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Feasibility of an 8-item questionnaire for early diagnosis of inflammatory bowel disease in primary care

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Abstract

Aims: Diagnosis of inflammatory bowel disease (IBD) is often associated with a diagnostic delay. Although faecal calprotectin is a helpful screening tool, the widespread use in primary care (PC) may not be appropriate due to the low prevalence of IBD in this setting. To increase pretest probability for a positive calprotectin test, an 8-item questionnaire (CalproQuest) was tested for its feasibility and acceptability in PC.

Methods: Population: PC patients with unspecific gastrointestinal complaints for at least 2 weeks. The CalproQuest consists of four major and four minor questions specific for IBD. It is considered positive if greater than or equal to two major or one major and two minor criteria are positive. Primary outcome: feasibility of CalproQuest, secondary outcome: patient's acceptance of stool sampling.

Results: Of 95 patients with a complete CalproQuest 52 (54.7%) were positive, 39 (41.1%) fulfilled two major and 13 (13.7%) one major and greater than or equal to two minor criteria. Twenty-seven general practitioners completed 83 (87.4%) questionnaires on feasibility which was assessed positive. Eighty-two patients (86.3%) completed questionnaires on acceptance which was high.

Conclusion: The CalproQuest is a feasible instrument for assessing IBD in PC. Further prospective studies concerning validity and cost effectiveness of a combined use with the calprotectin test in this setting are necessary.

KEYWORDS

calprotectin, Crohn's disease, diagnostic delay, early diagnosis, feasibility, general practitioner, inflammatory bowel disease, primary care, ulcerative colitis

1 | INTRODUCTION

Abdominal pain is one of the most frequent symptoms in primary care (PC).[1,2] In the United States, where respective data have been collected, 2.5 million consultations due to abdominal pain were recorded per year.[3] General practitioners (GP) often face the diagnostic challenge of identifying patients in need for further diagnostics and differentiating patients with inflammatory bowel disease (IBD) from

Abbreviations: Crohn's disease, (CD); Indeterminate colitis, (IC); Inflammatory bowel disease, (IBD); Irritable bowel syndrome, (IBS); Ulcerative colitis, (UC); 8-item questionnaire to increase pretest-probability for a positive test result of the faecal Calprotectin test, (CalproQuest); General Practitioner, (GP)
Trial registration number: ISRCTN66310845.

functional disorders such as irritable bowel syndrome (IBS). Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC) represent the three subtypes of IBD.[4] Estimated prevalence of IBD in the Swiss population is 205 cases per 100 000 (0.2%).[5] Meanwhile, the prevalence of IBS in Europe and North America is estimated at 10% to 15%.[6] Symptoms similar to IBS are frequently reported in patients before IBD is diagnosed.[7] Difficulties in recognizing early IBD, especially in PC, lead to considerable diagnostic delay in IBD,[4] which has been shown to be correlated with an increased risk of bowel stenosis and CD-related intestinal surgery.[8]

The gold diagnostic standard for IBD is endoscopy. However, not every patient with abdominal discomfort or pain in PC can be investigated by means of an invasive endoscopic exam. Therefore, different non-invasive markers were developed to reduce the number of necessary endoscopies and hence to increase the likelihood of positive endoscopic results. Several studies, mainly originated in specialist care, have shown that faecal calprotectin reflects intestinal inflammation in patients with known IBD.[9,10-12,13-15] It has also been shown to differentiate IBD from IBS due to its good negative predictive value in discriminating IBD versus IBS, depending on the cutoff value used.[16,17,18.19] Although calprotectin tests are easily accessible and reimbursed in Switzerland, this diagnostic test is not routinely performed in PC. The reasons here have not yet been systematically elaborated; we assume the following considerations to play a role: (1) the low prevalence of IBD in general practice. When analysing the reasons for encounter in PC, it becomes clear that digestive disorders are frequent complaints with a prevalence of 5% to 7%.[20,21] Considering the population-based prevalence of 10% to 15% of IBS compared with 0.2% of IBD, IBS is much more common in PC. (2) This consideration combined with the large amount of differential diagnosis for a positive calprotectin test besides IBD (esophagitis, gastritis, gastric ulcers, celiac disease, polyps and carcinomas, infections gastroenteritis, diverticulitis, microscopic and ischemic colitis, NSAR enteropathy, use of proton pump inhibitors, lactose intolerance) narrows the utility of the calprotectin test in this setting, besides (3) the relatively high costs (currently about 60 Euros).

