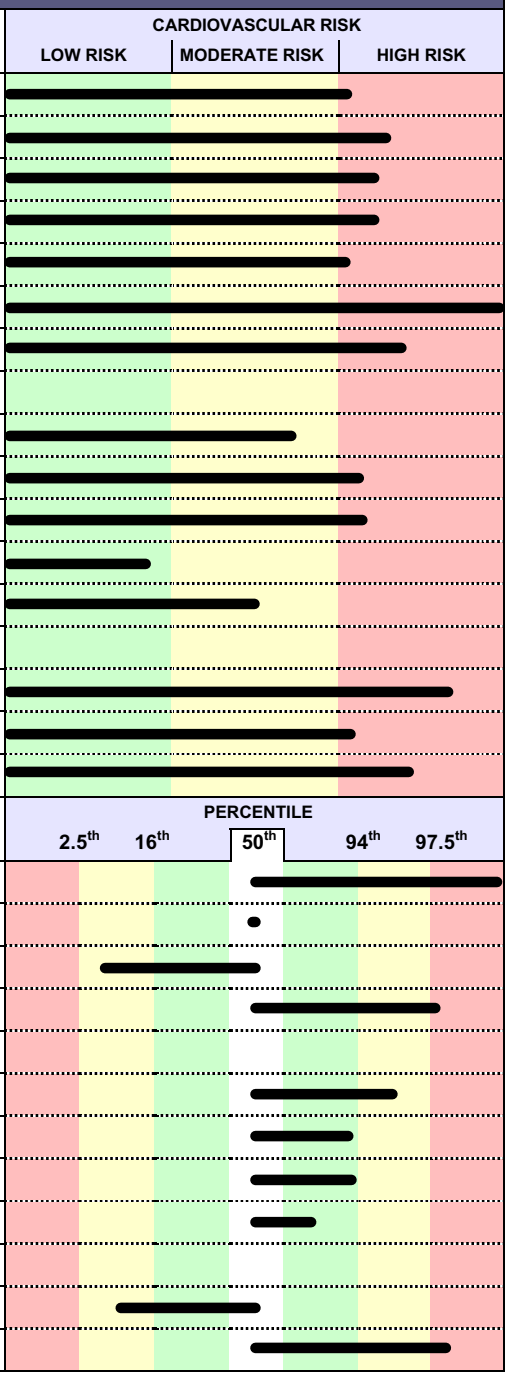
DOCTOR'S DATA INC

LAB #: B000000-0000-0
PATIENT: Sample Patient
ID: PATIENT-S-00002
SEX: Female
DOB: 1/11/1941

CLIENT #: 12345
DOCTOR:
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174

Comprehensive Cardiovascular Risk Profile

LIPIDS	RESULT	UNIT	REFERENCE INTERVAL
Total Cholesterol; serum	244	mg/dL	< 200
HDL Cholesterol; serum	35	mg/dL	> 60
LDL Cholesterol; serum	154	mg/dL	< 100
Oxidized LDL; serum	67	U/L	< 45
Small dense LDL Cholesterol*; serum	47	mg/dL	< 35
Lp(a); serum	110	mg/dL	< 30
Triglycerides; serum	220	mg/dL	< 150
RATIOS			
Total Cholesterol : HDL-C	6.9		< 4.0
LDL-C : HDL-C	4.4		< 2.0
Oxidized LDL : HDL-C	1.9		< 0.8
Small dense LDL-C : LDL-C	0.30		< 0.34
Apo B : Apo A-1	1.0		< 0.8
RISK FACTORS/INFLAMMATORY MARKERS			
Homocysteine; serum	25.3	µmol/L	< 11.0
CRP (Hs); serum	4.5	mg/L	< 1.0
HbA1c; whole blood	8.0	%	< 5.8
Cystatin C; serum	2.9	mg/L	0.5- 1.5
Ferritin; serum	79	ng/mL	10- 150
Iron; serum	62.0	µg/dL	50- 170
Fibrinogen; plasma	608	mg/dL	260- 590
CARDIOPROTECTIVE NUTRIENTS			
CoQ10; plasma	1.8	mg/L	0.5- 2.0
Vitamin E (α-Tocopherol); plasma	19	mg/L	6.5- 27
Vitamin E (γ-Tocopherol); plasma	1.6	mg/L	0.06- 3.8
Magnesium; red blood cells	52	µg/g	39- 59
LIPOPROTEINS			
Apolipoprotein A-1; serum	133	mg/dL	115- 220
Apolipoprotein B; serum	138	mg/dL	50- 130



SPECIMEN DATA

Comments:
Date Collected: 4/8/2012
Date Received: 4/9/2012
Date Completed: 4/19/2012
Methodology: Chemistry Analyzer, Oxidized LDL by EIA, CoQ10 and Vitamin E by HPLC, RBC Mg by ICP-MS

<dl: less than detection limit

*For Research Use Only. Not for use in diagnostic procedures.

