Policy Number	**MED207.136**
Policy Effective Date	**06/15/2024**
Policy End Date	**12/31/2025**

Measurement of Long Chain Omega-3 Fatty Acids in Red Blood Cell Membranes as a Cardiac Risk Factor

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Measurement of long chain omega-3 fatty acids in red blood cell membranes, including but not limited to its use as a cardiac risk factor, **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Epidemiologic studies have reported that subjects who eat a diet high in fish have a reduced risk of sudden cardiac death. Fish are rich in long chain omega-3 fatty acids, and it has been hypothesized that these fatty acids may be responsible for the beneficial effect. Long chain omega-3 fatty acids may be detected in the red cell membrane using gas chromatography. It has been suggested this measurement may be clinically useful as a cardiac risk factor for sudden cardiac death.

Rationale

This policy was originally developed in 2005 and has been updated with searches of scientific literature through April 15, 2024. The following is a summary of the key literature to date.

A literature search identified many observational studies exploring the relationship between fish consumption and coronary heart disease (CHD) mortality in different populations of patients. (1-6) These studies suggest that mortality from CHD may be reduced by including fish as a regular part of the diet. However, the search did not identify any published articles that explored how the measurement of red blood cell membrane omega-3 fatty acids may be used to improve patient management. For example, studies establishing the diagnostic parameters of omega-3 fatty acids (i.e., the definition of normal, high, and low values), were not identified. It has been suggested that measurement of omega-3 fatty acids may be incorporated into a cardiac risk panel in patients with a prior cardiac event. There were no studies that focused on this application of this laboratory test. Improved risk prediction does not by itself result in better health outcomes; to improve outcomes clinicians must have the tools to translate this information into clinical practice. Now, patients with coronary artery disease are offered the general dietary recommendation to increase fish consumption, a recommendation not based on red blood cell membrane levels of omega-3 fatty acids.

The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) trial compared fish oil capsules plus statins to statins alone in 18,645 patients with hypercholesterolemia. In this primary and secondary prevention study, if hypercholesterolemia remained uncontrolled, the dose of the statin could be raised by protocol. No measurements of the efficacy of fish oil treatment were performed and the dose remained constant throughout the study. The fish oil plus statin group had 18% (p=0.132) and 19% (p=0.015) fewer non-fatal (primary and secondary, respectively) cardiac events over a mean of 4.6 years compared to the statin only group. (7)

In 2014, Grieger et al. published an 8-week randomized, parallel study of 80 participants, which was stratified by CRP (<3 mg/L vs. ≥3 mg/L) on entry to the study. Compliance was measured using 3-day weighed food records in weeks 1 and 7 of the study. A 12-h fasting blood sample was taken at baseline and 8-weeks for erythrocyte fatty acids as confirmation of compliance, and measurement of serum cytokines and lipids. Blood pressure was measured at both time points. They concluded that eight weeks consumption of four servings of fish per week did not affect serum cytokine concentrations, blood pressure or lipids compared to a diet low in fish. In healthy older adults with low inflammatory burden, they reported that their results do not

support that short-term consumption of mixed fish has a beneficial effect on selected cardiovascular biomarkers. (8)

In a multiethnic population-based cross-sectional study of 998 asymptomatic men aged 40-49 years (300 US-White, 101 US-Black, 287 Japanese American, and 310 Japanese in Japan), Mahajan et al. (2019) examined the relationship of serum long-chain n-3 polyunsaturated fatty acids (LCn-3PUFAs) to aortic calcification (measured by electron-beam computed tomography and quantified using the Agatston method) using Tobit regression and ordinal logistic regression after adjusting for potential confounders. (9) Overall, 56.5% participants had an aortic calcification score (AoCaS) > 0. The means (SD) of total LCn-3PUFAs, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were 5.8% (3.3%), 1.4% (1.3%), and 3.7% (2.1%), respectively. In multivariable-adjusted Tobit regression, a 1-SD increase in total LCn-3PUFAs, EPA, and DHA was associated with 29% (95% CI = 0.51, 1.00), 9% (95% CI = 0.68, 1.23), and 35% (95% CI = 0.46, 0.91) lower AoCaS, respectively. Results were similar in ordinal logistic regression analysis. There was no significant interaction between race/ethnicity and total LCn-3PUFAs, EPA or DHA on aortic calcification. Authors concluded that this study showed the significant inverse association of LCn-3PUFAs with aortic calcification independent of conventional cardiovascular risk factors among men in the general population. This association appeared to be driven by DHA but not EPA. A notable study limitation is that it examined healthy men aged 40-49 years in Japan and the US; therefore, the results of the study cannot be generalized to females, other populations, or age groups. Follow-up population-based studies are needed to further clarify the effect of LCn-3PUFAs on the incidence and progression of atherosclerosis.

