KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

PLAC Test

- Predicting the Risk of Coronary Heart Disease (Lp-PLA2)

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	MolDX: Biomarkers in Cardiovascular Risk Assessment (L36362) *This test is not covered when included in a CV risk assessment panel per Medicare LCD.*
Local Coverage Article	Billing and Coding: MolDX: Biomarkers in Cardiovascular Risk Assessment (A57055)

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

Recent research suggests that inflammation plays a role in the development and progression of atherosclerosis. This observation, together with the advances in inflammatory biomarkers research, has led to the emergence of dozens of novel biomarkers that may potentially aid in predicting an individual's risk for cardiovascular disease. Among these novel biomarkers are C-reactive proteins, lipoprotein associated phospholipase A2 (Lp-PLA2), homocysteine, fibrinogen, plasminogen, interleukin-6 (IL-6), IL-18, and many others (Anderson 2008, Khakpour 2009, Packard 2009).

A novel biomarker for cardiovascular risk has clinical utility if it independently provides risk information above and beyond that provided by conventional risk factors, is easy to obtain and interpret in a primary care setting, is highly specific, accurately reproducible and contributes to patient management particularly through more accurate risk stratification and guidance in the choice of therapy (Oldgren 2007, Lerman 2008, Khakpour 2009).

Lp-PLA2, also known as platelet activating factor acetyl-hydrolase, has been proposed to be a more specific marker for vascular inflammation. It is an enzyme secreted by macrophages, monocytes, T-lymphocytes, and mast cells. Over two thirds of Lp-PLA2 circulate in the bloodstream bound to low-density lipoprotein cholesterol, and the rest travels bound to high-density and very low-density lipoproteins. For several years there has been a lot of debate on whether the enzyme has a pro- or anti-atherogenic mechanism. One viewpoint suggests that it plays a role in the production of proinflammatory mediators including oxidized free fatty acids and lysophosphatidylcholine, and another view implies that that the enzyme could be protective by reducing

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inflammation and predisposition to thrombosis in blood through its hydrolysis of platelet activating factor (Anderson 2008, Wilensky 2009).

The diaDexus PLAC test is a second generation of the enzyme-linked immunoassay (ELISA) test used in many of the population studies that investigated the association of Lp-PLA2 with cardiovascular diseases. It is based on the standard principle of a sandwich enzyme immunoassay using two specific high affinity monoclonal antibodies directed against Lp-PLA2 that show no cross-reactivity with other phospholipases. A set of Lp-PLA2 calibrators is used to plot a standard curve of absorbance (y-axis) versus Lp-PLA2 concentration in ng/ml (x-axis) from which the Lp-PLA2 concentration in the test sample can be determined. This concentration of the enzyme in each sample and control is then interpolated from the standard curve using a point-to-point curve fit with appropriate calibration curve fitting software. The test has a minimum detection limit of 1.3 ng/ml and the expected Lp-PLA2 concentrations are 120-342 ng/ml for females and 131-376 ng/ml for males. PLAC test is classified under the Clinical Laboratory Improvement Amendments (CLIA) 88 as a high-complexity test and must be run in CLIA-certified-high-complexity laboratories (Hoogerveen 2005, FDA Website).

PLAC test, diaDexus, Inc, San Francisco, CA, was cleared by the FDA in 2003, for the quantitative determination of Lp-PLA2 in human plasma to be used in conjunction with clinical evaluation and patient risk assessment as an aid for predicting risk for coronary heart disease, and ischemic stroke associated with atherosclerosis (FDA website).