Data assessing the diagnostic accuracy of the calprotectin in the PC setting are scarce. In this setting, the pretest probability for a positive calprotectin is naturally low due to low prevalence of IBD. It is hence not astonishing that studies from PC indicate a questionable diagnostic accuracy.[22-25] To increase pretest-probability for a positive calprotectin test and hence to increase its utility in the PC setting, an 8-item questionnaire (CalproQuest) was tested for its feasibility in PC.

2 | METHODS AND ANALYSIS

2.1 | Ethics, trial registration, informed consent, and funding

- Ethics: The study protocol was approved by the Ethics Committee of the Kanton Zurich (reference KEK-ZH-number 2013-0516).
- The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.
- Trial registration number: ISRCTN66310845.
- Written, informed consent was obtained from each patient included in the study.
- Funding: This project is supported by grants from the IBDnet, Swiss Research and Communication Network on Inflammatory Bowel Disease, and the "Gottfried und Julia Bangerter-Rhyner-Stiftung," fund of the Swiss Academy of Medical Sciences. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

2.2 | Study design

This study is a part of the prospective diagnostic ALERT trial (VAlidation of an 8-item questionnaire predictive for a positive caLprotectin tEst and Real-life implemenTation in PC to reduce diagnostic delay in IBD), consisting of two independent parts A and B, conducted by gastroenterologists (A) and GPs (B). The details of the study design, including recruitment of patients and physicians, administration of patient records, informed consent, and confidentiality have been published previously.[26] Patients included in the study presented at their GP because of ongoing unspecific gastrointestinal symptoms for at least 2 weeks (abdominal pain, bloating, stool irregularities, diarrhoea). The study design and including the study flow is shown in Figure 1.

2.3 | Inclusion and exclusion criteria

Inclusion criteria:

- ≥18 years
- GP visit due to on-going unspecific gastrointestinal symptoms (abdominal pain, bloating, stool irregularities, diarrhoea) for at least 2 weeks
- No earlier diagnostic procedures (endoscopy) for the current episode

2.4 | Informed consent

Exclusion criteria:

- <18 years
- Known further/other abdominal pathologies as, eg, cancer
- Previous abdominal surgeries
- Treatment with steroids (topical and/or oral) and/or amino salicylates within 30 days prior inclusion into this study
- Endoscopic examination within 3 years prior screening

2.5 | Procedure (see also Figure 1)

- Patients were subjected to CalproQuest.

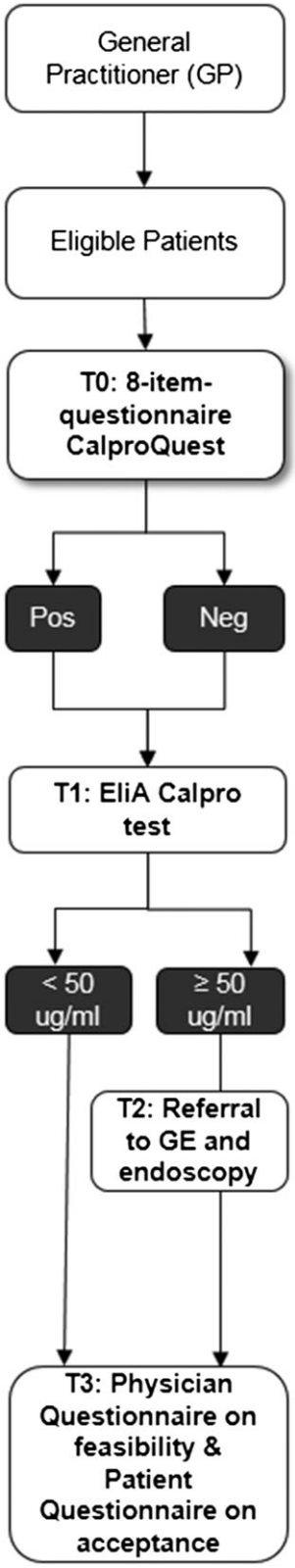

FIGURE 1 Study flow feasibility of CalproQuest Legend: Neg = negative; Pos = positive. GP: General practitioner

