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Published in:
Inflammatory Bowel Diseases

DOI:
10.1097/MIB.0000000000001082

Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide

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Background: In asymptomatic patients with inflammatory bowel disease (IBD), "monitoring" involves repeated testing aimed at early recognition of disease exacerbation. We aimed to determine the usefulness of repeated fecal calprotectin (FC) measurements to predict IBD relapses by a systematic literature review.

Methods: An electronic search was performed in Medline, Embase, and Cochrane from inception to April 2016. Inclusion criteria were prospective studies that followed patients with IBD in remission at baseline and had at least 2 consecutive FC measurements with a test interval of 2 weeks to 6 months. Methodological assessment was based on the second Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist.

Results: A total of 1719 articles were identified; 193 were retrieved for full text review. Six studies met eligibility for inclusion. The time interval between FC tests varied between 1 and 3 months. Asymptomatic patients with IBD who had repeated FC measurements above the study's cutoff level had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months. Patients with repeated normal FC values had a 67% to 94% probability to remain in remission in the next 2 to 3 months. The ideal FC cutoff for monitoring could not be identified because of the limited number studies meeting inclusion criteria and heterogeneity between selected studies.

Conclusions: Two consecutively elevated FC values are highly associated with disease relapse, indicating a consideration to proactively optimize IBD therapy plans. More prospective data are necessary to assess whether FC monitoring improves health outcomes.

(Inflamm Bowel Dis 2017;23:894–902)

Key Words: fecal calprotectin, disease monitoring, inflammatory bowel disease

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis (UC), is a chronic, relapsing, and remitting disorder of the gastrointestinal tract. The ultimate goal in IBD is to restore disease remission as early as possible and to prevent disease progression and resistance to pharmacotherapies.[1] The concept of "monitoring" involves repeated testing aimed at early recognition of disease recurrence and timely adjustment of therapy plans.[1]

The ideal monitoring test should be noninvasive, simple to conduct, and easily interpretable.[2] It should detect an imminent disease flare—often undetectable by symptom-based reporting alone—and makes provision for proactive treatment optimization.

In Table 1, several frequently used targets for disease monitoring are compared and evaluated for their suitability as a monitoring test in IBD. Although the gold standard for determining mucosal inflammation is endoscopy with histological confirmation,[3] there is a need for clinically useful biomarkers for monitoring purposes because it is unrealistic, costly, and potentially harmful to perform regular, invasive endoscopies.[23] This rationale is particularly true in children affected by IBD[8,9,24] and patients with concomitant irritable bowel syndrome.[10,25]

Calprotectin is a protein released by activated or damaged granulocytes, monocytes, macrophages, and epithelial cells.[26] It represents 60% of cytosolic protein in granulocytes and is resistant to metabolic degradation. Fecal calprotectin (FC) levels are related to neutrophil migration to the gastrointestinal tract.[26,27] FC is a more sensitive marker of active disease compared with the other frequently used surrogate markers (C-reactive protein)[12] and symptom-based clinical scoring systems,[4] including Crohn's Disease Activity Index (CDAI),[28] Harvey–Bradshaw Index,[29] Pediatric CDAI,[30] Simple Clinical Colitis Activity Index,[31] and the Pediatric Ulcerative Colitis Activity Index(PUCAI).[32] FC represents a practical monitoring test in IBD because testing can be done at home, and the protein is stable at room temperature for at least 3 days.[33]

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication December 31, 2016; Accepted February 6, 2017.

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Author disclosures are available in the Acknowledgments.

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DOI 10.1097/MIB.0000000000001082

Published online 3 April 2017.

