Faecal Calprotectin in Suspected Paediatric Inflammatory Bowel Disease

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ABSTRACT

Objectives: The diagnostic accuracy of faecal calprotectin (FC) concentration for paediatric inflammatory bowel disease (IBD) is well described at the population level, but not at the individual level. We reassessed the diagnostic accuracy of FC in children with suspected IBD and developed an individual risk prediction rule using individual patient data.

Methods: MEDLINE, EMBASE, DARE, and MEDION databases were searched to identify cohort studies evaluating the diagnostic performance of FC in paediatric patients suspected of having IBD. A standard study-level meta-analysis was performed. In an individual patient data meta-analysis, we reanalysed the diagnostic accuracy on a merged patient dataset. Using logistic regression analysis we investigated whether and how the FC value and patient characteristics influence the diagnostic precision. A prediction rule was derived for use in clinical practice and implemented in a spreadsheet calculator.

Results: According to the study-level meta-analysis (9 studies, describing 853 patients), FC has a high overall sensitivity of 0.97 (95% confidence interval [CI] 0.92–0.99) and a specificity of 0.70 (0.59–0.79) for diagnosing IBD. In the patient-level pooled analysis of 742 patients from 8 diagnostic accuracy studies, we calculated that at an FC cutoff level of 50 μg/g there would be 17% (95% CI 15–20) false-positive and 2% (1–3) false-negative results. The final logistic regression model was based on individual data of 545 patients and included both FC level and age. The area under the receiver operating characteristic curve of this derived prediction model was 0.92 (95% CI 0.89–0.94).

Conclusions: In high-prevalence circumstances, FC can be used as a noninvasive biomarker of paediatric IBD with only a small risk of missing cases. To quantify the individual patients' risk, we developed a simple prediction model based on FC concentration and age. Although the derived prediction rule cannot substitute the clinical diagnostic process, it can help in selecting patients for endoscopic evaluation.

Key Words: adolescent, child, infant, inflammatory bowel diseases, leukocyte L1 antigen complex, meta-analysis

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As many as 25% of all inflammatory bowel disease (IBD) cases present in childhood. Given the impact of the disease and its therapy, a reliable and timely diagnosis is mandatory (1). The reference standard, endoscopic evaluation with biopsies (2), is, however, invasive, not without risks, and also costly.

Faecal calprotectin (FC) has been investigated as a surrogate marker of neutrophil influx into the bowel lumen and a noninvasive diagnostic test for IBD (3,4).

van Rheenen et al (5) published a study-level meta-analysis on the diagnostic accuracy of FC for IBD in both children and adults. Based on the calculated summary estimates for specificity,

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sensitivity, and likelihood ratios (LRs), they concluded that the test is a useful screening tool for identifying those patients most likely needing endoscopic evaluation. A key problem is, however, that this meta-analysis was based on aggregate data and did not account for different cutoff levels or different patient characteristics (6).

By contrast, individual patient data (IPD) meta-analysis allows using the original test results as continuous data rather than as dichotomous classification data. In addition, the effect of patient characteristics on test accuracy can be evaluated and quantified (6,7).

We undertook the present study to update the study-level meta-analysis on the diagnostic performance of FC for paediatric IBD and to complement it with an individual-level meta-analysis. We also sought to develop a prediction model for IBD based on calprotectin level and readily available patient variables.

METHODS

The research was conducted in accordance with the Code of Conduct for Medical Research of the Dutch Federation of Biomedical Scientific Societies (8). Identification, selection, and appraisal of the relevant studies were carried out independently, by 2 reviewers (P.L.J.D. and M.P.A.B.). Disagreements were resolved through discussion.

Search Methods for Identification of Studies

A systematic search was performed initially from inception to December 2010 in MEDLINE (Ovid), EMBASE (Ovid), the Database of Abstracts of Reviews of Effects (DARE) of the Centre for Reviews and Dissemination (9), and the MEDION database of the University of Maastricht (10). The electronic search was last updated on April 1, 2012. We refrained from using a diagnostic search filter (11,12) or language restrictions. Details of the search are given in an online-only document (eText 1, *http://links.lww.com/MPG/A396*). Duplicate articles identified in both Medline and Embase were manually deleted. The reference lists of selected studies were checked for further relevant studies.