Medical Technology Assessment Committee (MTAC)

PLAC Test in Detecting Risk of Coronary Heart Disease

02/11/2004: MTAC REVIEW

Evidence Conclusion: Ballantyne et al's study was nested in a large prospective study. It included both men and women 45-64 years of age. In this sub-study CHD patients were compared to a random sample of 785 subjects (minus 45 cases with CHD), and not to the whole study population. The authors do not provide explanation why they selected such a design. There were several significant differences in the base-line characteristics between the cases, and non- cases. Adjustments were made for several of these variables, not for all. Other variables not adjusted for in the analysis may be potential confounders. Overall, it showed that the highest tertile of Lp-PLA_2 enzyme was associated with a higher CHD risk among patients with LDL cholesterol level <130 mg/dL. Packard's study was a case control nested in the WOSCOPS study. Participants were men 45-64 years of age, with baseline LDL cholesterol level 174 –232 mg/dL. Cases were those who developed a coronary event, and controls were men from the same cohort who did not develop a coronary event during the follow-up. Overall the results showed that lipoprotein-associated phospholipase A_2 was significantly associated with coronary events, independent of the other variables studied. Blake's study on the other hand did not detect a significant association between the enzyme and the risk of cardiovascular events among women. It was also a case control nested in a large trial, "Women's Health Study" that only enrolled women 45 years of age or older. The case control study was small, and the power might have been insufficient to detect a significant association. The different findings between the two studies may also indicate that lipoprotein-associated phospholipase levels may be predictive of coronary events in men but not women. The three studies reviewed examined Lp-PLA_2 as a marker or risk predictor for coronary events but did not study the implication of identifying this risk factor on the management of the patients or in improving the net health outcome.

Articles: The search yielded 25 articles, the majority of which were news, review articles, and tutorials. The search did not reveal any RCTs. The studies embedded in larger prospective cohort studies were identified. All three were critically appraised: Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase High sensitivity C-reactive protein, and risk incident coronary heart disease in middle-aged men and women in the atherosclerosis risk in communities (ARIC) study. *Circulation* 2004; 109:837-842. See Evidence Table. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein- associated phospholipase A_2 as an independent predictor of coronary heart disease. N Engl J Med 2000; 343:1148-1155. See Evidence Table. Blake GJ, Dada N, Fox JC, et al. A prospective evaluation of lipoprotein- associated phospholipase A_2 levels and the risk of future cardiovascular events in women. J Am Coll Cardiol 2001; 38:1302-1306**.** See Evidence Table.

The use of PLAC Test in detecting risk of coronary heart disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/05/2009: MTAC REVIEW

PLAC Test in Detecting Risk of Coronary Heart Disease

Evidence Conclusion: *Lp-PLA2 as a marker for predicting future CVD risk* in the last decade, a number of epidemiologic studies investigated the association between plasma Lp-PLA2 and the cardiovascular disease risk.

