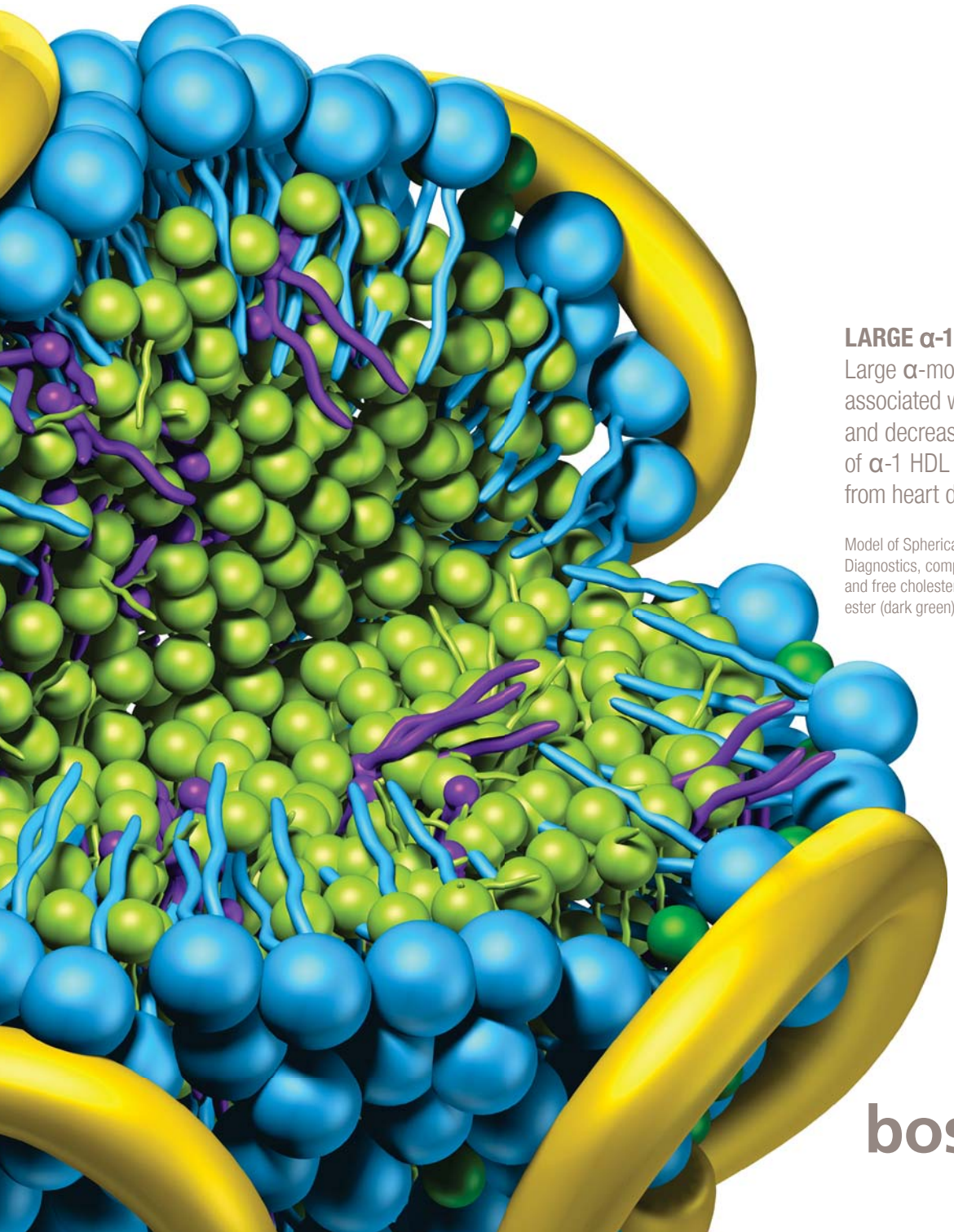
BOSTON HEART HDL MAP®

ASSESSING AND TREATING SUBPOPULATION ABNORMALITIES



LARGE α-1 HDL

Large α-mobility HDL particles are associated with healthy HDL maturation and decreased CVD risk. High levels of α-1 HDL are a marker of protection from heart disease.

Model of Spherical Lipoprotein developed by Boston Heart Diagnostics, composed of protein (yellow), phospholipids (blue), and free cholesterol (green) on the surface, and cholesteryl ester (dark green) and triglyceride (purple) in the core.