Study Selection

Only cohort studies evaluating the diagnostic performance of FC concentration in paediatric patients suspected of having IBD were considered for review. Other study designs, such as case-control, are indeed prone to spectrum bias (13). In addition, the following inclusion criteria were applied: FC measurement and reference standard available for all of the paediatric participants (or a follow-up period long enough to exclude IBD), and sufficient data to calculate 2×2 tables.

Data Abstraction

The following data were extracted from each study on a predesigned form: the spectrum of the studied population (indication for testing, age, and sex), details of the index and reference test, and counts in the 2×2 table.

IPD Sets

For the IPD meta-analysis, we contacted the authors of the selected studies and invited them to share the raw, deidentified study data (FC level, age, sex, and final diagnosis). The raw data were checked for internal consistency against the summary results published in the original article. Some small discrepancies were found, discussed with the authors, and ascertainable divergences were corrected.

Quality Assessment

The quality of the included studies was assessed using the revised QUADAS tool (14). Because the calprotectin assay is an objective measurement, 3 of 14 items were omitted: blinded interpretation of the index test, availability of clinical data, and reporting of uninterpretable results. Two reviewers independently answered the 11 remaining questions in the affirmative, in the negative, or as being unclear.

Data Synthesis and Statistical Analysis

Literature-Based Meta-Analysis

The aggregate data meta-analysis was performed in Stata/SE version 11.2 (StataCorp, College Station, TX) using the Midas command (15). Accordingly, summary statistics for all of the diagnostic performance indices were calculated within the bivariate mixed-effects logistic regression modelling framework. Between-study heterogeneity of the results was assessed graphically by using forest plots of the diagnostic odds ratios (ORs), and statistically by using the χ^2 test of homogeneity and the inconsistency index (I^2) (16). An I^2 value $>50\%$ was taken to indicate significant heterogeneity. The potential for publication bias was estimated by using a Deeks' funnel plot. As recommended, $P<0.1$ was considered statistically significant (17). A hierarchical summary receiver operating characteristic graph with 95% confidence interval (CI) region and 95% prediction region was constructed.

Individual Patient-Based Meta-Analysis

Although we largely prefer the analytical approach using logistic regression, we also evaluated the diagnostic performance of FC based on the merged individual data. The diagnostic performance was calculated through the MedCalc software, version 11.5.01. (MedCalc Software, Mariakerke, Belgium).

Logistic Regression Analysis: Predicted Probability

The contribution of calprotectin concentration and age as continuous variables, and sex and study as categorical variables, to the diagnosis of IBD was explored using stepwise forward (LR) binary logistic regression analysis. The logit and logistic commands in Stata/SE 10.1 were used. An entry probability for each variable was set at 0.05. A clinical prediction rule was derived from the final regression model (see eText 1, *http://links.lww.com/MPG/A396*, for calculation details).

RESULTS

Description of Studies

Our search (Fig. 1) returned 161 citations. After removal of 36 duplicates and because 104 of the abstracts were considered not pertinent, 23 records were retrieved as full texts. An additional 4 studies were excluded because of the inappropriateness of the population studied. Insufficient information was available for constructing a 2×2 table from 3 studies. Eventually, 8 cohort studies fulfilled the inclusion criteria (18–25). A ninth relevant population-based cohort study was discovered in a recently published diagnostic meta-analysis (5). The original study (26) does not provide data to construct a 2×2 table, but the meta-analysis does.