- Patients obtained faecal samples to measure calprotectin levels. Besides the possible diagnostic utility concerning the patient's complaints, the calprotectin was measured also in order to test for patient acceptance of stool sampling. No statement is possible concerning the validation of the CalproQuest with the calprotectin measures due to under powering.

- Patients completed the questionnaire on acceptance of stool sampling and physicians completed the questionnaire on feasibility of CalproQuest in daily practice.

- According to the current standard of care, patients with calprotectin levels ≥50 μg/g were referred to a gastroenterologist for endoscopic examination. It was at the discretion of the GP to follow this advice. The GP was informed about results of the endoscopy, and he forwarded these results to the study center.

2.6 | CalproQuest

CalproQuest is an 8-item IBD questionnaire consisting of four major and four minor questions specific for IBD (Table 1). The CalproQuest is considered positive, if greater than or equal to two major criteria or one major criterion and two minor criteria are answered positively. We assumed that a positive CalproQuest result might predict calprotectin levels ≥50 μg/g. Calprotectin levels above 50 μg/g are indicative for ongoing intestinal inflammation and call for further endoscopic examination.

2.7 | Faecal calprotectin

Faecal calprotectin levels were measured at the University Hospital Zurich. Specimens from outpatients were sent to the laboratory by post. The calprotectin test is called EliA calprotectin (Thermo Fisher Scientific) and uses the FEIA method (fluorescence enzyme immunoassay) on a fully automated system called Phadia 100. The EliA calprotectin Wells are coated with monoclonal antibodies to calprotectin. If present in the patient's specimen, calprotectin binds to the coated antibodies. After washing away non-bound components, enzyme-labelled antibodies against human calprotectin (EliACalprotectin Conjugate) are added to form a calprotectin-conjugate complex. After incubation, non-bound conjugate is washed away,

TABLE 1 CalproQuest (8-item IBD questionnaire)

Type	Criteria	Yes (1)	No (0)	Comment
Major	Does the patient suffer from abdominal pain at least 3 times a week for at least 4 weeks? Does the patient suffer from diarrhoea (more than three bowel movements daily) for 7 consecutive days? Does the patient have diarrhoea at night-time/does the patient awake from sleep because of abdominal pain or diarrhoea? Does the patient report bloody stool?			
Minor	Does the patient report mucus in stool for more than 4 weeks? Does the patient report unwanted weight loss (5% of normal body weight over 6 months)? Does the patient present with fever or report fever over the last 4 weeks (temperature > 38°C)? Does the patient report fatigue over the last 4 weeks?			

and the bound complex is incubated with a development solution. After stopping the reaction, the fluorescence in the reaction mixture is measured. The higher the response value, the more calprotectin is present in the specimen. To evaluate test results, the response for patient samples is compared directly with the response for calibrators.

2.8 | Questionnaires

The contents of the physician's questionnaire on feasibility and acceptance of CalproQuest in PC and the patient questionnaire on acceptance of stool sampling are provided within the Figures 2 and 3.

3 | PRIMARY AND SECONDARY OUTCOMES

Primary outcome: Feasibility of CalproQuest in daily PC practice.

Secondary outcome: Patient-reported acceptance of stool sampling.