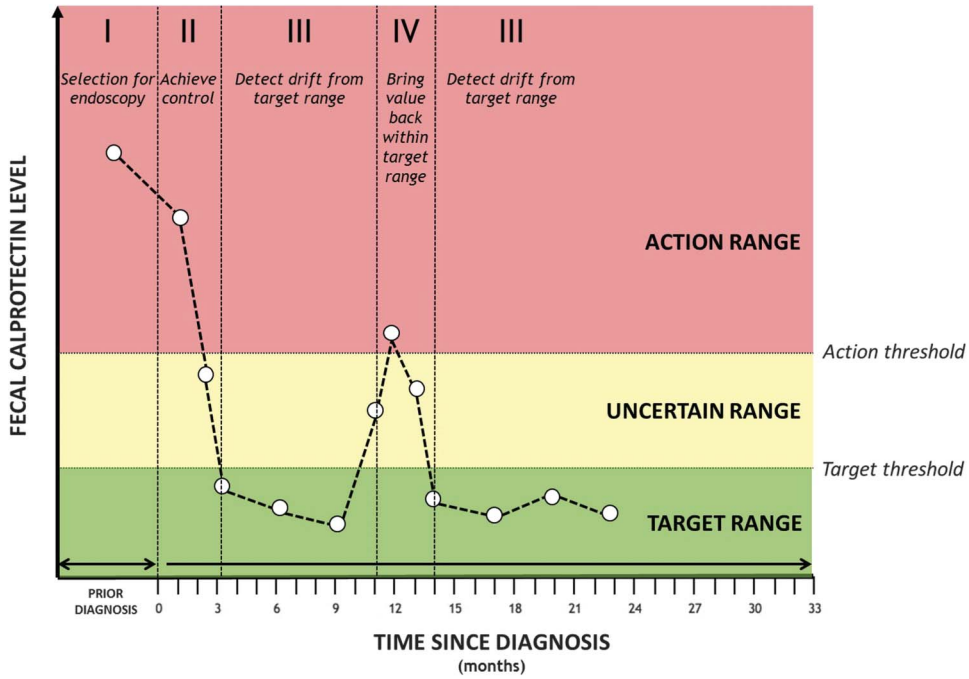

FIGURE 1. Conceptual model of FC monitoring in patients with IBD. Figure adapted from "Do Not Read Single Calprotectin Measurements in Isolation When Monitoring Your Patients with Inflammatory Bowel Disease" by P.F. van Rheenen, Inflammatory bowel disease, 20:1416 to 7. Copyright 2014 by the Wolters Kluwer Health, Inc. Adapted with permission.

A general construct for FC-based disease monitoring in patients with IBD is shown in Figure 1, which illustrates the 4 phases of disease monitoring.[1,34] Repeated FC measures are used to longitudinally track changes in a patient's condition over time. In phase I, IBD is suspected, but neither endoscopically confirmed nor treated. In phase II, induction therapy is introduced to achieve disease control, resulting in patient response. Phase III begins with disease remission with continuation of maintenance therapy.

TABLE 1. Markers of Disease Activity Used in Patients with IBD

	Validity (Correlation with Gold Standard)	Responsiveness to Changes in Condition	Signal-to-Noise Ratio (Ability to Differentiate Changes in Condition from Background Variability)	Practicality
Endoscopy	Gold standard	Gold standard	Gold standard	Low Requires bowel preparation and in children general anesthesia
Symptom-based clinical indices	Poor[3–7]	Moderate Affected by subjectivity[8,9]	Moderate Risk of false-positive results (irritable bowel syndrome) and false-negative results (dissimulation)[10,11]	High Easy to perform; noninvasive
C-reactive protein	Moderate[3–5,12]	Moderate Late position in disease progression pathway[12–14]	Moderate Risk of false-positive results (acute infections and other inflammatory conditions) and false-negative results (normal C-reactive protein, despite active disease)[13]	High Quick result; but requires venepuncture
FC	Good[11,12,15–18]	Good Rises quickly in case of relapse; falls rapidly with successful treatment[19]	Moderate Risk of false-positive results[20,21]	High Possible reluctance by patients for repeated stool collection.[22]

