Biomarkers (Novel) in Risk Assessment and Management of Cardiovascular Disease

I. Description

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). This biomarkers assessed here are those that have the most evidence in support of their use in clinical care, including apolipoprotein B (apo B), apolipoprotein Al (apo Al), apolipoprotein E (apo E), B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein (HDL) subclass, leptin, low-density lipoprotein (LDL) subclass, and lipoprotein (a). These biomarkers have been studied as an alternative or addition to standard lipid panels for risk stratification in CVD or as treatment targets for lipid-lowering therapy.

The evidence for the use of nontraditional lipid and other biomarker measurements, including apo B, apo Al, apo E, lipoprotein A, subclasses of LDL and HDL, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin, in individuals who are asymptomatic with risk for CVD includes systematic reviews, meta-analyses, and large, prospective cohort studies that have evaluated the association of these lipid and other markers with cardiovascular outcomes. Relevant outcomes are overall survival, other test performance measures, change in disease status, morbid events, and medication use. Evidence from cohort studies and meta-analyses of these studies suggests that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. In particular, apo B and apo Al have been identified as adding some incremental predictive value. However, it has not been established that the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of nontraditional lipid and other biomarker measurements, including apo B, apo Al, lipoprotein (a), subclasses of LDL and HDL, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin, in individuals with hyperlipidemia managed with lipid-lowering therapy includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes
are overall survival, change in disease status, morbid events, and medication use. In particular, apo B, apo AI, and apo E have been evaluated as markers of success of lipid-lowering treatment success, and evidence from the intervention arms from several randomized controlled trials suggests that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins, surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with “normal” levels of total and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Other non-lipid markers have been identified as having an association with cardiovascular disease (CVD) including B-type naturetic peptide, cystatin C, fibrinogen and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting for therapy.

Apolipoprotein B

Apolipoprotein B (apo B) is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B\textsubscript{100}, constitutes the apo B found in LDL and very-low-density lipoproteins (VLDL). Because both LDL and VLDL each contain 1 molecule of apo B, measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Because LDL particles can vary both in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety of both size and numbers of LDL particles. Thus, it has been postulated that apo B is a better measure of the atherogenic potential of serum LDL than LDL concentration.

Two basic techniques are used to measure LDL particle concentration. Particle size can be determined by gradient gel electrophoresis, or the number of LDL particles can be measured using nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy is based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus, NMR can quantify the number of LDL particles of a specific size (i.e., small dense LDL) and can provide a measurement of the total number of particles.

Apolipoprotein AI

HDL contains two associated apolipoproteins, i.e., AI and AII. HDL particles can also be classified by whether they contain apolipoprotein AI (apo AI) only or whether they contain both apo AI and apolipoprotein AII (apo AII). All lipoproteins contain apo AI and some also contain apo AII. Because
all HDL particles contain apo AI, this lipid marker can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number.

Direct measurement of apo AI has been proposed as more accurate than the traditional use of HDL level in evaluation of the cardioprotective, or “good,” cholesterol. In addition, the ratio of apo B/apo AI has been proposed as a superior measure of the ratio of proatherogenic (i.e., “bad”) cholesterol to anti-atherogenic (i.e., “good”) cholesterol.

Apolipoprotein E

Apolipoprotein E (apo E) is the primary apolipoprotein found in VLDLs and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The apolipoprotein E (APOE) gene is polymorphic, consisting of three alleles (e2, e3, and e4) that code for three protein isoforms, known as E2, E3, and E4, which differ from one another by one amino acid. These molecules mediate lipid metabolism through their different interactions with the LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the APOE phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various APOE genotypes are more atherogenic than others and that APOE measurement may provide information on risk of CAD above traditional risk factor measurement. It has also been proposed that the APOE genotype may be useful in the selection of specific components of lipid-lowering therapy, such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. APOE genotype may be one factor that determines an individual’s degree of response to interventions such as statin therapy.

Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is an amino acid polypeptide that is secreted primarily by the ventricles of the heart when pressure to the cardiac muscles increases or there is myocardial ischemia. Elevations in BNP levels reflect deterioration in cardiac loading levels and may predict adverse events. BNP has been studied as a biomarker for managing heart failure and predicting cardiovascular and heart failure risk.

Cystatin C

Cystatin C is a small serine protease inhibitor protein that is secreted from all function cells found throughout the body. It has primarily been used as a biomarker of kidney function. Cystatin C has also been studied to determine whether it may serve as a biomarker for predicting cardiovascular risk. Cystatin C is encoded by the CST3 gene.

Fibrinogen

Fibrinogen is a circulating clotting factor and precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Fibrinogen levels have been shown to be associated with future risk of CVD and all-cause mortality.
HDL Subclass

HDL particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size/density and/or on the apolipoprotein composition. Using size/density, HDL can be classified into HDL₂, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL₃, which are smaller, denser particles. HDL contains two associated apolipoproteins (AⅠ and AⅡ). HDL particles can also be classified by whether they contain apo AⅠ only or they contain both apo AⅠ and apo AⅡ. There has been substantial interest in determining whether subclasses of HDL can be used to provide additional information on cardiovascular risk compared with HDL alone.

An alternative to measuring the concentration of subclasses of HDL (e.g., HDL₂ and HDL₃) is direct measurement of HDL particle size and/or number. Particle size can be measured by NMR spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo AⅠ has used HDL particle number as a surrogate, based on the premise that each HDL particle contains one apo AⅠ molecule.

LDL Subclass

Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly inherited disorder associated with a more atherogenic lipoprotein profile, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly seen in type II diabetes and is one component of the “metabolic syndrome,” defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. Presence of the metabolic syndrome is considered by ATP III to be a substantial risk-enhancing factor for CAD.

LDL size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profile than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding to use a combination of two or more drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test, LDL-C is not a direct measure of LDL, but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the
bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL-C level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL-C represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic than larger particles. Therefore, for patients with elevated numbers of LDL particles, cardiac risk may be further enhanced when the particles are smaller versus larger.

Two techniques are most commonly used for measuring LDL particle concentration: the surrogate measurement of apo B or direct measurement of the number of particles using NMR. NMR signals distinguish lipoprotein subclasses of different size. Thus NMR can directly measure the number of LDL particles of a specific size (i.e., small dense LDL) and can measure the total number of particles. Thus, NMR is proposed as an additional technique to assess cardiac risk.

**Leptin**

Leptin is a protein secreted by fat cells that has been found to be elevated in heart disease. Leptin has been studied to determine if it has any relationship with the development of CVD.

**Lipoprotein A**

Lipoprotein (a) (Lp[a]) is a lipid-rich particle similar to LDL. Apo B is the major apolipoprotein associated with LDL; in Lp(a), however, there is an additional apolipoprotein A (apo A) covalently linked to the apo B. The apolipoprotein (a) molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of CVD. Levels of Lp(a) are relatively stable in individuals over time but vary up to a 1,000-fold between individuals, presumably on a genetic basis. The similarity between Lp(a) and fibrinogen has stimulated intense interest in Lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated Lp(a) levels. Therefore, it has been proposed that levels of Lp(a) may be an independent risk factor for CAD.

II. **Criteria/Guidelines**

Measurement of novel lipid and non-lipid risk factors (i.e., apolipoprotein B, apolipoprotein AI, apolipoprotein E, B-type natriuretic peptide, cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, lipoprotein[a]) as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease is not covered because it is not known to be effective in improving health outcomes.

III. **Administrative Guidelines**

The provider cannot bill or collect charges for these services unless a written acknowledgement of financial responsibility, specific to the service, is obtained from the Member prior to the time services are rendered. Modifier code GA should be appended to the CPT when billing for these services.
IV. Scientific Background

Introduction
A large body of literature has accumulated on the utility of novel lipid risk factors in the prediction of future cardiac events. The evidence reviewed here consists of systematic reviews, meta-analyses, and large, prospective cohort studies that have evaluated the association of these lipid markers with cardiovascular outcomes. A smaller amount of literature is available on the utility of these markers as a marker of treatment response. Data on treatment response is taken from randomized controlled trials (RCTs) that use one or more novel lipid markers as a target of lipid-lowering therapy. This evidence review was developed in 2010 and updated periodically with reviews of the literature through searches of the MEDLINE database. The most recent update covered the period through August 10, 2015.

