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Acceptabilité de la calprotectine fécale chez les patients atteints de maladies inflammatoires chroniques de l'intestin : impact d'un dispositif alternatif de prélèvement des selles (étude ACCALMI)

Giulia Pasi

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FACULTÉ DE MÉDECINE

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Pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

HEPATO-GASTRO-ENTEROLOGIE

par

Giulia PASI

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**ACCEPTABILITÉ DE LA CALPROTECTINE FECALE CHEZ LES PATIENTS
ATTEINTS DE MALADIES INFLAMMATOIRES CHRONIQUES DE L'INTESTIN :
IMPACT D'UN DISPOSITIF ALTERNATIF DE PRÉLÈVEMENT DES SELLES
(ÉTUDE ACCALMI)**

Président : Monsieur le Professeur Arnaud BOURREILLE

Directeur de thèse : Madame le Docteur Catherine LE BERRE

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Table of contents

ABSTRACT	9
INTRODUCTION.....	12
1. Clinical utility of FC	12
<i>1.1. Assistance for the diagnosis of IBD in patients with gastrointestinal symptoms</i>	12
<i>1.2. Prediction of response to treatment</i>	13
<i>1.3. Monitoring mucosal healing and histological remission</i>	13
<i>1.4. Prediction of clinical relapse</i>	14
<i>1.5. Therapeutic de-escalation aid</i>	14
<i>1.6. Detection of post-operative recurrence in CD</i>	14
2. Variability of FC	15
<i>2.1. Pre-analytical phase of FC measurement</i>	15
<i>2.2. Analytical phase of FC measurement</i>	17
3. Acceptability and compliance with FC testing	18
4. Lessons from CRC screening	18
5. Objectives	19
MATERIALS AND METHODS.....	20
1. Study design and population	20
2. Ethics	20
3. Stool collection devices	21
4. Questionnaire administration	21
5. Demographic and clinical data collection	22
6. FC measurements	23
7. Study outcomes	23
8. Statistics	24
<i>8.1. Sample size calculation</i>	24
<i>8.2. Data analysis</i>	24
RESULTS	26
1. Description of the study population	26
<i>1.1. Patient demographics and characteristics at enrolment</i>	26
<i>1.2. Disease activity at the time of FC testing</i>	29
<i>1.3. Conditions for FC testing</i>	31
2. Acceptability of FC testing	32
<i>2.1. Missing data</i>	32
<i>2.2. Difference in FC acceptability</i>	32
<i>2.3. Verbatim feedback to argue acceptability rating</i>	35

2.4. <i>Factors associated with better acceptability</i>	36
2.5. <i>Compliance with FC testing</i>	38
DISCUSSION	39
CONCLUSION	44
SUPPLEMENTARY DATA	45
Supplementary Table 1. Factors and conditions associated with elevated FC levels.	45
Preliminary study: Agreement Between ProciseFCP™ and Bühlmann fCAL® turbo	46
<i>Methods</i>	46
<i>Results</i>	49
<i>Discussion</i>	53
<i>Conclusion</i>	54
REFERENCES.....	55
RÉSUMÉ.....	61

Acceptability of fecal calprotectin in patients with inflammatory bowel disease: impact of an alternative collection device for stool sampling (the ACCALMI study)

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Lay Summary:

The ACCALMI study showed that a sampling bottle significantly improves the acceptability and compliance of fecal calprotectin testing in IBD patients compared to a conventional container, making it easier and more comfortable to use. This innovative device could lead to better disease monitoring and improved health outcomes.

ABSTRACT

Background: Fecal calprotectin (FC) is a non-invasive biomarker that guides treatment decisions in inflammatory bowel diseases (IBD). Low compliance may hinder routine testing, with stool collection being the primary obstacle for patients. The objective of the ACCALMI study was to compare acceptability and compliance with FC testing using an alternative collection device (sampling bottle) to a conventional container for stool sampling in patients with IBD.

Methods: In this prospective study, patients were randomly assigned to either the standard laboratory method (Bühlmann fCAL® turbo) or the ProciseFCP™ assay. Acceptability was assessed using both qualitative and quantitative scales. Factors associated with improved FC acceptability, and compliance with FC testing, were analyzed. Importantly, only the stool sampling procedure was evaluated, not the general satisfaction with the ‘point-of-care’ assay.

Results: The ProciseFCP™ device significantly improved acceptability compared to the standard method, both on the ordinal scale (OR 2.69, $p < 0.001$) and the visual analog scale, although for the latter it did not reach the predefined threshold of a 30-point difference (95% CI: 19.7 to 44.7). The alternative collection device and living more than 50 km from the hospital were the only factor associated with better acceptability. Embarrassment and discomfort associated with the conventional stool container were mitigated by the sampling bottle. Compliance was similar and high in both groups (80%).

Conclusions: The ACCALMI study demonstrates that a sampling bottle offers a patient-friendly alternative to the conventional stool container, significantly enhancing patient’s acceptability with stool collection. These findings support the integration of patient-centric innovations in diagnostic testing to improve the monitoring and management of IBD.

Keywords: Crohn's disease; Ulcerative colitis; Monitoring; Biomarker; Compliance.

Abbreviations

BMI, Body mass index; CD, Crohn's disease; CI, Confidence interval; CRC, Colorectal cancer; CRP, C-reactive protein; EIM, Extra-intestinal manifestation; ELISA, Enzyme-linked immunosorbent assay; FC, Fecal calprotectin; FIT, Fecal immunochemical test; gFOBT, guaiac Fecal occult blood test; GNEDS, Groupe Nantais d'éthique en santé ; IBD, Inflammatory bowel disease; IBD-U, IBD-Unclassified; IQR, Interquartile range; NA, Not applicable; NPV, Negative predictive value; NSAIDs, Non-steroidal anti-inflammatory drugs; OR, Odds ratio; PGA, Physician global assessment; PtGA, Patient global assessment; POC, Point-of-care; PPIs, Proton pump inhibitors; PRO, Patient-reported outcomes; SD, Standard deviation; SES-CD, Simple Endoscopic score for Crohn Disease; TNF, Tumor Necrosis Factor; UC, Ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; VAS, Visual analog scale.

INTRODUCTION

The therapeutic objectives for inflammatory bowel diseases (IBD) have significantly evolved in the last decade. Initially focused on achieving clinical remission, the paradigm has shifted to include endoscopic remission, as outlined in the STRIDE consensus in 2015¹. More recently, the updated STRIDE-II consensus has made these therapeutic targets even stricter², leading the patients to undergo numerous examinations throughout their lives reflecting the chronic nature of their disease. However, the patient's convenience is taken into consideration with the addition of biomarker normalization as a therapeutic target in itself². Fecal calprotectin (FC) is a surrogate non-invasive marker for neutrophil infiltration in the intestinal mucosa, and elevated FC levels are indicative of intestinal inflammation³.

1. Clinical utility of FC

There is substantial evidence supporting the utility of FC for diagnosing IBD, predicting therapy response and monitoring disease activity or post-operative recurrence (*Table 1*). It is the most extensively studied fecal biomarker in IBD. However, interpreting its levels must consider its lack of specificity, as high concentrations can occur in various gastroenterological conditions unrelated to IBD (*Supplementary Table 1*).

1.1. Assistance for the diagnosis of IBD in patients with gastrointestinal symptoms

FC can help physicians in distinguishing IBD and irritable bowel syndrome by identifying those most likely to require endoscopy. Several meta-analyses and systematic reviews showed an overall sensitivity of 80 to 98% and specificity of 68 to 96% for FC cutoff values ranging from 30 to 100 $\mu\text{g/g}$ in adults^{4,5}. Most studies recommend a threshold of 50 $\mu\text{g/g}$ with an excellent negative predictive value (NPV) for diagnosing IBD. An FC level below 40 $\mu\text{g/g}$ is associated with less than 1% probability of having IBD⁵. Using FC is cost-effective, as it

reduces the number of unnecessary colonoscopies by about two-thirds, saving approximately 400 euros per patient^{4,6}.

1.2. Prediction of response to treatment

With STRIDE-II, normalizing FC has been defined as an intermediate treatment target in both ulcerative colitis (UC) and Crohn's disease (CD)². A post-hoc analysis of the GEMINI and VARSITY trials showed that a post-induction FC concentration below 250 µg/g in patients with UC was associated with a higher probability of achieving long-term clinical, endoscopic, and histological remission and a reduced probability of colectomy and UC-related hospitalizations⁷. In CD, FC normalization is slower, but a reduction of at least 50 % of its baseline level at week 12 is predictive of favorable long-term outcomes⁸.

1.3. Monitoring mucosal healing and histological remission

FC levels correlate with the degree of endoscopic and histologic inflammation⁹. In STRIDE-II, it is suggested to use a cutoff value of 150 µg/g to identify endoscopic healing². A value of FC < 100 µg/g is highly correlated with histological remission and Mayo endoscopic subscore of 0 in UC and with SES-CD < 3 in patients with colonic IBD¹⁰. A meta-analysis of 13 studies, including 744 UC patients and 727 CD patients, reported an overall area under the curve of 0.89 (95% confidence interval [CI] 0.86–0.92) for discriminating quiescent and endoscopically active IBD¹¹. FC is also positively correlated to the Lewis score in small bowel capsule endoscopy, effectively predicting significant inflammatory activity, but with a lower cutoff value in exclusively ileal disease (100 µg/g)¹².