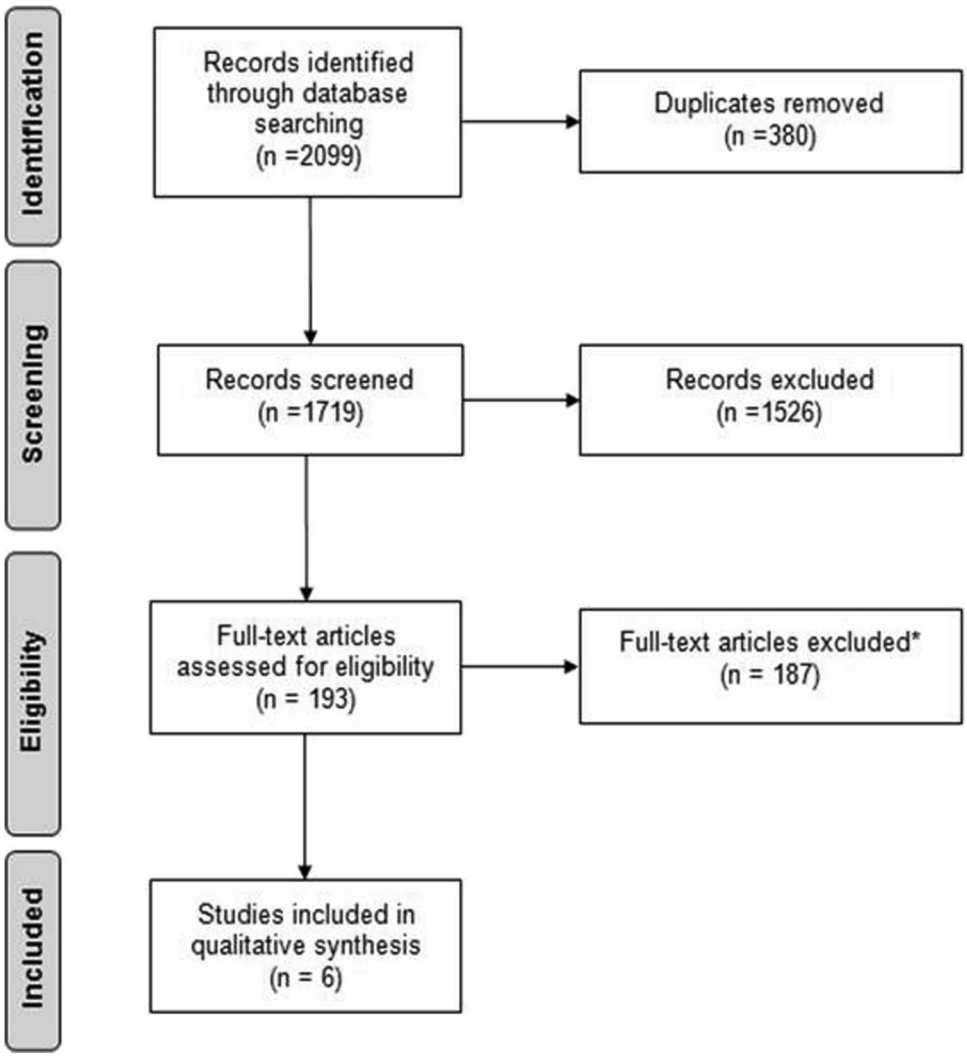

FIGURE 2. Flow diagram systematic literature search. Reasons for exclusion at last stage (*): serial measurements of FC not reported (n = 69); Congress abstract (n = 53); patients had active disease at baseline (n = 29); FC test interval out of desired range (<2 weeks or >6 months) (n = 14); narrative review, editorial, letter to editor, or comment (n = 7); FC test results within 6 months before relapse not reported (n = 7); FC cutpoint not reported (n = 3); language other than English (n = 3); and less than 10 participants (n = 2).

The goal of monitoring in this phase is to detect deviations from the target range, indicating the start of phase IV. In phase IV, therapy is adjusted to re-establish disease control and bring FC levels back to the target range.

Given this background and clinical need for a standardized approach to noninvasive IBD monitoring, we performed a systematic review to evaluate whether FC monitoring could be used to detect imminent disease flares and sustained remission.

METHODS

Eligible studies were those that followed at least 10 patients with IBD in remission at baseline (monitoring phase III) and presented at least 2 consecutive FC measurements. We accepted FC test intervals between 2 weeks and 6 months. Studies that did not report the use of a FC cutoff (either predefined or based on receiver operating characteristic curves) were excluded from analysis.