Cholesterol, Total High

The level of plasma total cholesterol in this sample is higher than expected. A high level of plasma total cholesterol is considered to an independent CVD risk factor. According to the lipid hypothesis (Virchow, 1856) lipid accumulation in arterial walls causes cardiovascular disease and, as has been further refined, higher concentrations of low-density lipoprotein (LDL) cholesterol and lower concentrations of high- density lipoprotein (HDL) cholesterol promote the development of atheromatous plaque in arteries which is associated with the development of cardiovascular disease. While high total and LDL cholesterol levels have been correlated with increased CVD risk, recent research indicates that much more sensitive CVD risk factors include small, dense LDL (sdLDL) cholesterol, the percentage of total LDL cholesterol present in sdLDL (sdLDL cholesterol:LDL cholesterol), oxidized LDL, lipoprotein(a) and the ratio of LDL to HDL cholesterol.

A change in diet, in addition to other lifestyle modifications, may help reduce blood cholesterol but debate is ongoing as to whether or not dietary changes reducing dietary saturated fat and cholesterol, can lower blood cholesterol levels, and thus reduce the likelihood of development of coronary artery disease leading to coronary heart disease. The rationale is that any reduction to dietary cholesterol intake could be counteracted by the organs compensating to try to keep blood cholesterol levels constant. Interestingly, a 2009 study of patients with acute coronary syndromes found an association of hypercholesterolemia with better mortality outcomes. High total cholesterol levels may be lowered by consumption of an appropriate amount of omega-3 fatty acids from fish, flax seed oil, and other sources. The recommendation for adults in the U.S. is for dietary intake of up to 3 grams of omega-3-containing oils per day.

The American Heart Association recommends testing cholesterol every five years for people aged 20 years or older. Cholesterol levels should be tested at least every five years if a person has total cholesterol of 200 mg/dL or more, or if a man over age 45 or a woman over age 50 has HDL cholesterol less than 40 mg/dL, or there are other risk factors for heart disease and stroke (cholesterol measurements that are reported in mg/dL are easily converted to mmol/L as 1 mmol/L is 38.665 mg/dL).

National Health Service (2009) High Cholesterol. Accessed 21 Sep 2011 at www.nhs.uk/conditions/cholesterol/Pages/Introduction.aspx

Warnick GR, Knopp RH, Fitzpatrick V, Branson L (1990). Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin. Chem. (36): 15-9.

HDL Cholesterol Low

The level of high-density lipoprotein cholesterol (HDL-C) in this sample is lower than expected. Low HDL-C is considered to be an independent CVD risk factor. Low levels of HDL-C (below 40 mg/dL for men, below 50 mg/dL for women) increase the risk for atherosclerotic disease. Also, in middle aged adults, low levels of HDL-C were associated with poor memory and, decreasing levels of HDL-C over a five year follow-up period were associated with decline in memory. Interpretation of the relative risk associated with low HDL-C should include consideration of the LDL-C: HDL-C ratio, the levels of small dense LDL-C and oxidized LDL.

Certain changes in lifestyle may have a positive impact on raising HDL levels:

- Aerobic exercise
- Weight loss

Nicotinic Acid supplementation
Smoking cessation
Removal of trans fatty acids from the diet
Mild to moderate alcohol intake
Addition of soluble fiber to diet
Consumption of omega-3 fatty acids such as fish oil or flax oil
Increased intake of cis-unsaturated fats and cholesterol.

Most saturated fats increase HDL cholesterol to varying degrees but also raise the levels of total and LDL cholesterol. A high-fat, adequate-protein, low-carbohydrate ketogenic diet may have similar response to taking niacin as described below (lowered LDL and increased HDL) through beta-hydroxybutyrate coupling the Niacin receptor 1.

Certain drugs and supplements may increase the HDL-C level but no incremental increase in HDL-C has been proven to improve health. Pharmcological therapy may include fibrates and niacin (vitamin B3). Niacin 1- to 3-gram/day increased HDL-C levels by 10-30% according to one study. Both fibrates and niacin may increase homocysteine levels and elevated homocysteine is a CVD risk factor. Magnesium supplementation may raise HDL-C levels. While the use of statins is effective against high levels of LDL cholesterol, it has little or no effect in raising HDL-C.

Cholesterol Levels. American Heart Association. Accessed 21 Sep 2011 at www.heart.org/HEARTORG/Conditions/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp

Singh-manoux, A; Gimeno, D; Kivimaki, et al. (2008) Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study. Arteriosclerosis, Thrombosis, and Vascular Biology (28):1556-62.

Rader, D J. (2004) Raising HDL in Clinical Practice: Clinical Strategies to Elevate HDL. Accessed 21 Sep 2011 at http://cme.medscape.com/viewarticle/479499_5.

Rosanoff A, Seelig MS (2004) Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. J Am Coll Nutr) (23):501S-505S.

Brewer, H B. (2005) Raising HDL-Cholesterol and reducing cardiovascular risk: an expert interview with H. Bryan Brewer, Jr, MD. Accessed 21 Sep 2011 at http://cme.medscape.com/viewarticle/520393.