3.1 | Statistical analysis

Likert-bar plots visualize feasibility of the CalproQuest and the patient-reported acceptance. For the comparison of symptoms of

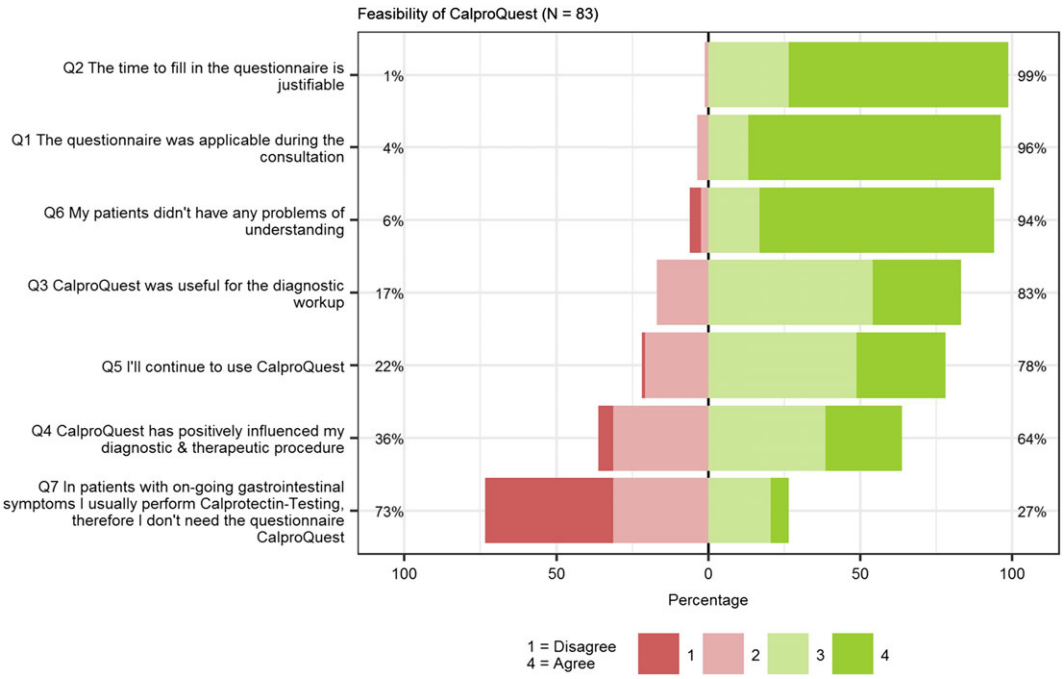

FIGURE 2 Feasibility of CalproQuest in daily primary care practice Legend: Four-level Likert scale: 1 (Strongly disagree) to 4 (Strongly agree)