Identification and Selection of Studies

We searched for studies published in Medline, Embase, and the Cochrane Library. The search strategy for Medline was ("Leukocyte L1 Antigen Complex"[Mesh] or "calprotectin"[tw] or "calgranulin"[tw]) and ("Inflammatory Bowel Diseases"[Mesh] or "inflammatory bowel disease"[tw] or "inflammatory bowel diseases"[tw] or "IBD"[tw] or "Crohn"[tw] or "Colitis"[tw]). For Embase, we used ("calgranulin"/exp or "calprotectin"/exp) and ("enteritis"/exp or "inflammatory bowel disease"/exp or "inflammatory bowel diseases"/exp or "ibd" or "crohn" or "colitis"/exp).

TABLE 2. Study Characteristics of Selected Studies

Study	No. Patients in Follow-up	Age Group	Study Aim (Prospective if Not Otherwise Specified)	Type of IBD; Remission at Baseline	Proportion of Patients with Relapse	Median Duration of Follow-up (in Months)	Frequency of Diagnostic Testing (Scoring Method)			
							FC	Endoscopy	Clinical Activity Score	C-reactive Protein
Dabritz et al,[37] Germany	181	AC	Monitoring disease activity	UC (120); CD (61)	34%	10	Every 3 months or when suspicion of relapse		Every 3 months or when suspicion of relapse (P) CDAI, (P) UCAI	Every 3 months or when suspicion of relapse
De Vos et al,[19] Belgium, Norway	87	A	Monitoring disease activity	UC (87)	33%	12 or relapse	Every month	Baseline, week 52 (Sigmoidoscopy, Mayo endoscopic subscore)	Every 2 months or when suspicion of relapse (Partial Mayo score)	Every 2 months or when suspicion of relapse
Jauregui-Amezaga et al,[38] Spain	64	A	Evaluating accuracy of HR-rectosigmoidoscopy	UC (64)	27%	12 or relapse	Every 3 months	Baseline, 12 months or relapse (HR-rectosigmoidoscopy)	Every 3 months (Mayo score)	Every 3 months
Lasson et al,[39] Sweden	91	A	RCT comparing FC-based pharmacological intervention and usual care	UC (91), control group (40), intervention group (51)	Intervention group 35%; usual care 50%; overall 42%	18	Every month	Baseline (Sigmoidoscopy)	Baseline (Mayo score)	
Molander 2015,[40] Finland	49	A	Monitoring and predicting disease activity after stopping anti-TNF therapy	UC (28); CD (16); IBD-U (5)	31%	12	0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 months or when suspicion of relapse	0, 4, 12 and months or when suspicion of relapse (ileocolonoscopy SES-CD or Mayo endoscopic subscore (UC))	0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 months or when suspicion of relapse (HBI [CD] or partial Mayo [UC])	0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 months or when suspicion of relapse
Yamamoto et al,[41] Japan	80	A	Monitoring disease activity	UC-proctitis: (80)	30%	10	Every 2 months	Baseline and when suspicion of relapse (endoscopy, UC-DAI score)	Every 2 months (UC-DAI score, PGA)	Every 2 months
Total	552				33.3%					

A, adults; C, children; CD, Crohn's disease; HBI, Harvey–Bradshaw Index; IBD-U, IBD-unclassified; N, number of participants; (P)CDAI, (Pediatric) Crohn's disease activity index; PGA, physicians global assessment; (P)UCAI, (Pediatric) ulcerative colitis activity index; RCT, randomized controlled trial; SES-CD, simple endoscopic score for Crohn's disease; TNF, tumor necrosis factor; UC-DAI, ulcerative colitis disease activity index.

TABLE 3. QUADAS-2 Checklist

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Dabritz et al[37]	☺	☺	☹	☺	☺	☺	☹
De Vos et al[19]	?	☹	☺	☺	☺	☺	☹
Jauregui-Amazega et al[38]	?	☹	☺	☺	☺	☺	☺
Lasson et al[39]	☺	☹	☹	☹	☺	☺	☹
Molander et al[40]	?	☹	?	☹	☺	☺	☹
Yamamoto et al[41]	☺	☹	☺	☺	☺	☺	☺

☺ = low risk of bias; ☹ = high risk of bias; ? = unclear risk of bias.

