Coverage Guidelines

NMR LipoProfile® and NMR LipoProfile®-II Tests

Disclaimer:
Please note that Baptist Health Plan updates Coverage Guidelines throughout the year. A printed version may not be most up to date version available. The health plan reserves the right to review and update this policy as needed. Refer to the website to ascertain that you are utilizing the most current available version. Clinical guideline policies are not intended to serve as treatment guidelines or treatment recommendation. Treating providers must use their own clinical judgment in rendering care to their patient population.

For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern. In addition, coverage for Medicare Advantage members may differ. This is a result of applicable coverage statements by the Center for Medicare and Medicaid Services (CMS). The National Coverage Determinations, Local Coverage Determinations, and Local Medical Review Policies may be found at the CMS website, http://www.cms.gov. Please note that for all plans, the member’s health plan benefits that are in effect on the rendered date of service must be used in coverage determinations.

DEFINITION

Determination of lipoprotein particle size and number using advanced lipoprotein tests (ALTs) is of particular importance to improve cardiovascular risk prediction. The LipoProfile® test (LabCorp Corporation, Burlington NC) is one of a number of advanced cardiovascular assays that may yield valid clinical prognostic indicators of future cardiovascular disease. The test uses nuclear magnetic resonance (NMR) imaging to measure the number and size of lipoprotein particles in the blood: i.e., it measures low-density lipoprotein (LDL) particle number and size, high- density lipoprotein (HDL) and very low- density lipoprotein (VLDL) parameters.¹

In 2014 LipoScience, Inc (the creator of the test) was acquired by LapCorp). With further development of the technology associated with the test a second generation assay termed NMR LipoProfile II® evolved that purported greater accuracy in both number and size measurement of LDL (an especially critical value in predicting cardiovascular risk).²

COVERAGE CRITERIA
Baptist Health Plan considers the NMR LipoProfile and the NMR LipoProfile II tests to be investigational and therefore not medically necessary.

**MEDICAL BACKGROUND**

Nuclear magnetic resonance (NMR) spectroscopy measures the number and size of lipoprotein particles instead of their cholesterol or triglyceride content, but its clinical utility is uncertain.\(^3\)

A contemporary narrative review presented the pros and cons of NMR diagnosis in cardiovascular disease and rendered the following assessment of its usefulness:\(^4\)

> “Early epidemiological studies suggest promise, however, this is an emerging field and more data is required before we can determine the clinical utility of these measures to improve disease prediction and treatment.”

An uncontrolled observational study of 82 patients referred to a tertiary care preventive cardiology clinic assessed the efficacy of the NMR LipoProfile test, the Vertical Auto Profile (VAP) cholesterol test, or gradient gel electrophoresis.\(^5\) Lipid profiles were obtained and Framingham risk scores were calculated. Patients were stratified by Adult Treatment Panel guidelines as being at low, intermediate, or high risk. The study included 56 men and 26 women with a mean age of 54 +/- 11 years. In the entire cohort of 82 patients, only 31 (38%) were at non-HDL goal, only 21 (26%) were at goals for both non-HDL and HDL, and only 18 (22%) were at goal for non-HDL, HDL, and triglycerides. When considering each of the risk factor strata, 19 of 43 (44%) low-risk patients were at non-HDL goal and 12 of these also had a small LDLPS. Only 8 of 18 (44%) intermediate-risk patients were at non-HDL goal and 7 of these (88%) had small LDLPS. Finally, only four high-risk patients were at non-HDL goal and three of these (75%) had small low-density lipoprotein particle size (LDLPS). The authors surmised that the LDLPS could alter subsequent therapeutic recommendations for a small cohort of patients who have reached target lipid values.