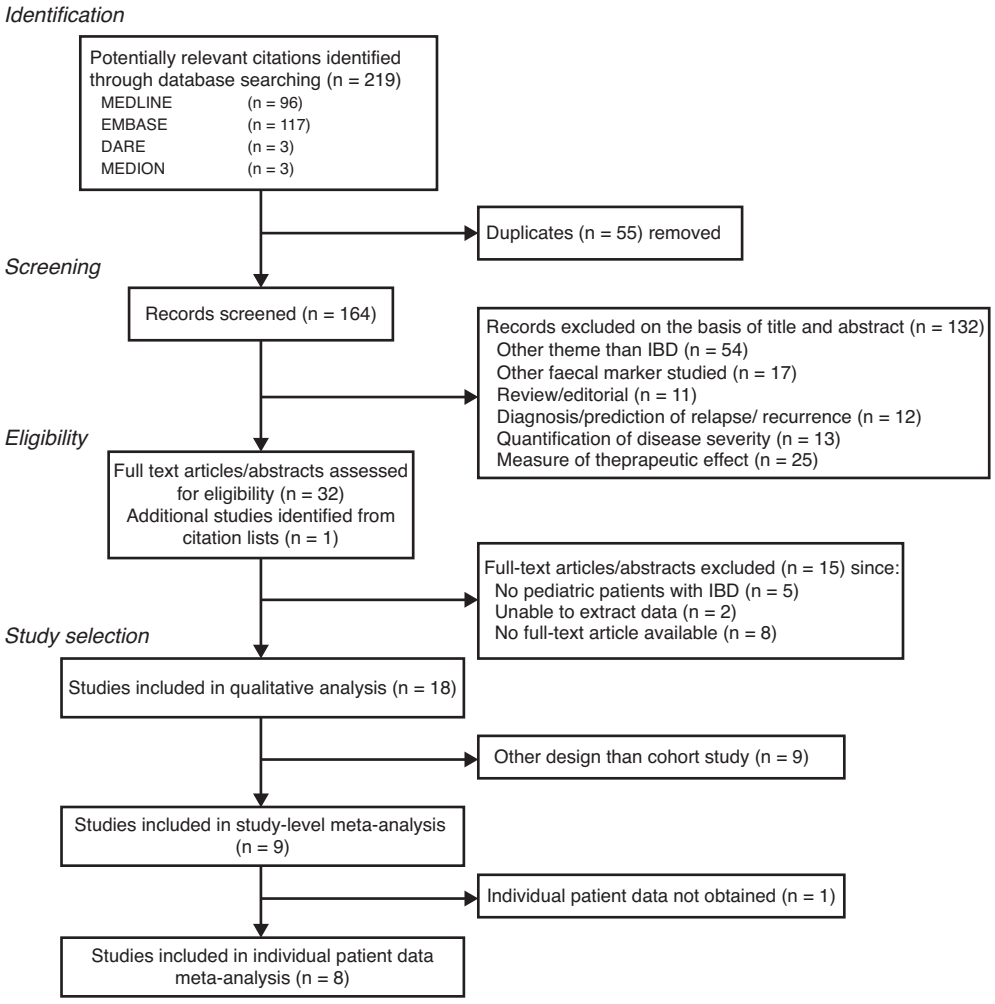

FIGURE 1. Flowchart showing the search for and selection of papers evaluating FC in children with suspected IBD. The final search was carried out on April 1, 2012. FC = faecal calprotectin; IBD = inflammatory bowel disease.

The authors of 8 cohort studies (18–25) were willing to share a dataset with IPD (age, sex, calprotectin concentration, and final diagnosis). Age and sex were not available from the Diamanti et al study owing to a computer crash. The authors of the Ashorn et al article (18) provided data on 31 additional patients recruited after the publication of their study results. In the most recently published study (25), not all of the patients underwent endoscopy, but a sufficiently extended follow-up period (disease-free period of 6 months) should minimise the risk of verification bias (27). To completely eliminating this type of bias, we excluded the 43 patients without histologically confirmed IBD from the IPD meta-analysis. The Norwegian group (26) justified their refusal by arguing that the data will again be used for their own follow-up study. None of the authors are aware of missed (un)published diagnostic accuracy studies fulfilling the selection criteria.

Characteristics of Included and Excluded Studies

All 9 included cohort studies (18–26) were undertaken in referral centres for paediatric gastroenterology and involved 853 patients from the toddler age group to young adults. Table 1 summarises the characteristics of the study population, a description of the applied index and reference tests, and the findings. In 1 study (19) 4 patients were excluded because infectious gastroenteritis was the final diagnosis. Upon enquiry, none of the authors were aware of similar patients in whom readily available diagnostic investigation could have prevented unjustified study entry and unnecessary false-positive or true-negative cases. Another study (24) contained 16 patients whose calprotectin results were expressed as greater or less than a numerical value. These test results were substituted by a value midway between the reported numerical value and a higher or lower value present in the dataset. This procedure is unlikely to influence the test accuracy parameters because 14 of the 16 adjusted values were situated in the highest or lowest quintile. The bar graph in eFigure 1 (*http://links.lww.com/MPG/A395*) is a representation of the quality of the 9 selected cohort studies (18–26).