1.4. Prediction of clinical relapse

Longitudinal monitoring of FC is useful in predicting relapse as it can identify patients at higher risk while their disease is still clinically inactive. FC levels start rising approximately 3 months before a relapse becomes clinically apparent¹³. Asymptomatic patients with consistently abnormal FC values have a 53–83% probability of clinical relapse within the 2–3 months¹⁴. On the other hand, patients with repeatedly normal FC measurements have a 67–94% probability of remaining in clinical remission over that same period. The CALM study in 2017 demonstrated that timely escalation of therapy, based on clinical symptoms and biomarkers (including an FC > 250 µg/g) in patients with early CD, led to better clinical and endoscopic outcomes than symptom-driven decisions alone¹⁵.

1.5. Therapeutic de-escalation aid

Therapeutic de-escalation is a daily challenge in managing patients with IBD, and FC serves as a prognostic factor for the risk of relapse in patients for whom it is considered. The STORI trial found that a baseline FC level above 300 µg/g was associated with higher risk of relapse after discontinuing infliximab therapy in CD patients receiving concomitant thiopurines¹⁶. Another multicenter study showed that an FC threshold of 200 µg/g highly predicted clinical relapse within 6 months¹⁷. The SPARE study, assessing the discontinuation of infliximab or immunosuppressant therapy in CD patients on combination therapy, involved bimonthly FC assessments. An FC level above 250 µg/g necessitated optimization, and levels over 300 µg/g were consistently linked to relapse¹⁶.

1.6. Detection of post-operative recurrence in CD

A post-hoc analysis of the POCER study indicated that FC was higher in patients with disease recurrence (Rutgeerts score \geq i2) than in those in remission (275 vs 72 µg/g; $p <$

0.001)¹⁸. This was significantly correlated with the presence and severity of CD recurrence. A threshold below 100 µg/g could avoid systematic ileocolonoscopies in 30% of patients after intestinal resection for CD, with a sensitivity of 95% and a NPV of 93%¹⁹.

Table 1. Suggested cut-off values of fecal calprotectin according to the indication.

Indication	Cut-off value (µg/g)
Assistance for the diagnosis of IBD (vs IBS)	50
Prediction of response to treatment (week 12)	UC: 250 / CD: ≥50% decrease
Monitoring endoscopic healing	Ileal disease or post-operative setting: 100 Colonic disease: 150
Monitoring histological remission	100

Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel disease; IBS, Irritable bowel syndrome; UC, Ulcerative colitis.

2. Variability of FC

The FC testing process includes pre-analytical and analytical phases, each critical to the accuracy of the results and potentially causing high intra-individual variability²⁰.

2.1. Pre-analytical phase of FC measurement

2.1.1. Timing

The optimal timing for stool collection is unclear. Some studies suggest a preference for sampling the first bowel movement of the day, as FC concentrations tend to rise with the time between bowel movements²¹. However, other studies showed that FC values widely vary between motions and that the highest or lowest FC values may also vary during the day^{22,23}. For now, patients' convenience should drive the collection timing. The analysis of only one stool sample is sufficient because intra-stool variability is low²⁴. Two commonly used drugs, namely non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs), have been identified as factors that can elevate FC levels²⁵. They should therefore be discontinued 4 weeks before FC testing for PPIs and 2 weeks for NSAIDs²⁰.

2.1.2. Stool collection

With most FC assays, stools should be collected in dedicated clean containers, without additives and avoiding any accidental contamination with urine or water. At least 100 mg of feces should be collected for traditional methods²⁰. Stool consistency can impact the level of FC with higher concentrations in liquid stools²¹. Thus, sampling of normally formed feces should be preferred and stool consistency should be taken into account when interpreting the results²⁰. However, it is unknown whether the influence of liquid stools on FC values is due to technical aspects of the collection, sampling heterogeneity, or increased disease activity.

2.1.3. Storage

Stool storage at room temperature is preferably limited to 3 days, although up to 1 week is still acceptable. Prolonged storage may result in decreased FC concentrations²¹. If the sample cannot be processed within 7 days, feces should be stored in a freezer at -20 C° by the laboratory for later processing²⁰.

2.1.4. Extraction

Sample pre-treatment is necessary to extract calprotectin from the feces. The gold standard method involves weighing a set amount of feces into the buffer²⁶. Variability in FC values has been observed due to different extraction devices and procedures^{27,28}. Moreover, significant differences in FC values have been noted when the analyzed sample was extracted from a single location of the feces²⁹. It is therefore recommended to use a mix of four different extractions from the same²⁰.

2.2. Analytical phase of FC measurement

All existing assays rely on immunochemical techniques using antibodies targeting different calprotectin epitopes. Detection methods include chemiluminescent, fluorescent, or immunoturbidimetric methods. Most of the kits use quantitative analysis since qualitative analysis has weak clinical value. Manual or semi-automated quantitative enzyme-linked immunosorbent assay (ELISA) is the standard quantitative test, but it is time consuming (more than 8 hours per test) and most laboratories only perform it every 1 or 2 weeks to analyze 35–40 samples at a time and therefore reduce costs. Automated tests are now available and allow individual analysis at any time. Point-of-care (POC) rapid tests (e.g. Quantum Blue®, ProciseFCP™) have lately been developed and allow to obtain a quantitative or semi-quantitative level of FC within 30 min. Finally, it is now also possible for the patient himself to measure FC at home by using a smartphone application (e.g. IBDoc®, QuantOnCal®, and CalproSmart™)³.

The proliferation of these tests raises concerns about inter-assay variability, as incomplete harmonization may compromise appropriate clinical use of FC. The diagnostic accuracy of automated tests³⁰ and POC tests^{31,32} seems equivalent to the traditional ELISA method but there is insufficient evidence to support the use of one specific FC test over another²⁰. Indeed, a comparative study evaluated three rapid POC tests, two standard ELISA tests, and one automated fluoroimmunoassay, and showed that all methods significantly correlated with comparable clinical performance for IBD diagnosis, but showed up to 5-fold quantitative differences between assays³³. Regarding home-based tests, a comparative study showed that IBDoc® FC measurements were in agreement with measurements made by the POC test Quantum Blue® and standard ELISA analysis as long as concentrations were < 500 µg/g³⁴. This finding was confirmed by another head-to-head study comparing the three home tests mentioned above to their companion ELISA tests, demonstrating substantial agreement at low

FC levels ($< 500 \mu\text{g/g}$) with percentages of 87%, 82%, and 76%, respectively, but a substantial decrease in concordance was observed at higher FC values ($> 500 \mu\text{g/g}$)³⁵.

Therefore, all existing FC assays share comparable diagnostic accuracy, but achieving quantitative agreement in absolute FC levels, especially at higher values, remains difficult. The high variability between the available methods suggests that they should not be interchangeable. Serial FC monitoring in a given patient should ideally be performed using the same method in the same laboratory³. Results, particularly when considering thresholds, must be interpreted carefully and cross-referenced with clinical and other biological parameters. In case of doubt, a new dosage on another stool sample should be performed.

3. Acceptability and compliance with FC testing

Despite the diagnostic potential of FC, challenges persist in its routine application, primarily related to the acceptability of the testing process. Patient compliance with stool sampling remains low, around 35%³⁶. This reluctance is mainly attributed to embarrassment associated with stool collection, sense of discomfort, and challenges in transporting the sample³⁷. This highlights the need for more patient-friendly testing methods. In response to these challenges, innovations in sample collection and transportation have been explored, mirroring developments seen in fecal immunochemical tests (FIT) for colorectal cancer (CRC) screening.

4. Lessons from CRC screening

Participation in CRC screening widely varies across Europe, ranging from 20 to 55%³⁸. In France, it remains low at around 32%, well below the European target of 45%³⁹. Barriers to compliance mirror those observed in the management of IBD, including low awareness of CRC signs and screening, reluctance to handle stool samples, and logistical challenges in samples submission^{40,41}. The search for occult blood in stools was previously performed with a guaiac-

based fecal occult blood test (gFOBT). The gFOBT involved collecting two pea-sized samples of feces from each of three separate bowel movements within a period of 10 days and placing them under a flap (window) on a card that was then posted back to the screening center.

The gFOBT has now been largely supplanted by the FIT with higher patient satisfaction due to the simplicity of the procedure: it involves using a stick that is reinserted and hygienically sealed into a small tube containing a preservative buffer solution, and requires only one stool sample⁴²⁻⁴⁵. In England, a large comparative pilot study found that adopting FIT increased participation rate by over 7 percentage points, particularly among patients who had not previously responded, with their participation rates nearly doubling⁴⁶. This was not observed in France following the switch to the FIT in 2015, but several factors may be involved such as a shortage of screening kits⁴⁷. A recent review showed that countries using FIT generally have higher participation rates (49.5%) compared to those using gFOBT (33.2%)⁴⁸.

These findings indicate that adherence to a fecal sample device is a major issue and that improving satisfaction with the stool sample collection process could be an effective approach to increase participation rates in fecal testing.

5. Objectives

To date, most studies evaluating alternative tests to the standard ELISA test focused on their accuracy, but not on patient satisfaction regarding the sampling kit. Yet, the best test is the one patients will do⁴⁹. Similar to what has been done for CRC screening, it is essential to identify patient preferences for stool collection devices to enhance FC acceptability and compliance. The primary objective of the ACCALMI study was to compare IBD patients' acceptability between a sampling bottle from a new POC FC assay (ProciseFCP™) and a conventional container used for Bühlmann fCAL® turbo. Secondary objectives were to analyze factors associated with improved acceptability and to compare compliance between both groups.

