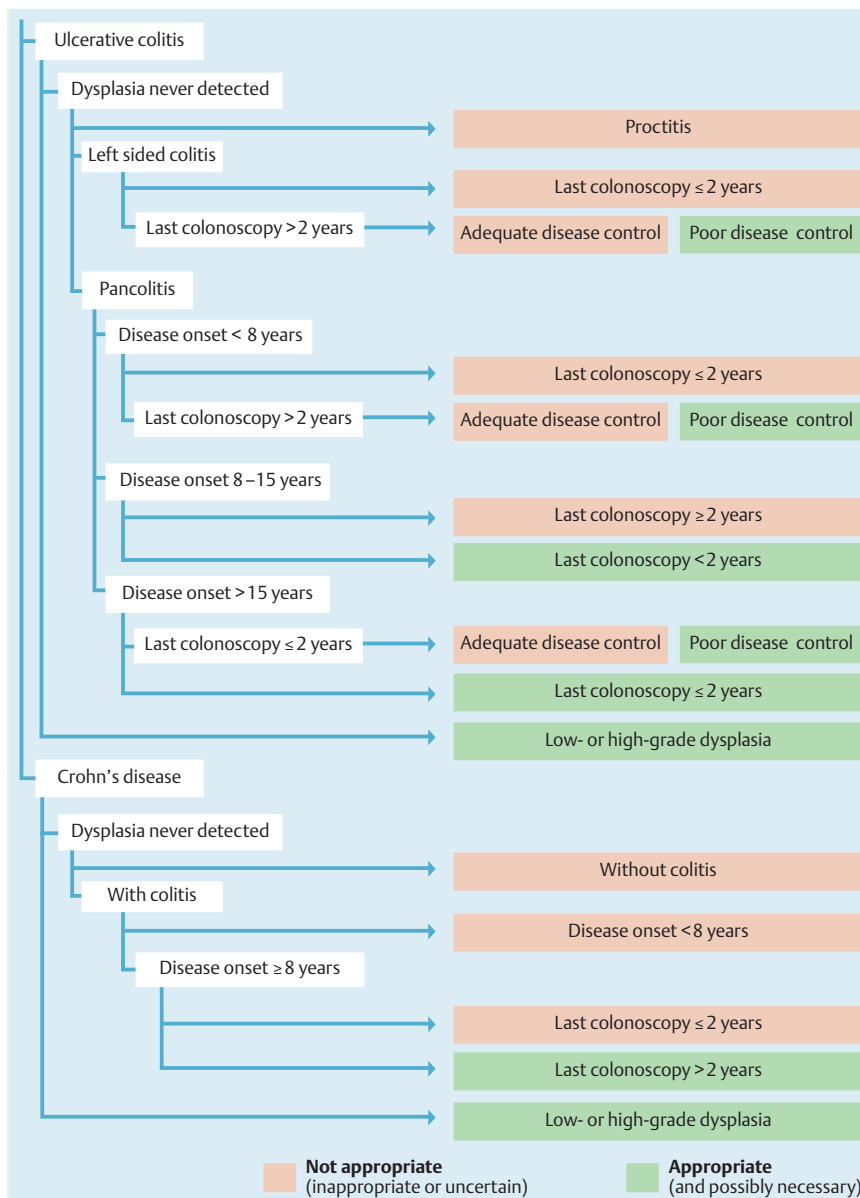
Fig. 4a Appropriateness ratings of clinical indications for performing colonoscopy for surveillance for colorectal cancer in patients with known inflammatory bowel disease (simplified decision tree). Copyright © 2008 IUMSP/CHUV, Lausanne, Switzerland – EPAGE II.

lonoscopy in IBD patients (○ **Fig. 4a**) was generally appropriate after a period of 2 years. In the presence of dysplasia at previous colonoscopy, it was not only appropriate but necessary (mandating colonoscopy). More detailed results presenting the four main categories of appropriateness (inappropriate, uncertain, appropriate, and both appropriate and necessary, that is, mandating colonoscopy) can be found online (**Figs. e1b, e2b, e3b, e4b**).

Conclusions: Literature review
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Chronic diarrhea
Caution is necessary in the interpretation of results from the literature on the appropriateness of colonoscopy for patients with chronic diarrhea. Primary studies are of modest quality. Most of them have a small sample size and are retrospective case series, without a control group. Variations in results can be explained by the heterogeneity existing in the studies in outcomes measured, study design, definitions, indications for colonoscopy, and/or inclusion criteria, thus reflecting the discrepancies in and the evolution of the definition of chronic diarrhea. Direct comparison of

results between studies is therefore difficult and hence guidelines on this must be interpreted with caution, being mainly based on modest evidence, expert opinion, and consensus. The role of diagnostic colonoscopy thus remains uncertain but, if this procedure is performed and findings are macroscopically normal, multiple biopsies should be taken to exclude microscopic colitis.

