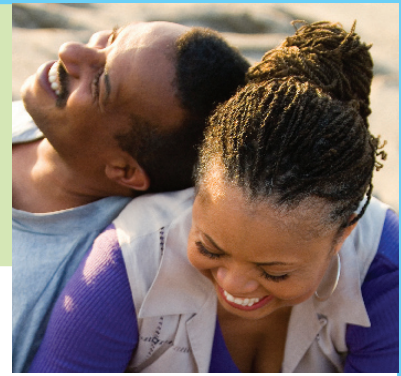


PROVIDER DATA SHEET

CardioMetabolic Profile I in Blood Spot



The Problem

The incidence of cardiovascular disease (CVD), obesity and type 2 diabetes mellitus (DM2) is rising at an alarming rate. CVD is the leading cause of mortality for both men and women in the United States; obesity, insulin resistance and DM2 significantly predispose individuals to developing CVD, yet these conditions are potentially avoidable. If we are to make an impact on the serious health and economic consequences of these diseases, we need to identify risk early enough for people to make lifestyle modifications or seek medical help, and avoid becoming a part of the rising statistics.

What is CardioMetabolic Risk?

Cardio-metabolic risk has been defined as “the cluster of modifiable risk factors and markers that identify individuals at increased risk for cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease) and type 2 diabetes¹.” The National Cholesterol Education Program (NCEP)'s Adult Treatment Panel III (ATP III) has identified the metabolic syndrome/insulin resistance syndrome as a major risk factor for CVD². The National Heart, Lung and Blood Institute and the American Heart Association in a 2003 conference³ agreed that CVD is the primary clinical outcome of metabolic syndrome; when the Framingham Heart Study investigators analyzed their data according to the NCEP-ATP III criteria for the conference, the metabolic syndrome predicted about 25% of all new-onset CVD and the presence of metabolic syndrome was highly predictive of new-onset DM2. NCEP-ATP III criteria for identifying metabolic syndrome include:

- hypertension/elevated blood pressure
- abdominal obesity
- atherogenic dyslipidemia (low HDL cholesterol, elevated triglycerides, elevated LDL cholesterol)
- prothrombotic/pro-inflammatory state
- insulin resistance/glucose intolerance

Advantages of a Simple Blood Spot Test to Assess CardioMetabolic Risk

- A simple, almost painless finger prick provides the few drops of blood required, which are collected on the filter paper provided
- Convenient sample collection at home - no phlebotomist required

- Easy shipment of samples by regular mail for analysis - samples are stable for several weeks at room temperature
- Dried blood spots carry no infection risk - infectious agents are inactivated when dry
- Excellent correlation with serum/plasma and whole blood assays

Clinical Utility

The blood spot cardiometabolic risk assessment panel allows early detection of major indicators associated with metabolic/insulin resistance syndrome. Used as a screening panel this can allow clinicians to recommend appropriate treatments to reduce the overall risk and potentially avoid the onset of DM2 and CVD. Regular testing can also be used for risk assessment and monitoring in patients being treated for DM2. Screening along with clinical assessment can be of reliable predictive value for determining the overall cardiometabolic risk.

Which Biomarkers are Included in the Profile?

High Sensitivity C-Reactive Protein (hs-CRP)

C-reactive protein (CRP) is an established marker of inflammation and has recently been suggested to be an important contributor to pro-inflammatory and pro-thrombotic elements of CVD risk. Extremely high CRP levels are seen in acute inflammatory states, but the small elevations that are indicative of the pro-inflammatory and pro-thrombotic states implicated in the metabolic syndrome require high sensitivity assays, and are thus referred to as hs-CRP levels. These high sensitivity assays have recently been developed for use with blood spots^{4,5,6}.