MATERIALS AND METHODS

1. Study design and population

The ACCALMI study was a single-center, prospective, randomized, superiority and unblinded study led in the Nantes University Hospital from July 2023 to April 2024. At that time, FC testing was not reimbursed by the public healthcare system in France.

Patients were recruited consecutively in the outpatient department during a scheduled visit with their referent IBD specialist if an FC test was prescribed as part of standard care. Patients aged over 18, with an established diagnosis of IBD (CD, UC or IBD-unclassified), could be included regardless of disease activity, location and ongoing treatment. Non-inclusion criteria included uncertain IBD diagnosis, legal incapacity, or physical, psychological, and mental status interfering with the patient's ability to sign the informed consent or to self-collect stools at home.

Patients were randomly assigned to either the standard Bühlmann fCAL® turbo method or the POC ProciseFCP™ (ProciseDx Inc.) method in a 1:1 ratio using a computer-generated randomization sequence, without stratification criteria. Participants were asked to return the stool sample at their next visit to the hospital within a delay established by their physician.

2. Ethics

Eligible patients were proposed to participate to the study during the visit with their IBD specialist. Patient information was provided both orally and in writing. Oral informed consent was then obtained from each patient and documented in the patient's clinical record.

This non-interventional study was approved by the local Research Ethics Committee (Groupe Nantais d'Éthique dans le Domaine de la Santé [GNEDS]) on February 8th, 2023 (number 23-24-02-080).

3. Stool collection devices

At the time of randomization, all patients were orally instructed on proper sample collection procedures. Patients randomized in the standard Bühlmann fCAL® turbo arm were provided with a 150 mL, plain, transparent, plastic container (referred to as “conventional container”) in which to deposit their stool sample for FC testing. The conventional container comprises a short sampling probe (2 cm) attached to a cap (*Figure 1*). Patients randomized in the ProciseFCP™ arm were provided with the Procise Stool Collection Device™, a sampling bottle consisting of a small tube comprising a thin and long sampling probe (4.6 cm long) with a grooved, spiraling tip and a twistable structure to open the cap (*Figure 1*). In this arm, patients were also provided with an information leaflet to guide sample collection, as well as a feces catcher, a hygienic, easy-to-use, biodegradable piece of flushable paper with two adhesive strips to secure to the toilet seat. Both containers were supplied with a transparent plastic bag for transport.



Figure 1. Illustrations of collection devices provided at the time of randomization.

Left: Conventional container; Right: Procise Stool Collection Device™.

4. Questionnaire administration

Patients received a questionnaire to complete during stool collection and were instructed to return it with the stool sample at their next hospital visit. Patients rated the clinical activity of their disease at the time of collection using a visual analog scale (VAS) between 0 and 10 (patient global assessment [PtGA]) as well as IBD-related disability using the IBD-Disk. They had to describe the appearance of their stools at the time of collection according to the Bristol

classification. They also reported whether they were aware of the FC test's usefulness (yes/no), if they previously performed FC testing (yes/no) and, if applicable, where it was performed (hospital lab/private lab/both). If non-compliance occurred in the past, they were asked to report the reason (forgetfulness, difficulty to perform sampling, refusal to handle stools, constipation, misunderstanding of test relevance, instructions not understood, other). Acceptability of the FC testing performed for the study was assessed using a semi-quantitative 4-item ordinal scale (method considered as 'poor', 'average', 'good', or 'very good') and a VAS ranging from 0 (absolutely unacceptable method) to 10 (totally acceptable method). Patients were then asked to argue their rating (verbatim feedback).

5. Demographic and clinical data collection

Clinical data were collected at baseline, including type of IBD (CD, UC or IBD-unclassified), age at diagnosis, disease duration, disease location and behavior according to Montreal classification, presence of extra-intestinal manifestations (EIM), history of intestinal resection, presence of stoma, ongoing disease-related treatments, number of previous biologic therapies, body mass index (BMI), smoking status and level of C-reactive protein (CRP) if available.

Educational level was recorded, assuming it might influence the patient's ability to understand and follow medical instructions and, consequently, affect FC acceptability. It was categorized into three groups: 'Below or baccalaureate level' (French high school diploma), 'Bachelor's degree,' and 'Master's degree or PhD'. Similarly, distance between home and hospital (< 10 km, 10-50 km, > 50 km) was also collected as the study was carried out at a time when FC testing was not reimbursed when performed in private laboratories.

When the patient brought his stool back to the hospital, a medical assessment of disease activity (physician global assessment [PGA]) was performed on a semi-quantitative 4-item

ordinal scale ('inactive', 'mildly active', 'moderately active', 'severely active'), either by the referent IBD specialist if stools were returned during a consultation, or on a phone call by a gastroenterology trainee in charge of the study if stools were returned some other time.

To assess compliance with FC testing, the number of patients who required at least one reminder to bring their FC sample to their next hospital visit was recorded. Reminders were given via phone calls, emails, or directly by the physician during consultations.

6. FC measurements

All analyses were conducted by trained laboratory personnel of the biochemical department of Nantes University Hospital following the manufacturer's instructions. Calibration and quality control procedures were performed as recommended. POC FC assays for patients randomized in the ProciseFCP™ arm were deliberately not carried out in a 'real-time' manner at the time the patient returned his/her stool sample. As with the conventional technique, samples were transported to the laboratory for subsequent analysis. Thus, only the stool sampling procedure was evaluated here, not the general satisfaction with the ability to obtain rapid results.

Due to the wide variability between different FC assay kit, a preliminary study was conducted to validate the ProciseFCP™ method against the standard Bühlmann fCAL® turbo on an independent cohort of IBD patients. Methods and results of this preliminary study conducted by the biochemical department of Nantes University Hospital (AA, DM, TD, HC) are presented in *Supplementary data*.

7. Study outcomes

The primary outcome was an improvement in patient's acceptability defined by an increase of one category in the semi-quantitative 4-item ordinal scale using the ProciseFCP™ device as compared to the conventional container. Secondary outcomes were (i) an improvement in

patient's acceptability using the ProciseFCP™ device defined by an increase $\geq 30\%$ in the mean VAS score as compared to the conventional container; (ii) the demographic, clinical, and activity factors associated with improved acceptability of the sampling method; (iii) an improvement in compliance to FC testing using the ProciseFCP™ device as compared to the conventional technique.

8. Statistics

8.1. Sample size calculation

Prior to the start of the study, the expected rates of acceptability for each assay method were estimated. For the conventional container, it was anticipated that 20% of participants would exhibit poor acceptability, 50% average acceptability, 25% good acceptability, and 5% very good acceptability. In contrast, for the Procise™ device, the estimated distribution included 5% poor acceptability, 20% average acceptability, 50% good acceptability, and 25% very good acceptability. These assumptions guided the sample size calculation to ensure the study's statistical power and precision. With an objective to detect potential differences in acceptability rates between the two methods, a minimum of 74 participants per arm were required. Accounting for a conservative estimate of 5% of participants lost to follow-up, the decision was made to include 78 patients per arm. This resulted in a total sample size of 156 patients.

8.2. Data analysis

Continuous variables are described using means and standard deviations (SD); categorical variables are described as raw counts and percentages.

Acceptability assessed using the ordinal scale was analyzed with an ordinal logistic regression model. The randomization arm (ProciseFCP™ or reference) was the independent

variable, and results are presented as odds ratios (OR) with 95% confidence intervals (CI) and p-values.

To compare the distribution of patient acceptability scores assessed by VAS between the two study arms, a Wilcoxon signed-rank test was used. CI were calculated using a bootstrap method, as the acceptability scores assessed by VAS did not follow a normal distribution. BCa (bias-corrected and accelerated) intervals were chosen.

Missing values are systematically presented. Two analyses were conducted: a per-protocol analysis and a full analysis set (FAS), with missing values replaced using the maximum bias technique. In the reference group, missing acceptability data were adjusted to 'very good' on the ordinal scale and 10 on the VAS, while in the ProciseFCP™ group, missing acceptability data were adjusted to 'poor' on the ordinal scale and 0 on the VAS.

To analyze demographic, clinical, and disease activity factors associated with better acceptability, an ordinal regression model with evaluation of acceptability on the ordinal scale was employed. The candidate characteristics included randomization arm, age at inclusion, gender, educational level, home-hospital distance, type of IBD, disease duration, PGA, PtGA, awareness of FC utility, and prior testing of FC.

Compliance was assessed by comparing the proportion of patients in each group who brought their FC sample to their next hospital visit with or without needing a reminder, using a chi-squared test.

Analyses were performed using RStudio. For all statistical analyses, $\alpha = 0.05$ was considered as an acceptable threshold for type I error.

RESULTS

1. Description of the study population

1.1. Patient demographics and characteristics at enrolment

Between May 2023 and August 2023, 156 patients were enrolled and randomly assigned to either the reference method or the ProciseFCPTM method for FC assay. Clinical characteristics of patients at enrolment are described in **Table 2** and were similar between both groups.