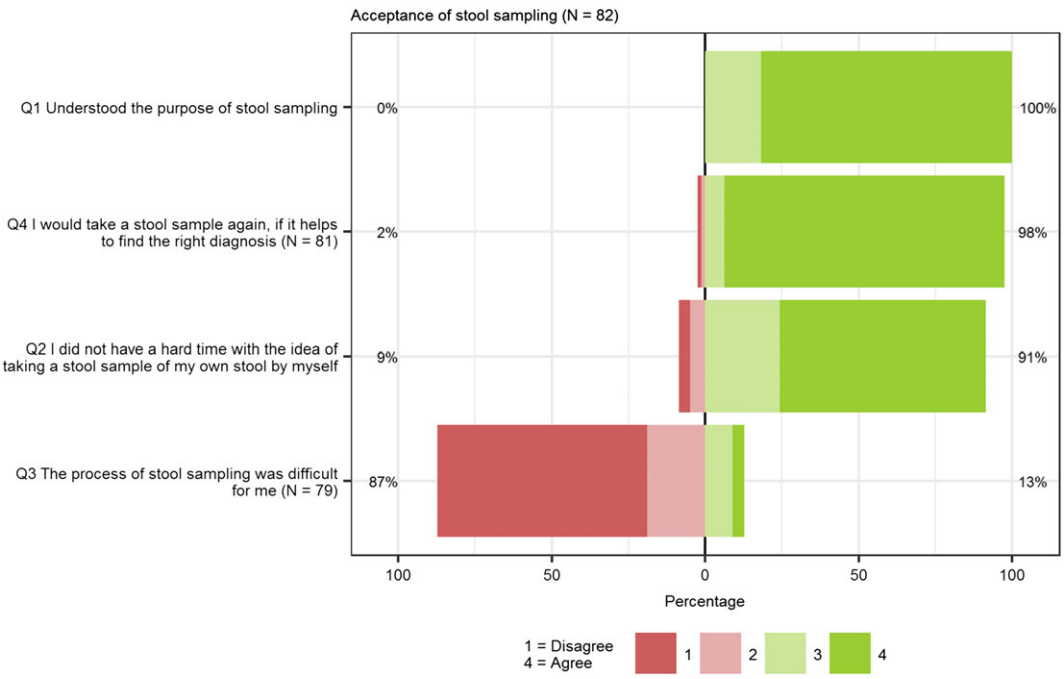

FIGURE 3 Patient-reported acceptance of stool sampling Legend: Four-level Likert scale: 1 (Strongly disagree) to 4 (Strongly agree)

patients with a positive or negative calprotectin, a Chi-square test was performed. $P < 0.05$ is considered statistically significant. Statistical analysis was performed with R (R version 3.3.2).[27]

4 | RESULTS

4.1 | Population

Recruitment of GPs started in October 2014 and ended in November 2016. Recruitment was performed by means of information events as well as mailings and personal contacts of the involved team. Therefore, no actual non-responder list was compiled. The study flow and Consort statement is shown in Figure 1 and Appendix A1. From 40 GPs, which were initially instructed, 35 finally agreed to participate and recruited patients. During study, one GP dropped out. The 34 GPs were mainly male (25, 73.5%), with a mean age of 49.4 years and working in practice since mean 12.4 years, mainly in group practices (30, 85.7%). Twenty-six (76.5%) GPs had used a calprotectin test before participating in the study.

The 34 GPs recruited between one and seven patients (mean 3.1), in total 98. From the 98 CalproQuests, 95 were complete. Eighty-four patients (mean [SD] age 38.0 [14.5] years, 57.1% female) with complete CalproQuests underwent calprotectin testing. From the 95 CalproQuests, 52 (54.7%) were positive, 39 (41.1%) fulfilled two major criteria, and 13 (13.7%) fulfilled one major and greater than or equal to two minor criteria. In 15 (15.8%), faecal probe concentrations of ≥50 μg/g calprotectin were found. In 9 (9.5%), the CalproQuest was likewise positive. The most common symptoms were abdominal pain (78, 80.4%) and diarrhoea (37, 38.1%). The most common minor criteria were fatigue (55, 56.7%) and slime in faeces (28, 28.9%). The distribution of symptoms did not show any significant difference between patients with calprotectin concentrations above or below 50 μg/g ($P = 0.8896$).

Since according to the study protocol, it was not mandatory for the GP to send patients with a positive Calprotectin to endoscopic evaluation, the data we received concerning endoscopic and histologic findings is far from complete. GPs sent the results of five endoscopies to the study center, of which four showed either no pathological findings or diverticulosis and/or polyps/adenomas, one showed evidence of CD.

4.2 | Primary outcome: Feasibility of CalproQuest in daily primary health care practice

Twenty-seven GPs completed or partially completed 83 (87.4%) questionnaires consisting of seven items. The detailed distribution of answers concerning feasibility of the CalproQuest is shown in Figure 2. All items concerning feasibility were assessed positive on the four-level even-point Likert scale. Only few GPs stated that they prescribe calprotectin tests in patients with ongoing gastrointestinal symptoms regularly and therefore do not need the CalproQuest.

4.3 | Secondary outcome: Patient-reported acceptance of stool sampling

Eighty-two patients (86.3%) completed or partially completed the patient questionnaire consisting of a four-level even-point Likert scale with seven items. All patients understood the rationale of faeces collection, and the patient-reported acceptance of stool sampling was high (Figure 3).

5 | DISCUSSION

Our study showed that the CalproQuest is a feasible instrument for the assessment of IBD in PC and that the patient reported acceptance of and understanding for stool sampling was high.