LDL Cholesterol High

The level of low-density lipoprotein cholesterol (LDL-C) in this sample is higher than expected. A high level of LDL-C is considered to be an independent CVD risk factor. LDL-C poses an increased risk for cardiovascular disease especially when the LDL particles are metabolized to small, dense LDL and oxidized LDL. Small, dense LDL penetrate the endothelium more readily than larger LDL and are more susceptible to oxidation in the intima. A complex set of biochemical reactions regulates the oxidation of LDL particles, chiefly stimulated by presence of necrotic cell debris and free radicals in the endothelium. The levels of small, dense LDL-C and oxidized LDL are not correlated with the level of LDL-C therefore all three factors should be considered in the assessment of CVD risk.

Statins reduce high levels of LDL-C by inhibiting the enzyme HMG-CoA reductase which is the rate-limiting step in cholesterol biosynthesis. To compensate for the decreased cholesterol availability, synthesis of

hepatic LDL receptors is increased, resulting in an increased clearance of LDL particles from the blood. Fibrates reduce absorption of cholesterol, thus can further lower LDL-C levels when combined with statins. Niacin (vitamin B3), lowers LDL-C by selectively inhibiting hepatic diacyglycerol acyltransferase 2, reducing triglyceride synthesis and the rate of release of very low density lipoproteins (VLDL) by the liver: VLDL are the direct precursors of LDL. Some tocotrienols, especially delta- and gamma-tocotrienols, are being promoted as non-prescription statin-like alternatives to treat high cholesterol, as a result of in vitro studies. In particular, gamma-tocotrienol appears to be another HMG-CoA reductase inhibitor, and can reduce cholesterol production. As with statins, this decrease in intra-hepatic (liver) LDL-C levels may induce hepatic LDL-C receptor up-regulation, also decreasing plasma LDL-C levels. Stains or any other compounds that inhibit cholesterol biosynthesis by inhibiting the enzyme HMG-CoA reductase also inhibit the biosynthesis of CoQ10 therefore warranting exogenous supplementation with CoQ10. High LDL-C levels may be lowered by consumption of an appropriate amount of omega-3 fatty acids from fish, flax seed oil, and other sources. The recommendation for adults in the U.S. is for dietary intake of up to 3 grams of omega-3-containing oils per day.

Oxidized LDL High

The level of oxidized low density lipoproteins (ox-LDL) is higher than expected in this sample. Elevated ox-LDL is a very strong independent CVD risk factor. Unlike normal LDL ox-LDL are directly involved in the initiation and progression of atherosclerotic lesions in coronary arteries that can result in CVD. Elevated levels of ox-LDL are associated with accelerated atherogenesis, atherosclerosis, acute myocardial infarction and stable and unstable angina. Importantly, the levels of total cholesterol are not necessarily higher than normal in patients with unstable CAD. Elevated ox-LDL has also been associated with metabolic syndrome, impaired glucose tolerance/insulin resistance and untreated overt hypothyroidism. Other factors that appear to increase levels of ox-LDL include a diet that is high in trans- fats and smoking.

Low density lipoproteins (LDL), the major carriers of circulating cholesteryl esters, are susceptible to oxidation of the constituent apolipoproteins B (apo B) moiety by reactive oxygen radicals, oxidized macrophages, lipoxygenase and peroxynitrite. When the LDL protein (apo B) is oxidized it becomes antigenic and the ox-LDL particles are taken up excessively by the unregulated ”scavenger” or ”ox-LDL receptors” on monocyte-derived macrophages. Native LDL (un-oxidized) are not involved in the unregulated uptake process and ox-LDL is present in macrophages in atherosclerotic lesions but not in normal arteries. Once macrophages breach the arterial endothelial barrier (damaged) the excessive uptake of lipids from ox-LDL contributes to their entrapment in the sub-endothelial space. The trapped lipid-laden ”foam” cells elicit biosynthesis and release of factors by the arterial wall that are pro-inflammatory and chemotactic for other monocytes, perpetuating the atherosclerotic process with further injury to the arteries. Injury to the sub-endothelial vessel wall results in decreased production of nitric oxide (NO) and decreased elasticity of the arteries and, the damaged lipid-laden arteries eventually narrow restricting the flow of blood. Ox-LDL impairs endothelium dependent vasodilatation via several mechanisms including decreased transport of L-arginine into cells, increased superoxide (O2-) production, and inhibition of NO synthesis and activity.

Increased antioxidant protection and amelioration of oxidative stress would be expected to decrease levels of atherogenic ox-LDL. An oral liposomal glutathione preparation has been demonstrated to decrease the extent of ox-LDL uptake, macrophage cholesterol mass and, decreased the atherosclerotic lesion area in a rodent model of atheroscerosis.

Steinberg D. (1997) Oxidative modification of LDL and athersclerosis. Circulation (95):1062-71.

Holvoet P et al. (1998) Ox-LDL and malondialdehyde-modified LDL in patients with acute coronary

syndromes and stable CAD. Circulation (98):1487-94.

Schulze PC, Lee RT. (2005) Oxidative stress and athersclerosis. Curr Atheroscler Rep (7):242-8.

