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), choline, and L-carnitine, 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, including reverse cholesterol transport and platelet aggregation. Elevated levels of TMAO may identify:

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

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, atheroerotic burden, and incidence of major adverse cardiovascular events (MACE: myocardial infarction, stroke, or death). Elevated levels of TMAO are associated with increased risk of cardiovascular disease and MACE. 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. 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. Elevated TMAO is associated with a 5-year mortality risk in patients with type 2 diabetes mellitus, coronary artery disease (CAD), or peripheral artery disease (PAD), and a 7-year mortality risk in patients admitted to the emergency room, with acute coronary syndrome.

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, which may lead to transient elevations. 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.

Elevated levels of TMAO may identify:

- Gut dysfunction
- Risk of adverse cardiac events
- Individuals who may benefit from intensive dietary intervention
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess lifestyle habits.**
  - Consider implementing a Mediterranean or plant-based diet.\(^5\)
  - Consider limiting the intake of foods rich in TMAO 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).\(^12,14\) Levels increase with depth of habitat.\(^12,13\) These food sources may falsely elevate TMAO levels,\(^*\) 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 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.\(^8\)

- **Assess clotting risk.\(^2,7\)**
  - Consider antiplatelet therapy,\(^7\) 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).

### Implementation 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.\(^19\)

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**References**