The Adult Treatment Panel III (ATP III) guidelines note that to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria to assess their clinical significance:

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

A 2002 TEC Assessment summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor independently contributes to risk assessment compared to established risk factors.
- Determination of how the novel risk assessment will be used in the management of the patient, compared with standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Each of the individual novel lipid risk factors will be judged separately against these criteria to determine whether health outcomes are improved through measurement of the novel lipid risk factor.

Systematic Reviews and Meta-Analyses
Thanassoulis and colleagues in 2014 reported on a meta-analysis of seven placebo-controlled statin trials to evaluate the relationship of statin-induced reductions in lipid levels to reduction of coronary heart disease (CHD) risk. Each of the trials included low-density lipoprotein cholesterol
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(LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and apo B values assessed at baseline and 1-year follow-up. In both frequentist and Bayesian meta-analyses, reductions in apo B were more closely related to CHD risk reduction from statins than LDL-C or non-HDL-C.

In 2013, van Holten and colleagues reported on a systematic review of 85 articles with 214 meta-analyses to compare serological biomarkers for risk of CVD. Predictive potential for primary CVD events was strongest with lipids with a ranking from high to low found with: C-reactive protein (CRP), fibrinogen, cholesterol, apo B, the apo A/apo B ratio, HDL, and vitamin D. Markers associated with ischemia were more predictive of secondary cardiovascular events and included from high to low result: cardiac troponins I and T, CRP, serum creatinine, and cystatin C. A strong predictor for stroke was fibrinogen.

Tzoulaki and colleagues reported on meta-analyses on biomarkers for CVD risk to examine potential evidence of bias and inflation of results in the literature. Included in the evaluation were 56 meta-analyses, with 49 reporting statistically significant results. Very large heterogeneity was seen in 9 meta-analyses, and small study effects were seen in 13 meta-analyses. Significant excess of studies with statistically significant results was found in 29 meta-analyses (52%). The authors report only 13 meta-analyses with statistical significant results that had more than 1000 cases and no evidence of large heterogeneity, small-study effects, or excess significance.

In a 2012 systematic review, Willis and colleagues evaluated whether validated CVD risk scores can identify patients at risk for CVD for participation in more intensive intervention programs for primary prevention. The authors were unable to perform a meta-analysis due to the heterogeneity of the studies. The evidence was considered not strong enough to draw definitive conclusions, but the authors noted lifestyle interventions with higher intensity may have potential for lowering CVD risk.

**Apolipoprotein B**

**Apo B as a Predictor of Cardiovascular Risk**

In 2012, Robinson and colleagues published results of a Bayesian random-effects meta-analysis of RCTs to compare the effectiveness of lowering apo B versus LDL-C and non-HDL-C for reducing CVD, CHD, and stroke risk. Included in the analysis were 131,134 patients from 25 RCTs including 12 trials on statins, 5 on niacins, 4 on fibrates, 1 on simvastatin plus ezetimibe, 1 on aggressive versus standard LDL and blood pressure targets, and 1 on ileal bypass surgery. In the analysis of all trials, each apo B decrease of 10 mg/dL resulted in a 6% decrease in major CVD risk and a 9% decrease in CHD risk prediction, but stroke risk was not decreased. Decreased apo B levels were not superior to decreased non-HDL levels in decreasing CVD (Bayes factor [BF]=2.07) and CHD risk (BF=1.45) prediction. When non-HDL-C plus LDL-C decrease were added to apo B decrease, CVD risk prediction improved slightly (BF=1.13) but not CHD risk prediction (BF=1.03) and stroke risk prediction worsened (BF=0.83). In summary, the addition of apo B decrease did not consistently add information to LDL, non-HDL, or LDL/non-HDL decreases to improve CVD risk prediction when analyzed across lipid-modifying treatments of all types. Sniderman and colleagues reported on 9,345 acute myocardial infarction patients compared with 12,120 controls in the standardized case-control INTERHEART study. The authors reported discordance in the levels of cholesterol contained
in apo B and non-HDL-C. In contrast to the Robinson study above, apo B was found to be more accurate than non-HDL-C as a marker for cardiovascular risk.

The Emerging Risk Factors Collaboration published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154,544 individuals. Risk prediction was examined for a variety of traditional and non-traditional lipid markers. For apo B, evidence from 26 studies on 139,581 individuals reported that apo B was an independent risk factor for cardiovascular events, with an adjusted hazard ratio (HR) of 1.24 (95% confidence interval [CI]: 1.19-1.29). On reclassification analysis, when apo B and apo A1 were substituted for traditional lipids, there was no improvement in risk prediction. In fact, there was a slight worsening in the predictive ability, evidenced by a decrease in the C-statistic of -0.0028 (p<0.001), and a decrease in the net reclassification improvement of -1.08% (p<0.01).

The Quebec Cardiovascular Study evaluated the ability of levels of apo B and other lipid parameters to predict subsequent CAD events in a prospective cohort study of 2,155 men followed for 5 years. Elevated levels of apo B were found to be an independent risk factor for ischemic heart disease after adjustment for other lipid parameters (risk ratio [RR]=1.40; 95% confidence interval [CI]: 1.2 to 1.7). In patients with an apo B level of greater than 120 mg/dL, there was a 6.2-fold increase in the risk of cardiovascular events.

The Apolipoprotein Mortality Risk Study (AMORIS) was another prospective cohort study that followed up 175,000 Swedish men and women presenting for routine outpatient care over a mean of 5.5 years. This study found that apo B was an independent predictor of CAD events and was superior to LDL-C levels in predicting risk, both for the entire cohort and in all subgroups examined. Risk ratios for the highest quartile of apo B levels were 1.76 in men (p<0.0001) and 1.69 in women (p<0.001).

A cohort study of 15,632 participants from the Women’s Health Initiative provided similar information in women. In this analysis, the HR for developing CHD in the highest versus the lowest quintiles was greater for apo B (2.50; 95% CI: 1.68 to 3.72) than LDL-C (1.62; 95% CI: 1.17 to 2.25), after adjustment for traditional cardiovascular risk factors.

The Copenhagen City Heart Study prospectively evaluated 9,231 asymptomatic persons from the Danish general population followed for 8 years. Individuals with total apo B levels in the top one-third (top tertile) had a significantly increased relative risk of cardiovascular events compared with patients in the lowest one-third, after controlling for LDL-C and other traditional cardiovascular risk factors (RR=1.4, 95% CI: 1.1 to 1.8 for men; RR=1.5, 95% CI: 1.1 to 2.1 for women). This study also compared the discriminatory ability of apo B with that of traditional lipid measures, by using the area under the curve (AUC) for classifying cardiovascular events. Total apo B levels had a slightly higher AUC compared with LDL-C (0.58 vs. 0.57, respectively); however, this difference in AUC was not statistically significant.

At least one large prospective cohort study, the Atherosclerosis Risk in Communities (ARIC) study, concluded that apo B did not add additional predictive information above standard lipid measures. The ARIC study followed 12,000 middle-aged individuals free of CAD at baseline for 10 years. While apo B was a strong univariate predictor of risk, it did not add independent predictive value above traditional lipid measures in multivariate models.
The ratio of apo B/apo Al has also been proposed as a superior measure of the ratio of pro-atherogenic (i.e., “bad”) cholesterol to anti-atherogenic (i.e., “good”) cholesterol. This ratio may be a more accurate measure of this concept, compared to the more common total cholesterol (TC)/HDL ratio. A number of epidemiologic studies have reported that the apo B/apo Al ratio is superior to other ratios, such as TC/HDL-C, or non-HDL-C/HDL-C.

Kappelle and colleagues used data from the prospective PREVEND cohort to evaluate the predictive value of the apo B/apo Al ratio independent of other traditional risk factors, including albuminuria and CRP. Among 6,948 individuals without previous heart disease and who were not on lipid-lowering drugs, the adjusted HR for a high apo B/apo Al ratio was 1.37 (95% CI: 1.26 to 1.48). This HR was not significantly different from the TC/HDL-C ratio of 1.24 (95% CI: 1.18 to 1.29), and was not significantly changed after further adjustment for triglycerides.