Fuhrman B et al. (2002) Oxidative stress increases the expression of the CD36 scavenger receptors and the cellular of oxidized LDL in macrophages fro atherosclerotic mice: protective role of antioxidants and paraoxonase. Atherosclerosis (161):307-16.

Rosenblat M et al. (2007) Anti-oxidant and anti-atherogenic properties of liposomal glutathione: Studies in vitro, and in atherosclerotic apo-E deficient mice. Atherosclerosis (195):e61-e68.

Rajasekaran NS et al. (2005) Chronic depletion of glutathione (GSH) and minimal modification of LDL in vivo: its prevention by glutathione mono ester (GME) therapy. BBA (1741):103-12.

Ryoo S et al. (2006) Oxidized LDL-dependent endothelial arginase II activation contributes to impaired nitric oxide signaling. Circ Res (99):951-60.

Oxidized LDL and maldondialdehyde-modified LDL.www.oxldtest.com/

Small dense LDL Cholesterol High

The level of small, dense low-density lipoprotein cholesterol (sdLDL-C) in this sample is higher than expected. Small, dense LDL (sdLDL) is an extremely atherogenic LDL subtype that is considered to be a powerful independent CVD risk factor (National Cholesterol Education Program Adult Treatment Panel III). SdLDL-C levels are also independently associated with increased risk for Type-2 diabetes and smaller LDL may be more prevalent in patients with acute myocardial infarction, angina pectoris and other forms of non-coronary arterial disease. SdLDL-C is associated with obesity, metabolic syndrome, pre-diabetes, insulin resistance, renal dysfunction, hepatic steatosis and dietary trans-fatty acids.

Levels of sdLDL-C are not correlated with LDL-C levels and one can have elevated sdLDL-C but ”optimal” LDL-C levels. Thus it is important to evaluate the percentage of total LDL-C that is present as sdLDL-C (see the sdLDL-C: LDL-C ratio in this report).

Distinct from normal LDL, sdLDL are apolipoprotein B rich and depleted of cholesteryl esters (hydrophobic core). The smaller sdLDL, compared to more buoyant normal LDL, more readily penetrate the arterial endothelial wall, are more prone to oxidation and, are taken up in an unregulated manner by macrophage scavenger receptors that results in accelerated foam cell formation. Aberrant triglyceride metabolism that results in increased triglyceride levels/flux is involved in the formation of sdLDL that involves very low density lipoproteins, triglyceride- enriched HDL, the plasma cholesteryl ester transfer protein and the enzymatic activity of lipoprotein lipase (hydrolysis of plasma lipoprotein triglycerides). Accordingly, sdLDL concomitant with elevated plasma triglycerides and low HDL-C comprise an atherogenic lipid phenotype that that is associated with type 2 diabetes and metabolic syndrome.

Elevated sdLDL-C may be lowered with lifestyle modification (e.g. diet, weight loss, exercise) and appropriate control of diabetes/insulin resistance. Drugs that lower sdLDL-C include niacin, fenofibrate and combinations of fibrates and statins. It should be noted that statins alone do not lower sdLDL and statins actually increase sdLDL-C when plasma triglycerides are low.

Menys VC, Liu Y, Mackness M et al (2003) Measurement of plasma small-dense LDL concentration by a

simplified ultracentrifugation procedure and immunoassay of lipoprotein B. Clinica Chimica Acta (334):95-106.

National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) final report. "Third report of the National Chlesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report". (2002) Circulation(82):3143-3421.

Kobas S, Hirano T, Kondo T et al (2002) Significance of small dense low-density lipoproteins and other risk factors in patients with various types of coronary heart disease. Am Heart J(144):1026-35.

Hulthe J, Bokemark L, Wikstrand J et al. (2000). The metabolic syndrome, LDL particle size, and atherosclerosis: Atherosclerosis and insulin resistance (AIR) study. Arterioscler Thrombo Vasc Biol(20):2140-47

Tall AR. (1993) Plasma cholesteryl ester transfer protein. J lipid Res(34):1255-74.
Rizzo M, Berneis K. (2005) Lipid triad or atherogenic lipoprotein phenotype: a role in cardiovascular prevention(c) J Atherocsler Throm(12):237-9.

Ito MK. (2004) The metabolic syndrome: Pathology, clinical relevance, and use of niacin. Ann Pharmacolther(38):277-85.

Berneis K, Jeanneret C, Muser J et al. (2005) Low-density lipoprotein size and subclasses are markers of

Lp(a) High

The level of lipoprotein(a) [Lp(a)] in this sample is higher than expected. High Lp(a) is a possible risk factor in atherosclerotic heart disease and stroke. High Lp(a) predicts risk of early atherosclerosis, but in advanced atherosclerosis, Lp(a) is an independent risk factor not dependent on low-density lipoprotein (LDL). Lp(a) then indicates a coagulant risk of plaque thrombosis.

Lp(a) levels are higher in people of African descent compared to Caucasians but, in people of African descent the higher levels of Lp(a) do not appear to be associated with increased CVD risk.