Summary Results for All Included Studies

Literature-Based Meta-Analysis

A summary of test accuracy estimates is shown in Table 2. The Cochran Q test and the I^2 values are indicative for substantial heterogeneity (28). Figure 2 shows a forest plot of the diagnostic OR and the pooled estimate for the 9 cohort studies (18–26). The

TABLE 1. Characteristics and 2 × 2 data of all included studies

References	Patient characteristics: Setting, location	Patient characteristics: Spectrum	Patient characteristics: Age range or mean (SD), y	Patient characteristics: Female/male (n)	Index test	Cutoff value (μg/g)	Reference test	Prev	TP	FP	FN	TN
Ashorn et al (18)	Children's Hospital, University of Helsinki, Helsinki, Finland	Suspicion of IBD	5.8–19.9	50	PhiCal Test	100	Histopathology	0.80	39	1	5	10
								0.84	62	1	10	13
Berni Canani et al (19)	Paediatric Gastroenterology Unit, Naples, Italy	Children referred for initial assessment of suspected IBD	Non-IBD 11.0 (3.3) CD 14.5 (5.1) UC 11.0 (5.0)	21/24	Calprest	95.3	Standard diagnostic criteria, including histopathology	0.60 ↓ 0.66	25	2 ↓ 0	2	16 ↓ 14
Diamanti et al (20)	Paediatric Gastroenterology and Nutrition Unit, Rome, Italy	Children referred for recurrent abdominal pain and altered bowel habits	Non-IBD 1–1 IBD 1–18	88/109	Calprest	100 160	Histological examination	0.59 0.59	117 117	26 16	0 0	54 64
Fagerberg et al (21)	Department of Gastroenterology, Stockholm and Paediatrics, Västerås, Sweden	Scheduled for colonoscopy to rule out IBD; no bacterial gastroenteritis	IBD 6.7–17.8 Non-IBD 6.5–17.3	19/17	Calprest	50	Conventional histopathological criteria for diagnosis of IBD	0.56	20	2	0	14
Henderson et al (22)	Paediatric Gastroenterology Department, Edinburgh, UK	Children evaluated for suspected bowel inflammation	IBD 12.6, IQR 9.5–14.0 Non-IBD 9.3, IQR 5.2–12.7	79/111	PhiCal Test	50	Complete endoscopic evaluation + biopsies, small bowel imaging plus follow-up of ≥12 mo	0.48	89	55	2	44
Kolho et al (23)	Children's Hospital, University of Helsinki, Helsinki, Finland	Children undergoing colonoscopy	0.9–18 9.8 (4.7)	29/28	Phical Test	50 100	Colonoscopy + histology	0.54 0.54	28 27	10 8	3 4	16 18
Perminow et al (26)	Southeastern Norway	Children with suspected IBD (treatment naive)	IBD 0.8–17.9 Non-IBD 1.9–18	95	?	160	Histopathological (Porto criteria)	0.63	54	14	6	21
Sidler et al (24)	Gastroenterology Outpatient Clinic, Randwick, Australia	Symptoms suggestive of an organic gut disease	Non-IBD 2.2–15.5 IBD 2.4–16	24/37	PhilCal test	50	Standard diagnostic criteria, including histopathology	0.51	31	10	0	20
Van de Vijver et al (25)	Department of Paediatric Gastroenterology, Groningen, the Netherlands	Clinical suspicion of IBD	IBD 6–18 Non-IBD 6–18	61/56	Calpro ELISA test	50	Esophagogastroduodenoscopy and ileocolonoscopy including histopathological verification or 6 mo follow-up	0.36	42	20	0	55

CD = Crohn disease; ELISA = enzyme-linked immunosorbent assay; FN = false-negative; FP = false-positive; IBD = inflammatory bowel disease; IQR = interquartile range; TN = true-negative; TP = true-positive; UC = ulcerative colitis.