Educational levels were also globally similar, with 27.5% (19/69) of patients in the reference group and 29.8% (17/57) in the ProciseFCPTM group who finished their studies at or before the baccalaureate level, 37.7% (26/69) and 42.1% (24/57) having completed a Bachelor's degree, respectively, and 34.8% (24/69) and 28.1% (16/57) having completed a Master's degree or PhD equivalent, respectively.

Distance from home to hospital was also roughly equally distributed between the reference and the ProciseFCPTM groups, with 29.5% (23/78) and 26.9% (21/78) of patients living within 10 km of the hospital, 41.0% (32/78) and 38.5% (30/78) living between 10 and 50 km from the hospital, and 29.5% (23/78) and 34.6% (27/78) living more than 50 km from the hospital, respectively.

Table 2. Clinical characteristics of patients at enrolment.

	Reference group (n=78)	ProciseFCP™ group (n=78)
Type of IBD, n (%)		
• CD	57 (73.1)	59 (75.6)
• UC	18 (23.1)	15 (19.2)
• IBD-unclassified	3 (3.8)	4 (5.1)
Male gender, n (%)	33 (42.3)	35 (44.9)
Age at baseline [years], mean (SD)	38.7 (12.3)	40.9 (14.8)
Disease duration [years], mean (SD)	13.5 (10.8)	12.8 (10.1)
BMI [kg/m ²], mean (SD)	25.1 (5.1) ^a	25.4 (5.5)
Smoking status, n (%)		
• Current smokers	13 (16.9) ^b	14 (19.7) ^c
• Ex-smokers	20 (26.0) ^b	14 (19.7) ^c
• Never smokers	40 (51.9) ^b	42 (59.2) ^c
• Cannabis users	4 (5.2) ^b	1 (1.4) ^c
Disease location in CD, n (%), [£]		
• Ileal (L1)	19 (33.3)	17 (29.3) ^{\$}
• Colonic (L2)	9 (15.8)	17 (29.3) ^{\$}
• Ileocolonic (L3)	29 (50.9)	24 (41.4) ^{\$}
Disease behavior in CD, n (%)		
• Inflammatory (B1)	34 (59.6)	31 (53.4) ^{\$}
• Stricturing (B2)	11 (19.3)	14 (24.1) ^{\$}
• Penetrating (B3)	12 (21.1)	13 (22.4) ^{\$}
Disease location in UC, n (%)		
• Proctitis (E1)	2 (11.1)	1 (7.1) ^b
• Left-sided colitis (E2)	9 (50.0)	9 (64.3) ^b
• Extensive colitis (E3)	7 (38.9)	4 (28.6) ^b
Perineal location in CD, n (%)	20 (35.1)	19 (32.2)
EIM*, n (%)	27 (34.6)	23 (29.5)
• Rheumatologic	15 (19.2)	11 (14.1)
• Cutaneous	15 (19.2)	13 (16.7)
• Hepatobiliary	1 (1.3)	3 (3.8)
• Ocular	4 (5.1)	4 (5.1)
History of bowel resection, n (%)	26 (33.3)	22 (28.2)
Existing stoma, n (%)	1 (1.3)	1 (1.3)
Number of previous biologics, mean (SD)	1.0 (1.5)	1.0 (1.4)
Ongoing IBD-related medications, n (%)		
• None	7 (9.0)	10 (12.8)
• Oral and/or topical 5-ASA	9 (11.5)	7 (9.0)

• Corticosteroids	2 (2.6)	0 (0.0)
• Immunosuppressant monotherapy	1 (1.3)	1 (1.3)
• Anti-TNF monotherapy	27 (34.6)	28 (35.9)
• Anti-TNF + immunosuppressant	6 (7.7)	6 (7.7)
• Vedolizumab	6 (7.7)	5 (6.4)
• Ustekinumab	12 (15.4)	16 (20.5)
• Risankizumab	2 (2.6)	1 (1.3)
• Combiotherapy	3 (3.8)	2 (2.6)
• Jak inhibitors	2 (2.6)	1 (1.3)
• Leukapheresis	1 (1.3)	1 (1.3)

Abbreviations: ASA, Aminosalicylates; BMI, Body mass index; CD, Crohn's disease; EIM, Extra-intestinal manifestation; IBD, Inflammatory bowel disease; SD, Standard deviation; TNF, Tumor necrosis factor; UC, Ulcerative colitis.

[§] One patient had exclusive perineal location.

[‡] 5 patients in each group also had an upper gastrointestinal location (L4).

*A patient could have experienced more than 1 extra-intestinal manifestation.

Number of missing data: ^a, 2; ^b, 1; ^c, 7.

1.2. Disease activity at the time of FC testing

Table 3 describes disease activity markers in both groups at the time of FC testing. According to their physician (PGA), the vast majority of patients (79.6%) were inactive or mildly active, with numerically slightly more patients with mildly active disease in the reference group as compared to the ProciseFCP™ group.

Endoscopic assessment in the last 3 months was available in only 17 cases (10.9%), with 8/17 patients (47.0%) in endoscopic remission as defined by the STRIDE-II consensus (SES-CD < 3 or UCEIS ≤ 1)².

In the overall population (14 missing data), mean (\pm SD) FC value was 318 (\pm 472) μ g/g and median value [interquartile range, IQR] was 86 [40-322] μ g/g. There were three cases of non-conformity FC test results in the ProciseFCP™ group, compared to none in the reference group. For two of these cases, the residual buffer was below the recommended limit, and both patients reported issues with the green cap loosening during the test. The third non-conforming result was due to insufficient quantity of stool, which might be linked to difficulty in filling the grooves on the rod, although this patient did not report having liquid stools.

Table 3. Markers of disease activity at the time of FC testing.

	Reference group (n=78)	ProciseFCP™ group (n=78)
Physician global assessment [PGA], n (%)		
• Inactive	37 (50.7) ^a	47 (63.5) ^b
• Mildly active	21 (28.8) ^a	12 (16.2) ^b
• Moderately active	12 (16.4) ^a	13 (17.6) ^b
• Severely active	3 (4.1) ^a	2 (2.7) ^b
Biological parameters, mean (SD)		
• Fecal calprotectin [$\mu\text{g/g}$]	357.9 (512.7) ^a	275.5 (424.9) ^{d,§}
• CRP [mg/L]	4.5 (4.3) ^c	4 (6.3) ^e
Patient global assessment [PtGA] using VAS from 0 to 10, mean (SD)	3.5 (2.4) ^f	3.7 (2.5) ^g
IBD-Disk, mean (SD)	32.9 (20.3) ^d	35.7 (19.3) ^h
• Abdominal pain	3.3 (2.6)	4 (3.1)
• Regulating defecation	3.4 (3.0)	4.5 (3.5)
• Interpersonal interactions	2.3 (2.9)	2.5 (2.9)
• Education and work	3.2 (3.3)	3.6 (3.0)
• Sleep	4.3 (3.2)	4.5 (3.4)
• Energy	5.4 (2.9)	5.9 (3.1)
• Emotions	4.5 (3.2)	4 (2.9)
• Body image	3.6 (3.3)	3.8 (3.0)
• Sexual functions	3.1 (3.1)	2.9 (2.9)
• Joint pain	3.7 (3.2)	3.6 (3.2)
IBD-Disk overall score < 40, n (%)	44 (63.8) ^d	39 (59.1) ^h

Abbreviations: CRP, C-reactive protein; IBD, Inflammatory bowel disease; PGA, Physician global assessment; PtGA, Patient global assessment; SD, Standard deviation; VAS, Visual analog scale.

Number of missing data: ^a, 5; ^b, 4; ^c, 13; ^d, 9; ^e, 14; ^f, 11; ^g, 6; ^h, 12.

[§] Missing data for the ProciseFCP™ group include 6 tests not performed and 3 non-conforming results.

1.3. Conditions for FC testing

According to Bristol classification, 39.2% of patients (49/125) had normal stool consistency (Bristol 3-4) (26/63 [41.3%] in the reference group and 23/62 [37.1%] in the ProciseFCP™ group), while 33.6% (42/125) had very loose or liquid stools (Bristol 6-7) (19/63 [30.2%] in the reference group and 23/62 [37.1%] in the ProciseFCP™ group). The mean (\pm SD) Bristol score was 4.5 (\pm 1.5) in the reference group, and 4.4 (\pm 1.8) in the ProciseFCP™ group.

Table 4 describes prior experience of FC testing. In the overall population, 80.1% of patients were aware of FC usefulness; 94.2% had prior FC testing, of whom 57.9 % admitted a previous lack of compliance, mainly driven by forgetfulness and the stool sampling in itself (difficulty or refusal to perform it), each of these reasons representing about one-third of prior compliance failures.

Table 4. Prior experience of FC testing.

	Reference group (n=78)	ProciseFCP™ group (n=78)
Awareness of FC usefulness, n (%)	51 (72.9) ^a	62 (87.3) ^b
Prior FC testing, n (%)	74 (94.9)	71 (93.4) ^c
Site of previous FC testing, n (%)		
• Hospital laboratory	65 (87.8)	57 (80.3)
• Private laboratory	0 (0)	3 (4.2)
• Both	9 (12.2)	11 (15.5)
Prior lack of compliance to FC testing, n (%)	52 (70.3)	32 (45.1)
Reasons why FC was not performed before*, n (%)		
• Forgetfulness	18 (34.6)	12 (37.5)
• Difficulty to perform sampling	11 (21.2)	9 (28.1)
• Refusal to handle stools	5 (9.6)	1 (3.1)
• Constipation	8 (15.4)	5 (15.6)
• Misunderstanding of test relevance	2 (3.8)	1 (3.1)
• Instructions not understood	2 (3.8)	0 (0.0)
• Other	6 (11.5) [£]	4 (12.5) [§]

Abbreviations: FC, Fecal calprotectin.