Lipoprotein(a) is structurally similar to LDL but distinct due to the linkage between its constituent apolipoprotein(a) and apolipoprotein B. Apolipoprotein(a) has structural similarities with plasminogen and tPA (tissue plasminogen activator) and it competes with plasminogen for its binding site. However Lp(a) does not have fibrinolytic activity leading to reduced fibrinolysis. Also because Lp(a) stimulates secretion of plasminogen activator inhibitor-1 (PAI-1) it leads to thrombogenesis. In addition, because of its LDL-like cholesterol content, Lp(a) contributes to atherosclerosis.

Lp(a) concentrations in plasma are highly heritable and mainly controlled by the apolipoprotein(a) gene. Lp(a) concentrations may be affected by disease states, but are only slightly affected by diet, exercise, and other environmental factors. Commonly prescribed lipid-reducing drugs have little or no effect on Lp(a) concentration.

Vegetarians in one homogeneous tribal population of Tanzania have higher levels of Lp(a) than fish eaters raising the possibility that pharmacologic amounts of fish oil supplements may be helpful to lower the levels of Lp(a). Niacin (nicotinic acid) and aspirin are two relatively safe, easily available and inexpensive drugs known to significantly reduce the levels of Lp(a) in some individuals with high Lp(a). Some studies have

shown that regular consumption of moderate amounts of alcohol leads to significant decline in plasma levels of Lp(a) while other studies have not confirmed this observation.

Danesh J, Collins R, Peto R (2000) Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. Circulation (102):1082-5.

Smolders B, Lemmens R, Thijs V. (2007) Lipoprotein (a) and stroke: a meta-analysis of observational studies. Stroke (38): 1959-66.

Schreiner PJ, Morrisett JD, Sharrett AR, et al. (1993) Lipoprotein(a) as a risk factor for preclinical atherosclerosis Arterioscle. Thromb (38):826-33.

Berg K (1963) A new serum type system in man - the Lp system. Acta Pathol Microbiol Scand (59): 369-82.

Sharpe PC, Young IS, Evans AE (May 1998) Effect of moderate alcohol consumption on Lp(a) lipoprotein concentrations. Reduction is supported by other studies. BMJ (Clinical Research Ed.) 316:1675.

Triglycerides High

The level of triglycerides (TG) in this sample is higher than expected. High TG levels have been associated with the development of atherosclerosis and thus an increased risk of heart disease and stroke.

Diets high in carbohydrates, with carbohydrates accounting for more than 60% of the total energy intake, can increase triglyceride levels. Heavy consumption of alcoholic beverages can elevate triglycerides levels. The correlation is stronger for those with higher BMI (28+) and insulin resistance is a primary suspect cause of the phenomenon of carbohydrate-induced hypertriglyceridemia. Consumption of carbohydrates with a high glycemic index may cause insulin overproduction and increase triglyceride levels in women and adverse changes associated with carbohydrate intake, including triglyceride levels, are stronger risk factors for heart disease in women than in men.

Triglyceride levels are reduced by exercise, omega-3 fatty acids from fish, flax seed oil, and other sources. The recommendation for adults in the U.S. is for dietary intake of up to 3 grams of omega-3-containing oils per day. Omega-3 fatty acid consumption should be balanced with omega-6 fatty acids, in an omega-6 to omega-3 ratio between 1:1 and 4:1 (up to 4 grams omega-6 for every 1 gram of omega-3). Carnitine and fibrates may be useful in lowering blood triglyceride levels. The DDI Red Blood Cell Fatty Acids test provides one's ratio of omega-6 to omega-3 fatty acids.

Dietary Glycemic Load and Index and Risk of Coronary Heart Disease in a Large Italian Cohort. Archives of Internal Medicine. http://archinte.ama-assn.org/cgi/content/abstract/170/7/640.

Fish and Omega-3 Fatty Acids. American Heart Association.
http://www.americanheart.org/presenter.jhtml(c)identifier=4632.

Daley CA, Abbott, A, Doyle, P et al. (2004) A literature review of the value-added nutrients found in grass-fed beef products. California State University, Chico (College of Agriculture).

Total Cholesterol : HDL-C High

The ratio of plasma total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) is higher than

expected in this sample. The TC: HDL-C ratio is considered to be a CVD risk factor. Plasma cholesterol is transported predominantly by low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The majority of total cholesterol is associated within the hydrophobic core of LDL and, total and LDL cholesterol (LDL-C) levels are considered to be CVD risk factors. HDL-C is inversely associated with CVD risk but the clinical significance of a level of HDL-C is more predictive when viewed in context with total lipoprotein cholesterol. For example if one has a normal level of HDL-C in the presence of a high level of TC the predictive value of that level of HDL-C may be significantly marginalized.

LDL-C : HDL-C High

The ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) is higher than expected in this sample. The LDL-C: HDL-C ratio is considered to be a CVD risk factor. Plasma cholesterol is transported predominantly by low-density (LDL) and to a lesser extent by high-density lipoproteins (HDL). The majority of total cholesterol is associated within the hydrophobic core of LDL and LDL-C is considered to be CVD risk factor. HDL-C is inversely associated with CVD risk but the clinical significance of the level of HDL-C has more value when viewed in context with LDL-C. For example if one has a normal level of HDL-C but an elevated level of LDL-C the predictive value of that level of HDL-C may be significantly marginalized.