Some studies have tested the use of apo B in a multivariate risk prediction model in which both traditional risk factors and apolipoprotein measures were included as potential predictors. Ridker and colleagues published the Reynolds Risk Score, based on data from 24,558 initially healthy women enrolled in the Women’s Health Study and followed for a median of 10.2 years. A total of 35 potential predictors of CVD were considered as potential predictors, and 2 final prediction models were derived. The first model was the best fitting model statistically, and included both apo B and the apo B/apo Al ratio as 2 of 9 final predictors. The second model, called the “clinically simplified model,” substituted LDL-C for apo B and total/HDL cholesterol for apo B/apo Al. The authors developed this simplified model “for the purpose of clinical application and efficiency” and justified replacing the apo B and apo B/apo Al measures as a result of their high correlation with traditional lipid measures (r=0.87 and 0.80, respectively).

Ingelsson and colleagues used data from 3,322 individuals in the Framingham Offspring Study to compare prediction models with traditional lipid measures to models that include apolipoprotein and other nontraditional lipid measures. This study reported that the apo B/apo Al ratio had similar predictive ability as traditional lipid ratios with respect to model discrimination, calibration, and reclassification. The authors also reported that the apo B/apo Al ratio did not provide any incremental predictive value over traditional measures.

**Apo B as a Treatment Target**

A number of RCTs of statin therapy have examined the change in apo B on treatment in relation to clinical CAD outcomes and compared whether apo B is a better predictor of outcomes than LDL-C.

Boekholdt and colleagues published an individual patient-level meta-analysis of on-treatment levels of traditional and non-traditional lipids as a measure of residual risk. A total of 8 studies enrolling 62,154 participants were included. The adjusted HR for each 1 standard deviation (SD) increase in apo B was 1.14 (95% CI: 1.11 to 1.18), which did not differ significantly from LDL-C (HR=1.13, 95% CI: 1.10 to 1.17, p=0.21). The HR for HDL-C was 1.16 (95% CI: 1.12 to 1.19), which was significantly greater than LDL-C or apo B (p=0.002). In a subsequent report from this meta-analysis, Boekholdt and colleagues evaluated the LDL-C, non-HDL-C, and apo B levels of 38,153 patients allocated to the statin therapy groups. Despite statin therapy, reductions in levels of LDL-C, non-HDL-C, and apo B from baseline to 1 year showed large interindividual variation.
In 2013, Ballantyne and colleagues reported on a post hoc analysis of 682 patients with acute coronary syndrome from the randomized, phase 3 study Limiting Undertreatment of Lipids in Acute Coronary Syndrome with Rosuvastatin (LUNAR) study. The LUNAR subanalysis examined apo B in relation to LDL-C and non-HDL-C under intensive statin therapy with rosuvastatin or atorvastatin. The treatment target for apo B of 80 mg/dL correlated with an LDL-C of 90 mg/dL and non-HDL-C of 110 mg/dL at baseline and with an LDL-C of 74 mg/dL and non-HDL-C of 92 mg/dL with statin therapy. Independent of triglyceride status, non-HDL-C was found to have a stronger correlation with apo B than LDL-C and could be an adequate surrogate of apo B during statin therapy.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated lipid parameters among 6,605 men and women with average LDL and low HDL cholesterol levels who were randomly assigned to receive either lovastatin or placebo. Baseline LDL and HDL cholesterol as well as apo B levels were predictive of future coronary events. However, in the treatment group, post-treatment levels of LDL-C and HDL-C were not predictive of subsequent risk, while post-treatment apo B levels were predictive.

In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, the relationship between on-treatment apo B levels and clinical outcomes was examined in 9,140 patients randomized to pravastatin or placebo and followed for a mean of 6.1 years. The adjusted HR for apo B levels (2.10; 95% CI: 1.21 to 3.64, p=0.008) was higher than that for LDL-C (1.20; 95% CI: 1.00 to 1.45, p=0.05). Also, the proportion of the treatment effect explained by on-treatment apo B levels (67%) was higher than that for LDL-C levels (52%).

Kastelein and colleagues combined data from 2 RCTs, the Treating to New Targets (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trials, to compare the relationship between response to lipids, apo B levels, and other lipid measures. This analysis included 18,889 patients with established coronary disease randomly assigned to low- or high-dose statin treatment. In pairwise comparisons, the on-treatment apo B level was a significant predictor of cardiovascular events (HR=1.24; 95% CI: 1.13 to 1.36, p<0.001), while LDL level was not. Similarly, the ratio of apo B/apo A1 was a significant predictor of events (HR=1.24; 95% CI: 1.17 to 1.32), while the total/HDL-C was not. In another publication that reported on the TNT study, the on-treatment apo B level was also a significant predictor of future events (adjusted HR=1.19, 95% CI: 1.11 to 1.28). In this study, the known baseline variables performed well in discriminating future cases from non-cases, and the addition of apo B was not associated with additional risk.

Mora and colleagues measured on-treatment lipid levels to assess the prediction of residual risk while on statin therapy. Using data from the JUPITER trial, on-treatment levels of LDL-C, non-HDL-C, high-sensitivity CRP (hs-CRP), apo B, and apo A1 were used to predict subsequent cardiovascular events. The HRs for cardiovascular events were similar among all the lipid measures, ranging from 1.22 to 1.31, with no significant differences between measures. The residual risk declined overall with a decreasing level of LDL-C, with the lowest risk seen in individuals achieving an LDL-C of less than 70 mg/dL.

**Section Summary: Apolipoprotein B**

The evidence suggests that apo B provides independent information on risk assessment for CVD and that apo B may be superior to LDL-C in predicting cardiovascular risk. Numerous large
prospective cohort studies and nested case-control studies have compared these measures, and most have concluded that apo B is a better predictor of cardiac risk than LDL-C. However, some meta-analyses have concluded that apo B is not a better predictor of cardiac risk than HDL or non-HDL combined with LDL. There is also greater uncertainty around the degree of improvement in risk prediction and whether the magnitude of improvement is clinically significant. While there have been attempts to incorporate apo B into multivariate risk prediction models, at present, apo B is not included in the models that are most commonly used in routine clinical care, such as the Framingham risk model and the Prospective Cardiovascular Munster Study (PROCAM) Score.

As a marker of response to cholesterol-lowering treatment, apo B may be more accurate than LDL-C and may provide a better measure of the adequacy of anti-lipid therapy than does LDL-C. Post-hoc analyses of RCTs of statin treatment have reported that on-treatment levels of apo B are more highly correlated with clinical outcomes than standard lipid measures. Whether the degree of improvement in assessing treatment response is clinically significant has yet to be determined.

It is not yet possible to conclude that the use of apo B levels will improve outcomes in routine clinical care. Improved ability to predict risk and/or treatment response does not by itself result in better health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. No studies have demonstrated improved health outcomes by using apo B in place of LDL-C for either risk assessment and/or treatment response. The most widely used risk assessment models, such as the Framingham prediction model, and the most widely used treatment guidelines, the ATP III guidelines, do not provide the tools necessary for clinicians to incorporate apo B measurements into routine assessment and management of hyperlipidemic patients. This lack creates difficulties in interpreting and applying the results of apo B and/or apo B/apo A measurements to routine clinical care.

**Apolipoprotein AI**

**Apo Al as a Predictor of CVD**

The Emerging Risk Factors Collaboration published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154,544 subjects. Risk prediction was examined for a variety of traditional and nontraditional lipid markers. For apo A1, evidence from 26 studies on 139,581 subjects reported that apo A1 was an independent risk factor for reduced cardiovascular risk, with an adjusted HR for cardiovascular events of 0.87 (95% CI: 0.84 to 0.90). On reclassification analysis, when apo B and apo A1 were substituted for traditional lipids, there was no improvement in risk prediction. In fact, there was a slight worsening in the predictive ability, evidence by a decreased in the C statistic of -0.0028 (p<0.001) and a decrease in the net reclassification improvement of -1.08% (p<0.01).

The Apolipoprotein-Related Mortality Risk Study (AMORIS) followed up 175,000 Swedish men and women for 5.5 years and reported that decreased apo A1 was an independent predictor of CAD events. The AFCAPS/TexCAPS investigated lipid parameters among 6,605 men and women with average LDL-C and low HDL-C who were randomized to receive either lovastatin or placebo. This study also reported that levels of apo A1 and the apo B/apo A1 ratio were strong predictors of CAD events.
The Copenhagen City Heart Study was a prospective cohort study of 9,231 asymptomatic persons from the Danish general population. The apo B/apo AI ratio was reported to be an independent predictor of cardiovascular events, with an HR similar to that for TC/HDL-C. This study also compared the discriminatory ability of the apo B/apo AI ratio with that of traditional lipid measures, using the AUC for classifying cardiovascular events. The apo B/apo AI ratio had a slightly higher AUC than the TC/HDL-C ratio (0.59 vs. 0.58, respectively), but this difference was not statistically significant.