Harris et al. (2021) conducted a meta-analysis to examine the associations between circulating levels of the n-3 PUFAs and mortality. (11) The analysis was done with individual-level data from 17 prospective cohorts. Over a median of 16 years of follow-up, 15,720 deaths occurred among 42,466 individuals. Risk for death from all causes was significantly lower (by 15–18%) in the highest vs the lowest quintile for circulating long chain (20–22 carbon) omega-3 fatty acids. Approximately 30% of the deaths were attributed to cardiovascular disease (CVD), 30% to cancer, and the remaining 39% to all other causes. The authors concluded that in a global pooled analysis of prospective studies, LC n-3 PUFA levels were inversely associated with risk for death from all causes and from CVD, cancer, and other causes. Potential limitations included the hazard ratios (HRs) reported (instantaneous relative risk) may be modestly different than the cumulative relative risk and most individuals were White, potentially lowering generalizability to other races/ethnicities. Additionally, the study did not address whether measurement of LC n-3 PUFA levels improved patients care and outcomes.

In a systematic review and meta-analysis, Zheng et al. (2022) sought to determine the role of LC n-3 PUFAs in the incidence of heart failure (HF). (12) Thirteen studies met inclusion criteria and were included in the meta-analysis. Eight studies on dietary LC n-3 PUFA intake and incident HF included n = 316,698 (11,244 incident HF cases), with a median follow-up of 10.7 years, for analysis. The studies showed that a higher dietary intake of LC n-3 PUFAs was associated with a lower risk of HF (highest versus lowest quintile: HR = 0.84, 95% CI = 0.75–0.94). Six studies,

evaluating the association between circulating LC n-3 PUFA concentrations and the risk of HF comprising of n = 17,163 (2520 HF cases) with a median follow-up of 9.7 years, showed that higher circulating LC n-3 PUFA concentrations were associated with a lower risk of HF. Higher circulating docosahexaenoic acid (DHA) concentrations were associated with a decreased risk of HF (top versus bottom quintile: HR = 0.44, 95% CI = 0.26–0.77). The associations between eicosapentaenoic acid (EPA) (HR = 0.58, 95% CI = 0.26–1.25), DHA (HR = 0.66, 95% CI = 0.24–1.82), and the risk of HF were not significant. The authors concluded higher LC n-3 PUFA concentrations measured by dietary intake or circulating biomarkers are associated with a lower risk of developing HF. Comparably, higher circulating LC n-3 PUFA concentrations appeared to play a protective role in the risk of HF. Future randomized controlled trials are required to evaluate whether LC n-3 PUFAs are effective in the primary prevention of HF. Limitations in the study included single measurement of LC n-3 PUFAs was performed in the observational studies and the association between individual LC n-3 PUFAs (DHA, EPA, and DPA) and the risk of HF are limited. Furthermore, comparison to other predictors of HF and the clinical utility of LC n-3 PUFA measurement are not addressed in this study.

Summary of Evidence

There are multiple published studies addressing the potential benefits of adding omega-3 fatty acids to one's diet. However, there is a lack of scientific evidence regarding how the measurement of long-chain omega-3 fatty acids would affect management and improve clinical outcomes of individuals at risk for, or patients with coronary heart disease.

Practice Guidelines and Position Statements

American College of Cardiology (ACC)/American Heart Association (AHA)

The 2019 ACC/AHA guidelines on the primary prevention of cardiovascular risk do not address long-chain omega-3 fatty acids to assess initial cardiovascular disease (CVD) risk. (10)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	84999
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/31/2025	Document became inactive.
06/15/2024	Document updated with literature review. Coverage unchanged. Added references 11 and 12.
07/01/2023	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. Added reference 10.
01/01/2022	Reviewed. No changes.
01/15/2021	Document updated with literature review. Coverage unchanged. Added reference 9.
09/15/2019	Reviewed. No changes.
05/15/2018	Document updated with literature review. Coverage unchanged.
06/15/2017	Reviewed. No changes.
06/01/2016	Document updated with literature review. Coverage unchanged.
05/15/2015	Reviewed. No changes.
04/15/2014	Document updated with literature review. Coverage unchanged.
05/01/2011	Document updated with literature review. Coverage unchanged.
11/01/2009	Policy updated with literature review. No change in coverage position.
09/14/2007	Revised/Updated Entire Document
07/01/2005	New Medical Document