HDL Function Panel with HDL*fx* pCAD Score (HDL*fx* Test)

CPT Code **82172 x5***
Order Code **37812**
Specimen Type **Serum**
Tube Type **Gel-barrier tube (SST, Tiger Top)**

The HDL*fx* test evaluates:

- HDL function
- Risk of coronary artery disease (CAD) by the pCAD score

Importance of HDL function:

- More informative for cardiovascular disease (CVD) risk than HDL-C levels
- Identifies risk for presence of atherosclerosis and cardiovascular events

Description

HDL cholesterol particles are considered to be cardioprotective because of their anti-atherogenic properties, which include increasing reverse cholesterol transport, promoting endothelial nitric oxide production, and anti-inflammatory and antithrombotic effects.[1-3] Low HDL-C, a component of metabolic syndrome, is predictive of cardiovascular risk, but clinical trials have shown therapeutically increased HDL-C levels do not reduce rates of cardiovascular events.[4-6] These findings led to an understanding that the physiological impact of HDL may be dependent on its functionality, more so than low or high HDL-C levels.[7,8] The importance of HDL function to CVD is highlighted by findings that patients who have the highest cholesterol efflux capacity (CEC), a marker of HDL function, have a 67% reduction in cardiovascular risk compared to the lowest quartile CEC.[9]

The HDL*fx* test enables high-throughput and rapid assessment of HDL function.[10] It measures 5 proteins bound to apoA1-associated lipoprotein particles (AALPs) that are used to calculate the HDL*fx* pCAD score, which correlates with traditional measures of CEC.[11] The HDL*fx* pCAD score is also clinically validated to predict CAD risk.[12]

Clinical Use

Through assessment of HDL function, the HDL*fx* test provides additional information about CVD risk. A better understanding of HDL function will add clinical value to the assessment of HDL-C and provide additional insight into CVD risk that is not evident with HDL-C levels alone. The HDL*fx* test is appropriate for patients who have 1 or more risk factors for the development of CVD.

Clinical Significance

HDL*fx* Test Subcomponents‡	Clinical Significance
AALP ApoA-1	Decreased serum levels are associated with CHD[13]
AALP ApoC-1	Decreased levels in HDL particles of patients with CHD[14]
AALP ApoC-2	Elevated serum levels in patients with CHD[15]
AALP ApoC-3	Elevated levels in HDL particles of patients with CAD[16]
AALP ApoC-4	Elevated levels in HDL particles of patients with CAD[17]

The HDL*fx* pCAD score is calculated from subcomponents of the HDL*fx* test and has been validated in clinical studies to identify:

- Patients with CAD, independent of conventional CV risk factors[12]
- Female patients with increased risk of myocardial infarction within 1 to 2 years[11]
- Increased risk of cardiovascular death among those with CAD over a 4-year follow-up[12]

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RELATIVE RISK

HDL*fx* pCAD Score

≤0.90 Low	>0.90 High

Based on a population of patients diagnosed with CAD (defined as having a coronary lesion consistent with 50% blockage or more; N=149) and a study control group of healthy individuals without CAD (N=69), a pCAD score greater than 0.90 indicates high risk for having atherosclerosis with a clinical sensitivity of 76% and clinical specificity of 75%. Case and control samples were selected from the Fairbanks Institute for Healthy Communities biobank cardiovascular disease study with analysis performed by Cleveland HeartLab.