- Overweight, obese, insulin resistant and diabetic individuals typically have elevated CRP levels⁷
- Studies have shown correlations between elevated CRP and increased risk of future heart attacks, ischemic stroke, and peripheral arterial disease^{8,9,10,11}

(continued inside)

- Elevated CRP levels have been found to predict the development of DM2¹²
- Increased CRP levels, which correlate inversely with insulin sensitivity, have been found in individuals with polycystic ovarian syndrome and may be a marker of early cardiovascular risk in these patients^{13,14}
- Lifestyle changes such as aerobic exercise, weight loss and smoking cessation have been known to lower CRP
- Medications like aspirin and statins can lower CRP levels^{11,15}
- Levels below 3.0 mg/L are considered to be normal; 3.1 to 10 mg/L is elevated, in the context of CVD risk, and above 10 mg/L is very high, more likely indicating an acute inflammatory event due to infection or trauma

Insulin

Dried blood spot technology has effectively been used for measurement of insulin levels^{16,17,18}. The requirement to measure fasting insulin makes convenient blood spot collection at home especially advantageous to patients.

- High fasting insulin levels are a good indicator of insulin resistance, which occurs when the cellular response to the presence of insulin is impaired resulting in a reduced ability of tissues to take up glucose for energy production. Chronically high insulin levels are seen as the body attempts to normalize blood sugar levels
- High fasting insulin indicates the presence of insulin resistance whether or not the patient shows glucose intolerance
- The normal range for fasting insulin is 1 – 15 μ IU/mL, but levels between 2 and 6 μ IU/mL are optimal

Hemoglobin A1c (HbA1c)

HbA1c is a measure of red blood cell hemoglobin glycation, indicating mean glycemia over the previous 3 months, which is the lifespan of circulating red blood cells. It can therefore indicate impaired glucose tolerance even when occasional fasting plasma glucose measurements are normal¹⁹.

- The American Diabetes Association's recommendation is to measure HbA1c every 3-6 months; normal levels are 4 - 6%
- Levels of HbA1c above 6% in diabetics are associated with an increased risk of developing complications such as eye, kidney, and heart disease, nerve damage, and stroke, therefore treatment should aim to keep levels below 7%²⁰
- An HbA1c of more than 6% can predict CVD and DM2 in high-risk individuals^{21,22,23}

Triglycerides

Hypertriglyceridemia, a triglyceride level >150 mg/dL, is an established indicator of atherogenic dyslipidemia and is often found in untreated DM2 and obesity.

- Studies have shown that levels above 200 mg/dL indicate an increased risk of heart disease and stroke^{24,25}
- Some studies have shown that fasting triglyceride levels lower than 100 mg/dL should be considered as a more optimal cutoff in coronary heart disease risk assessment²⁶
- The NCEP-ATP III defines levels of 150 mg/dL or above as one of the diagnostic criteria for metabolic syndrome

Total Cholesterol and LDL Cholesterol

In addition to the inclusion of elevated LDL cholesterol as one of the criteria for diagnosing the metabolic syndrome, high LDL cholesterol has consistently been identified as a strong component of coronary heart disease risk because of its contribution to coronary atherosclerosis. However, as with other risk factors, high cholesterol and LDL cholesterol are more significant when other cardiometabolic parameters are already abnormal, or in patients who already have diabetes or cardiovascular disease. The American Diabetes Association and the American College of Cardiology Foundation recently released a consensus statement on lipoprotein management in patients with cardiometabolic risk²⁷.

The current NCEP-ATP III recommendations² for cholesterol levels are:

Total cholesterol (mg/dL):	<200 desirable 200 - 239 borderline high >240 high
LDL cholesterol (mg/dL):	<100 optimal 100 - 129 near optimal 130-159 borderline high 160 - 189 high >190 very high.

Because LDL cholesterol levels are regarded as a better predictor of cardiovascular disease risk than total cholesterol, **the American Diabetes Association recommends the following cutoffs for LDL cholesterol in patients at high risk²⁷:**

Highest risk patients, including those with known CVD or diabetes plus one or more additional major CVD risk factor:
<70 mg/dL

High-risk patients, including those without diabetes or CVD but having 2 or more additional major CVD risk factors:
<100 mg/dL

