invasive procedure. Just as in the case of "exertional angina", the root cause of acute coronary syndromes is atherosclerotic plaque in the coronary arterial vasculature.

Accordingly, the initiation and progression of atherosclerotic plaques are the root cause of the clinical manifestations of atherosclerotic CAD and CHD. Thus, there remains a need for improved diagnostic methods for detecting an atherosclerotic plaque and for diagnosing atherosclerotic CAD.

SUMMARY

The disclosure provides non-invasive methods for evaluating a human subject for having atherosclerotic coronary artery disease (ASCAD) or as having a coronary atherosclerotic plaque. ASCAD includes, for example, atherosclerosis. The methods include measuring the levels of each analyte within a panel of analyte biomarkers in a biological sample obtained from a subject, wherein the panel of analyte biomarkers is selected from the group consisting of:

(i) a panel of biomarkers comprising valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose;

(ii) a panel of biomarkers comprising acisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide;

(iii) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose;

(iv) a panel of biomarkers comprising glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE;

(v) a panel of biomarkers comprising o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate;

(vi) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate);

(vii) a panel of biomarkers comprising N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated);

(viii) a panel of biomarkers comprising N.acetylglycine and 3.ethylphenylsulfate;

(viv) a panel of biomarkers comprising serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate;

(x) a panel of biomarkers comprising acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate;

(xi) a panel of biomarkers comprising N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate and salicylate;

(xii) a panel of biomarkers comprising asparagine, taurine, acisoga, 1.oleoylglycerol (18:1), cholesterol and 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid and propionylglycine (C3), wherein the levels, including relative levels, or the occurrences of the plurality of analyte biomarkers are indicative of having ASCAD and/or for the presence of a coronary atherosclerotic plaque.

In one aspect, there is provided a method for evaluating a human subject for having atherosclerotic coronary artery disease (ASCAD) or as having a coronary atherosclerotic plaque, the method comprising:

measuring the levels of each analyte within a panel of analyte biomarkers in a biological sample that has been obtained from a subject, wherein the panel of analyte biomarkers is selected from the group consisting of:

(i) a panel of biomarkers comprising valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose;

(ii) a panel of biomarkers comprising acisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide;

(iii) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose;

(iv) a panel of biomarkers comprising glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE;

(v) a panel of biomarkers comprising o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate;

(vi) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate);

(vii) a panel of biomarkers comprising N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated);

(viii) a panel of biomarkers comprising N.acetylglycine and 3.ethylphenylsulfate;

(viv) a panel of biomarkers comprising serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate;

(x) a panel of biomarkers comprising acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate;

(xi) a panel of biomarkers comprising N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate and salicylate;

(xii) a panel of biomarkers comprising asparagine, taurine, acisoga, 1.oleoylglycerol (18:1), cholesterol, 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid and propionylglycine (C3);

comparing the measured levels of the analytes in the biological sample with one or more reference samples, wherein the references are representative of matched human subjects; and

identifying the subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque if measured levels of the analytes in the biological sample are increased or decreased relative to the amounts of the analytes in the reference samples.

Any of the panels above may further include the analysis of age and gender.

In another embodiment, the disclosure provides a method comprising measuring by mass spectrometry the levels of each of a plurality of metabolites in a blood sample obtained from a human subject, wherein the plurality of metabolites is selected from the group consisting of (i) valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose; (ii) cisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide; (iii) N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose; (iv) glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE; m(v) o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate; (vi) N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate); (vii) N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated); (viii) N.acetylglycine and 3.ethylphenylsulfate; (viv) serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate; (x) acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate; (xi) N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate, salicylate; and(xii) asparagine, taurine, acisoga, 1.oleoylglycerol

(18:1), cholesterol, 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid, and propionylglycine (C3).