*A patient could have more than one reason.

[£]Home-hospital distance, fear, price, lack of available container.

[§]Home-hospital distance, unwillingness.

Number of missing data: ^a, 8; ^b, 7; ^c, 2.

2. Acceptability of FC testing

2.1. Missing data

The number of missing data for FC acceptability was similar in both groups with a total of 13 instances – 7 in the reference group and 6 in the ProciseFCP™ group. Reasons for missing data included an inability to meet the study's timeline (1 participant in each group), unreturned questionnaires despite FC being performed (2 in the reference group), forgotten stool samples during appointments (2 in the reference group and 3 in the ProciseFCP™ group), and interrupted follow-ups due to reasons external to the study (2 in each group).

2.2. Difference in FC acceptability

2.2.1. Ordinal scale (primary outcome)

On per protocol analysis, the ProciseFCP™ group had significantly higher acceptability ratings than the reference group, with 1.4% versus 7.0% rating it as 'poor', 12.5% versus 46.6% as 'average', 66.7% versus 40.8% as 'good', and 19.4% versus 5.6% as 'very good', respectively (OR 2.69 (95% CI [1.83, 4], $p < 0.001$) (*Figure 2*).

After imputing missing data with maximum bias replacement (FAS analysis), the acceptability rates remained higher in the ProciseFCP™ group than in the reference group, with 6.4% versus 9.0% rating it as 'poor', 42.3% versus 11.5% as 'average', 37.2% versus 61.5% as 'good', and 14.1% versus 17.9% as 'very good', respectively (OR 1.48 (95% CI [1.05, 2.09], $p = 0.026$).

Consequently, the primary outcome of improved acceptability, defined as an increase of one category in the semi-quantitative 4-item ordinal scale, was achieved.

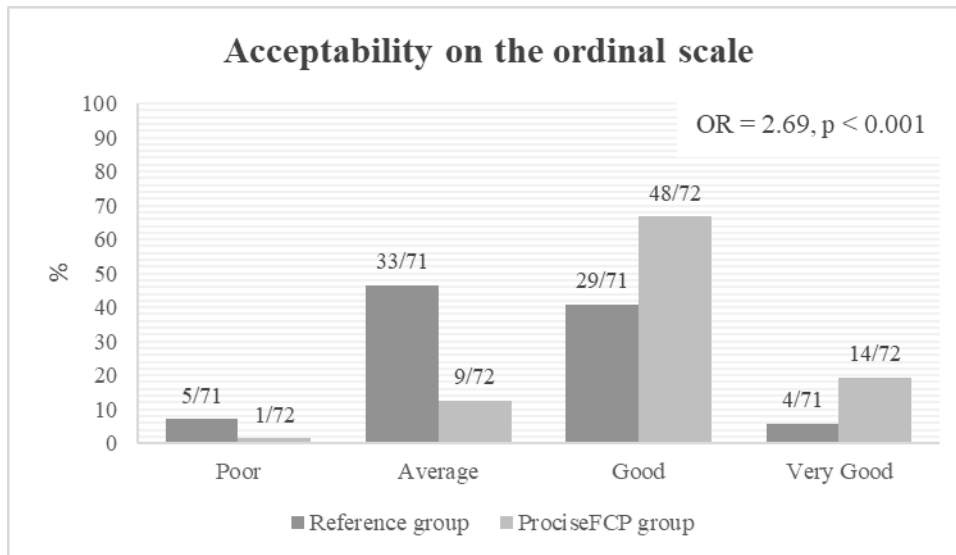


Figure 2. Acceptability of FC testing assessed by the ordinal scale (per protocol analysis).
Abbreviations: OR, Odds ratio.

2.2.2. Visual analog scale

On per protocol analysis, the mean (\pm SD) acceptability score was 6.1 (\pm 2.3) in the reference group and 7.9 (\pm 1.9) in the ProciseFCPTM arm ($p < 0.001$), i.e. an increase of 30.04% (95% CI: 19.7 to 44.7) (**Figure 3**). Despite the significant improvement in acceptability scores, the secondary outcome – increase $\geq 30\%$ in the mean VAS score – was not reached because the confidence interval includes the 30% threshold.

The same was true after imputing missing data with maximum bias replacement (FAS analysis). The mean (\pm SD) acceptability score was 6.4 (\pm 2.4) in the reference group compared to 7.3 (\pm 2.8) in the ProciseFCPTM group ($p < 0.001$), i.e. an increase of 13.4% (95% CI: 1.2 to 27.2).

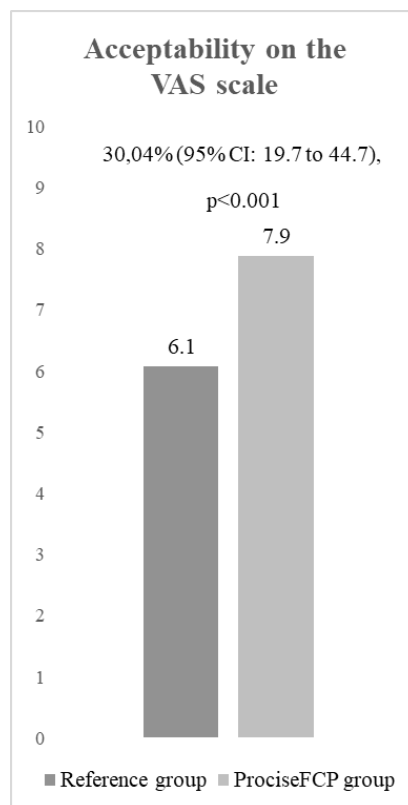


Figure 3. Mean VAS for the assessment of FC acceptability (per protocol analysis).

Abbreviations: CI, Confidence interval; FC, fecal calprotectin; VAS, Visual analog scale.

2.3. Verbatim feedback to argue acceptability rating

Reasons for low acceptability of FC test (< 5 using VAS) in the reference group were similar to those cited in the literature: the invasive nature of the procedure, lack of privacy, unclear instructions, and no reimbursement for tests outside the hospital (at the time of the study), adding financial and logistical frustrations. Participants found the procedure uncomfortable and messy, highlighting difficulties in staying clean and handling fecal matter. Transporting samples in non-opaque containers compromised discretion. Patients described the process as awkward, embarrassing, and sometimes humiliating.

Among the 71 patients in the ProciseFCP™ group who had previously undergone an FC assay using a conventional container, 38 (53.5%) indicated a preference for this method, 5 (7.0%) preferred the reference method, 26 (36.6%) found them similar and 2 did not answer. Patients who preferred the ProciseFCP™ device appreciated its ease of performance (even though some patients mentioned difficulties in case of liquid stools due to issues with the tube's handling) and transport, as well as its eco-friendly components like the biodegradable stool catcher. Those favoring the reference method cited excessive preparation time, more complex handling using the ProciseFCP™ device compared to simple collection pots, and technical issues like the bottom green cap detaching or becoming unscrewed during use.

2.4. Factors associated with better acceptability

In univariate analysis, over the candidate characteristics tested, a significant interaction with the randomization arm was found for gender and disease duration. Female patients exhibited significantly lower acceptability of FC testing (OR 0.54, $p=0.022$). However, a positive interaction was observed between female sex and the ProciseFCP™ arm (OR 2.14, $p=0.047$), indicating that the impact of ProciseFCP™ on FC acceptability was more pronounced in females. Conversely, longer disease duration was associated with higher acceptability (OR 1.03, $p=0.011$), but there was a significant negative interaction between disease duration and being in the ProciseFCP™ group suggesting that the positive effect of the ProciseFCP™ device on acceptability decreases as disease duration increases (OR 0.96, $p=0.048$). Long home-hospital distance ($> 50\text{km}$) was also associated with higher acceptability (OR 2.20, $p = 0.026$) in univariate analysis with no interaction between the arm and the home-hospital distance.

In multivariate analysis, the only factors significantly influencing FC acceptability were being in the ProciseFCP™ group and living > 50 km to the hospital (**Table 5**). Female sex tended to be associated with lower acceptability but this did not reach statistical significance.

Table 5. Factors influencing FC acceptability on ordinal scale (multivariate analysis).

Characteristics	OR	95% CI	p-value
Randomization arm			
Reference group	-	-	-
ProciseFCP™ group	3.99	1.12, 14.5	0.034
Age	0.99	0.97, 1.01	0.4
Gender			
Male	-	-	-
Female	0.47	0.21, 1.05	0.068
Educational level			
Baccalaureate level or under	-	-	-
Bachelor's degree	0.81	0.42, 1.56	0.5
Master's degree or PhD equivalent	1.09	0.57, 2.08	0.8
Home-hospital distance			
< 10 km	-	-	-
10 – 50 km	1.14	0.49, 2.65	0.8
> 50 km	2.99	1.25, 7.30	0.015
Disease duration	1.03	0.99, 1.07	0.15
Type of IBD			
UC	-	-	-
CD	0.64	0.33, 1.23	0.2
IBD-unclassified	1.03	0.31, 3.47	> 0.9
PGA			
Inactive	-	-	-
Mildly active	0.67	0.34, 1.28	0.2
Moderately active	0.70	0.32, 1.51	0.4
Severely active	0.60	0.15, 2.35	0.5
IBD-Disk overall score < 40	1.43	0.78, 2.65	0.3
PtGA < 4	0.62	0.29, 1.31	0.2
Awareness of FC usefulness	0.99	0.52, 1.90	>0.9
Prior testing of FC	2.57	0.75, 8.90	0.14

Abbreviations: CD, Crohn's disease; CI, Confidence interval; FC, Fecal calprotectin; IBD, Inflammatory bowel disease; OR, Odds ratio; PGA, Physician global assessment; PtGA, Patient global assessment; UC, Ulcerative colitis.