Oxidized LDL : HDL-C High

The ratio of oxidized low-density lipoprotein (ox-LDL): high-density lipoprotein cholesterol (HDL-C) is higher than expected in this sample. Ox-LDL is a very atherogenic form of LDL and is considered to be an independent CVD risk factor. When the apolipoproteins B moiety of LDL becomes oxidized the protein is recognized as a foreign antigen that is rapidly taken up by the unregulated ”scavenger” or ”ox-LDL receptors” on monocyte-derived macrophages. When the phagocytic cells residing in the arterial intima engulf excessive amounts of oxLDL they become foam cells that initiate and perpetuate the atherogenic process.

HDL-C is an independent, inversely related CVD risk factor due to its role in ”reverse cholesterol transport” that presumably transports excess cholesterol from the periphery back to the liver for elimination in the bile. The relative significance of the level of HDL-C has more value when viewed in context with the level of atherogenic ox-LDL. For example if one has a normal level of HDL-C but an elevated level of ox-LDL the predictive value of that level of HDL-C may be significantly marginalized. Clinical efforts to lower the ratio of ox-LDL:HDL-C might include increased consumption of antioxidant-rich foods or supplements and identification of and removal of the source of oxidative stress. An oral liposomal glutathione preparation has been demonstrated to decrease the extent of ox-LDL uptake, macrophage cholesterol mass and, decreased the atherosclerotic lesion area in a rodent model of atherosclerosis.

Steinberg D. (1997) Oxidative modification of LDL and athersclerosis. Circulation (95):1062-71.

Holvoet P et al. (1998) Ox-LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable CAD. Circulation(98):1487-94.

Schulze PC, Lee RT. (2005) Oxidative stress and athersclerosis. Curr Atheroscler Rep (7):242-8.

Rosenblat M et al. (2007) Anti-oxidant and anti-atherogenic properties of liposomal glutathione: Studies in vitro, and in atherosclerotic apo-E deficient mice. Atherosclerosis (195):e61-e68.

Apo B : Apo-A1 High

The ratio of apolipoproteins B (apoB): apolipoproteins A-1 (apoA-1) is higher than expected. The ratio of constituent apoB (LDL) to apoA-1 (HDL) may provide a better indicator of CVD risk than the levels of cholesterol associated the with the two lipoprotein subfractions.

Apo B is the sole apolipoprotein of low-density lipoproteins (LDL) and LDL cholesterol is an independent CVD risk factor. LDL-C becomes particularly atherogenic when its constituent apoB moiety is oxidized by reactive oxygen radicals, oxidized macrophages, lipoxygenase and peroxynitrite. The most atherogenic sub-types of LDL are the small, dense LDL (sdLDL) that contain much less cholesterol per apo B than the more buoyant cholesteryl ester-rich LDL. Therefore the level of apo B likely provides a better indication of CVD risk than LDL-C.

In sharp contrast the level of high-density lipoprotein cholesterol (HDL-C) is an independent CVD risk factor. ApoA-1 is a primary apolipoprotein associated with high-density lipoproteins HDL) and is an obligatory cofactor for the enzyme lecithin-cholesterolacyl transferase (LCAT) that converts readily exchangeable free cholesterol into cholesteryl esters that are sequestered in the core of HDL particles that are subsequently transported to the liver for excretion. The HDL-apoA-1 mediated process has been referred to as ”reverse cholesterol transport” and appears to be protective against atherogenesis.

Steinberg D. (1997) Oxidative modification of LDL and athersclerosis. Circulation (95):1062-71.

Holvoet P et al. (1998) Ox-LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable CAD. Circulation (98):1487-94.

Menys VC, Liu Y, Mackness M et al. (2003) Measurement of plasma small-dense LDL concentration by a simplified ultracentrifugation procedure and immunoassay of lipoprotein B. Clinica Chimica Acta (334):95-106.

National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) final report. ”Third report of the National Chlesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report”. (2002) Circulation (82):3143-3421.

Kobas S, Hirano T, Kondo T et al. (2002) Significance of small dense low-density lipoproteins and other risk

Homocysteine High

The level of homocysteine (Hcys) in this sample is higher than expected. Homocysteine levels of 10-12µmol/L are common in western populations. Homocysteine levels higher than 6µmol/L have been linked to cardiovascular disease but lowering Hcys levels may not improve outcomes. However, the HOPE-2 study found that giving folic acid, B6 and B12 reduced the risk of stroke by 25%. Homocysteine values higher than 20µmol/L may be found in the elderly and/or may indicate a general B vitamin deficiency. Elevated Hcys has been associated with increased fractures in the elderly (it does not affect bone density but instead interferes with collagen cross-linkages).