TABLE 2. Numerical results of the literature-based meta-analysis (FC for the diagnosis of IBD)

Parameter	Estimate (95% CI)	Cochran-Q (P)		Inconsistency (I^2) (%) (95% CI)
Sensitivity	0.97 (0.92–0.99)	30.21	0.00	73.52 (55.84–91.20)
Specificity	0.70 (0.59–0.79)	34.33	0.00	76.70 (61.62–91.77)
DOR	86 (25–300)	1133.20	0.00	99.29 (99.14–99.45)
LR+	3.2 (2.3–4.5)	39.24	0.00	66.87 (66.87–92.36)
LR−	0.04 (0.01–0.12)	21.09	0.01	62.06 (34.57–89.56)

Test performance parameters and their 95% CI along with Cochran-Q and inconsistency are presented in the table. CI = confidence interval; DOR = diagnostic odds ratio; FC = faecal calprotectin; IBD = inflammatory bowel disease; LR+ = likelihood ratio of a positive test; LR− = likelihood ratio of a negative test.

average prevalence of IBD in the cohort studies was 0.54. Accordingly, the posttest probability of a positive calprotectin test could be estimated to be 0.79 (95% CI 0.72–0.85). The posttest probability of a negative calprotectin test is 0.05 (0.01–0.14). Figure 3 shows the hierarchical summary receiver operating characteristic graph with 95% CI region and 95% prediction region.

Publication bias was assessed by Deeks' funnel plot asymmetry test for small study effect/publication bias. The non-significant slope ($P = 0.62$) indicates that no significant bias was found.

Individual Patient-Based Meta-Analysis

IPD on final diagnosis and FC were collated from 742 children from 8 studies (18–25). The studies were significantly different with respect to age ($P = 0.004$, 1-way analysis of variance [ANOVA] test), mean FC concentration ($P < 0.001$, 1-way ANOVA test), and area under the receiver operating characteristic (ROC) curve (AUC; $P = 0.001$, 1-way ANOVA). The pretest probability ranged from 0.51 (95% CI 0.39–0.63) to as high as 0.84 (0.75–0.90).

In the pooled dataset of all of the children, the ''optimal'' cutoff value (the value with the highest accuracy – minimal false-negative and false-positive results) for FC was 212 μg/g corresponding with a sensitivity of 0.90 (95% CI 0.87–0.93), a specificity of 0.85 (0.81–0.88), a positive LR of 5.99 (4.6–7.8), and a negative LR of 0.11 (0.09–0.20). The AUC of FC for the diagnosis of paediatric IBD was 0.94 (95% CI 0.92–0.95).

Logistic Regression Analysis: Predicted Probability

The results of the logistic regression analysis (eText 1, *http://links.lww.com/MPG/A396*) disclosed that calprotectin concentration, age, and study centre were independent predictors of IBD. The influence of study centre (LR test significant) confirms heterogeneity across the studies.

Outside the 8 study centres, a regression equation containing a term related to the study centre is not of use; therefore, the impact of study centre on the diagnosis was omitted from the final regression model: $\text{logit}(P) = S = -3.294 + 0.004 \times \text{FC} + 0.175 \times \text{AGE}$, where the explanatory variable FC is the FC concentration in micrograms per gram and AGE is the age in years. The predictivity of this simplified model was evaluated by ROC curve analysis. The estimated AUC for the final model was calculated to be 0.92 (95% CI 0.89–0.94). The logistic model using calprotectin concentration and age predicts IBD correctly in 85.5% (466/545) of children (sensitivity 0.81; 95% CI 0.76–0.85), specificity 0.92 (0.88–0.95), positive predictive value 0.93 (0.89–0.96), and negative predictive value 0.73 (0.72–0.83).