Clarke and colleagues published a prospective cohort study of 7,044 elderly men enrolled in the Whitehall Cardiovascular Cohort from London, England. Measurements of apolipoprotein levels were performed on 5,344 of these individuals, and patients were followed for a mean of 6.8 years. The authors reported that the apo B/apo AI ratio was also a significant independent predictor (HR=1.54; 95% CI: 1.27 to 1.87), with similar predictive ability as the TC/HDL ratio (HR=1.57; 95% CI: 1.32 to 1.86).

The addition of the apo B/apo AI ratio to the Framingham risk model resulted in a statistically significant improvement in predictive value for cardiovascular events (AUC, 0.594 vs. 0.613, respectively; p<001). However, the authors concluded that this increment in predictive value was likely to be of little clinical value. In this analysis, individuals with apo AI levels in the highest quartile had a decreased risk of cardiovascular events compared with those in the lowest quartile (adjusted odds ratio [OR]=0.62; 95% CI: 0.43 to 0.90).

Ridker and colleagues compared the predictive ability of apo AI and the apo B/apo AI ratio with standard lipid measurements. Measurements of apo AI and the apo B/apo AI ratio had similar predictive ability to standard lipid measurements but were no better. The HR for future cardiovascular events was 1.75 (95% CI: 1.30 to 2.38) for apo AI compared with 2.32 (95% CI: 1.64 to 3.33) for HDL-C. The HR for the ratio of apo B/apo AI was 3.01 (95% CI: 2.01 to 4.50) compared with an HR of 3.18 (95% CI: 2.12 to 4.75) for the ratio of LDL-C/HDL-C.

Some researchers have attempted to develop multivariate risk prediction models intended for clinical care, in which both traditional risk factors and apolipoprotein measures were included as potential predictors. Ridker and colleagues published the Reynolds Risk Score, based on data from 24,558 initially healthy women enrolled in the Women’s Health Study and followed for a median of 10.2 years. A total of 35 potential predictors of cardiovascular disease were considered potential predictors, and two final prediction models were derived. The first model was the best-fitting model statistically and included both apo B and the apo B/apo AI ratio as 2 of 9 final predictors. The second model, called the “clinically simplified model,” substituted LDL-C for apo B and TC/HDL-C for apo B/apo AI. The authors developed this simplified model “for the purpose of clinical application and efficiency” and justified replacing the apo B and apo B/apo AI measures as a result of their high correlation with traditional lipid measures (r=0.87 and 0.80, respectively).

Ingelsson and colleagues used data from 3,322 individuals in the Framingham Offspring Study to compare prediction models with traditional lipid measures to models that include apolipoprotein and other nontraditional lipid measures. This study reported that the apo B/apo AI ratio had similar predictive ability compared with traditional lipid ratios with respect to model discrimination, calibration, and reclassification. The authors also reported that the apo B/apo AI ratio did not provide any incremental predictive value over traditional measures.
A nested case-control study, performed within the larger European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) cohort study, evaluated the predictive ability of the apo B/apo A1 ratio in relation to traditional lipid measures. The EPIC-Norfolk study is a cohort study of 25,663 patients from Norfolk, U.K. The case-control substudy enrolled 869 patients who had developed CAD during a mean follow-up of 6 years and 1,511 control patients without CAD. The authors reported that the apo B/apo A1 ratio was an independent predictor of cardiovascular events after controlling for traditional lipid risk factors and the Framingham Risk Score (FRS; adjusted OR=1.85; 95% CI: 1.15 to 2.98). However, the authors also reported that this ratio was no better than the TC/HDL ratio for discriminating between cases and controls (AUC, 0.673 vs. 0.670, respectively; p=0.38).

**Apo A1 as a Treatment Target**

A number of studies have evaluated the utility of the apo B/apo A1 ratio as a marker of treatment response in RCTs of statin treatment. Kastelein and colleagues combined data from two RCTs, the TNT and IDEAL trials, to compare the relationship between response to lipids, apo B/apo A1 ratio, and other lipid measures. This analysis included 18,889 patients with established coronary disease randomized to low- or high-dose statin treatment. In pairwise comparisons, the ratio of apo B/apo A1 was a significant predictor of events (HR=1.24; 95% CI: 1.17 to 1.32) while the TC/HDL-C was not.

The PROVE-IT TIMI study randomized 4,162 patients with acute coronary syndrome (ACS) to standard statin therapy or intensive statin therapy. While the on-treatment ratio of apo B/apo A1 ratio was a significant predictor of cardiac events (HR for each standard deviation [SD] increment 1.10, 95% CI: 1.01 to 1.20), it was not superior to LDL-C (HR=1.20, 95% CI: 1.07 to 1.35) or the TC/HDL ratio (HR=1.12; 95% CI: 1.01 to 1.24) as a predictor of cardiac events.

Preliminary studies of infusions of reconstituted apo A1 have demonstrated plaque regression in a small number of patients with ACS. Based on this research, there is interest in developing synthetic apo A1 mimetic proteins, and such agents are in the drug development stage. These types of agents would likely target patients with residual cardiac risk following maximal statin therapy, especially patients with low HDL levels.

**Section Summary: Apolipoprotein A1**

The current evidence generally indicates that measurement of apo A1 and the apo B/apo A1 ratio, is as good as or better than currently used lipid measures such as LDL and HDL. Some experts have argued that the apo B/apo A1 ratio is superior to the LDL/HDL ratio as a predictor of cardiovascular risk and should supplement or replace traditional lipid measures as both a risk marker and a treatment target. However, there is substantial uncertainty regarding the degree of improvement that these measures provide. The evidence suggests that any incremental improvement in predictive ability over traditional measures is likely to be small and of uncertain clinical significance.

The use of apo A1 and the apo B/apo A1 ratio as a target of treatment response to statins may also be as good as or better than the traditional measure of LDL. However, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking apo A1 to clinical decision making, both in risk assessment and treatment response, are...
currently not available. Apo AI has not been incorporated into quantitative risk assessment models or treatment guidelines that can be used in clinical practice, such as the ATP III. The ATP III practice guidelines continue to tie clinical decision making to conventional lipid measures, such as TC, LDL-C, and HDL-C. Therefore, it is not yet possible to conclude that these measures improve outcomes or that they should be adopted in routine clinical care. There is continued interest in developing new therapeutic agents that raise HDL, and apo AI mimetics are currently in development for this purpose.

**Apolipoprotein E**

**Apo E as a Predictor of CVD**

A large body of research has established a correlation between lipid levels and the underlying APOE genotype. For example, in population studies, the presence of an apo e2 allele is associated with the lowest cholesterol levels and the apo e4 allele is associated with the highest levels.

Numerous studies have focused on the relationship between genotype and physiologic markers of atherosclerotic disease. A number of small- to medium-sized cross-sectional and case-control studies have correlated apo E with surrogate outcomes such as cholesterol levels, markers of inflammation, or carotid intima-media thickness. These studies have generally shown a relationship between apo E and these surrogate outcomes. Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of TC and LDL-C levels.

Some larger observational studies have correlated APOE genotype with clinical disease. The ARIC study followed up 12,000 middle-aged individuals free of CAD at baseline for 10 years. This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik and colleagues reported that APOE polymorphisms were associated with LDL levels and carotid intima-media thickness but were not predictive of incident CAD.

A meta-analysis published by Bennet and colleagues summarized the evidence from 147 studies on the association of APOE genotypes with lipid levels and cardiac risk. Eighty-two studies included data on the association of apo E with lipid levels, and 121 studies reported the association with clinical outcomes. The authors estimated that patients with the apo e2 allele had LDL levels that were approximately 31% less than those patients with the apo e4 allele. When compared with patients with the apo e3 allele, patients with apo e2 had an approximately 20% decreased risk for coronary events (OR=0.80; 95% CI: 0.70 to 0.90). Patients with the apo e4 had an estimated 6% higher risk of coronary events that was of marginal statistical significance (OR=1.06; 95% CI: 0.99 to 1.13).

