

# New blood-based test, 7 alpha-hydroxy-4-cholesten-3-one (7AlphaC4), for bile acid malabsorption/bile acid diarrhea in inflammatory bowel disease or unspecified diarrhea



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## Introduction

Serum 7AlphaC4 (7-alpha-hydroxy-4-cholesten-3-one) is a diagnostic test for bile acid (BA) malabsorption (BAM) or bile acid diarrhea (BAD) and the only available blood-based test for BAM/BAD. Concentrations >48 ng/mL have a high positive predictive value (PPV) of 82% for BAD and high likelihood of responding to BA sequestrants.<sup>1</sup> In BAM, less BAs re-enter enterohepatic circulation and more BAs spill into the colon increasing motility and secretion. Less reabsorbed BA means less negative feedback and an ensuing increase in hepatic BA synthesis. As BA synthesis increases, blood levels of 7AlphaC4, a BA precursor, also increase. This 7AlphaC4 test performed on a random blood collection as a surrogate measure of stool BA aims to simplify the investigation and thereby, improve recognition of BAM/BAD which may often be overlooked in IBD and other patients with more than one possible etiology of diarrhea.

## Methods

We assessed the distribution of numeric serum 7AlphaC4 results (in ng/mL) in 712 patient samples using an in-house developed method utilizing protein precipitation followed by liquid chromatography with tandem mass spectrometry. Reference range of this validated assay is 1.8 – 57 as determined using sera of 120 non-disease individuals.

## Results

Analysis of 712 patient samples yielded a mean ( $\pm$  standard deviation) 7AlphaC4 of  $36.2 \pm 50.1$  ng/mL (range, undetectable (<0.5) to 549); 37.6% were low at <15 (associated with a NPV of 85%); 21.3% were high at >48. Most 7AlphaC4 was ordered in the general or urgent medical setting (42.8%), by gastroenterologists (27.8%) or infectious disease specialists (9.3%). Other testing in order of frequency included: tTG IgA or other celiac tests, fecal calprotectin, fecal pancreatic elastase, stool PCR for 22 GI pathogens, fecal fat, C. difficile toxin, Giardia, H.pylori, and stool lactoferrin. Most common International Classification of Diseases (ICD) codes were: diarrhea unspecified, noninfectious gastroenteritis and colitis, abdominal distension, unspecified abdominal pain, irritable bowel syndrome with diarrhea (IBS-D), change in bowel habit, other fatigue, gastroesophageal reflux, functional diarrhea.

| Serum 7AlphaC4 concentration (ng/mL) | Percentage of total patient results | Interpretation                               |
|--------------------------------------|-------------------------------------|--|
| < 15                                 | 37.6%                               | Low;<br>Associated with 85% NPV for BAM/BAD  |
| 15 – 48                              | 41.1%                               | Normal;<br>Does not help rule in/out BAM/BAD |
| > 48                                 | 21.3%                               | High;<br>Associated with 82% PPV for BAM/BAD |

Table 1. Distribution of all serum 7AlphaC4 results.