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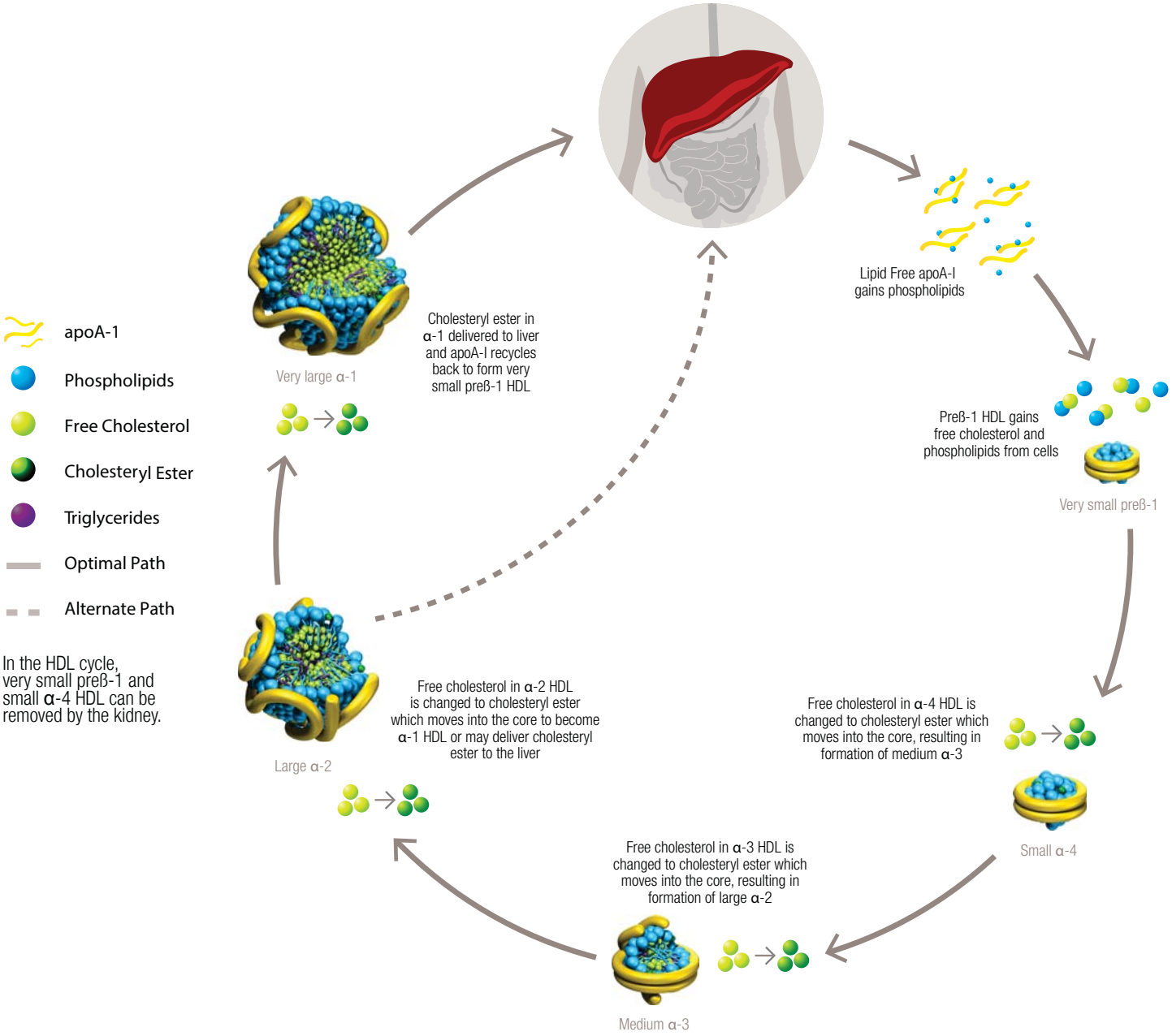
BOSTON HEART HDL MAP®

FORMATION OF HDL PARTICLES

HDL particles begin as free circulating apoA-I, which is made in the liver and intestine. Lipid free apoA-I gains phospholipids and becomes a very small HDL particle, called preß-1. These particles begin to collect free cholesterol and additional phospholipids from cells and progressively grow into larger HDL particles (small α-4, medium α-3, large α-2 and very large α-1). The conversion of free cholesterol on the HDL particle surface into cholesteryl ester results in the growth of HDL particles as the cholesteryl ester moves into the HDL particle core. When HDL particles become large α-2 or very large α-1 they dump cholesteryl ester to the liver or to triglyceride rich lipoproteins, the apoA-I then recycles back as a small HDL particle again.