2.5. Compliance with FC testing

The number of patients needing at least one reminder to bring their FC sample to their next hospital visit was similar between both groups: 16 patients (20.5%) in the reference group, compared to 15 patients (19.2%) in the ProciseFCP™ group.

DISCUSSION

The ACCALMI study is the first randomized study to compare an alternative collection device to a conventional container for stool sampling in more than 150 patients with IBD in terms of acceptability and compliance to fecal calprotectin testing. The Procise Stool Collection Device™ was associated with better acceptability without any difference in compliance. The only factors that had a significant impact on FC acceptability were belonging to the ProciseFCP™ group and residing more than 50 km away from the hospital.

FC is considered by physicians as an easy-to-use and non-invasive biomarker. However, patients often find stool collection less acceptable compared to other monitoring tools like wireless capsule endoscopy or magnetic resonance enterography³⁷. Reasons for this include embarrassment (43.0%), feeling of dirtiness (23.0%), and challenge of transporting the sample (17.7%)³⁷. A study in Nancy, France, revealed that only one-third of patients complied with FC testing, primarily due to forgetfulness (76%)³⁶. Another study led in the same center several years later and evaluating FC home monitoring through IBDoc® showed that two-thirds of patients performed the test, doubling compliance compared to the previous study, with 85% of satisfied patients, highlighting the importance to consider more patient-friendly stool testing methods⁵⁰. A large survey led on 585 patients across the UK, Europe, and Australia explored patients' perception and barriers to FC testing, of whom 76% had prior FC testing experience. Of them, 37% rated FC testing as difficult, particularly those aged < 49 years with short disease duration (< 3 years). In this survey, “sample collection” (67%) was the most commonly reported reason to explain difficulty to perform FC testing. Patient recommendations for improvements focused on collection kits, providing information leaflets to aid sample collection, and ease of access for sample drop, suggesting that the sampling device plays an important role in non-compliance to fecal testing⁵¹. In response, easier stool sampling kits have been developed.

In our study, the median [IQR] acceptability score on the VAS scale was 6 [5-8] in the

reference group and 8 [7-10] in the ProciseFCP™ arm. Comparatively, a nationwide survey of IBD patients in France found that the reference method received higher acceptability scores, with a median VAS of 7.7 [4.6-9.3] for patients with CD and 8.1 [5.7-9.4] for patients with UC³⁷. This indicates that while the ProciseFCP™ system significantly improves acceptability in our study, the reference method was rated more favorably in other studies, suggesting variability in patient preferences and experiences across different cohorts.

In the ACCALMI study, among the patients randomized in the ProciseFCP™ group who had previously undergone an FC assay using a conventional container, 55.1% indicated a preference for the new method, mainly due to its ease of performance and transport, as well as its stool catcher provided with the kit, leading to reduced manipulation of stools. Importantly, only the sampling device was studied here, but not the overall experience with a point-of-care test performed directly during consultation. Therefore, acceptability could probably increase even further with the result of FC obtained in real time, although the reimbursement of FC testing in private laboratories by the public healthcare system since February 2024 somewhat addresses this issue because patients now carry out the test prior to their consultation.

In our study, the only factors significantly influencing FC acceptability in multivariate analysis were being in the ProciseFCP™ group and living more than 50 km from the hospital. In univariate analysis and similar to other studies, longer disease duration was correlated to better FC acceptability⁵¹. This may be due to an effect of habituation to medical examinations and patients with a long-standing disease may have observed that certain FC results influence their doctors' decisions, increasing their acceptability of these tests. Besides, there was a significant negative interaction between disease duration and being in the ProciseFCP™ group, suggesting that while the sampling bottle enhances acceptability as compared to the

conventional container, its effect is less pronounced in patients with longer disease histories who are accustomed and somewhat “resigned” to unappealing examinations.

In univariate analysis female gender was associated with lower acceptability of FC testing, in line with the survey by Buisson et al.³⁷. However, a positive interaction between gender and the ProciseFCP™ suggests that the use of this specific collection device can help mitigate lower acceptability among females.

Residing more than 50 km away from the hospital was also associated with higher acceptability. One explanation may be that patients who live far away and still choose to be followed at the university hospital are potentially more compliant and willing to travel long distances and undergo multiple tests to receive care at a tertiary center. Another factor in the balance is the means of transport used to come to the hospital. Given the impact of transporting the stool sample on FC acceptability³⁷, it is likely that patients living far from the hospital come by car more often than patients living closer who may use public transportation, potentially leading to an understandable feeling of discomfort with transporting a stool sample in their bag. With the reimbursement of FC tests in France since February 2024, compliance with this examination is expected to improve, as patients will be able to perform the FC test at any laboratory close to their home.

In our study, the ProciseFCP™ method was not associated with better compliance with FC testing than the reference method, although it is important to note a difference in prior lack of compliance in favor of the reference group, which might have masked an effect of the sampling device on compliance. Another bias may come from high rates of compliance in both groups, with 93% of patients returning their samples, significantly higher than the 30% compliance rate reported in the Nancy study³⁶. The number of patients reporting knowledge of the purpose of FC was high (72% in the reference arm and 87% in the ProciseFCP™ arm), which could partly

explain the better compliance and acceptability. By contrast, in the Nancy study, conducted in 2015 i.e. at the start of the calprotectin era, 82% of patients reported that they had not been aware of FC before being asked to perform the test, which may have contributed to the low rate of compliance³⁶. That being said, the prospective and randomized design of our study might not be ideal for evaluating compliance, and an observational study could provide better insights into patient behavior.

The main strength of our study is its prospective and randomized design, although limited by its single-center setting. However, some limitations must be pointed out.

First, satisfaction data regarding the stool catcher and the information leaflet provided with the Procise Stool Collection DeviceTM were not collected. This may limit the comprehensiveness of the comparison. Is the difference between both methods linked to the sampling method or the supplied accessories? However, previous studies have shown mixed experiences with fecal collection devices, with no significant increase in participation rates when using additional collection aids. In a study from the UK, participants in the National Health Service Bowel Cancer Screening Programme reported mixed experiences with fecal collection devices, with only a small proportion finding them helpful⁵². Similarly, another study evaluating the use of a feces collection paper in a FIT-based CRC screening program found no significant increase in participation rates compared to FIT-only groups⁵³. Participants who were supplied with a collection paper rated stool collection as equally easy and unpleasant as those who had not received a collection paper.

Another limitation of our study is that patients were not stratified based on prior FC testing. However, this approach ensures representation of the population seen in our hospital, as it consecutively includes all patients meeting the inclusion and exclusion criteria who accepted to participate to the study. Moreover, although prior awareness of FC (which concerned only 18%

of patients) has been associated with better compliance with FC testing in the Nancy study³⁶, this factor did not emerge in our study, in which the vast majority of patients were aware of FC utility and already performed FC testing outside the scope of the study.

Patient-reported outcomes (PRO)-2 were not specifically collected as we focused on the Bristol stool scale, which we believe is the most pertinent parameter within PRO-2 that can influence FC levels and acceptability. While PRO-2 includes additional symptoms namely abdominal pain in CD and rectal bleeding in UC, these symptoms are not known to significantly affect FC testing and levels. Additionally, we measured symptoms using the IBD-Disk, which provides a similar comprehensive assessment of the patient's condition.

Finally, a medico-economic analysis on a larger population over the long term would be necessary before implementing and reimbursing such a device in clinical practice, as its cost is three times higher than the reference method.

CONCLUSION

The ACCALMI study is the first randomized study to compare acceptability and compliance with fecal calprotectin testing using an alternative collection device (sampling bottle) to a conventional container for stool sampling in patients with IBD. The ProciseFCP™ method significantly improved acceptability compared to the standard test, with higher ratings on both ordinal and visual analog scales, even though the objective of 30% improvement was not reached for the latter. The alternative collection device was the only factor associated with better acceptability in this study, due to its simplified collection and handling process, which reduces the manipulation of stools – a major barrier to compliance with fecal tests. This highlights the importance of considering patient preferences and satisfaction when implementing FC testing in clinical practice, although no difference in compliance was found between both methods. Addressing technical issues such as the handling of liquid stools and ensuring the integrity of the sample collection process remain areas for improvement.

SUPPLEMENTARY DATA

Supplementary Table 1. Factors and conditions associated with elevated FC levels.

Adapted from^{3,54,55}.