**Apo E as a Predictor of Response to Therapy**

Apo E has been investigated as a predictor of response to therapy by examining apo E alleles in the intervention arm(s) of lipid-lowering trials. Some data have suggested that patients with an apo e4 allele may respond better to diet-modification strategies. Other studies have suggested that response to statin therapy may vary with APOE genotype and that the e2 allele indicates greater responsiveness to statins.
Chiodini and colleagues examined differential response to statin therapy according to APOE genotype, by reanalyzing data from the GISSI study according to APOE genotype. GISSI was an RCT comparing pravastatin with placebo in 3,304 Italian patients with previous myocardial infarction (MI). Patients with the apo e4 allele treated with statins had a greater response to treatment as evidenced by lower overall mortality (1.85% vs. 5.28%, respectively, p=0.023), while there was no difference in mortality for patients who were not treated with statins (2.81% vs. 3.67%, respectively, p=0.21). This study corroborated results reported previously but does not provide evidence that changes in treatment should be made as a result of APOE genotype.

In 2008, additional published studies were identified that evaluated APOE genetic status as a predictor of response to lipid-lowering therapy. Donnelly and colleagues reported on 1,383 patients treated with statins from the Genetics of Diabetes Audit and Research in Tayside, Scotland (Go-DARTS) database. The researchers reported on the final LDL levels and percentage of patients achieving target LDL according to APOE genetic status. LDL levels following treatment were lower for patients who were homozygous for apo e2 than for patients homozygous for apo e4 (0.6 ± 0.5 mmol/L vs. 1.7 ± 0.3 mmol/L, p<0.001). All patients who were homozygous for apo e2 reached their target LDL level compared with 68% of patients homozygous for apo e4 (p<0.001).

Vossen and colleagues evaluated response to diet and statin therapy by apo E status in 981 patients with CAD who were enrolled in a cardiac rehabilitation program. These authors reported that patients with an apo e4 allele were more responsive to both diet and statin therapy than were patients with an apo e2 allele. The overall response to treatment was more dependent on baseline LDL levels than APOE genetic status, with 30% to 47% of the variation in response to treatment explained by baseline LDL, compared with only 1% of the variation explained by APOE status.

**Section Summary: Apolipoprotein E**

The evidence suggests that APOE genotype may be associated with lipid levels and CAD but is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered a relatively poor predictor of CAD, especially compared with other established and emerging clinical variables and does not explain a large percent of the interindividual variation in TC and LDL levels. Moreover, apo E has not been incorporated into standardized cardiac risk assessment models and was not identified as one of the important “emerging risk factors” in the most recent ATP III recommendations.

The evidence on response to treatment indicates that APOE genotype may be a predictor of response to statins and may allow clinicians to better gauge an individual’s chance of successful treatment, although not all studies are consistent in reporting this relationship. At present, it is unclear how this type of information will change clinical management. Dietary modifications are a universal recommendation for those with elevated cholesterol or LDL levels, and statin drugs are the overwhelmingly preferred agents for lipid-lowering therapy. It is unlikely that a clinician will choose alternative therapies, even in the presence of an APOE phenotype that indicates diminished response.

None of the available evidence provides adequate data to establish that APOE genotype or phenotype improves outcomes when used in clinical care.
B-Type or Brain Natriuretic Peptide

The use of brain natriuretic peptide (BNP) levels for monitoring and managing established heart failure patients has been frequently studied and has demonstrated value. Studies on the use of BNP for determining cardiovascular risk in the asymptomatic population, however, are limited. In the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research [EISNER] study, Shaw and colleagues evaluated BNP and coronary artery calcium levels in 2,458 asymptomatic adults. BNP levels ranging from 40 to 99.9 and 100 pg/mL or higher had a 2.2 to 7.5 relative hazard for a cardiovascular event compared with BNP levels of less than 40 pg/mL (p<0.001). Other large population cohort studies have shown a relationship between elevations in BNP levels and future risks of cardiovascular events or heart failure. In a cohort study of 5,067, Melander and colleagues found adding CRP and BNP to a risk model of conventional factors increased the C statistic for cardiovascular events by 0.007 (p=0.04) and for coronary events by 0.009 (p =0.08). In a cohort study of 3,346 patients without heart failure, Wang and colleagues found BNP levels above the 80th percentile (20.0 pg/mL for men; 23.3 pg/mL for women) were associated with multivariable-adjusted HRs of 1.62 for death (p=0.02), 1.76 for a first major cardiovascular event (p=0.03), 1.91 for atrial fibrillation (p=0.02), 1.99 for stroke or transient ischemic attack (p=0.02), and 3.07 for heart failure (p=0.002). However, any gains over use of conventional risk factors appear to be minimal.

Section Summary: Brain Natriuretic Peptide

BNP levels appear to be associated with cardiovascular risks. However, no evidence was identified demonstrating that the use of BNP testing in clinical care improves outcomes.

Cystatin C

Ito and colleagues evaluated the value of adding cystatin C to FRS variables to predict CVD risk in 6,653 adults without clinical CVD from the Multi-Ethnic Study of Atherosclerosis. Cardiovascular risk prediction did not improve with the addition of cystatin C to FRSs. Lee and colleagues conducted a meta-analysis of 14 studies consisting of 22,509 participants from predominantly high cardiovascular risk patients to evaluate the relationship between elevated cystatin C levels and CVD risk. Higher levels of cystatin C were associated with greater risk of CVD (RR=2.62; 95% CI: 2.05 to 3.37; p<0.001), CHD (RR=1.72; 95% CI: 1.27 to 2.34; p<0.001), and stroke (RR=1.83; 95% CI: 1.12 to 3.00; p=0.02) after adjusting for known cardiovascular risk factors. In 2015, Luo and colleagues reported results of a meta-analysis of studies evaluating the role between cystatin C and cardiovascular and all-cause mortality in the general population. The study included nine prospective studies with a total of 39,854 patients. Across the six studies that reported cardiovascular mortality-specific outcomes, the pooled adjusted HR of cardiovascular mortality, comparing the highest and lowest cystatin C categories, was 2.74 (95% CI: 2.04 to 3.68; p=0.021).

Section Summary: Cystatin C

Several meta-analyses have reported that higher levels of cystatin C are associated with higher cardiovascular risk and higher risk of cardiovascular death. In contrast, in one large cohort, cystatin C did not improve risk prediction of CVD. No evidence was identified demonstrating that the use of cystatin C testing in clinical care improves outcomes.
Fibrinogen

Kenge and colleagues evaluated data from nine prospective, community-based cohorts from the British and Scottish general population-based health surveys. In the analysis of a total of 33,091 adults, of whom 1,006 had diabetes, fibrinogen was found to be positively associated with a higher risk of CVD by 34% (95% CI: 26% to 42%) and all-cause mortality by 30% (95% CI: 26% to 35%). The relationship with cardiovascular mortality and a higher fibrinogen produced HRs (95% CI) of 1.48 (1.21 to 1.81) in subjects with diabetes and 1.31 (1.23 to 1.39) in those without diabetes. The interaction between fibrinogen and CVD risk was not significantly different between the diabetic and nondiabetic populations (p=0.47). Despite improved predictive accuracy, the addition of fibrinogen to established risk factors was reported to not be clinically important.

In 2014, Willeit and colleagues reported results of a patient-level meta-analysis from 20 prospective studies to assess the association between a number of inflammatory markers, including fibrinogen, and atherosclerosis among patients without preexisting CVD. Included studies were prospective cohort studies from the PROG-IMT collaboration, which included participants from the general population and reported at least two visits with measurements of common carotid artery intima-media thickness (CCA-IMT) as a marker of preclinical atherosclerosis, along with at least one inflammatory marker (hsCRP, leukocyte count, and/or fibrinogen). Overall, the authors included 20 studies with 49,087 participants, of which 13 studies (35,096 participants) reported fibrinogen levels. In cross-sectional analysis, a 1 SD higher baseline fibrinogen level was associated with higher CCA-IMT (mean=0.0073 mm; 95% CI: 0.0047 to 0.0097; p<0.001). However, in longitudinal analysis, neither the baseline level of any of the inflammatory markers evaluated nor their progression was associated with progression of CCA-IMT.