Deficiencies of riboflavin (vitamin B2), folic acid (vitamin B9), pyridoxine (B6) and/or cobalamin (B12) can lead to deficient recycling of Hcys and resultant high Hcys levels. Supplementation of these vitamins will reduce

Hcys levels. Intense, prolonged exercise may raise plasma Hcys levels. Chronic consumption of alcohol may also result in increased plasma levels of Hcys. Elevations of Hcys occur in hereditary homocystinuria and in cases of methylene-tetrahydrofolate reductase (MTHFR) polymorphism (common; about 1 in 10 people; and linked to increased incidence of thrombosis and cardiovascular disease). Due to high methylation capacity women in their reproductive years may have Hcys levels 10-15% less than those of men the same age. The DDI Methylation Profile provides important information regarding aberrant methionine metabolism and metabolic processing of Hcys.

Martí-Carvajal AJ, Sola I, Lathyris D, Salanti G (2009) Homocysteine lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev (4):CD006612.

Lonn E, Yusuf S, Arnold MJ, et al. (2006) Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease. N Engl J Med (354):1567-77.

McLean RR et al. (2004) Homocysteine as a predictive factor for hip fracture in older persons. NEJM (350):2042-2049.

van Meurs JB et al. (2004) Homocysteine levels and the risk of osteoporotic fracture. NEJM (350):2033-2041.

Selhub, J (1999) Homocysteine metabolism. Ann Rev Nutr (19):217-246.

Bleich S, Carl M, Bayerlein K, Reulbach U, et al. (2005) Evidence of increased homocysteine levels in alcoholism: the Franconian Alcoholism Research Studies (FARS). Alcohol Clin Exp Res (29):334-336.

CRP (Hs) High

The level ofh ighly sensitive C-reactive protein (Hs-CRP) in this sample is higher than expected. Elevated Hs-CRP is an independent, non-specific risk factor for atherosclerotic disease. Patients with moderately high Hs-CRP concentrations are more likely to develop stroke, myocardial infarction and severe peripheral vascular disease. In coronary artery disease, arterial damage results from white blood cell invasion and inflammation within the vessel wall. Hs-CRP is a general marker for inflammation and infection so it can be used as a very rough proxy for heart disease risk. Since many conditions can cause elevated Hs-CRP, it is not a very specific indicator. Nevertheless, a level above 2.4 mg/L has been associated with a doubled risk of a coronary event compared to levels below 1 mg/L. Moderately elevated levels of hs-CRP (less than about 7 mg/L) are associated with increased CVD risk. Statin drugs (cholesterol lowering) reduce hs-CRP levels however there is no evidence that this is useful for determining statin benefit.

Elevations of Hs-CRP in the absence of clinically significant inflammation can occur in renal failure. Patients with chronically elevated basal levels of Hs-CRP are at an increased risk of diabetes and hypertension. Hs-CRP levels may be elevated in colon cancer and levels increase slightly later in pregnancy as well as with aging.

Examples of Hs-CRP elevation include: mild inflammation and viral infections (10-40 mg/L); active inflammation and/or bacterial infection (40-200 mg/L); severe infection and/or burns (>200 mg/L). When using hs-CRP to monitor these conditions, note that Hs-CRP returns to normal more quickly than does the erythrocyte sedimentation rate (ESR).

C-reactive protein (CRP) is synthesized in the liver; levels rise in response to inflammation and thus, by definition, CRP is an ”acute-phase” protein. Apart from liver failure there is little that interferes with CRP

production. The role of CRP is to bind to phosphocholine on the surface of dead or dying cells activating the complement system via the C1Q complex.

The acute phase response develops in a wide range of acute and chronic inflammatory conditions (bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; coronary artery disease; malignancy; and tissue injury or necrosis) which cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. During the acute phase response, levels of CRP rapidly increase within 2 hours of acute insult, reaching a peak at 48 hours. With resolution of the acute phase response, CRP declines with a relatively short half-life of 18 hours.

Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. J Clin Invest 111: 1805-12.

Hemoglobin A1c High

The blood level Hemoglobin A1c (HbA1c) in this sample is higher than expected. A high HbA1c generally represents poor glucose control. Persistent elevations in blood sugar (and, therefore, HbA1c) increase the risk of long-term vascular complications from diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy, gangrene, and gastroparesis. Poor blood glucose control also increases the risk of short-term complications of surgery such as poor wound healing.

HbA1c (%)	(mmol/mol)	eAG (estimated average glucose) (mmol/L)	(mg/dL)
5	31	5.4 (4.2-6.7)	97 (76-120)
6	42	7.0 (5.5-8.5)	126 (100-152)
7	53	8.6 (6.8-10.3)	154 (123-185)
8	64	10.2 (8.1-12.1)	183 (147-217)
9	75	11.8 (9.4-13.9)	212 (170-249)
10	86	13.4 (10.7-15.7)	240 (193-282)
11	97	14.9 (12.0-17.5)	269 (217-314)
12	108	16.5 (13.3-19.3)	298 (240-347)

A meta-analysis to identify the effect of two different kinds of training programs (combined aerobic and eccentric resistance exercise program and aerobic exercise only) on the glycated hemoglobin levels of individuals with type 2 diabetes found that combining resistance exercise with aerobic exercise improved the glucose control more than just aerobic exercise alone. The average effect of the training programs reduced glycated hemoglobin by 9 mmol/mol (0.8%), similar to results of long-term diet and drug or insulin therapy(1).