Infectious conditions	Inflammatory conditions
- Infectious diarrhea (viral, bacterial, parasitic)	- IBD
- Helicobacter pylori gastritis	- Auto-immune enteropathy
- Lung infections	- Cirrhosis
	- Cystic Fibrosis
	- Diverticulitis
	- Eosinophilic colitis/enteritis
	- Gastroesophageal reflux disease
	- Juvenile polyp
	- Microscopic colitis
	- Peptic ulcer
	- Celiac disease
	- Proctitis after radiation therapy
	- Pouchitis
Neoplasms	
- Colonic and gastric polyps	
- Colorectal cancer	
- Gastric carcinoma	
- Intestinal lymphoma	
	Other
	- Age: < 9 years or > 65 years
	- Lifestyle: Obesity, physical inactivity
	- Bowel preparation for colonoscopy
	- Food allergy (untreated)
	- Perianal disease
	- Rheumatologic diseases

Abbreviations: FC, Fecal calprotectin; IBD, Inflammatory bowel disease; NSAIDs, Non-steroidal anti-inflammatory drugs; PPIs, Proton pump inhibitors.

Preliminary study: Agreement Between ProciseFCP™ and Bühlmann fCAL® turbo

Validation of an analytical method is an essential prerequisite in any laboratory to ensure the reliability and quality of results before any routine use. This principle also applies to the use of off-site medical biology devices. Until now, the ProciseFCP™ assay had been validated only by ProciseDx Inc. for distinguishing irritable bowel syndrome from IBD⁵⁶. An external validation on an independent cohort of IBD patients was therefore necessary. Thus, prior to the start of the ACCALMI study, the ProciseFCP™ method was validated by the Biochemistry Laboratory at Nantes University Hospital (AA, DM, TD, HC). This validation aimed to confirm the method's reliability and performance, ensuring that there would be no clinico-biological impact on patients participating in the ACCALMI study.

Methods

Sample collection, preparation and storage

A total of 43 samples, collected between January and March 2023, were analyzed using both the ProciseFCP™ and Bühlmann fCAL® turbo methods for comparison. The samples were provided by both inpatients and outpatients who had been prescribed an FC assay. Samples were extracted daily and stored at 4°C before being analyzed once a week using the Bühlmann fCAL® turbo method. For the ProciseFCP™ method, samples were extracted and analyzed immediately after stool collection to simulate the real-world conditions of device use as closely as possible. The samples included a variety of consistencies: liquid, soft, pasty, and hard stools. Clinical data from the patients who provided the samples were not collected.

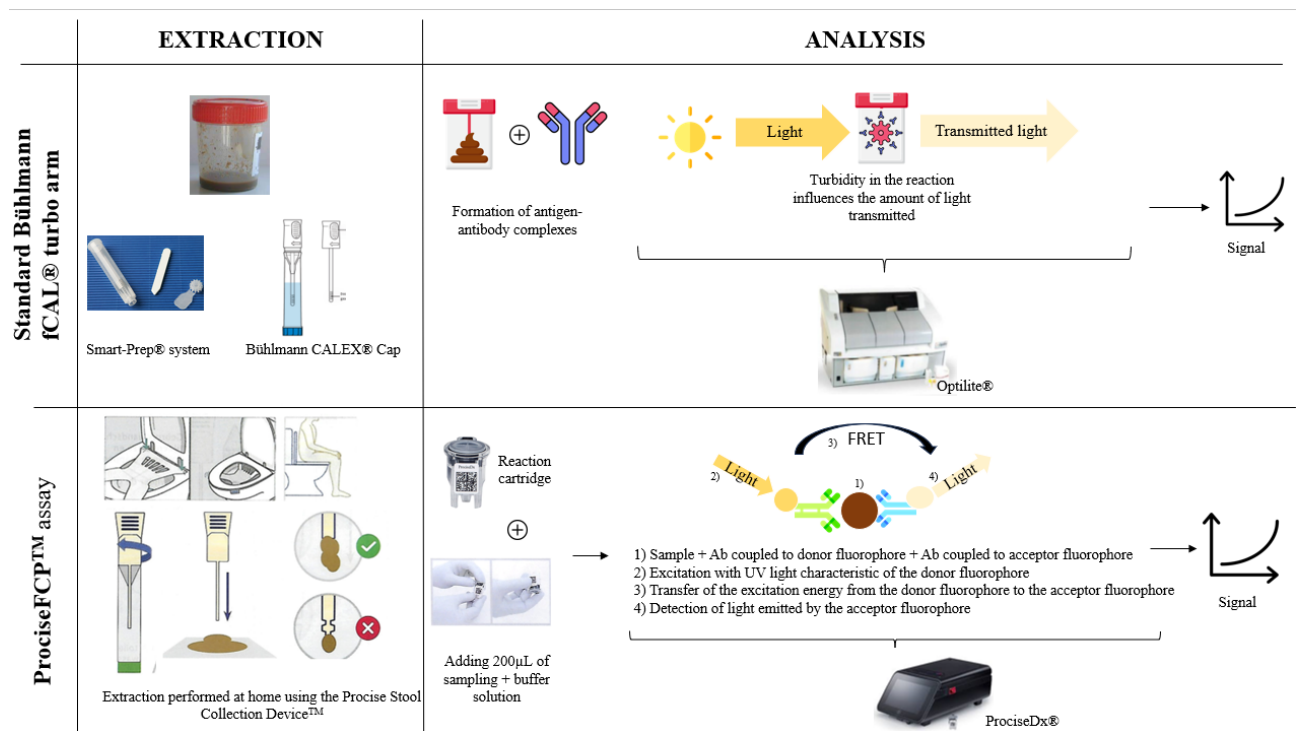
Extraction and analysis process for both methods

FC was measured using the immunoturbidimetric method Bühlmann fCAL® turbo on the Optilite® device and the ProciseFCP™ test, according to the manufacturer's instructions. *Supplementary Figure 1* describes the extraction and analysis process for both devices. For the standard Bühlmann fCAL® turbo, three types of extraction devices were employed based on the stool consistency, using either the Bühlmann CALEX® Cap or the Smart-Prep® system. The CALEX Cap® consists of a rod with six grooves. It was inserted into the stool sample at 3 to 5 different points. Once the grooves were completely filled, the rod was reintroduced into the device, homogenized by vortexing until the stools were completely dissolved, centrifuged, and 500 µL of this mixture were taken for analysis on Optilite® analyzer. The Smart-prep® device was used for hard-to-extract waxy stools. Finally, in the case of liquid stools, 10 µL of stools were taken using a pipette and transferred directly into the CALEX Cap® system. The Optilite® analyzer utilizes immunoturbidimetry technology, which means that polystyrene nanoparticles beads sensitized with calprotectin-specific antibodies are brought into contact with the sample, forming an immune complex that disrupts the reaction medium. The intensity of light transmitted through the medium is measured, directly proportional to the FC concentration of the sample.

In the preliminary study, extraction for the ProciseFCP™ assay was performed by the laboratory personnel. In the ACCALMI study, it was performed at home by the patient himself. Sampling followed the same principle as the CALEX Cap® system: a rod with grooves was inserted into the stools at five different points and was reintroduced into the device. The ProciseFCP™ assay employs an immunological analysis by fluorescence resonance energy transfer (FRET) method: the sample is brought into contact with a reagent consisting of rabbit monoclonal antibody labeled with a donor fluorophore and mouse monoclonal antibody labeled with an acceptor fluorophore. This combination specifically recognizes calprotectin and forms

a complex that is excited by UV light at a wavelength characteristic of the donor fluorophore, which transfers its excitation energy to the acceptor fluorophore. This acceptor fluorophore emits light energy, detected in direct proportion to the degree of formation of the donor/acceptor complex.

Both manufacturers recommend using the following thresholds for interpreting results: for Bühlmann fCAL® turbo, < 60 µg/g indicates IBD negative, 60 to 180 µg/g is doubtful, and > 180 µg/g is IBD positive; for ProciseFCP™, < 50 µg/g indicates IBD negative, 50 to 120 µg/g is IBD doubtful, and > 120 µg/g is IBD positive.



Supplementary Figure 1. Extraction and analysis process for both methods.

In the preliminary study, extraction for the ProciseFCP™ assay was performed by the laboratory personnel. In the ACCALMI study, it was performed at home by the patient himself.

Abbreviations: Ab, Antibody; FRET, Fluorescence resonance energy transfer.

Statistics

The correlation between Bühlmann fCAL® turbo and ProciseFCP™ assays was assessed using Spearman's rho correlation coefficient. The intermediate imprecision of both assays was calculated. Statistical analyses and graphics were performed using R Studio and Microsoft Excel.

Results

Analytical phase

Intra-assay variability (coefficient of variation [CV]) was assessed by performing five repeated measurements on the same stool sample extracted using the ProciseFCP™ kit, with the same reagent lot, the same calibration, and over a short time interval (within one day). Intra-assay variability was obtained with the CV of 2.54%, which is acceptable according to the limits set by the laboratory (CV of 7.5%).

The reproducibility study, usually performed by carrying out the repeated quality control analysis, in different series with different technicians and at different times, could not be carried out. In fact, the device does not provide an exact value, but only indicates whether the control is successful or not. In addition, the constraints due to the stability of FC made it difficult to find an alternative.