The probability of having IBD is determined by the equation: $P = \exp(S)/(1 + \exp(S))$. We programmed an Excel spreadsheet (eFile1, *http://links.lww.com/MPG/A397*) computing the probability (with CI) of having IBD for each combination of FC, age, and disease prevalence. Figure 4 illustrates that assuming a disease prevalence of 56%, an FC of 700 μg/g in a 6-year-old child corresponds to an IBD probability of 64% (95% CI 52–71). This prediction lacks precision and the posttest probability is hardly improved compared with the average pretest probability. In a 17-year-old adolescent the same test result makes the diagnosis

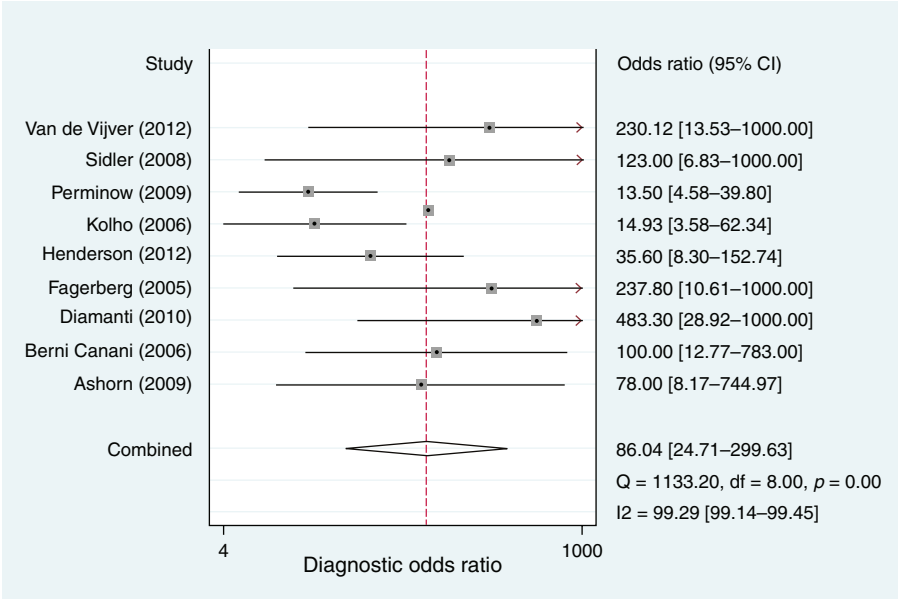

FIGURE 2. Forest plot of diagnostic OR of each individual cohort study, pooled odds ratio, Cochran-Q test heterogeneity and I^2 statistic for inconsistency. CI = confidence interval; OR = odds ratio.

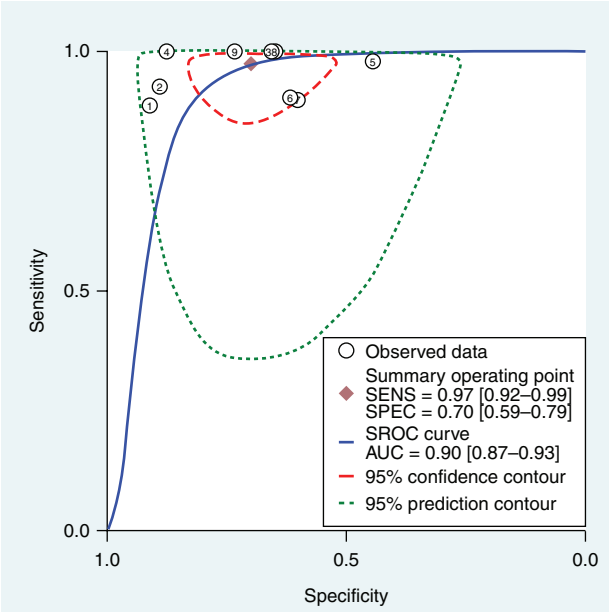

FIGURE 3. Summary ROC space of sensitivity and specificity for FC in the diagnosis of paediatric IBD. The circles depict the observed bivariate pairs of sensitivity and specificity of the 9 diagnostic cohort studies (18–26). The blue solid line is the summary ROC curve. The diamond is the bivariate summary point. The red dashed line triangle is the bivariate boundary of the 95% CI region for the bivariate summary point, and the green dotted line encloses the 95% prediction region. The study numbers correspond to those reported in Table 1. AUC = area under the ROC curve; CI = confidence interval; FC = faecal calprotectin; IBD = inflammatory bowel disease; SROC = summary receiver operating characteristic.

quite probable, but ruling out IBD at this age and this pretest probability is practically impossible.