Hemoglobin A1c (HbA1c) or glycated hemoglobin, assesses the average plasma glucose concentration over a prolonged period of time; testing is recommended for both (a) checking blood sugar control in people who might be pre-diabetic and (b) monitoring blood sugar control in patients with more elevated levels, termed diabetes mellitus. The HbA1c level is proportional to average blood glucose concentration over the previous four weeks to three months. Glycated hemoglobin is formed in a non-enzymatic glycation pathway by the exposure of hemoglobin glucose in plasma.

Normal levels of glucose produce a normal amount of glycated hemoglobin. The 2010 American Diabetes Association Standards of Medical Care in Diabetes state that HbA1c = 48 mmol/mol (=6.5%) is one of the criteria for the diagnosis of diabetes. Laboratory results may be variable in many circumstances, such as after blood loss, for example, after surgery, blood transfusions, anemia, or high erythrocyte turnover; in the

presence of chronic renal or liver disease; after administration of high-dose vitamin C; or erythropoetin treatment (3).

Marcus RL, Smith S, Morrell G, et al. (2008) Comparison of combined aerobic and high-force eccentric resistance exercise with aerobic exercise only for people with type 2 diabetes mellitus. Phys Ther 88:1345-54.

Executive summary: Standards of medical care in diabetes-2010. Diabetes Care (33) (Suppl 1):S4-10.

Geistanger A, Arends S, Berding C, et al. (2008) Statistical methods for monitoring the relationship between the IFCC reference measurement procedure for hemoglobin A1c and the designated comparison methods in the United States, Japan, and Sweden. Clin Chem (54):1379-85.

Cystatin C High

The level of cystatin C in this sample is higher than expected. High cystatin C indicates a reduced glomerular filtration rate (GFR). If kidney function and GFR decline, the blood levels of cystatin C rise. Cystatin C is not a direct CVD risk factor but renal disease is associated with increased incidence of CVD. It has been suggested that elevated cystatin C is a sensitive predictor of risk of developing chronic kidney disease, thereby signaling a state of 'preclinical' kidney dysfunction. An elevated level of cystatin C may warrant further renal testing such as the DDI six hour creatinine clearance test.

Increased levels of cystatin C may be associated with the increased risk of death (independent of renal dysfunction), with several types of cardiovascular disease (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) and healthy aging. Mutations in the cystatin 3 gene are responsible for the Icelandic type of hereditary cerebral amyloid angiopathy, a condition predisposing to intracerebral hemorrhage, stroke and dementia.

The prevalence of increased levels of cystatin C in the United States was 9.6% in subjects of normal weight, increasing in overweight and obese individuals (2). In Americans aged 60 and 80 and older, serum cystatin C is increased in 41% and more than 50%, respectively.

Shlipak MG, Katz R, Sarnak MJ et al. (2006) Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med (145):237-46.

Muntner P, Winston J, Uribarri J, et al. (2008) Overweight, obesity, and elevated serum cystatin C levels in adults in the United States. Am J Med (121):341-348.

Kottgen A, Selvin E, Stevens LA, et al. (2008) Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis (51):385-394.

Fibrinogen High

The level of fibrinogen in this sample is higher than expected. Elevated fibrinogen has been identified as an independent risk factor cardiovascular disease. Since fibrinogen is an acute phase protein, it may be elevated in association with any form of inflammation.

Fibrinogen is the principal protein of the vertebrate blood clotting cascade. It is a soluble plasma protein made in the liver that is converted by thrombin into fibrin during blood coagulation. During the coagulation cascade the zymogen prothrombin is activated to the serine protease thrombin, which is responsible for

converting fibrinogen into fibrin. Fibrin is then cross linked by factor XIII to form a clot. Factor XIIIa stabilizes fibrin further by incorporation of fibrinolysis inhibitors and by binding to adhesive proteins of various cells. Both activation of factor XIII by thrombin and plasminogen activator (t-PA) are catalyzed by fibrin

Stec JJ, Silbershatz H, Tofler GH, Matheney TH, Sutherland P, Lipinska I, Massaro JM, Wilson PFW, Muller JE, D'Agostino RB, Sr, (2000). Association of Fibrinogen With Cardiovascular Risk Factors and Cardiovascular Disease in the Framingham Offspring Population. Circulation (102):1634-1638.

Apolipoprotein B High

The level of apolipoprotein B (apoB) in this sample is higher than expected. ApoB is the sole apolipoprotein constituent of low-density lipoproteins (LDL) and apoB and LDL-cholesterol are CVD risk factors. High levels of apoB can lead to plaque formation in arteries (atherosclerosis) leading to coronary and cerebrovascular disease if that apoB is associated with oxidized or small, dense LDL particles. Elevated apoB may be a better indicator of heart disease risk than either total cholesterol or LDL-cholesterol levels.