TMAO
(Trimethylamine N-oxide)

CPT Code **82542***
Order Code **C524**
Specimen Type **Serum**
Tube Type **Tiger Top**

Elevated levels of TMAO may identify:

- Gut dysfunction
- Risk of adverse cardiac events
- Individuals who may benefit from intensive dietary intervention

Description

Gut microbes live symbiotically within the human digestive tract and play important roles in host defense, immunity, and nutrient processing and absorption. This diverse community is unique to each person and is influenced by both acute and chronic dietary exposures to various food sources.

Nutrients, such as phosphatidylcholine (also known as lecithin),[1,2] choline,[3] and L-carnitine,[4] are abundant in animal-derived products, such as red meat, egg yolk, and dairy products. When consumed, these nutrients are processed by gut bacteria, resulting in the release of various metabolites, including TMA (trimethylamine), into the blood. TMA is then transported to the liver, where it is converted into TMAO (trimethylamine N-oxide). TMAO regulates various physiological processes involved in the development and progression of atherosclerosis,[1,4] including reverse cholesterol transport[5] and platelet aggregation.[3,6]

Clinical Use

TMAO may be measured in individuals with one or more risk factors for the development of cardiovascular disease and/or individuals whom may benefit from intensive dietary intervention.

Clinical Significance

- There is a dose-response relationship between TMAO and platelet aggregation,[3] atherosclerotic burden,[1] and incidence of major adverse cardiovascular events (MACE: myocardial infarction, stroke, or death).[2,7,8]
- For every 10 µmol/L-increase in TMAO, there is a 7.6% increase in relative risk of mortality.[8]
- In stable individuals, undergoing elective cardiac evaluation, elevated TMAO levels are associated with increased risk of cardiovascular disease[1] and MACE.[2]
  - Increased plasma L-carnitine (a dietary precursor to TMAO) is associated with cardiovascular risk only when TMAO is simultaneously elevated via the metabolism by specific gut microbes.[4]
  - In a subset of this population considered 'low risk' (<65 years old, <100mg/dL LDL-C, normal blood pressure, non-smokers), elevated TMAO remained a significant predictor of MACE risk.[2]
- Elevated TMAO is associated with a 5-year mortality risk in patients with type 2 diabetes mellitus,[9] coronary artery disease (CAD),[10] or peripheral artery disease (PAD),[11] and a 7-year mortality risk in patients admitted to the emergency room, with acute coronary syndrome.[7]

Testing Frequency

TMAO testing is determined by an individual's medical history, but it may be performed semi-annually or annually, as necessary. If the initial test result is abnormal, then follow-up testing may be performed within 3-6 months following treatment.

Specimen Type

The TMAO test should be performed on a serum specimen. Patients should fast overnight and refrain from consuming fish, other seafood, or fish oil supplements the day before the blood draw, as fish naturally produce TMAO,[12,13] which may lead to transient elevations.[14] If the patient is on antibiotics, they should finish their medication, and wait one month before testing for TMAO.

Commercial Insurance or Medicare Coverage

Coverage guidelines have not been established or posted by CMS (Medicare & Medicaid). We have reviewed the larger carriers (Aetna, United Healthcare, Cigna, Blues) and information is limited or has not been posted.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103
p 866.358.9828 | f 866.869.0148
clevelandheartlab.com | knowyourrisk.com | chlcme.com

ClevelandHeartLab®
Know your risk.

Quest Diagnostics™

RELATIVE RISK

TMAO
(μM)

<6.2 Low	6.2-9.9 Moderate	≥10.0 High

Treatment Considerations†

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviews by the treating practitioner.

✓ **Assess lifestyle habits.**

- Consider implementing a Mediterranean or plant-based diet.[15]
- Consider limiting the intake of foods rich in TMA precursors, such as red meat, egg yolk, and dairy products.[1-4,14,16] Some energy drinks may also contain L-carnitine.
- Consider recent consumption of seafood (within 24 hours prior to blood draw).
  - Many types of seafood naturally contain TMAO (particularly saltwater fish, sharks, rays, mollusks, and crustaceans),[12-14] and levels increase with depth of habitat.[12,13] These food sources may falsely elevate TMAO levels,[14] whereas cardiovascular risk is associated with gut microbiota-derived TMAO.[1-4]

✓ **Assess dietary supplementation.**

- Consider discontinuing the use of choline-, phosphatidylcholine-, or L-carnitine- containing supplements in individuals with elevated TMAO levels.[1-4]
- Decreased diversity of gut microbiota may be associated with high levels of TMAO,[16] therefore probiotic/prebiotic supplementation may be considered to promote gut biodiversity.