DISCUSSION

This systematic review has provided an updated aggregate data meta-analysis confirming the high diagnostic accuracy of FC for the detection of IBD in referral centres for paediatric gastroenterology. In addition, a meta-analysis using individual participant data enabled us to develop an algorithm predicting that the probability of having IBD depends on the FC level and the age of the child. This was previously not recognised.

The literature-based meta-analysis indeed confirms that FC has an excellent overall sensitivity of 0.97 (95% CI 0.92–0.99) and a modest specificity of 0.71 (0.59–0.80) for diagnosing paediatric IBD. A first observation is that, owing to the relatively small number of pooled investigated patients, the imprecision of the predictive values is considerable.

In addition, although we used recommended, robust state-of-the-art statistical methodology (29), the estimation of summary points does not hold true if the included studies have used different threshold values (30). For the clinician, it is not evident at which cutoff value the calculated summary estimates of the test accuracy measures apply. Therefore, we recalculated the diagnostic performance of FC using merged IPD. The ''optimal'' cutoff for the whole group equals 212 μg/g. Taking into account the pretest probability and the LRs, the clinician can now better interpret a test result and discuss the predictive value with the patient and his or her parents. We should, however, realise that the predictive values or LRs are applicable to the whole group of patients presenting with a test result above or below the threshold and that dichotomising carries with it a loss of information for the individual child (31). This drawback can be overcome by using logistic regression analysis, a technique that allows taking into consideration patient-level covariates as well.

The contribution of age in the prediction of IBD turned out to be significant. FC concentrations have been shown to be higher in preschool children, especially infants, than in older children (32,33). This age dependency does not seem to play an important role in our logistic regression model because there is no significant correlation between age quartile and FC in non-IBD subjects ($r = -0.06$, $P = 0.34$). In contrast, the prevalence of IBD is significantly increased with higher age quartile (χ^2 test, $P < 0.0001$), suggesting that the age factor corrects for the age-dependent prevalence.

Our literature search revealed some of the well-known shortcomings in the quality and reporting of diagnostic research (27). We had to exclude nearly half of the paediatric accuracy studies because they used a case-control design known for introducing spectrum bias (13). None of the studies prespecified a target value for sensitivity, specificity, predictive accuracy, and a minimal acceptable lower confidence limit, enabling sample size calculation

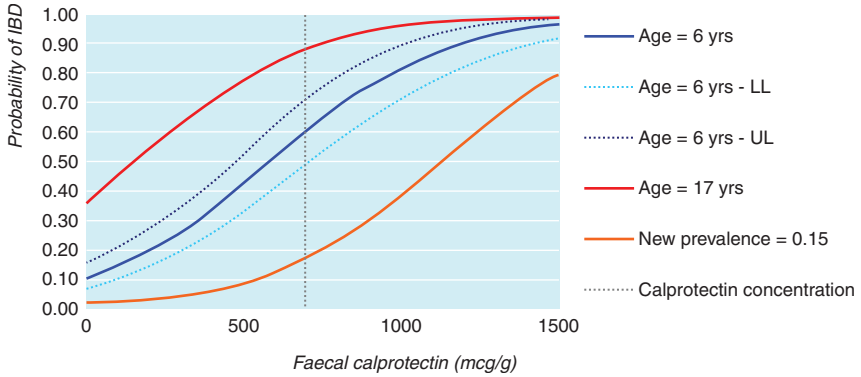

FIGURE 4. Plots of the predicted probabilities as a function of FC concentration, age, and disease prevalence. This figure illustrates that age has an important additional value for calprotectin testing for the diagnosis of IBD. CI = confidence interval; FC = faecal calprotectin; IBD = inflammatory bowel disease; LL = lower limit of 95% CI; UL = upper limit of 95% CI.

(34,35). Admittedly, neither did we define a target region within which the summary estimates of our meta-analysis should fall. We suggest that the absence of a predefined target makes authors undeservedly enthusiastic about the diagnostic value of an index test.

Our meta-analysis differs in some aspects from the study of van Rheenen et al (5). They included 1 study that we excluded (36), whereas we added 3 new studies totalling 404 participants (20,22,25). Golden (personal communication, March 18, 2010) discouraged us from using her group's data (36) because Magne Fagerhol's original assay, measuring calprotectin as milligrams per litre assay buffer, does not correlate well with the new commercial assays expressing the results as micrograms per gram faeces.