Samples for which a significant difference was observed between the values obtained from Bühlmann fCAL® turbo and ProciseFCP™ were extracted again from the stool sample and analyzed using ProciseFCP™ to determine if this variability was due to the extraction process. This verification was conducted for 5 patients, allowing to study the variability of both, the pre-analytical and analytical phases. Inter-assay variability shows a variation of 7.5% (CV) on average between two measurements carried out by qualified personnel on values ranging from

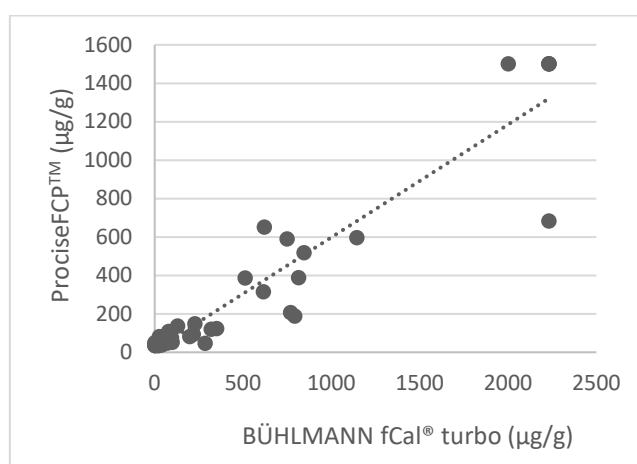
38 µg/g to 556 µg/g. The results show that the variability between the two measurements is acceptable and that the clinical interpretation based on the thresholds remains consistent, except for one patient, who went from a negative result to a doubtful result (*Supplementary Table 2*).

Supplementary Table 2. Repeated analysis on the ProciseFCP™, performed in cases of significant discrepancies between the values obtained from Bühlmann fCAL® turbo and ProciseFCP™ assays (n = 5).

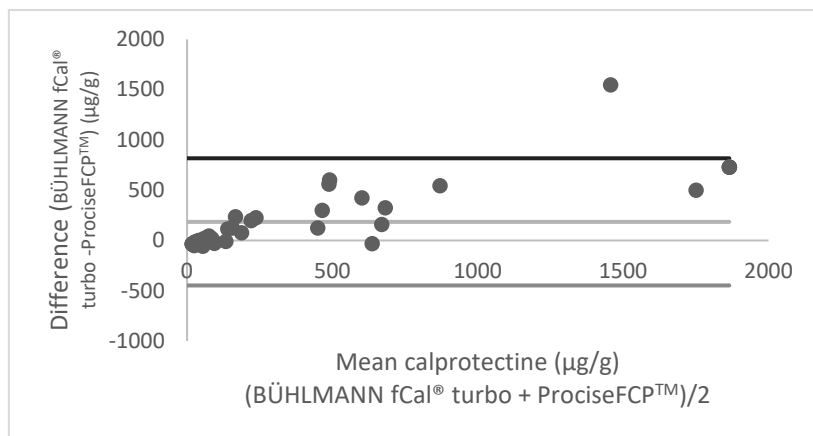
Measure n°1 (µg/g)	82	123	518	49	38
Measure n°2 (µg/g)	61	132	556	53	44

Concordance

Forty-three samples were analyzed using the Bühlmann fCAL® turbo method, yielding values ranging from 40 µg/g (the limit of quantification) to 2000 µg/g (the linearity limit of this method). These samples were also analyzed using the ProciseFCP™ method, which produced values ranging from 34 µg/g to 1500 µg/g, within the linearity range of this system. *Supplementary Figure 2* illustrates the correlation between FC measurements obtained with these two methods, showing a Spearman correlation coefficient of 0.94. The data revealed a consistent bias of 185 µg/g, indicating that the ProciseFCP™ method tends to provide lower values compared to the reference method (*Supplementary Figure 3*). This study demonstrates that, from an analytical perspective, the two methods are not equivalent.



Supplementary Figure 2. Correlation of FC measurements between Bühlmann fCAL® turbo and ProciseFCP™ assays (n = 43).



Supplementary Figure 3. Bland-Altman Plots for comparing Bühlmann fCAL® turbo and ProciseFCP™ assays (n = 43).

Bland-Altman plot showing the difference between ProciseFCP™ and Bühlmann fCAL® turbo in relation to the average values of the assays for all FC values (n = 43). The central line is the bias (mean of the differences), the upper and lower lines are the upper and lower 95% limits of agreement.

To determine whether this difference between the two methods had a clinical impact on patients, a contingency table was created (*Supplementary Table 3*). Of the 43 analyses compared, 33 were concordant (76.7%), while 10 samples (23.2%) led to different interpretations. Among these 10 samples, classification discrepancies were primarily found in the grey zone, with 9 samples (20.9%) classified as either negative/doubtful or doubtful/positive pairs. Only one sample (2.3%) showed a major classification error, being classified as positive by the Bühlmann fCAL® turbo method (284 µg/g) and negative by the ProciseFCP™ assay (43 µg/g).

Supplementary Table 3. Concordance and Discrepancies between Bühlmann fCAL® turbo and ProciseFCP™ measurements.

		ProciseFCP™			Total
		Negative (< 50 µg/g)	Doubtful (50-120 µg/g)	Positive (> 120 µg/g)	
Bühlmann fCAL® turbo	Negative (< 80 µg/g)	13	5	0	18
	Doubtful (80-160 µg/g)	0	4	1	5
	Positive (> 160 µg/g)	1	3	16	20
Total		14	12	17	43

Concordance (76.7%) is marked in green, misclassification without clinical consequences (20.9%) in orange, and serious misclassification (2.3%) in red.

Liquids stools

Given the challenges associated with extraction, a detailed analysis of liquid stool samples was conducted. A subsequent analysis, focusing exclusively on liquid stool samples (n=6), revealed the same pattern: a positive bias was observed, but the overall interpretation remained consistent, with no serious misclassifications and only two misclassifications without clinical consequences.

Discussion

The ProciseFCP™ method exhibits some analytical differences compared to the Bühlmann fCAL® turbo method. The fixed bias and occasional misclassifications observed suggest that the two methods are not entirely equivalent from an analytical standpoint. However, the clinical impact of these differences is minimized due to the different interpretation thresholds established by the suppliers. The ProciseFCP™ method demonstrates acceptable variability and can be reliably used in clinical practice, provided its limitations are recognized.

It is important to keep in mind that in this preliminary study, the tests were performed by skilled laboratory technicians, but in a clinical setting, the extraction is performed by patients

themselves, which could introduce more variability in the analyses. It would be interesting to compare the result of FC extracted by the patient and measured with the ProciseFCP™ assay in parallel with an extraction and analysis carried out in the laboratory on the Bühlmann fCAL® turbo in order to study the variability in real conditions of use of the ProciseFCP™ assay. It would be also interesting to follow patients over an extended period to assess the coherence between the results obtained and the clinical evolution of the patients, which was not done in this study.

As shown in the literature, all existing FC assays share comparable diagnostic accuracy, but achieving quantitative agreement in absolute FC levels, especially at higher values, remains difficult. The high variability between the available methods suggests that these instruments for FC measurement should not be interchangeable. Serial FC monitoring in a given patient should ideally be performed using the same method in the same laboratory².

Conclusion

The ProciseFCPTM method shows some analytical differences from the Bühlmann fCAL® turbo, including fixed bias and occasional misclassifications, but remains reliable for clinical use due to adjusted interpretation thresholds, as long as its limitations are acknowledged.

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Titre de Thèse : ACCEPTABILITÉ DE LA CALPROTECTINE FÉCALE CHEZ LES PATIENTS ATTEINTS DE MALADIES INFLAMMATOIRES CHRONIQUES DE L'INTESTIN : IMPACT D'UN DISPOSITIF ALTERNATIF DE PRÉLÈVEMENT DES SELLES (ETUDE ACCALMI)

RÉSUMÉ

L'étude ACCALMI a comparé l'acceptabilité de la calprotectine fécale (CF) chez les patients atteints de MICI en utilisant le système ProciseFCP™, qui comporte un dispositif de recueil alternatif, et le système de référence utilisant un pot de recueil de selles standard. Le dispositif ProciseFCP™ améliore significativement l'acceptabilité sur une échelle ordinale (OR 2,69 ; IC 95 % [1,83 ; 4], $p < 0,001$) et sur une échelle visuelle analogique, sans atteindre le seuil fixé d'une différence de 30 % (IC 95 % : 19,7 ; 44,7). L'observance était similaire dans les deux groupes. Ces résultats plaident pour l'intégration d'innovations centrées sur le patient dans les tests diagnostiques et de suivi pour améliorer la gestion des MICI.

MOTS-CLÉS

Maladie de Crohn, Rectocolite hémorragique, Surveillance, Biomarqueur, Observance.

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THESIS TITLE: ACCEPTABILITY OF FECAL CALPROTECTIN IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE : IMPACT OF AN ALTERNATIVE COLLECTION DEVICE FOR STOOL SAMPLING (THE ACCALMI STUDY)

SUMMARY

The ACCALMI study compared the acceptability of fecal calprotectin (FC) in patients with IBD using the ProciseFCPTM system, which includes an alternative collection device, and the reference system using a standard stool collection container. The ProciseFCPTM device significantly improved acceptability on an ordinal scale (OR 2.69; 95% CI [1.83; 4], $p < 0.001$) and on a visual analog scale, without reaching the predefined threshold of a 30% difference (95% CI: 19.7; 44.7). Adherence was similar in both groups. These results support the integration of patient-centered innovations in diagnostic and follow-up tests to improve the management of IBD.

KEYWORDS

Crohn's disease, Ulcerative colitis, Monitoring, Biomarker, Adherence