Bile Acid Malabsorption/ Bile Acid Diarrhea:

7AlphaC4 is a diagnostic blood-based marker

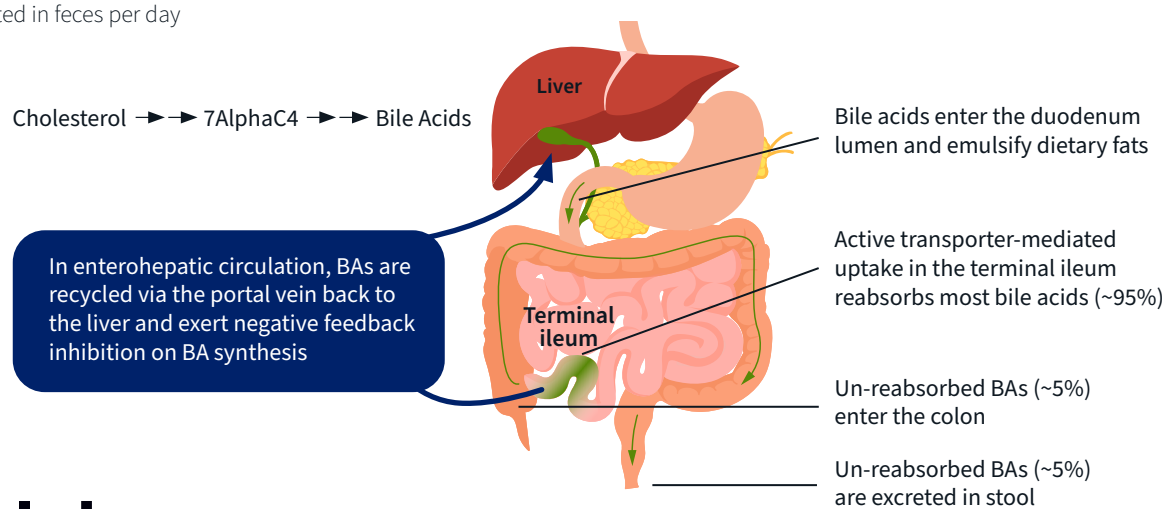
Chronic diarrhea (loose or liquid stool, three or more times a day, lasting longer than four weeks) **affects up to 5% of the population** at any given point in time.[4-6] Causes include neoplasms, food intolerances, certain systemic diseases, chronic infections, irritable bowel syndrome (IBS), inflammatory 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 exclusion[4]
- **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



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]

labcorp

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 synthesis[4]
- As hepatic BA synthesis increases, blood levels of 7AlphaC4 also increase[4]
- Serum 7AlphaC4 has high sensitivity (90%) and specificity (79%) for BAM/BAD[2]
- 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 sequestrants[10]
- up to 50% of functional diarrhea or diarrhea-predominant irritable bowel syndrome (IBS-D)[13]
- 35% of microscopic colitis[14]
- 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 disease[15-18]

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.

References

1. Walters JRF. Making the Diagnosis of Bile Acid Diarrhea. *Am J Gastroenterol*. 2020 Dec;115(12):1974-1975.
2. Sauter GH, Münzing W, von Ritter C, Paumgartner G. Bile acid malabsorption as a cause of chronic diarrhea diagnostic value of 7α- hydroxy-4-cholesten-3-one in serum. *Dig Dis Sci*. 1999 Jan;44(1):14-19.
3. Borup C, Wildt S, Rumessen J, et al. Biochemical Diagnosis of Bile Acid Diarrhea: Prospective Comparison With the 75Seleno-Taurohomocholic Acid Test. *Am J Gastroenterol*. 2020 Dec;115(12):2086-2094.
4. DiBaise JK. Does Your Patient Have Bile Acid Malabsorption? *Pract Gastroenterol*. 2020 May:12-26.
5. Hammer HF. Management of Chronic Diarrhea in Primary Care: The Gastroenterologists' Advice. *Dig Dis*. 2021;39(6):615-621.
6. Schiller LR, Pardi DS, Sellin JH. Chronic Diarrhea: Diagnosis and Management. *Clin Gastroenterol Hepatol*. 2017 Feb;15(2):182-193.e3.
7. Barkun AN, Love J, Gould M, Pluta H, Steinhart H. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. *Can J Gastroenterol*. 2013 Nov;27(11):653-659.
8. Camilleri M, Nurko S. Bile Acid Diarrhea in Adults and Adolescents. *Neurogastroenterol Motil*. 2022 Apr;34(4):e14287.
9. Vijayvargiya P, Camilleri M. Update on Bile Acid Malabsorption: Finally Ready for Prime Time? *Curr Gastroenterol Rep*. 2018 Mar 26;20(3):10.
10. Wong BS, Camilleri M, Carlson P, et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol*. 2012 Sep;10(9):1009-1015.e3.
11. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. *Aliment Pharmacol Ther*. 2014 May;39(9):923-939.
12. Lyutakov I, Ursini F, Penchev P, et al. Methods for Diagnosing Bile Acid Malabsorption: A Systematic Review. *BMC Gastroenterol*. 2019 Nov 14;19(1)185.
13. Camilleri M, Nadeau A, Tremaine WJ, et al. Measurement of serum 7alpha-hydroxy-4-cholesten-3-one (or 7alphaC4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. *Neurogastroenterol Motil*. 2009 Jul;21(7):734-e43.
14. Vijayvargiya P, Camilleri M, Shin A, Saenger A. Methods for diagnosis of bile acid malabsorption in clinical practice. *Clin Gastroenterol Hepatol*. 2013 Oct;11(10):1232-1239.
15. Lenicek M, Duricova D, Komarek V, et al. Bile acid malabsorption in inflammatory bowel disease: assessment by serum markers. *Inflamm Bowel Dis*. 2011 Jun;17(6):1322-1327.
16. Kunstár E, Hegyi P, Rakonczay Z, et al. Is bile acid malabsorption really a common feature of Crohn's disease or is it simply a consequence of ileal resection? *Front Physiol*. 2011 Aug 17;2:28.
17. Nyhlin H, Merrick MV, Eastwood MA. Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. *Gut*. 1994 Jan;35(1):90-93.
18. Vítek L. Bile acid malabsorption in inflammatory bowel disease. *Inflammatory Bowel Dis*. 2015 Feb;21(2):476-483.

labcorp