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The majority were nested case-cohort studies, and the blood samples were taken only once at baseline and stored at ~ -70oC for up to 10 years before its analysis. The results were mainly presented in hazard ratios comparing the lowest with the highest tertile, quartile or quintile values. Several studies including West of Scotland Coronary Prevention Study (WOSCOPS), the Atherosclerosis Risk in Communities (ARIC) Study, and MONICA study found an association between elevated levels of Lp-PLA2 and increased risk for cardiovascular events in certain groups of patients. In the ARIC study however, the relative risk associated with the upper tertile of Lp-PLA2 became statistically insignificant when adjustments were made for traditional risk factors. Other studies including the Women's Health Study, GUSTO and FRISC did not show a significant association between Lp-PLA2 and CVD risk. A meta-analysis (Garza 2007) that pooled the results of 14 studies, showed a significant independent association between Lp-PLA2 and CVD risk. The results, however, do not provide evidence that measurement of Lp-PLA2 levels would improve risk stratification for CVD or add to the predictive value of the traditional risk factors and scoring systems used e.g. Framingham Risk Score. An analysis of the ARIC study (Folsom 2006) showed that the addition of Lp-PLA2 to the basic risk model increased the area under the receiver operating curve (AUC) from 0.774 to 0.780. Due to the large sample size, this small difference was statistically significant, but is of minor clinical significance. A statistically significant, independent association of a marker to CVD does not necessarily indicate that it improves the risk prediction beyond the traditional variables. Lp-PLA2 as therapeutic target There are no long-term published RCTs to date provide evidence that measuring LP-PLA2 would lead to meaningful changes in patient management, or improvement in clinical outcomes. In a multicenter placebo-controlled trial, Mohler and colleagues 2008 investigated the effect of darapladib, a selective Lp-PLA2 inhibitor, on the enzyme activity as well as on another panel of biomarkers. The study randomized 959 participants with stable CHD or risk equivalent, to receive a placebo or one of three doses of darapladib (40, 80, or 160mg daily), for 12 weeks, together with atorvastatin 20 or 80mg/day. The trial did not have hard clinical outcomes, instead Lp-PLA2 and other select biomarkers were used as surrogates of atherosclerosis risk, to assess the efficacy of the therapy. The results showed that darapladib given together with atorvastatin was associated with lower Lp-PLA2 activity, which appeared to be dose-dependent (darapladib 40,80, and 160 mg significantly inhibited Lp-PLA2 activity by 43%, 55%, and 66% respectively compared to placebo). This was observed in the two atorvastatin groups but without affecting the LDL levels. The study duration was too short to determine the long-term adverse events of the therapy, and its effect on CVD risk. (i.e. whether inhibition of Lp-PLA2 leads to accumulation of proinflammatory or prothrombotic factors). Intervention trials investigating the effect of LP-PLA2 inhibitors on coronary disease events are in progress. These include STABILITY trial on the effect of darapladib on CHD and FRANCIS-ACS trial that evaluates varespladib in patients with acute coronary syndrome. Diagnostic accuracy of PLAC test: The literature did not identify any study that examined the diagnostic accuracy, predictive values, or likelihood ratios of PLAC test in measuring LP-PLA2 among patients at different levels of cardiovascular disease risk. *Conclusion:* The current evidence suggests that Lp-PLA2 may be associated with vascular disease risk, but it is insufficient to show the association is causal, that measuring the enzyme level improves risk stratification for CVD, would have any impact on managing patients at high risk, or that inhibition therapy of Lp-PLA2 enzyme would improve health outcomes.

Articles: The search yielded around 33 articles. There was a meta-analysis, and a number of case control studies examining the association between Lp-PLA2 and CVD. The search also identified one randomized controlled trial on the effect of a selective Lp-PLA2 inhibitor of the enzyme activity (darapladib) in patients with CHD or risk equivalent, and another small RCT on the effect of the drug on the atherosclerotic plaque. The literature search did not reveal any published studies on the clinical benefits of screening for Lp-PLA2 in optimizing therapy and reducing cardiovascular risk, and/or events. There were also no studies on the diagnostic accuracy of PLAC test in assessing the Lp-PLA2 levels. The meta-analysis on the association between Lp-PLA2 and CVD risk, the ARIC study (FDA approval), and the RCT on the effect of darapladib on the enzyme activity in patients with CHD or risk equivalent were selected for critical appraisal: Garza CA, Montori VM, Connell JP, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review . Mayo Clin Proc.2007; 82:159-165. See Evidence Table. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase High sensitivity C-reactive protein, and risk incident coronary heart disease in middle-aged men and women in the atherosclerosis risk in communities (ARIC) study. Circulation 2004; 109:837-842. See Evidence Table. Mohler ER, Ballantyne CM, Davidson MH, et al. The effect of darapladib on plasma lipoprotein -associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease equivalent. The results of a multicenter, randomized double-blind, placebo-controlled study. J Am Coll Cardiol 2008; 51:1632-1641. See Evidence Table.

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Applicable Codes

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Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Dates Reviewed	Date Last Revised
02/11/2004	Initiated annual review because of Medicare criteria 04/04/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC,10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 11/06/2018MPC, 11/05/2019MPC, 11/03/2020MPC, 11/02/2021MPC, 11/01/2022MPC, 11/07/2023MPC	09/08/2015

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
08/04/2015	Changed Medicare links
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services

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