Treatment Considerations§

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner. Therapies that improve CEC or levels of subcomponents of the HDL*fx test may improve the* HDL*fx pCAD score and CAD risk, but further studies are needed to confirm. Most therapies do not directly target CEC, and findings may be confounded by other medications, patient characteristics, or the CEC evaluation test used.*

✓ **Treatment considerations for CEC**

- AALP ApoA-1 therapeutics improve CEC[18]
- Niacin has minimal effects on CEC[18]
- Fibrates may increase CEC[18]
- Statins minimally affect or decrease CEC[18]
- Diet and exercise may improve CEC, but more investigation is needed[18]
- Omega-3 fatty acids may improve CEC[19,20]

**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.*

‡ *Panel components may be ordered separately: AALP Apolipoprotein A1 order code 37838; AALP Apolipoprotein C1 order code 37864; AALP Apolipoprotein C2 order code 37865; AALP Apolipoprotein C3 order code 37866; AALP Apolipoprotein C4 order code 37867.*

§ *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. Rye KA, Barter PJ. Cardioprotective functions of HDLs. *J Lipid Res*. 2014;55:168-179. 2. Tosheska Trajkovska K, Topuzovska S. High-density lipoprotein metabolism and reverse cholesterol transport: strategies for raising HDL cholesterol. *Anatol J Cardiol*. 2017;18:149-154. 3. Besler C, Lüscher TF, Landmesser U. Molecular mechanisms of vascular effects of high-density lipoprotein: alterations in cardiovascular disease. *EMBO Mol Med*. 2012;4:251-68. 4. Grundy SM, Brewer HB Jr, Cleeman JI, et al. National Heart, Lung, and Blood Institute; American Heart Association. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*. 2004;109:433-438. 5. Chapman MJ, Ginsberg HN, Amarenco P, et al. European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345-1361. 6. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al. ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med*. 2017;376:1933-1942. 7. Shah AS, Tan L, Long JL, Davidson WS. Proteomic diversity of high density lipoproteins: our emerging understanding of its importance in lipid transport and beyond. *J Lipid Res*. 2013;54:2575-2585. 8. Mendivil CO, Furtado J, Morton AM, Wang L, Sacks FM. Novel pathways of apolipoprotein A-I metabolism in high-density lipoprotein of different sizes in humans. *Arterioscler Thromb Vasc Biol*. 2016;36:156-165. 9. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383-2393. 10. Collier TS, Jin Z, Topbas C, Brystrom C. Rapid affinity enrichment of human apolipoprotein A-I associated lipoproteins for proteome analysis. *J Proteome Res*. 2018;17:1183-1193. 11. Jin Z, Collier TS, Dai DLY, et al. Development and validation of apolipoprotein AI-associated lipoprotein proteome panel for the prediction of cholesterol efflux capacity and coronary artery disease. *Clin Chem*. 2019;65:282-290. 12. Natarajan P, Lyass A, Li Y, et al. Association of an HDL apolipoproteomic score with the presence of coronary atherosclerosis and incident cardiovascular death. *J Am Coll Cardiol*. 2019; 73:2135-2145. 13. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med*. 2006;259:481-492. 14. Yan LR, Wang DX, Liu H, et al. A pro-atherogenic HDL profile in coronary heart disease patients: an iTRAQ labelling-based proteomic approach. *PLoS One*. 2014;9:e98368. 15. Gerber Y, Goldbourt U, Cohen H, Harats D. Association between serum apolipoprotein C(II) concentration and coronary heart disease. *Prev Med*. 2002;35:42-47. 16. Luo M, Liu A, Wang S, et al. ApoCIII enrichment in HDL impairs HDL-mediated cholesterol efflux capacity. *Sci Rep*. 2017;7:2312. 17. Vaisar T, Pennathur S, Green PS, et al. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *J Clin Invest*. 2007;117:746-756. 18. Brownell N, Rohatgi A. Modulating cholesterol efflux capacity to improve cardiovascular disease. *Curr Opin Lipidol*. 2016;27:398-407. 19. Pizzini A, Lunger L, Demetz E, et al. The role of omega-3 fatty acids in reverse cholesterol transport: a review. *Nutrients*. 2017;9(10). 20. Ballantyne CM, Bays HE, Braeckman RA, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects on plasma apolipoprotein C-III levels in patients from the MARINE and ANCHOR studies. *J Clin Lipidol*. 2016;10:635-645.e1.

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