The literature review also highlights the fact that despite the modest quality of evidence, and although the presence of these symptoms probably does not enhance the pick-up rate of CRC per se, recommendations tend to consider screening purposes together with clinical symptoms as an indication for performing an evaluation colonoscopy. Colonoscopic evaluation may thus be justified for patients aged > 50 years with recent-onset chronic diarrhea or for any patients with such a complaint in association with alarm symptoms.

Known IBD
Assessment of the appropriateness of colonoscopy in management of known ulcerative colitis and Crohn's disease relies on modest evidence. Available primary studies in patients with

known IBD are aimed at evaluating the efficiency of specific treatments, rather than the general impact of colonoscopy on patient outcome. Expert opinion and consensus play an important role in the recommendations on colonoscopy in IBD [45,98]. Guidelines on the use of colonoscopy for surveillance in ulcerative colitis and Crohn's disease provide remarkably uniform recommendations, mostly relying on past studies [99] on CRC risk. The available evidence remains, however, modest. Considerable variation in the reported association between IBD and CRC might be due to differences in referral patterns, in follow-up, to differences in the methods of evaluating cancer risk, and to biological differences among the patients studied [45,100]. Surveillance of CRC in IBD has important limitations [98,100–102], including the possibility of a lead-time bias [100], limited patient compliance [103], variable endoscopic quality [104,105], poor interobserver agreement in histopathological interpretation, and disagreement in the management of dysplasia [45]. Although knowledge on the risk of CRC in ulcerative colitis and Crohn's disease does reveal some discrepancies, guidelines issue similar surveillance recommendations for both IBDs.

The appropriateness of colonoscopy in the management of known ulcerative colitis and Crohn's disease is in many cases debatable and depends on the evolution of the disease and on the therapeutic approach. Colonoscopy is useful in the preoperative phase and in the therapeutic management of short accessible strictures and of bleeding. In the future, endoscopic procedures might be indicated and systematically performed in order to monitor mucosal healing in patients where biological treatments are planned and/or under way [106,107]. Literature data support CRC surveillance in IBD, while at the same time recognizing its limitations. In the future, new techniques such as endomicroscopy and chromoendoscopy might considerably improve detection procedures for colonic dysplasia [108,109].

Conclusions: EPAGE II panel
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The EPAGE II panel criteria confirmed the appropriateness of diagnostic colonoscopy for diarrhea of at least 4 weeks' duration. They also suggest that, in addition to assessing the extent of IBD by colonoscopy, further colonoscopic examination is appropriate in the face of persistent or worsening symptoms. The indication for surveillance colonoscopy in IBD patients is generally considered appropriate after a lapse of 2 years; in the presence of dysplasia at previous colonoscopy, it is not only appropriate but necessary.

Acknowledgments
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Appendix: The EPAGE II Study Group
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See page 205.

Institutions

[1] Healthcare Evaluation Unit, Institute of Social and Preventive Medicine, University of Lausanne and Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[2] Department of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland
[3] Department of Surgery, University College London Hospitals, London, United Kingdom
[4] Department of Gastroenterology, University of Basle, Basle, Switzerland
[5] Cerner LifeSciences, Beverly Hills, USA
[6] The EPAGE II Study Group*

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The following figures and tables are available online:
www.thieme-connect.com/media/endoscopy/200903/supmat/
endo843.pdf

Fig. e1b Appropriateness ratings of clinical indications for performing colonoscopy in patients with uncomplicated chronic diarrhea (full decision tree).
Fig. e2b Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known ulcerative colitis, excluding surveillance for colorectal cancer (full decision tree).
Fig. e3b Appropriateness ratings of clinical indications for performing colonoscopy in patients for the evaluation of known Crohn's disease, excluding surveillance for colorectal cancer (full decision tree). SBFT, small-bowel follow through; CT/MRI, computed tomography/magnetic resonance imaging.
Fig. e4b Appropriateness ratings of clinical indications for performing colonoscopy for surveillance for colorectal cancer in patients with known inflammatory bowel disease (full decision tree).
Table e1 Studies investigating the diagnostic yield of colonoscopy in chronic diarrhea (1997 – February 2008).
Table e2 Guidelines on the appropriateness of diagnostic colonoscopy in chronic diarrhea.
Table e3 Studies investigating the association between diarrhea and colorectal cancer (CRC), 1997 – February 2008.
Table e4 Guidelines/reviews on the appropriateness of colonoscopy for the clinical management of known ulcerative colitis.
Table e5 Guidelines/reviews on the appropriateness of colonoscopy for the clinical management of known Crohn's disease.
Table e6 Guidelines/reviews on the use of colonoscopic surveillance for colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD).
Table e7 Meta-analyses, reviews, and studies investigating the association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) (1997 – February 2008).