The major difference between the results predicted by van Rheenen et al (5) and this article is the IPD meta-analysis. As already known, the collection of IPD is time-consuming and difficult. A high level of persuasiveness was needed to collect the raw study data from 8 of the 9 cohort studies. Consequently, we could use easily available patient characteristics and the original continuous calprotectin data instead of the dichotomised study results in a logistic regression analysis. It is also noteworthy that we detected and could correct small discrepancies between the raw data and the published data.

By publishing all of the available raw data (eTable 1, *http://links.lww.com/MPG/A398*), we comply with the appropriate and growing request to share complete data, allowing re-analysis by the reader and sequential meta-analysis if new studies appear. There is indeed a growing awareness that sharing data is an ethical obligation (37–42).

Compared with the systematic review of van Rheenen et al (5), the key strength of our study is the IPD meta-analysis. Although a literature-based meta-analysis provides a good overall impression of the diagnostic accuracy of the test, pooling of studies with different diagnostic thresholds (50–160 μg/g faeces) precludes the calculation of the predictive value at a self-selected threshold or the patient's result. Only IPD permits prediction based on numerical test results and adjustment for patient characteristics. Our prediction tool calculates an individualised disease risk with accompanying confidence range taking into account the FC concentration and the patient's age. In a paediatric gastroenterology referral centre, ruling out IBD is difficult in older children, whereas in younger patients a higher FC concentration is needed to obtain a posttest probability larger than the prevalence.

Our search methodology aimed to avoid language and citation bias, but we cannot exclude publication or reporting bias in our meta-analysis. Publication bias is probably even more of a problem for diagnostic and prognostic than for therapeutic studies (43,44). The effects of reporting bias in therapeutic meta-analyses have been shown to be substantial (45).

Our IPD meta-analysis may also experience availability bias. Data from 2 large studies are incomplete or unavailable. In this context, it is noteworthy that the study of Perminow et al (26) was not intended to be a diagnostic accuracy study and showed the lowest diagnostic OR.

We also recognise that the number of patients in the meta-analysis is limited. Therefore, the precision of the diagnostic accuracy measures and our predictive algorithm leaves room for improvement. Furthermore, the final logistic regression equation contains only 2 independent variables. This likely represents an oversimplification of a complex clinical diagnostic process, including information collected during history taking and physical examination. The user of the algorithm should be aware of this. Other laboratory test results, such as C-reactive protein, haemoglobin, and iron indicators, could improve diagnostic precision but were not available for this study. Clinical suspicion or ''gut feeling'' may also be of additional diagnostic value.

Finally, the between-study heterogeneity is of concern and not fully understood. Although the selection criteria are more or less the same (suspected IBD), between-study differences were shown for age and FC concentration. The prevalence of IBD varied from 51% to 84%, and the false-positive rate ranged from 0% to 29% suggesting dissimilar study entry criteria. We have also noticed that there was a negative, just significant linear correlation ($r = -0.71$, $P = 0.049$) between prevalence and the false-positive rate.

Differences in clinical laboratory measurement procedures for FC may be another source of heterogeneity (46). We know that even small analytic biases can indeed shift the laboratory values and lead to diagnostic misclassification (47,48).

Implications for Clinical Practice and Future Research

Despite the absence of validation, and given the mentioned concern about study heterogeneity and (reporting) bias, our predictive algorithm is presently the best available tool for predicting IBD in the individual child. As such it deserves a valid place in the decision-making process.

We nevertheless advocate a large prospective multicentre study to improve and refine the IBD screening tool. More data are needed to validate the prediction algorithm on a different dataset to improve the precision of the tool. Every effort should be made to standardise and harmonise calprotectin measurements, and the predictive value of other clinical variables and (faecal) biomarkers (49,50) should be investigated simultaneously.

CONCLUSIONS

Using an IPD meta-analysis and through regression modelling, we identified FC concentration and age as independently associated with the diagnosis of IBD. We developed a prediction rule that enables the practicing paediatric gastroenterologists to numerically interpret the FC value together with the patient's age. As such, this rule can be a valuable adjunct to the diagnostic armamentarium making physicians and patients/families better equipped to make personalised decisions.

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