Other studies have found an association between fibrinogen and cardiovascular risk including the EPIC-Norfolk cohort study and the Fibrinogen Studies Collaboration. In a report from the Fibrinogen Studies Collaboration, it was noted fibrinogen levels increased with age and were linked to established risk factors such as triglycerides, smoking and body mass index (BMI).

Section Summary: Fibrinogen

Reports from a number of cohort studies suggest that fibrinogen levels are associated with cardiovascular risk. However, no evidence was identified demonstrating that the use of fibrinogen testing in clinical care improves outcomes.

Leptin

Sattar and colleagues reported on a prospective study of 5,661 men and a systematic review of 7 prospective studies to evaluate the relationship between leptin and CVD. Leptin levels in the top third had an OR for CHD of 1.25 (95% CI: 0.96 to 1.62) compared with the bottom third. After adjusting for BMI, this decreased to 0.98 (95% CI: 0.72 to 1.34) suggesting any association of leptin with CVD is largely dependent upon BMI.

In 2014, Zeng and colleagues reported results of a meta-analysis of studies reporting the association between leptin levels and risk of CHD or stroke. The meta-analysis included 8 nested case-control studies with 1,980 patients and 11,567 controls. In pooled analysis, leptin levels were
significantly associated with pathogenic risk of CHD (OR=1.90; 95% CI: 1.06 to 3.43; p=0.032) and pathogenic risk of stroke (OR=2.14; 95% CI: 1.48 to 3.08; p<0.001).

Section Summary: Leptin

Two meta-analyses suggest that leptin levels are associated with CHD and stroke, although this association may be dependent on BMI. No evidence was identified demonstrating that the use of leptin testing in clinical care improves outcomes.

HDL Particle Size/Concentration

In the JUPITER RCT, 10,886 patients without CVD were randomized to rosvastatin or placebo and followed for a median of 2 years. Before randomization and 1 year after, levels of LDL-C, HDL-C, apo A1 and NMR-measured HDL size and HDL particle numbers were evaluated. Statistically significant changes in the median and 25th and 75th percentile values of HDL measures between baseline and year 1 values occurred in the rosvastatin and placebo groups for all levels (p<0.001) except for apo A1 and HDL particle size in the placebo group, which did not differ significantly (p=0.09 and 0.74, respectively). Changes in the rosvastatin group were all statistically significant compared with placebo for LDL-C, HDL-C, apo A1, and HDL particle size and number (p<0.001 for all). In the placebo group, inverse associations with CVD and HDL-C, apo A1, and HDL particle were seen. HDL particle number in the rosvastatin group had a greater association with CVD (HR=0.73, 95% CI: 0.57 to 0.93; p=0.01) than HDL-C (HR=0.82, 95% CI: 0.63 to 1.08; p=0.16) or apo A1 (HR=0.86, 95% CI: 0.67 to 1.10; p=0.22). This association remained after adjusting for HDL-C (HR=0.72, 95% CI: 0.53 to 0.97; p=0.03). HDL size was not significantly associated with CVD in risk-factor adjusted models.

Section Summary: HDL Particle Size/Concentration

One RCT has evaluated the association of HDL particle size and number as measured by NMR with residual CVD risk. While this study found an association with HDL particle (but not HDL size) and CVD, it is uncertain how NMR-measured HDL particle number would be used to change clinical management beyond information provided by traditional lipid measures. Therefore, there is no evidence that HDL size or HDL particle number measurement improves health outcomes.

LDL Subclass and LDL Particle Size/Concentration

LDL Subclass as an Independent Risk Factor for CVD

A nested case-control study from the Physician’s Health Study, a prospective cohort study of almost 15,000 men, investigated whether LDL particle size is an independent predictor of CAD risk, particularly compared with triglyceride levels. This study concluded that while LDL particle diameter was associated with risk of MI, this association was not present after adjustment for triglyceride level. Only triglyceride level was significant independently.

The Quebec Cardiovascular Study evaluated the ability of “nontraditional” lipid risk factors, including LDL size, to predict subsequent CAD events in a prospective cohort study of 2,155 men followed for 5 years. The presence of small LDL was associated with a 2.5 times increased risk for ischemic heart disease after adjustment for traditional lipid values, indicating a level of risk similar
to total LDL. This study also suggested an interaction in atherogenic risk between LDL size and apo B levels. In the presence of small LDL particles, elevated apo B levels were associated with a 6-fold increased risk of CAD, whereas when small LDL particles were not present, elevated apo B levels were associated with only a 2-fold increase in risk.

In 2005, Tzou and colleagues examined the clinical value of “advanced lipoprotein testing” in 311 randomly selected adults participating in the Bogalusa Heart Study. Advanced lipoprotein testing consisted of subclass patterns of LDL, i.e., the presence of large buoyant particles, intermediate particles, or small dense particles. These measurements were used to predict the presence of subclinical atherosclerosis, as measured ultrasonographically by carotid intimal-media thickness. In multivariate logistic regression models, substituting advanced lipoprotein testing for corresponding traditional lipoprotein values did not improve prediction of the highest quartile of carotid intimal-media thickness.

**LDL Subclass as a Predictor of Treatment Response**

Patients with subclass pattern B have been reported to respond more favorably to diet therapy than those with subclass pattern A. Subclass pattern B has also been shown to respond more favorably to the drugs gemfibrozil and niacin, with a shift from small, dense LDL particles to larger LDL particles. While statin drugs lower the overall concentration of LDL-C, there is no shift to the larger LDL particles.

Superko and colleagues reported that the response to gemfibrozil differed in patients with LDL subclass A compared with those with LDL subclass B. There was a greater reduction in the small LDL levels for patients with subclass B, but this did not correlate with clinical outcomes. Another study reported that atorvastatin treatment led to an increase in mean LDL size, while pravastatin treatment led to a decrease in LDL size.

These studies generally confirmed that small, dense LDL is impacted preferentially by fibrate treatment and possibly also by statin therapy. However, none of the studies demonstrated that preferentially targeting small, dense LDL leads to improved outcomes, compared with standard LDL targets that are widespread in clinical care.

Several trials with angiographic outcomes have examined the change in LDL particle size in relation to angiographic progression of CAD. The Stanford Coronary Risk Intervention Project (SCRIP) trial studied the relationship between small, dense LDL and the benefit of diet, counseling, and drug therapy in patients with CAD, as identified by initial coronary angiogram. Patients with subclass pattern B showed a significantly greater reduction in CAD progression than those with subclass pattern A. The Familial Atherosclerosis Treatment Study (FATS) randomized patients from families with premature CAD and elevated apo B levels. Change in LDL particle size correlated significantly with angiographic progression of CAD in this study. Fewer studies have evaluated clinical outcomes in relation to LDL particle size. In the Cholesterol and Recurrent Events (CARE) trial, survivors of MI with normal cholesterol levels were randomly assigned to lipid-lowering therapy or placebo. A post hoc analysis from this trial failed to demonstrate a correlation between change in particle size and treatment benefit.
Measurement of LDL Particle Size and Concentration by NMR

Similar to small dense lipoprotein particles, several epidemiologic studies have shown that the lipoprotein particle size and concentration measured by NMR is also associated with cardiac risk. For example, data derived from the Cardiovascular Health Study, Women’s Health Study, and PLAC-1 trial suggest that the number of LDL particles is an independent predictor of cardiac risk. Translating these findings into clinical practice requires setting target values for lipoprotein number. Proposed target values have been derived from the same data set (i.e., Framingham study) that was used to set the ATP III target goals for LDL-C. For example, the ATP III targets for LDL-C correspond to the 20th, 50th, and 80th percentile values in the Framingham Offspring Study, depending on the number of risk factors present. Proposed target goals for lipoprotein number correspond to the same percentile values, and LDL particle concentrations corresponding to the 20th, 50th, and 80th percentile are 1,100 nmol/L, 1,400 nmol/L, and 1,800 nmol/L, respectively.

Mora and colleagues evaluated the predictive ability of LDL particle size and number measured by NMR in participants of the Women’s Health Study, a prospective cohort study of 27,673 women followed over an 11-year period. After controlling for nonlipid factors, LDL particle number was a significant predictor of incident CVD, with an HR of 2.51 (95% CI: 1.91 to 3.30) for the highest compared with the lowest quintile. LDL particle size was similarly predictive of cardiovascular risk, with an HR of 0.64 (95% CI: 0.52 to 0.79). When compared with standard lipid measures and apolipoproteins, LDL particle size and number showed similar predictive ability but were not superior in predicting cardiovascular events.