We restricted our search to studies published in English only. Duplicate articles were manually deleted using RefWorks. For further relevant studies, we checked the reference lists of identified articles. The first selection of studies was performed by 1 reviewer (A.H.) on the basis of title and abstract. The full article of each potentially eligible study was then obtained. Two authors (A.H. and P.v.R.) independently assessed full manuscripts against the predefined inclusion criteria. Any disagreements were resolved by discussion, and consensus was reached with the third author (K.T.P.).

Data Extraction and Management

The following characteristics were extracted from each selected study: name of the first author, year of publication, country of origin, journal, study design criteria (prospective versus retrospective design), sample size (the number of patients in follow-up), baseline characteristics (type of IBD and age group), FC test characteristics (including cutoffs tested), reference standard (endoscopy), other markers of disease activity used (including symptom-based clinical indices and C-reactive protein), prevalence of disease flares, and the number of true positives, true negatives, false positives, and false negatives. Pooling of data was greatly jeopardized because of heterogeneity between studies and was therefore not undertaken.

Assessment of Risk of Bias and Applicability Concerns

The study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist included in systematic reviews.[35] In QUADAS, 4 key domains are rated for risk of bias and concerns regarding applicability to the review questions. The signaling questions in each domain were specifically tailored to our review questions (see Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B478). We did not calculate summary scores because their interpretation is problematic and potentially misleading.[36]

RESULTS

This review includes results of electronic searches up to April 21, 2016. A total of 1719 articles were identified, of which, 193 were retrieved for full text review. Of these, 187 were excluded for not meeting the eligibility criteria. Six articles were included in the final analysis (Fig. 2).

Study Characteristics

Study characteristics of included studies are presented in Table 2. All studies were published in the most recent 3 years, and all except 1 were from European countries. Sample size varied between 49 and 181 patients. All except 1 study included adult patients only.[37] The mean proportion of patients experiencing a disease flare during the observation period was 33.3% (184 of 552; range, 27%–50%), and the total observation period was 10 to 18 months. All studies included patients with UC of which 1 followed patients with disease exclusively confined to the rectum.[41] Two studies also included patients with Crohn's disease.[37,40] The time interval between consecutive FC tests varied between 1 and 3 months. One study compared control patients assigned to usual care with patients exposed to a FC-guided dose-escalation scheme with oral 5-aminosalicylates.[39] For the sake of clarity, we excluded the intervention group from our analysis because the number of relapses in the intervention group was directly influenced by the therapeutic intervention.

Methodological Quality of Included Studies

The methodological quality of the included studies is summarized in Table 3. All studies used a prospective design, enrolled patients with IBD in remission, used a commercially available FC assay, and tested FC during the initial remission period and periodically thereafter. One study used only clinical activity scores as reference standard instead of endoscopic evaluation.[37] In half of the studies, endoscopy was scheduled according to the protocol when relapse was suspected.[38,40,41] Differential verification was evident in 3 studies.[19,39,40] Substantial differences between studies were observed in clinical and endoscopic definitions of relapse and predefined FC cutoff levels.

Findings

Prognostic Value of Repeated FC Measurements for Relapse and Sustained Remission

All patients included in the final analysis collected the first feces sample while in remission. Most individual studies showed that asymptomatic patients with FC levels moving out of the normal range on the next measurement had higher risk of relapse within the next 2 to 3 months. When FC was elevated, the probability of relapse increased from 53% to 83%, as is shown in Table 4.[19,38–41] Consecutive normal FC values were associated with reduced risk of relapse, with 67% to 94% probability of remission in the next 2 to 3 months.

One study investigated the prognostic value of ≥2 consecutive measurements above the upper limit of normal,[19] whereas the others focussed on an upward trend of FC between 2 measurements.[37–41] As can be seen in Table 5, the former strategy resulted in the highest probability of relapse.

Optimal FC Cutoff for Monitoring Disease Activity

Probabilities of relapse and remission varied between studies, partly because different FC cutoffs were used. Variation in FC cutoffs could not explain all the difference. Patient variation, study design, and type of FC assay may also have contributed to the heterogeneity of the test accuracy. Because of the limited number of studies included in this systematic review, we were not able to derive the ideal cutoff point.