References

1. Watson K. Managing cardiometabolic risk: an evolving approach to patient care. *Crit Pathw Cardiol.* 2007; 6:5-14.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
3. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. 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;109:433-8.
4. McDade TW, Burhop J, Dohnal J. High sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. *Clin Chem* 2004; 50:652-4.
5. Cordon SM, Elborn JS, Hiller EJ, Shale DJ. C-reactive protein measured in dried blood spots from patients with cystic fibrosis. *J Immunol Methods* 1991;143:69-72.
6. Beesley R, Al Serouri A, Filteau SM. Measurement of C-reactive protein in dried blood spots on filter paper. *Trans R Soc Trop Med Hyg.* 2000;94:348-349.
7. Marques-Vidal P, Mazoyer E, Bongard V, Gourdy P, Ruidavets JB, Drouet L, Ferrieres J. Prevalence of insulin resistance syndrome in southwestern France and its relationship with inflammatory and hemostatic markers. *Diabetes Care* 2002;25:1371-7.
8. Shankar A, Li J, Nieto FJ, Klein BE, Klein R. Association between C-reactive protein level and peripheral arterial disease among US adults without cardiovascular disease, diabetes, or hypertension. *Am Heart J* 2007;154:495-501.
9. Church T S, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol* 2002;22:1869-76.
10. Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Toft E, Schmidt EB. C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. *Am J Cardiol* 2001;88:1139-42.
11. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New Engl J Med* 1997;336:973-9.
12. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327-34.
13. Boulman N, Levy Y, Leiba R, Shachar S, Linn R, Zinder O, Blumenfeld Z. Increased C-reactive protein levels in the polycystic ovary syndrome: a marker of cardiovascular disease. *J Clin Endocrinol Metab* 2004;89:2160-65.
14. Tarkun I, Arslan BC, Canturk Z, Turemen E, Sahin T, Duman C. Endothelial dysfunction in young women with polycystic ovary syndrome: relationship with insulin resistance and low-grade chronic inflammation. *J Clin Endocrinol Metab* 2004;89:5592-6.
15. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *New Engl J Med* 2001;344:1959-65.
16. Shields BM, Knight B, Shakespeare L, Babrah J, Powell RJ, Clark PM, Hattersley AT. Determinants of insulin concentrations in healthy 1-week-old babies in the community: applications of a blood spot assay. *Early Hum Dev* 2006;82:143-8.
17. Butter NL, Hattersley AT, Clark PM. Development of a blood spot assay for insulin. *Clin Chim Acta.* 2001;310:141-150.
18. Dowlati B, Dunhardt PA, Smith MM, Shaheb S, Stuart CA. Quantification of insulin in dried blood spots. *J Lab Clin Med* 1998;131:370-4.
19. Geberhiwot T, Haddon A, Labib M. HbA1c predicts the likelihood of having impaired glucose tolerance in high-risk patients with normal fasting plasma glucose. *Ann Clin Biochem.* 2005;42:193-5.
20. Saudek CD, Kalyani RR, Derr RL. Assessment of glycemia in diabetes mellitus: hemoglobin A1c. *J Assoc Physicians India* 2005;53:299-305.
21. Grant T, Soriano Y, Marantz PR, Nelson I, Williams E, Ramirez D, Burg J, Nordin C. Community-based screening for cardiovascular disease and diabetes using HbA1c. *Am J Prev Med* 2004;26:271-5.
22. Perry RC, Shankar RR, Fineberg N, McGill J, Baron AD; Early Diabetes Intervention Program (EDIP). HbA1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). *Diabetes Care* 2001;24:465-71.
23. Singer DE, Nathan DM, Anderson KM, Wilson PW, Evans JC. Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. *Diabetes* 1992;41:202-8.
24. Tirosh A, Rudich A, Shochat T et al. Changes in triglyceride levels and risk for coronary heart disease in young men. *Ann Intern Med* 2007;147:377-85.
25. O'keefe JH, Bell DS. Postprandial hyperglycemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. *Am J Cardiol* 2007;100:899-904 .
26. Ahmad I, Zhan M, Miller M. High prevalence of C-reactive protein elevation with normal triglycerides (100-149 mg/dL): are triglyceride levels below 100 mg/dL more optimal in coronary heart disease risk assessment? *Am J Med Sci* 2005;329:173-7.
27. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL; American Diabetes Association; American College of Cardiology Foundation. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 2008 ;31:811-22.