Rosenson and Underberg conducted a systematic review of studies on lipid-lowering pharmacotherapies in 2013 to evaluate changes in LDL particles pre- and post-treatment. Reductions in mean LDL particles occurred in 34 of the 36 studies evaluated. Percentage reductions of LDL particles in several statin studies were smaller than reductions in LDL-C. LDL particles and apo B changes were comparable in studies. The authors suggested the differences in LDL particle reductions with different lipid-lowering therapies demonstrate potential areas of residual cardiovascular risk which can be addressed with LDL particle monitoring.

In 2014, Toth and colleagues analyzed LDL-C and LDL particle levels and cardiovascular risk using commercial insurance and Medicare claims data on 15,569 high-risk patients form the HealthCore Integrated Research Database (HIRD). For each 100 nmol/L increase in LDL particle level, there was a 4% increase in risk of a CHD event (HR=1.04; 95% CI: 1.02 to 1.05; p<0.000). A comparative analysis, using 1:1 propensity score matching of 2,094 patients from the LDL-C target cohort (LDL-C level less than 100 mg/dL without a LDL particle level) and a LDL particle target cohort (LDL particle less than 1000 nmol/L and LDL-C of any level) found a lower risk of CHD or stroke in patients who received LDL particle measurement and were presumed to have received more intensive lipid-lowering therapy (HR=0.76; 95% CI: 0.61 to 0.96; at 12 months). A comparison of smaller LDL particle target groups at 24 (n=1242) and 36 (n=705) months showed similar reductions in CHD and stroke (HR=0.78, 95% CI: 0.62 to 0.97; and HR=0.75; 95% CI: 0.58 to 0.97; respectively).

Section Summary: LDL Subclass and LDL Particle Size/Concentration

Small LDL size is one component of an atherogenic lipid profile that also includes increased triglycerides, increased apo B, and decreased HDL. Some studies have reported that LDL size is an
independent risk factor for CAD, and others have reported that a shift in LDL size may be a useful marker of treatment response. However, the direct clinical application of measuring small, dense lipoprotein particles is still unclear. To improve outcomes, clinicians must have tools to translate this information into clinical practice. Such tools for linking levels of small, dense LDL to clinical decision making, both in risk assessment and treatment response, are currently not available. Published data are inadequate to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial patient outcomes.

A relatively small number of studies have evaluated the predictive ability of LDL particle size and number as measured by NMR. These studies do not demonstrate that NMR-measured particle size and/or number offer additional predictive ability beyond that provided by traditional lipid measures. NMR measures have been proposed as indicators of residual cardiovascular risk in patients treated with statins who have met LDL goals, but there is no evidence that these measures improve health outcomes when used for this purpose.

**Lipoprotein A**

**Lipoprotein A as a Predictor of Cardiovascular Risk**

Numerous prospective RCTs, cohort studies, and systematic reviews have evaluated lipoprotein (a) (Lp[a]) as a cardiovascular risk factor. The following are representative prospective trials drawn from the extensive literature on this topic.

The Emerging Risk Factors Collaboration published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154,544 individuals. Risk prediction was examined for a variety of traditional and non-traditional lipid markers. For Lp(a), evidence from 24 studies on 133,502 individuals reported that Lp(a) was an independent risk factor for reduced cardiovascular risk, with an adjusted HR for cardiovascular events of 1.13 (95% CI: 1.09 to 1.18). The addition of Lp(a) to traditional risk factors resulted in a small improvement in risk prediction, with an increase in the C statistic of approximately 0.002. A reclassification analysis found no significant improvement in the net reclassification index (0.05%, 95% CI: -0.59 to 0.70).

A systematic review by Genser and colleagues included 67 prospective studies on 181,683 individuals that evaluated the risk of CVD associated with Lp(a). Pooled analysis was performed on 37 studies that reported the endpoints of cardiovascular events. When grouped by design and populations, the relative risks for these studies, comparing the uppermost and lowest strata of Lp(a), ranged from 1.64 to 2.37. The RR for cardiovascular events was higher in patients with previous CVD compared with patients without previous disease. There were no significant associations found between Lp(a) levels, overall mortality, or stroke.

The Lipid Research Clinics (LRC) Coronary Primary Prevention Trial, one of the first large-scale RCTs of cholesterol-lowering therapy, measured initial Lp(a) levels and reported that Lp(a) was an independent risk factor for CAD when controlled for other lipid and non-lipid risk factors. As part of the Framingham Offspring Study, Lp(a) levels were measured in 2,191 asymptomatic men between the ages of 20 and 54 years. After a mean follow-up of 15 years, there were 129 CHD events, including MI, coronary insufficiency, angina, or sudden cardiac death. Comparing the Lp(a) levels of these patients with the other participants, the authors concluded that elevated Lp(a) was an
independent risk factor for the development of premature CHD (i.e., before age 55 years). The ARIC study evaluated the predictive ability of Lp(a) in 12,000 middle-aged individuals free of CAD at baseline who were followed up for 10 years. Lp(a) levels were significantly higher among patients who developed CAD than among those who did not, and Lp(a) levels were an independent predictor of CAD above traditional lipid measures.

Several RCTs on lipid-lowering therapies have found Lp(a) is associated with residual cardiovascular risk. In a subgroup analysis of 7,746 white patients from the JUPITER study, median Lp(a) levels did not change in either group of patients randomized to treatment with rosuvastatin or placebo during a median 2-year follow-up. Lp(a) was independently associated with a residual risk of CVD despite statin treatment (adjusted HR=1.27; 95% CI: 1.01 to 1.59; p=0.04). The LIPID RCT93 randomized 7,863 patients to pravastatin or placebo. Patients were followed for a median of 6 years. Lp(a) concentrations did not change significantly at 1 year. Baseline Lp(a) concentration was associated with total CHD events (p<0.001), total CVD events (p=0.002), and coronary events (p=0.03). In the AIM-HIGH study, Lp(a) levels in 1,440 patients at baseline and on simvastatin plus placebo or simvastatin plus extended-release niacin were significantly predictive of cardiovascular events with HRs ranging from 1.18 to 1.25.

Kamstrup and colleagues analyzed data from the Copenhagen City Heart Study, which followed up 9,330 individuals from the Copenhagen general population over a period of 10 years. This study reported a graded increase in risk of cardiac events with increasing Lp(a) levels. At extreme levels of Lp(a) above the 95\textsuperscript{th} percentile, the adjusted HR for MI was 3.6 (95% CI: 1.7 to 7.7) for women and 3.7 (95% CI: 1.7 to 8.0) in men. Tzoulaki and colleagues reported data from the Edinburgh Artery Study, which was a population cohort study that followed 1,592 individuals for a mean of 17 years. These authors reported that Lp(a) was an independent predictor of MI, with an OR of 1.49 (95% CI: 1.0 to 2.2) for the highest one-third versus the lowest one-third.

Zakai and colleagues evaluated 13 potential biomarkers for independent predictive ability compared to established risk factors, using data from 4,510 individuals followed up for 9 years in the Cardiovascular Health Study. Lp(a) was 1 of 7 biomarkers that had incremental predictive ability above established risk factors. The adjusted HR for each standard deviation increase in Lp(a) was 1.07 (95% CI: 1.0 to 1.12).

Some studies, however, have failed to demonstrate such a relationship. In the Physicians’ Health Study, initial Lp(a) levels in the 296 participants who subsequently experienced MI were compared with Lp(a) levels in matched controls who remained free from CAD. The authors found that the distribution of Lp(a) levels between the groups was identical. The European Concerted Action on Thrombosis and Disabilities (ECAT) study, a trial of secondary prevention, evaluated Lp(a) as a risk factor for coronary events in 2,800 patients with known angina pectoris. In this study, Lp(a) levels did not differ significantly among patients who did and did not have subsequent events, suggesting that Lp(a) levels were not useful risk markers in this population.

