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Comparison of clinical performance of fecal calprotectin of laboratory methods with lateral flow based POC and home tests

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Introduction

Endoscopy is the gold standard for detecting mucosal inflammation to differentiate between Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS). It also plays a major role in monitoring mucosal inflammation in diagnosed IBD patients. Fecal calprotectin has been established as an excellent surrogate biomarker of intestinal inflammation as it correlates well with endoscopic and histological scores. Most IBD diagnosis and treatment guidelines recommend using fecal calprotectin as an aid in diagnosis and in management of IBD. As there is no international standard to date, fecal calprotectin assay manufacturers rely on their own internal calprotectin standardization. Assays can be based on various technologies from enzyme-linked immunosorbent assays (ELISA), particle enhanced turbidimetric high throughput assays (PETIA), to rapid lateral flow assays (LFIA). LFIAs can be read by tabletop lateral flow readers or smartphone applications using the phone's camera to acquire an image, detect the test cassette and calculate a quantitative result. It is essential that the biomarker is measured comparably across all assay methods. In this work, different assay methods were compared with clinical samples using a clinically relevant assay range.

Methods

We measured 128 raw stool samples from an FDA submission study[1] obtained from patients that presented with signs and symptoms suggesting intestinal inflammation and underwent endoscopic evaluation to establish or exclude an IBD diagnosis. Samples were extracted with the BÜHLMANN CALEX® Cap stool preparation device. Each extract was then measured on the BÜHLMANN fCAL® ELISA (fCAL ELISA), BÜHLMANN fCAL® turbo (fCAL turbo), Quantum Blue® fCAL extended (QB fCAL) and the smartphone based IB*Doc*® fCAL home test. For the home test, two phones, iPhone 11 and Samsung Galaxy S7, were used to measure the test cassettes. Each sample was measured one time on each assay and Receiver Operating Characteristic (ROC) curve analysis was performed and total agreement between each method was calculated.

Conflict of Interest
All authors are employees of BÜHLMANN Laboratories AG.

Results

ROC curves were generated to assess the ability of each assay to differentiate between IBS and IBD with area under the curve (AUC) values ranging from 0.827 (Samsung Galaxy S7) to 0.835 (fCAL turbo). There was no significant difference between the methods (Figure 1). BÜHLMANN recommends cut-offs at 80 µg/g and 160 µg/g for IBS/IBD differentiation and 100 µg/g and 300 µg/g for IBD monitoring.

For all methods, the sensitivity at the cut-off level 80 µg/g was 90.8 % and specificity at 160 µg/g ranged from 67.3% to 82.2%. Sensitivity at a cut-off of 100 µg/g ranged from 85.5% to 88.2% and specificity at 300 µg/g ranged from 87.2% to 86.5% (Table 1). In addition to a cut-off at 300 µg/g, 250 µg/g is also a commonly used level in the assessment of IBD patients. Positive and negative percent agreement (PPA/NPA) between the smartphone-based home test and the BÜHLMANN fCAL® turbo and Quantum Blue® fCAL extended lateral flow assay were calculated for values in the measuring range of the assays. The PPA was above 90% and the NPA was above 88% for all methods.

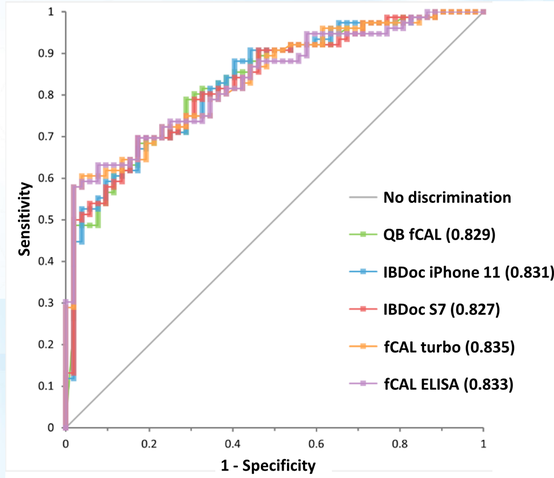

Figure 1: Receiver Operating Characteristic (ROC) Curve Analysis for different fecal calprotectin methods.

	IBDoc (iPhone 11)	IBDoc (Samsung S7)	QB fCAL	fCAL turbo	fCAL ELISA
Sensitivity at 80 µg/g	90.8%	90.8%	90.8%	90.8%	90.8%
Specificity at 160 µg/g	71.2%	82.7%	71.2%	71.2%	67.3%
Sensitivity at 100 µg/g	86.8%	88.2%	88.2%	85.5%	88.2%
Specificity at 300 µg/g	84.6%	82.7%	84.6%	86.5%	84.6%

Table 1: Sensitivity and specificity for IBS/IBD differentiation (80/160 µg/g) and IBD monitoring cut-off (100/300 µg/g) of different fecal calprotectin methods.

	Estimate of Percent Agreement between IBDoc and fCAL turbo		Estimate of Percent Agreement between IBDoc and QB fCAL	
	iPhone 11	Samsung S7	iPhone 11	Samsung S7
PPA at 100 µg/g	120/127 = 94.5%	121/126 = 96.0%	127/132 = 96.2%	128/131 = 97.7%
NPA at 100 µg/g	89/97 = 91.8%	86/97 = 88.7%	91/92 = 98.9%	88/92 = 95.7%
PPA at 250 µg/g	72/75 = 96.0%	71/74 = 95.9%	73/75 = 97.3%	73/74 = 98.6%
NPA at 250 µg/g	146/149 = 98.0%	142/149 = 95.3%	147/149 = 98.7%	144/149 = 96.9%

Table 2: Estimates of PPA and NPA between IB*Doc*® results and corresponding Quantum Blue® fCAL and fCAL turbo assay results.

Conclusion

The results presented here show that the four BÜHLMANN assays measure fecal calprotectin highly comparably and show an excellent clinical performance. This allows for the use of the methods interchangeably, depending on the needs of the patients and their care team.

[1]Berinstein, J.A. et al., 2019, The Clinical Accuracy of the BÜHLMANN fCAL ELISA in the Differentiation of Inflammatory Bowel Disease From Irritable Bowel Syndrome: A Multicenter Prospective Case-Control Study, Crohn's & Colitis 360