DISCUSSION

In this systematic review, we evaluated the utility of FC monitoring to detect imminent flares in asymptomatic patients with IBD. We identified only 6 studies meeting our inclusion criteria. Data collection were done prospectively in consecutive series of mostly patients with UC with quiescent disease at baseline. We found that there was poor consistency of reference standard use and definition of relapse between the studies. Two consecutively elevated FC levels appeared to be the best predictor for relapse, but this was systematically investigated in only 1 study.[19] An upward trend of FC out of the normal range was also prognostic for relapse, albeit with a lower probability of relapse.

Comparison with Other Reviews

We report the first systematic review that investigates the prognostic value of repeated FC measurements in asymptomatic patients with IBD. To date, there have been 2 meta-analyses of the diagnostic accuracy of a single FC measurement in almost exclusively symptomatic patients with previously diagnosed UC or Crohn's disease.[12,15] In these circumstances, symptom-based clinical indices and derangements in serological markers of inflammation would likely lead clinicians to intensify medical therapy. Inclusion of these studies may cause overestimation of the prognostic value of calprotectin relative to the practical situation, where a monitoring test is necessary to discriminate between those who

TABLE 4. Characteristics of Fecal Calprotectin Monitoring Studies

Study	FC Assay	Upper Limit of Normal Range (in µg/g)	Basis of Relapse Diagnosis	Pretest Probability of Relapse	Posttest Probability of Relapse		Time Between drift out of Normal Range to Relapse, mo	N per 100 patients			
					When Upward Trend in FC out of Normal Range (95% CI)	When Consecutive Values in Normal Range (95% CI)		True Positives	True Negatives	False Positives	False Negatives
Dabritz et al[37]	Immunodiagnostic	15	C	34%	63% (55–71)	12% (8–19)	2–3	27	51	15	7
De Vos et al[19]	PhiCal	300[a]	C&E	33%	83% (61–94)	20% (15–27)	3	17	63	4	16
Jauregui-Amazega et al[38]	Cerba internacional	250	E	27%	53% (33–73)	18% (12–26)	3	13	62	11	14
Lasson et al[39,b]	Buhlmann	300	C	50%	57% (47–67)	33% (15–58)	Unknown	40	20	30	10
Molander et al[40]	Calpro	200	E	31%	57% (36–76)	20% (12–30)	2–4	17	57	12	14
Yamamoto et al[41]	Canton	55	E	30%	66% (52–77)	6% (2–16)	2	26	56	14	4

[a]FC value above cutoff in 2 consecutive months.
[b]Only control group included in this table.
C, relapse defined as clinical relapse; C&E, relapse defined as both clinical relapse or endoscopic relapse; CI, confidence interval; E, relapse defined as endoscopic relapse.

TABLE 5. Implications of Fecal Calprotectin Test Results

Outcomes	Consequences	Importance[a]
True positives	Interpretation	Critical
	Patient has active disease, despite being symptom free	
	Presumed patient outcome	
	May benefit from shorter delay and potential early adjustment of therapy (intensify/switch/add)	
True negatives	Interpretation	Critical
	Patient is in remission	
	Presumed patient outcome	
	Benefit from reassurance	
False positives	Interpretation	Critical
	Patient is in remission, FC elevated	
	Presumed patient outcome	
	Detriment from exposure to overtreatment	
False negatives	Interpretation	Critical
	Patient has active disease, but it is not (yet) recognized	
	Presumed patient outcome	
	Detriment from delayed diagnosis and delayed adjustment of therapy	
	False reassurance leading to ignoring symptoms	
Inconclusive results	Interpretation	Critical
	Not sure whether this increase in FC is clinically relevant	
	Presumed patient outcome	
	Detriment from increased anxiety by uncertainty until next FC test result	
	May benefit from avoidance of overtreatment	
Complications of test	May be perceived as unsanitary	Not important
Resource utilization (cost)	Increases cost for ambulant diagnostic testing; however, endoscopy has much greater resource implications. FC-based home monitoring may reduce cost for out-patient health checks	Important

[a]GRADE recommends classifying each outcome as either "critical for decision making," "important but not critical for decision making," or "not-important."

have preclinical relapse and those with quiescent IBD. We moved away from single FC measurements that are read in isolation when relapse is suspected and focused on repeated FC measurements in asymptomatic patients to predict relapse.