BOSTON HEART HDL MAP®

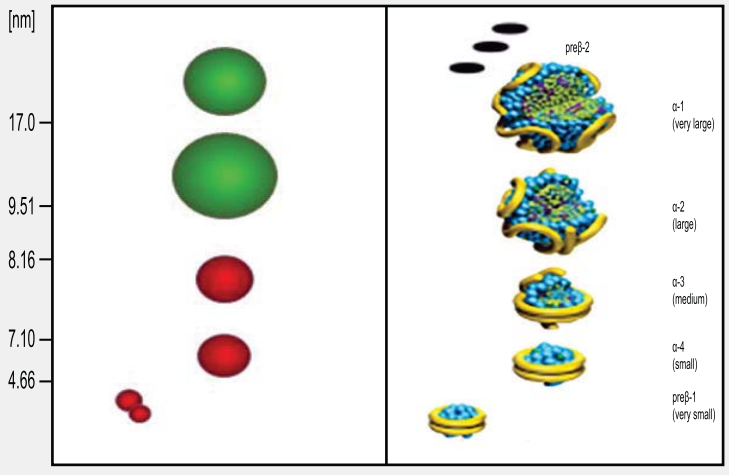
OVERVIEW OF THE HDL MAP

Standard HDL-C tests only measure the total amount of HDL-C contained by all HDL particles. Boston Heart's exclusive HDL Map test measures the amount of apoA-I in the five most significant subpopulations, resulting in a deeper understanding of a patient's CVD risk.[1-4] This exclusive method provides an accurate and consistent indication of reverse cholesterol transport by separating the larger, cardioprotective particles (α-1) most associated with decreased CVD risk from the smaller HDL particles which have been associated with increased risk.[1-4]

SCIENCE OF THE HDL MAP

The Boston Heart HDL Map test analyzes the distribution of HDL subpopulations in plasma using a proprietary gel electrophoresis technique which enables precise differentiation of HDL subparticles based on size.

Subsequent immunoblotting quantifies the amount of apoA-I, the main protein of HDL, in each of the five most important HDL subpopulations (very large α-1, large α-2, medium α-3, small α-4 and very small preβ-1), providing more accurate disease characterization than HDL-C alone.[2]



BOSTON HEART HDL MAP®

TREATMENT ALGORITHM FOR HDL SUBPOPULATION ABNORMALITIES

1 ASSESS FOR ABNORMAL TEST RESULTS

MALE FEMALE	**Low apoA-I in α-1 HDL level <25 mg/dL** **Low apoA-I in α-1 HDL level <35 mg/dL**
MALE FEMALE	**Low high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL** **Low high-density lipoprotein cholesterol (HDL-C) level <50 mg/dL**
ALL	**High triglyceride (TG) level >150 mg/dL**

2 ASSESS FOR ADDITIONAL CAUSES OF LIPID ABNORMALITIES

ADDITIONAL CAUSES OF LOW HDL CHOLESTEROL[5]

LIFESTYLE	CONDITIONS	MEDICATIONS
· Cigarette smoking · High sugar intake · Excess caloric intake · Excess alcohol intake (>2 drinks/day) · High trans fat intake · Physical inactivity	**Common Causes** · Elevated triglycerides[8]* · Diabetes mellitus* · Insulin resistance · Overweight/obesity · Kidney & liver dysfunction **Other Causes** · HIV · Polycystic ovarian syndrome · Acute or chronic inflammation · Hypothyroidism	· Non-selective beta blockers · Androgenic steroids · Progestins · Isotretinoin · Paradoxical response to fenofibrate and thiazolidinediones

ADDITIONAL CAUSES OF ELEVATED TRIGLYCERIDES[6]

LIFESTYLE	CONDITIONS	MEDICATIONS
· Cigarette smoking · High sugar intake · Excess caloric intake · Excess alcohol intake (>2 drinks/day) · Physical inactivity · High saturated fat intake, fried foods	**Common Causes** · Overweight/obesity · Insulin resistance · Diabetes mellitus · Alcoholism · Kidney dysfunction **Other Causes** · HIV · Cushing's disease · Pregnancy · Hypothyroidism	· Non-selective beta blockers · Thiazide diuretics · Androgenic steroids · Oral estrogens · Oral contraceptives · Isotretinoin · Protease inhibitors · Cyclosporin · Glucocorticosteroids

*Condition must be optimally controlled to successfully increase HDL.