Attempts to fine-tune the underlying technology for measurement of lipoprotein dimension and create greater credibility of particle-size assessment have gradually led away from the original LipoProfile assessment toward more sophisticated studies.\(^6\) One such technique uses a novel advanced lipoprotein test (Liposcale) based on two-dimensional diffusion-ordered 1H NMR spectroscopy. In a study of 177 plasma samples from healthy individuals the test showed a stronger correlation between the NMR-derived lipoprotein particle numbers and apolipoprotein concentrations than the LipoProfile(®) test. After converting LDL particle numbers to ApoB equivalents (milligrams per deciliter) the Liposcale model yielded similar values of LDL-ApoB to the LipoProfile(®) test (absolute mean bias of 8.5 and 7.4 mg/dl, respectively). In addition HDL particle number values were more concordant with the calibrated values determined using ion mobility. Finally, principal component analysis distinguished type 2 diabetic patients with and without atherogenic dyslipidemia (AD) on a second cohort of 307 subjects characterized using the Liposcale test (area under the curve = 0.88) and showed concordant relationships between variables explaining AD. The authors concluded that:

> “Liposcale showed a stronger correlation between the NMR-derived lipoprotein particle numbers and apolipoprotein concentrations than the LipoProfile(®) test commercialized by LipoScience.”
Other attempts to correlate the size of lipoprotein particles to the risk of coronary artery disease (CAD) have looked at atomic force microscopy (AFM) for evaluating the size of lipoproteins separated by ultracentrifugation. A small study found a significant difference in particle sizes determined by AFM between large LDL (20.6 ± 1.9 nm, mean ± SD) and small density LDL (16.2 ± 1.4 nm) obtained from six healthy volunteers (P < 0.05). The particle sizes determined by electron microscopy (EM) for the same samples were 23.2 ± 1.4 nm for large LDL and 20.4 ± 1.4 nm for sd-LDL. The difference between large LDL and sd-LDL detected by EM was also statistically significant (P < 0.05). In addition, the particle sizes of each lipoprotein fraction were significantly different between AFM and EM: P < 0.05 for large LDL and P < 0.05 for sd-LDL. The authors concluded that AFM can differentiate between small density LDL and large LDL particles by their size, and might be another option in lieu of NMR technology that is useful for evaluating risk for CAD.

A large controlled clinical trial (n=2940) assessed NMR-measured lipoproteins versus gel electrophoresis to determine if either modality was superior in measuring lipid particle size. There was generally overall agreement between NMR and electrophoresis with regard to HDL and LDL size, though there was some bias toward NMR with respect to cardiovascular heart disease risk.

The data with regard to NMR assessment of lipid particle size notwithstanding, there is still a need for better ways to measure these important contributors to heart disease. A narrative review noted there is surprisingly little consistency in the reliability of laboratory measurements of low-density lipoprotein cholesterol (LDL-C), citing its measurement as fraught with error. Despite the widespread belief that LDL-C is standardized and reproducible, available data suggest that results can vary significantly as the result of methods from different manufacturers’ tests. Similar problems with direct high-density lipoprotein cholesterol (HDL-C) assays raise concerns about the reliability of non-HDL-C measurement. The root cause of method-specific bias relates to the ambiguity in the definition of both LDL and HDL, and the heterogeneity of LDL and HDL particle size and composition. Apolipoprotein B appears to provide a more reliable alternative, but assays for it have not been as rigorously tested as direct LDL-C and HDL-C assays.

REGULATORY INFORMATION

Kentucky – No legislative mandates were found for coverage of the NMR LipoProfile or the NMR LipoProfile II Test.

Indiana – No legislative mandates were found for coverage of the NMR LipoProfile or the NMR LipoProfile II Test.

Tennessee – No legislative mandates were found for coverage of the NMR LipoProfile or the NMR LipoProfile II Test.

The Center for Medicare and Medicaid Services (CMS) has established a National Coverage Determination (NCD) for lipid assessment in the setting of cardiovascular risk that includes both screening and follow-up treatment testing of blood lipid levels by serum panel. The NCD makes no mention of lipid particle size assessment by NMR.
COVERAGE DETAIL

For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.

CODES INCLUDE BUT MAY NOT BE LIMITED TO THE FOLLOWING:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Coverage Information</th>
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<tbody>
<tr>
<td>83704</td>
<td>Lipoprotein, blood; quantitation of lipoprotein particle numbers and lipoprotein particle subclasses (eg, by nuclear magnetic resonance spectroscopy)</td>
<td>Not medically necessary or experimental/investigational</td>
</tr>
</tbody>
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REFERENCES


8. Arsenault B.J., Lemieux I., Despres J.-P., et al. Comparison between gradient gel electrophoresis and nuclear magnetic resonance spectroscopy in estimating coronary heart disease risk associated with LDL and HDL particle size. Clinical Chemistry. 56 (5) (pp 789-
798), 2010.