Based on our review, we found that FC levels start rising 2 to 3 months before a relapse becomes apparent, and therefore support the biological implausibility that a single FC measurement at baseline can predict the clinical course over a 12-month period, as was suggested in a meta-analysis by Mao et al.[42]

Cutoff Levels

Furthermore, we were not able to identify the best FC cutoff for monitoring purposes. Currently, there is no consensus among IBD experts about the range of FC associated with mucosal healing, indicating a need for prospective and randomized studies comparing monitoring strategies that vary in thresholds.

Clinical Implications

Table 5 elaborates on the specific outcomes when FC monitoring strategy leads to effective adjustments in IBD therapy from a patient's perspective. The underlying assumption here is that FC monitoring serves to improve patient-centered outcomes, representing a proactive approach to detecting indolent disease activity. Of note, when adopting FC monitoring, key questions most relevant to decision making are whether the numbers of false negatives (missed cases with relapse) and false positives (cases without disease activity who may receive treatment intensification) are acceptable within the new monitoring paradigm.

.Emerging evidence suggest that FC monitoring has the potential to result in less missed cases of asymptomatic patients with IBD with ongoing mucosal-level inflammation. In particular, patients with IBD who underreport symptoms and pediatric patients requiring anesthesia for each endoscopic evaluation are 2 subsets of patients who may benefit from FC monitoring. From a patient's perspective, bowel preparation for colonoscopy, repeated anesthesia, and incurring indirect costs are practical and important considerations in favor of FC monitoring. In addition, FC monitoring may serve as a feedback tool for better patient engagement, facilitating self-management strategies of their chronic condition.

Although there is no consensus on the optimal frequency of calprotectin retesting and cutoffs for treatment intensification, the authors of this article routinely monitor children with IBD using an enzyme-linked immunosorbent assay (ELISA) allowing quantification. A practical cutoff range could be as follows: levels below 250 μg/g as indicative for disease remission (green), levels above 500 μg/g as indicative for disease flare (red), whereas levels between 250 and 500 μg/g indicating need for more frequent calprotectin monitoring (yellow), as shown in Figure 1. This "traffic light" is currently being evaluated in a prospective multicenter telemonitoring program.[43] Future studies are needed to determine whether pre-emptive treatment intensification based on elevated FC levels will lead to long-term better patient outcomes, including reduction of hospitalizations, disability-associated costs, and loss of productivity. The first prospective trials with mesalamine dose

intensification[39,44,45] and infliximab dose interval adjustment[46] have already been performed with promising results.

Methodological Limitations of the Review

Although the methodology to conduct a systematic review and meta-analysis of diagnostic research is developed to a certain extent, at least for dichotomized tests, the systematic evaluation of a monitoring test is not bound to consensus guidelines. Although the articles we selected had to meet high methodological standards, we acknowledge several limitations. Significant heterogeneity in disease spectrum, study endpoints, FC cutoff levels, and quality of reporting are potentially confounding factors that may affect interpretation of the data and conclusions. Also, we restricted our search to studies published in English only, leading to potential bias.

CONCLUSIONS

This systematic review shows that the relapsing and remitting nature of IBD becomes less unpredictable with proactive FC monitoring in clinical practice, allowing early recognition of relapse before overt symptoms (or symptom reporting). Although FC monitoring may represent a more proactive strategy for treatment modifications in a treat-to-target approach, more robust data are necessary to determine whether it will improve decision-making and patient-centered outcomes.

ACKNOWLEDGMENTS

The authors thank Karin Sijtsma (medical librarian, University Medical Center Groningen) for help with the design of the optimal search strategy.

K. T. Park has received research support from BÜHLMANN Laboratories and served as a consultant for Inova Diagnostics. P. van Rheenen and A. Heida received research support from BÜHLMANN Laboratories for other ongoing studies. K. T. Park is supported by the National Institutes of Health (K08 DK094868) for this work.

All authors approved the final version of the manuscript.

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