3 Assess for family history of an HDL disorder and premature heart disease

- Collect family history about premature cardiovascular disease (CVD) identified as male first degree relative < age 55 and female first degree relative < age 65.
- Collect information about lipid disorders in family members, including parents, siblings and offspring. There are three disorders to look for:

DYSLIPIDEMIA	**Triglycerides greater than 150 mg/dL and HDL-C less than 40 mg/dL**
COMBINED HYPERLIPIDEMIA	**Triglycerides greater than or equal to 150 mg/dL and LDL-C greater than 160 mg/dL, usually with HDL-C less than 40 mg/dL**
ISOLATED LOW HDL-C	**Isolated HDL-C less than 40 mg/dL**

4 INTERPRET HDL MAP RESULTS

Initiate appropriate treatment after correcting contributing causes for low HDL-C and elevated triglycerides

PARAMETER/LAB VALUES	POTENTIAL DIAGNOSIS/CLINICAL SIGNIFICANCE	TREATMENT CONSIDERATIONS**
ApoA-I in α-1 HDL>35 mg/dL **ApoA-I in α-1 HDL>45 mg/dL**	· Optimal · Indicates excellent reverse cholesterol transport	No treatment changes or additions for optimizing HDL particles
ApoA-I in α-1 HDL≥25 but≤35 mg/dL **ApoA-I in α-1 HDL≥35 but≤45 mg/dL**	· Not optimal for CVD prevention · If CVD is not present, may consider treating only with lifestyle modification · If CVD is present, consider treating to optimal levels	**Lifestyle** · Weight reduction if needed · Exercise (>30 minutes/day) · Diet (low saturated fat (<7%), low cholesterol (<200 mg/day), low trans fat and low sugar) · Smoking cessation **Medications** · Use statin* to optimize LDL-C first; consider impact of statin on HDL particles [4, 7, 8] · Statin efficacy for beneficially modifying HDL in decreasing order: - Rosuvastatin · Atorvastatin · Simvastatin · Pravastatin · Lovastatin - Niacin* (2 grams/day) is the best agent for optimizing HDL [1, 9] - Fenofibrate* is the best agent for lowering triglycerides, especially in those with TG >500 mg/dL; can also use fish oil (≥ 4 g/day).
ApoA-I in α-1 HDL<25 mg/dL **ApoA-I in α-1 HDL<35 mg/dL**	· Abnormal levels associated with increased risk of heart disease	
ApoA-I in α-1 HDL<25 mg/dL and preß-1>25 mg/dL **ApoA-I in α-1 HDL<35 mg/dL and preß-1>25 mg/dL**	· Abnormal levels associated with increased risk of heart disease · Indicates a problem of HDL metabolism · Often associated with triglyceride levels >150 mg/dL	

*Niacin at a dose of 2 grams/day will increase apoA-I in large α-1 HDL by 100% or more. Potent statins such as rosuvastatin and atorvastatin will increase this parameter by 10-40%. Fibrates such as gemfibrozil or fenofibrate do not increase this parameter, but increase intermediate sized HDL particles such as α-3 and α-2 HDL. Statins are the best agents for lowering LDL and small dense LDL, niacin is the best agent for raising large HDL, and fibrates are the best agents for triglyceride lowering. However all of the above agents will lower triglyceride levels. The statin/niacin combination has been shown to be the most effective treatment regimen to promote regression of CVD or cardiovascular disease.[1] In order to achieve regression of cardiovascular disease, the apoA-I level in very large α-1 HDL should be >20 mg/dL in men and >30 mg/dL in women.

** Treatment Considerations are typically the first line treatment considerations by Boston Heart. A patient's healthcare provider must provide patient-specific treatment plans.

IMPACT OF DRUG CLASSES ON HDL PARTICLES & METABOLISM

HDL PARAMETER	NIACIN [1, 9]	STATINS [4, 7, 8]	FIBRATES [10, 11]
HDL-C	↑ **20–40%**	↑ **2–10%**	↑ **2–10%**
ApoA-I concentration	↑	—	—
α-1 particles	↑ **up to 115%**	↑ **12-36%**	**Slight** ↓
α-3 particles	—	—	**Slight** ↑
Preß-1 particles	↓**up to 30%**	↓**up to 40%**	—
Metabolism	↑ **apoA-I production** ↑ **ATP-binding cassette protein A1 (ABCA-1) expression in the liver**	↓**cholestryl ester transfer protein (CETP) activity** **No change in apoA-I kinetics**	↑ **gene expression of apoA-I, apoA-II & lipoprotein lipase (LPL)** ↑ **apoA-I fractional catabolic rate (FCR)**

BOSTON HEART DIAGNOSTICS

Boston Heart Diagnostics is transforming the treatment of cardiovascular disease by providing healthcare providers and their patients with novel, personalized diagnostics and integrated customized lifestyle programs that have the power to change the way clinicians and patients communicate about disease and improve heart health. Boston Heart looks beyond the "good" and "bad" cholesterol assessment that conventional labs provide to give a more complete picture of heart health. Founded by renowned cardiovascular researchers and led by seasoned lab and diagnostic executives, Boston Heart is one of the fastest growing health companies in the country.

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