The rationale for the ALERT trial is the reduction of diagnostic delay in IBD patients. Since most patients present to their GP with unspecific abdominal complaints first, improving diagnostic procedures for diagnosing IBD patients in PC is one of the most important starting points to reduce diagnostic delay. However, following factors render the optimal diagnostic procedure extremely challenging in PC: reasons of encounter for digestive disorders are common (5%-7%),[20,21,28,29] but the prevalence of IBD extremely low (0.2%),[5] compared with a much higher prevalence of functional disorders (10%-15%).[6] In this low prevalence setting, pretest probability for positive diagnostic test results such as the calprotectin are naturally low.[23] Since not all patients with unspecific gastrointestinal complaints can undergo invasive endoscopic examination, it is of utmost importance that other non-invasive diagnostic procedures are developed to reduce morbidity and mortality of a diagnostic delay in IBD. To increase pretest probability for a positive calprotectin test and hence to increase its utility in the PC setting, an 8-item questionnaire (CalproQuest) was tested for its feasibility in PC.

Very few studies currently exist to compare our findings. Danese et al published a 21-item questionnaire, which was developed by means of a systematic literature review in which CD specialists identified "red flags," ie, symptoms or sings suggestive of CD.[30] Healthy as well as known CD patients were subjected to the questionnaire and had to recall symptoms. The questionnaire was able to successfully discriminate functional disorders from CD. This questionnaire however was not yet prospectively validated and not tested for feasibility, which seems necessary considering large content compared with the 7 items of the CalproQuest.

Contradictory to findings from other studies,[31] our study population showed a high acceptance concerning stool sampling, probably due to good communication skills of the GPs in our study population. The diagnostic strategy of combining a questionnaire with faecal sampling to measure calprotectin levels therefore seems feasible in the Swiss PC setting.

5.1 | Strengths and limitations

In the PC setting, this is one of the few existing studies on the noninvasive assessment of IBD, almost none of the former studies are prospective and most originate from secondary and tertiary care.[32] To our knowledge, the ALERT trial is the first attempt of prospectively developing a questionnaire for the assessment of IBD in PC.

According to the sample size calculation, targeted number of 80 patients assumed necessary for the feasibility testing in our study was more than achieved ($n = 95$). We abstained from

restrictive inclusion criteria for the participation in the study. Therefore, patients represent the typical clientele with unspecific gastrointestinal complaints, which the GP is confronted with in daily practice. We therefore consider the study population to be representative. The distribution of participating GPs concerning age and gender was similar to the statistics of the Swiss Medical Association[33]; therefore, generalizability can be assumed. Nevertheless, a selection bias of motivated GPs as well as patients cannot be neglected.

6 | CONCLUSION

The CalproQuest is a feasible instrument for the assessment of IBD in PC. Further prospective studies concerning the validity and cost effectiveness of a combined use with the calprotectin test in this setting are necessary.

7 | ETHICS and INFORMED CONSENT

7.1 | Ethics

The study protocol was approved by the Ethics Committee of the Kanton Zurich (reference KEK-ZH-number 2013-0516).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Written, informed consent was obtained from each patient included in the study.

FUNDING

This project is supported by grants from the IBDnet, Swiss Research and Communication Network on Inflammatory Bowel Disease, and the "Gottfried und Julia Bangerter-Rhyner-Stiftung," fund of the Swiss Academy of Medical Sciences. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

T.R., S.V., and G.R. were the initiators for this study. T.R. is the trial sponsor. T.R., S.V., G.R., and N.Z. developed the questionnaires. S.H., R.T., S.M., and T.R. organized the recruitment of the practices. S.H., O.S., T.R., and R.T. were involved in the development of the study protocol. S.H. wrote and revised the study protocol. C.C. analysed the study data. C.C., T.R., N.S., and O.S. interpreted the study data. C.C. wrote and revised the final manuscript, and all authors read revised and approved it.

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APPENDIX A1

CONSORT
TRANSPARENT REPORTING of TRIALS