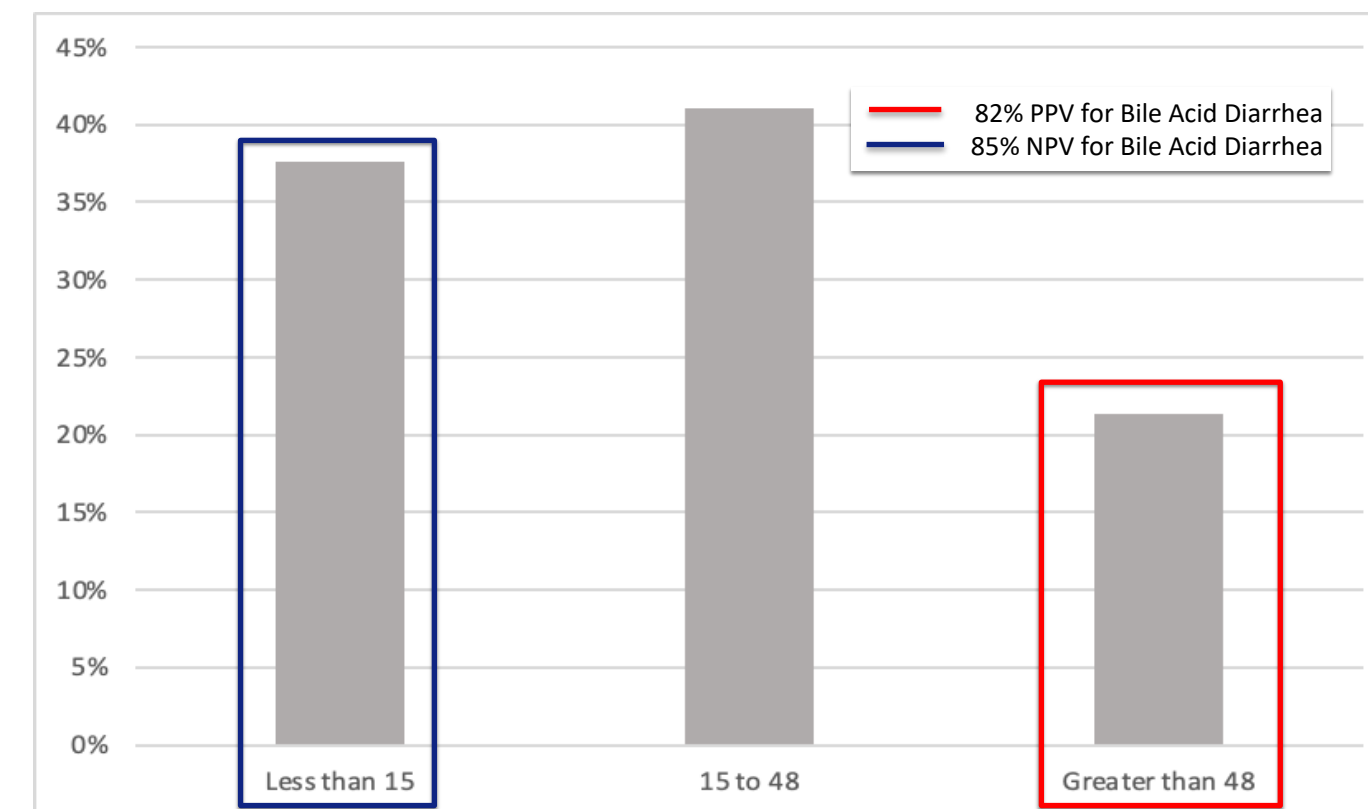
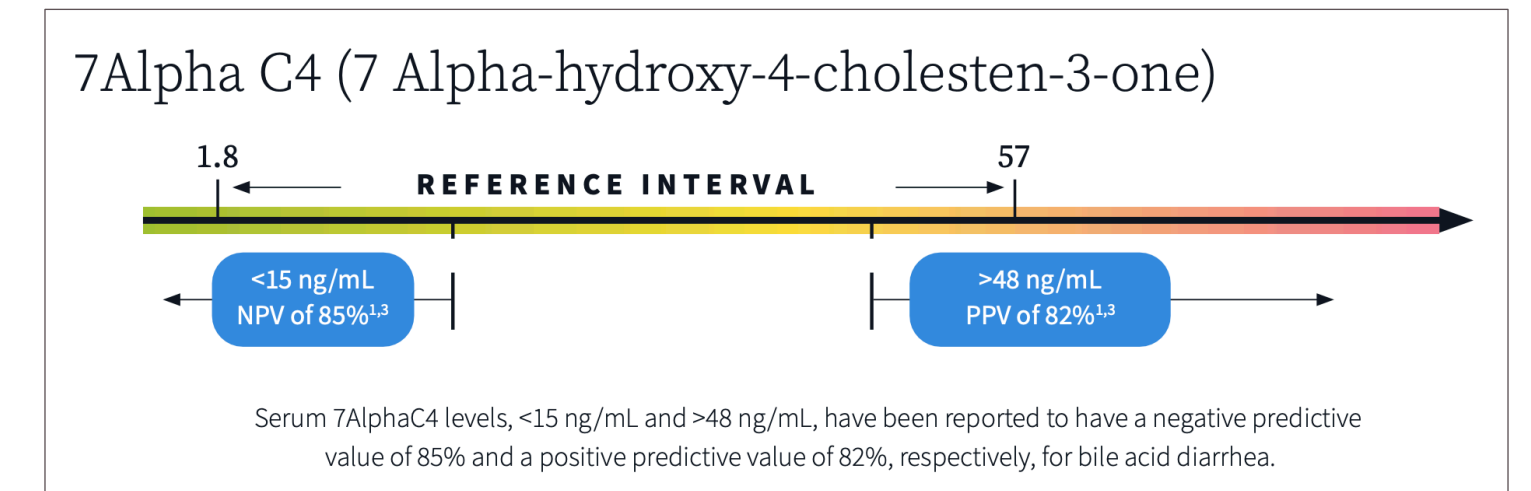


Figure 1. Distribution of serum 7AlphaC4 results (ng/mL).



## Results (continued)

Diagnosis codes are not known for all samples. However, of 50 patients with the highest 7AlphaC4 levels (>100), at least 20% had Crohn's (ileal resection status unknown). In 86 patients with known diagnoses, those with Crohn's with small intestine involvement had the highest mean 7AlphaC4 of  $83.9 \pm 77.1$  (n=27) compared to  $46.1 \pm 83.7$  in functional diarrhea (n=20),  $37.3 \pm 58.9$  in unspecified diarrhea (n=191),  $31.4 \pm 22.3$  in IBS-D (n=31), and  $22.1 \pm 10.8$  in UC (n=8).

## Summary and conclusions

More than half (58.9%) of all 7AlphaC4 results were low (< 15) or high (>48) and as such, potentially diagnostic, carrying a high NPV or high PPV for bile acids contributing to diarrhea. BAM/BAD may account for 30% of all chronic diarrhea cases, thereby, affecting 1-2% of the general population. Disruptions in BA homeostasis and reabsorption occur more frequently in IBD (up to 40%, with or without ileal resection). We observed that many of the highest 7AlphaC4 levels occurred in Crohn's patients. In summary, 7AlphaC4 is a new blood-based marker that provides quantitative evidence of the contribution of colonic BA toward diarrhea (and hence, a higher likelihood of responding to BA sequestrants), especially in patients with persistent diarrhea of more than one possible etiology.

## Reference

- Walters JRF. Making the Diagnosis of Bile Acid Diarrhea. Am J Gastroenterol. 2020 Dec;115(12):1974-1975.