

Bile Acid Malabsorption/ Bile Acid Diarrhea: 7AlphaC4 is a diagnostic blood-based marker

Key Highlights

- Serum 7AlphaC4 is a diagnostic blood test for bile acid diarrhea
- It is a surrogate measure of stool bile acids
- Elevated concentrations (> 57 ng/mL) are associated with excess colonic bile acids as the cause of diarrhea^{1,2}
- Concentrations > 48 ng/mL have been reported to have a positive predictive value (PPV) of 82% for bile acid diarrhea^{1,3}
- Bile acid diarrhea may still occur in the setting of lower 7AlphaC4 levels; values < 15 ng/mL carry a negative predictive value (NPV) of 85%^{1,3}

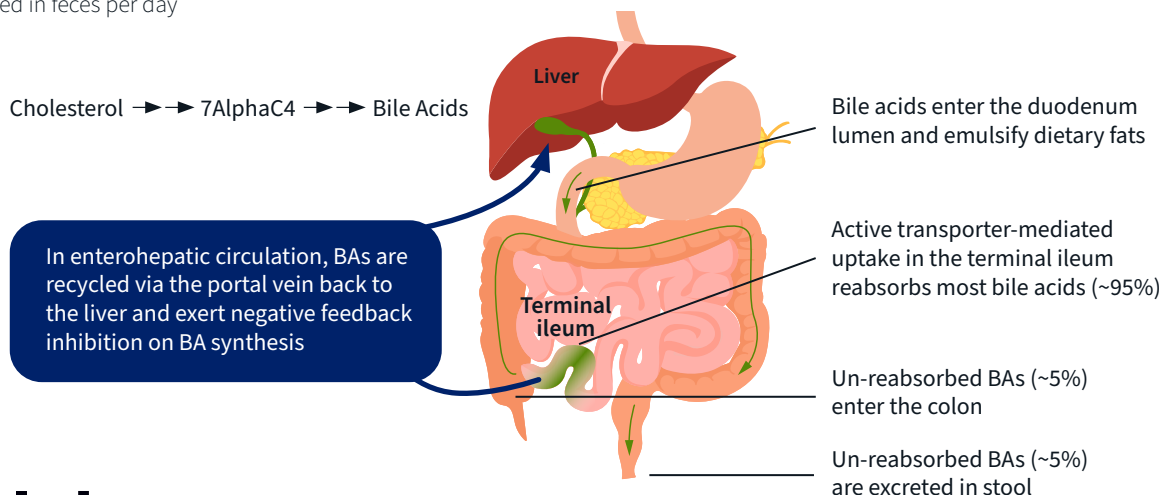
Chronic diarrhea (loose or liquid stool, three or more times a day, lasting longer than four weeks) **affects up to 5% of the population** at any given point in time.^{4,6} Causes include neoplasms, food intolerances, certain systemic diseases, chronic infections, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and malabsorption syndromes including bile acid malabsorption (BAM).^{5,6}

Bile acid malabsorption (BAM), also called **bile acid diarrhea (BAD)**:⁴

- is a common but under-recognized and under-investigated cause of chronic diarrhea^{4,7}
- is characterized by excess bile acids in the colon which stimulate motility and secretion, causing non-bloody diarrhea, urgency, and cramping^{4,8,9}
- is often diagnosed as IBS or functional diarrhea by exclusion⁴
- **occurs in about 30% of patients** with chronic diarrhea, affecting ~ 1% of the general population^{4,9}
- is very responsive to bile acid sequestration therapies^{7,10}

Bile acids (BAs) are detergent molecules that are necessary for intestinal absorption of dietary fats.^{4,11}

- BAs are synthesized from cholesterol in the liver, stored in the gallbladder, and then secreted into the duodenum during meals
- In the lumen of small intestine, BAs emulsify fats to facilitate lipid and fat-soluble vitamin absorption
- In healthy individuals, most BAs (~95%) are reabsorbed by active transporter-mediated uptake in the terminal part of the ileum and returned to the liver (via the portal venous system) in a recycling process known as *enterohepatic circulation*
- Only the remaining unabsorbed BAs (normally ~5%) reach the colon and are excreted in feces
- The typical bile acid pool of 2-3 grams cycles 4-6 times a day where only 0.3-0.5 grams are excreted in feces per day



7AlphaC4 is the only blood-based marker for BAM/BAD

7 Alpha-hydroxy-4-cholesten-3-one (7AlphaC4)

- is a BA precursor, an intermediate in BA biosynthesis from cholesterol^{2-4,11}
- In bile acid malabsorption,
 - less BAs re-enter enterohepatic circulation
 - more BAs spill into the colon where they increase motility and secretion, resulting in diarrhea^{4,8-9}
- Negative feedback regulates hepatic BA synthesis
 - less reabsorbed BAs in BAM lead to increased hepatic BA synthesis⁴
- As hepatic BA synthesis increases, blood levels of 7AlphaC4 also increase⁴
- Serum 7AlphaC4 has high sensitivity (90%) and specificity (79%) for BAM/BAD²
- correlates well with 7-day radioactive 75selenium homocholic acid retention test (SeHCAT) (not available in the US)^{4,11-12}

BAM or BAD can be idiopathic or secondary and co-existent with other gastrointestinal pathologies^{4,7-8,11}:

- **Type 1** (Secondary) – Ileal resection or ileal disease with impaired reabsorption of BAs. e.g. Crohn's disease, radiation ileitis, short bowel syndrome
- **Type 2** (Primary) – Idiopathic overproduction of BA. Many cases of functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS-D)
- **Type 3** (Non-ileal disease) – Altered BA homeostasis in bacterial overgrowth, microscopic colitis, pancreatitis, celiac disease, post-cholecystectomy, post-bariatric surgery, post-vagotomy, cystic fibrosis, hypertriglyceridemia and in patients on metformin therapy

Bile acid diarrhea occurs in:

- more than 30% of patients with unexplained chronic diarrhea that responds to BA sequestrants¹⁰
- up to 50% of functional diarrhea or diarrhea-predominant irritable bowel syndrome (IBS-D)¹³
- 35% of microscopic colitis¹⁴
- more than 40% of inflammatory bowel disease (IBD) patients, most frequently in post-ileal resection (62-100%) and Crohn's disease (CD) ileitis, but also in the absence of active inflammation or ileal disease¹⁵⁻¹⁸

Test Name	Test No.
7AlphaC4 (7 Alpha-Hydroxy-4-Cholesten-3-One)	520550
Synonyms: C4, 7AC4, 7C4, bile acid intermediate, bile acid synthesis surrogate	
Methodology: liquid chromatography- tandem mass spectrometry (LCMS/MS)	
Note: A morning blood collection after overnight fasting is recommended. For cholestasis of pregnancy, Bile Acids, Fractionated and Total, LC/MS-MS [503640] is a different test.	

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