✓ **Assess insulin-sensitivity.**

- If not at an optimal level,[9,17] consider insulin-sensitizing therapies described in the ADA guidelines for the management of pre-diabetes/diabetes.[18]

✓ **Assess clotting risk.**[3,7]

- Consider antiplatelet therapy,[3] if there is a history of CAD (i.e., myocardial infarction or revascularization) and/or a history of cerebrovascular disease (i.e., transient ischemic attack or stroke).

Implement global risk reduction strategies

✓ **Assess BMI.**

- If overweight/obese,[17] consider weight management strategies.

✓ **Assess LDL-C levels.**[4,5]

- If not at an optimal level, consider lipid-lowering therapies described in the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) Guidelines.[19]

** The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.*

† The treatment considerations are provided for informational purposes only and are not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

References

1. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature*. 2011; 472: 57–63. 2. Tang WHW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013; 368: 1575-1584. 3. Zhu W, Wang Z, Tang WHW, Hazen SL. Gut Microbe-Generated Trimethylamine N-Oxide From Dietary Choline Is Prothrombotic in Subjects. *Circulation*. 2017: 135: 1671-1673. 4. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013; 19: 576-585. 5. Warrier M, Shih DM, Burrows AC, et al. The TMAO-Generating Enzyme Flavin Monooxygenase 3 Is a Central Regulator of Cholesterol Balance. *Cell Reports*. 2015; 10: 326-338. 6. Zhu W, Gregory JC, Org E, et al. Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell*. 2016; 165: 111-24. 7. Li SX, Obeid S, Klingenberg R, et al. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J*. 2017; 0: 1-11. 8. Schiattarella GG, Sannino A, Toscano E, et al. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. *European Heart Journal*. 2017; 38: 2948-2956. 9. Tang WHW, Wang Z, Li XS et al. Increased Trimethylamine N-Oxide Portends High Mortality Risk Independent of Glycemic Control in Patients with Type 2 Diabetes Mellitus. *Clin Chem*. 2017; 63 (1): 297-306. 10. Senthong V, Wang Z, Li XS, et al. Intestinal Microbiota-Generated Metabolite Trimethylamine-N-Oxide and 5-Year Mortality Risk in Stable Coronary Artery Disease: The Contributory Role of Intestinal Microbiota in a COURAAGE-Like Patient Cohort. *J Am Heart Assoc*. 2016; 5: e002816. 11. Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WHW. Trimethylamine N-Oxide and Mortality Risk in Patients With Peripheral Artery Disease. *J Am Heart Assoc*. 2016; 5; e004237. 12. Kelly RH and Yancey PH. High Contents of Trimethylamine Oxide Correlating With Depth in Deep-Sea Teleost Fishes, Skates, and Decapod Crustaceans. *Bio Bull*. 1999; 196: 18-25. 13. Treberg JR and Driedzi WR. Elevated Levels of Trimethylamine Oxide in Deep-Sea Fish: Evidence for Synthesis and Intertissue Physiological Importance. *J Exp Zool*. 2002; 29: 39-45. 14. Krüger R, Merz B, Rist MJ, et al. Associations of current diet with plasma and urine TMAO in the KarMeN study: direct and indirect contributions. *Mol Nutr Food Res*. 2017; 61: 1700363. 15. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*. 2015; 65 (11): 1812-1821. 16. Cho CE, Taesuwan S, Malysheva OV, et al. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: A randomized controlled trial. *Mol Nutr Food Res*. 2017; 61: 1600324. 17. Schugar RC, Shih DM, Warrier M, et al. The TMAO-Producing Enzyme Flavin-Containing Monoxygenase 3 Regulates Obesity and the Beiging of White Adipose Tissue. *Cell Reports*. 2017; 19: 2451-2461. 18. American Diabetes Association: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Supplement 1). 19. Third report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *National Institutes of Health*. September 2002. NIH Publication No. 02-5215.

QuestDiagnostics.com