Some researchers have hypothesized that there is a stronger relationship between Lp(a) and stroke than for CHD. Similar to the situation with cardiac disease, most prospective studies have indicated that Lp(a) is an independent risk factor for stroke. In one prospective cohort study, Rigal and colleagues reported that an elevated Lp(a) level was an independent predictor of ischemic stroke in men (OR=3.55; 95% CI: 1.33 to 9.48) but not in women (OR=0.42; 95% CI: 0.12 to 1.26). In the ARIC
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prospective cohort study of 14,221 participants, elevated Lp(a) was a significant independent predictor of stroke in black women (RR=1.84; 95% CI: 1.05 to 3.07) and white women (RR=2.42; 95% CI: 1.30 to 4.53) but not in black men (RR=1.72; 95% CI: 0.86 to 3.48) or white men (RR=1.18; 95% CI: 0.47 to 2.90).

There also may be a relationship between Lp(a) as a cardiovascular risk factor and hormone status in women. Suk Danik and colleagues reported the risk of a first cardiovascular event over a 10-year period in 27,736 women enrolled in the Women’s Health Study. After controlling for standard cardiovascular risk factors, Lp(a) was an independent predictor of risk in women who were not taking hormonal replacement therapy (HR=1.77; 95% CI: 1.36 to 2.30; p<0.001). However, for women who were taking hormonal replacement therapy, Lp(a) levels were not a significant independent predictor of cardiovascular risk (HR=1.13; 95% CI: 0.84 to 1.53; p=0.18).

Several meta-analyses have also examined the relationship between Lp(a) levels and cardiovascular risk. Bennet and colleagues synthesized the results of 31 prospective studies with at least 1 year of follow-up and that reported data on cardiovascular death and nonfatal MI. The combined results revealed a significant positive relationship between Lp(a) and cardiovascular risk, with an OR for patients with Lp(a) in the top-third compared with those in the bottom-third of 1.45 (95% CI: 1.32 to 1.58). This analysis reported a moderately high degree of heterogeneity in the included studies (I²=43%), reflecting the fact that not all studies reported a significant positive association.

Smolders and colleagues summarized evidence from observational studies on the relationship between Lp(a) and stroke. Five prospective cohort studies and 23 case-control studies were included in this meta-analysis. Results from prospective cohort studies showed that Lp(a) added a modest amount of incremental predictive information (for the highest one-third of Lp(a), combined RR=1.22; 95% CI: 1.04 to 1.43). From case-control studies, an elevated Lp(a) level was also associated with an increased risk of stroke (combined OR=2.39; 95% CI: 1.57 to 3.63).

A patient-level meta-analysis of 36 prospective studies published between 1970 and 2009 included 126,634 participants. Overall, the independent association of Lp(a) with vascular disease was consistent across studies but modest in size. The combined RR, adjusted for age, sex and traditional lipid risk factor, was 1.13 (95% CI: 1.09 to 1.18) for CHD and 1.10 (95% CI: 1.02 to 1.18) for ischemic stroke. There was no association of Lp(a) levels and mortality.

Genetic studies have examined the association of various genetic loci with Lp(a) levels, and Mendelian randomization studies have examined whether Lp(a) is likely to be causative for CAD. In one such study, there were three separate loci identified for increased Lp(a) levels. Genetic variants were identified at two of these loci that were independently associated with coronary disease (OR=1.70; 95% CI: 1.49 to 1.95; and OR=1.92; 95% CI: 1.48 to 2.49). This finding strongly implies that elevated Lp(a) levels are causative of coronary disease, as opposed to simply being associated.

**Lipoprotein A as Treatment Target**

There is a lack of evidence to determine whether Lp(a) can be used as a target of treatment. Several randomized studies of lipid-lowering therapy have included measurements of Lp(a) as an intermediate outcome measurement. While these studies have demonstrated that Lp(a) levels are
reduced in patients receiving statin therapy, the data are inadequate to demonstrate how this laboratory test can be used to improve patient management.

**Section Summary: Lipoprotein A**

A large amount of epidemiologic evidence has determined that Lp(a) is an independent risk factor for CVD. The overall degree of risk associated with Lp(a) levels appears to be modest, and the degree of risk may be mediated by other factors such as LDL levels and/or hormonal status. There is considerable uncertainty regarding the clinical utility of measuring Lp(a), specifically how knowledge of Lp(a) levels can be used in clinical care of patients who are being evaluated for lipid disorders. There is scant evidence on the use of Lp(a) as a treatment target for patients with hyperlipidemia. The available evidence is insufficient related to impact on clinical outcomes.

**Summary of Evidence**

The evidence for the use of non-traditional lipid and other biomarker measurements including apo B, apo A1, apo E, lipoprotein A, subclasses of LDL and HDL, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin, in individuals who are asymptomatic with risk for CVD includes systematic reviews, meta-analyses, and large, prospective cohort studies that have evaluated the association of these lipid and other markers with cardiovascular outcomes. Relevant outcomes are overall survival, other test performance measures, change in disease status, morbid events, and medication use. Evidence from cohort studies and meta-analyses of these studies suggests that some of these markers are associated with increased cardiovascular risk and may provide some incremental accuracy in risk prediction. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established that the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of nontraditional lipid and other biomarker measurements, including apo B, apo Al, lipoprotein (a), subclasses of LDL and HDL, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin, in individuals with hyperlipidemia managed with lipid-lowering therapy includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are overall survival, change in disease status, morbid events, and medication use. In particular, apo B, apo Al, and apo E have been evaluated as markers of success of lipid-lowering treatment success, and evidence from the intervention arms from several randomized controlled trials suggests that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
Practice Guidelines and Position Statements

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute’s (NHLBI’s) National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) issued a position statement in 2001. Apo B, apo AI, lipid subclass, and lipoprotein (a) were listed as “emerging risk factors” for cardiovascular risk assessment, without specific recommendations for how these measures should be used in clinical practice. A 2004 update to these guidelines discussed the result of clinical trials of statin therapy.

In 2013, NHLBI published a systematic evidence review from the Cholesterol Expert Panel on managing blood cholesterol in adults. The review was used to develop joint guidelines by the American College of Cardiology and American Heart Association (ACC/AHA) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (see below).

American College of Cardiology and American Heart Association

ACC/AHA published guidelines in 2013 for the assessment of cardiovascular risk. Pooled cohort equations for estimating arteriosclerotic cardiovascular disease (ASCVD) were developed from sex- and race-specific proportional hazards models that included covariates of age, treated or untreated systolic blood pressure level, total cholesterol and HDL cholesterol levels, current smoking status, and history of diabetes. Additional risk factors evaluated included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease, and body mass index. None of these variables significantly improved discrimination for 10-year hard ASCVD risk prediction. Further research using state of the art statistical techniques (including net reclassification improvement and integrative discrimination index) are needed to examine the utility of novel biomarkers when added to these new pooled cohort equations in different populations and patient subgroups.

European Society of Cardiology et al

The 2012 guidelines on cardiovascular disease prevention from the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice indicate that apo B can be a substitute for LDL cholesterol, but its use does not improve risk assessment and apo B is not readily available. The use of lipoprotein (a) is not justified as a treatment target or for screening the general population.

American Diabetes Association and American College of Cardiology Foundation

In 2008, a publication from a consensus conference of the American Diabetes Association and the American College of Cardiology addressed lipoprotein management in patients with cardiometabolic risk. These guidelines included specific recommendations for incorporating apo B testing into clinical care for high-risk patients and recommended that, for patients with metabolic syndrome who are being treated with statins, both LDL-C and apo B should be used as treatment targets, with an apo B target of less than 90 mg/dL, even if target LDL has been achieved.

This consensus statement also commented on the use of LDL particle number in patients with cardiometabolic risk and on the limitations of the clinical utility of NMR measurement of LDL
particle number or size, including lack of widespread availability. They also mentioned that there is a need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.

**Canadian Cardiovascular Society**

A Canadian task force has also endorsed use of apo B as a treatment target and proposed a target apo B level of 90 mg/dL. These guidelines also recommended that a lipoprotein (a) concentration greater than 30 mg/dL with elevated LDL or other major risk factors may indicate the need for earlier and more intensive therapy to lower the LDL-C level. These guidelines were updated in 2006.

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force issued recommendations in 2009 on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD). They included lipoprotein (a) in its summary statement: “The evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events.”

**Medicare National Coverage**

There is no national coverage determination (NCD).

V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes § 432E-1.4), generally accepted standards of medical practice, and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA consider the application of this Medical Policy to the case at issue.

VI. References

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