In one embodiment, the disclosure provides methods for evaluating a human subject for having ASCAD or as having a coronary atherosclerotic plaque which comprises measuring the levels of each analyte within a panel of analyte biomarkers in a biological sample obtained from a subject, wherein the panel of analyte biomarkers is selected from the group consisting of:

(xiii) a panel of biomarkers comprising valylleucine, isoleucylvaline, glutamine-leucine, X-12212, glucuronate and glutamate;

(xiv) a panel of biomarkers comprising glucose, gamma-glutamyl transferase, uric acid, low density lipoprotein cholesterol, triglycerides, lipoprotein (a) mass , alkaline phosphatase, and apolipoprotein B;

(xv) a panel of biomarkers comprising glutamate, X-16132, isoleucylalanine, isoleucylphenylalanine, lipoprotein (a) mass, small dense low density lipoprotein cholesterol, X-12212. ADSGEGDFXAEGGGVR (SEQ ID NO: 1), glutamine, leucine, and threonylleucine;

(xv1) a panel of biomarkers comprising CER22.1, HexCER18:1, TG15:0, SM16:0, CER20:0, DHC20:1, and CER18:0;

(xvii) a panel of biomarkers comprising CER20:0, apolipoprotein B, SM16:0, lipoprotein (a) mass, DHC20L1, alkaline phosphatase, and CER18:0;

(xviii) a panel of biomarkers comprising glutamate, X-16132, isoleucylalanine, Lipoprotein (a) mass, X-12212, and glutamine-leucine;

(xix) a panel of biomarkers comprising oleic2, N-terminal pro-brain natriuretic peptide, lipoprotein (a) mass, insulin, glycated hemoglobin A1C, cismontaotl, small dense low density lipoprotein cholesterol, behenic2, adiponectin, and gamma-glutamyl transferase;

(xx) a panel of biomarkers comprising isoleucylalanine, glucuronate, glycine, isoleucylphenylalanine, mannose, X-21452, 1-oleoylglycerophosphoglycerol, X-21335, 7-methylxanthine, X-12729, acisoga, alpha-hydroxyisovaleroyl carnitine, 2-aminoadipate, X-18914, tigloylglycine, and pyridoxal;

(xxi) a panel of biomarkers comprising isoleucylalanine, glycine, isoleucylphenylalanine, oleic2, X-21335, methylxanthine, aminoadipate, mannose, acisoga, arachidonoyl.GPE.20.4, and triglycerides;

(xxii) a panel of biomarkers comprising DHC18:0, DG18:1n9, total diacylglycerol, TG20:3n9, CE20:4n6, CER18:1, DHC20:1, CE18:2n6, PL18:2n6, SM18:0, FA14:1n5, PL15:0, and CE16:0;

(xxiii) a panel of biomarkers comprising glycated hemoglobin A1C, total diacylglycerol, cismontotl, lipoprotein (a) mass, TG20.3n9, oleic2, DHC18.1, N-terminal pro-brain natriuretic peptide, gamma-glutamyl transferase, and CER18;

(xxiv) a panel of biomarkers comprising isoleucylalanine, glycine, cismontotl, lipoprotein (a) mass, X-21452, isoleucylphenylalanine, glycated hemoglobin A1C, X-21335, X7.methylxanthine, acisoga and X-12729; wherein the levels, including relative levels, or the occurrences of the plurality of analyte biomarkers are indicative of having atherosclerotic coronary artery disease (ASCAD) or the presence of a coronary atherosclerotic plaque.

Also provided in aspects of the disclosure are panels of biomarkers useful for evaluating a human subject for having ASCAD or as having a coronary atherosclerotic plaque. By a "panel of biomarkers" it is meant a collection, or combination, of two or more molecular entities, e.g. two, three, four, five, or more than five entities, whose representation in a sample is associated with ASCAD or a coronary atherosclerotic plaque. The panel of biomarkers described herein may be used to diagnose ASCAD or identify the presences of a coronary atherosclerotic plaque., to provide a prognosis to a patient having ASCAD or a coronary atherosclerotic plaque, to provide a prediction of the responsiveness of a patient with ASCAD or a coronary atherosclerotic plaque to a medical therapy, to monitor a patient having ASCAD or a coronary atherosclerotic plaque, to treat a patient having ASCAD or a coronary atherosclerotic plaque, etc.

In some embodiments, the methods further comprise of performing a comparison between the measured levels of the analytes in the biological sample with one or more reference samples, said references being representative of matched (e.g., age, gender, etc.) human subjects.

In some embodiments, the methods further include identifying a subject as having ASCAD or as having a coronary atherosclerotic plaque if the measured levels of the analytes in the biological sample are increased or decreased relative to the amounts of the analytes in the reference samples.

In some embodiments, the methods include instructing a healthcare professional (e.g., a physician, physician assistant, nurse practitioner, nurse and case

manager) to complete a non-invasive cardiovascular evaluation on a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque. The further non-invasive cardiovascular evaluation can confirm whether the subject has or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque.

In some embodiments, the methods further comprise of performing a non-invasive cardiovascular evaluation on a subject identified as having ASCAD or as having a coronary atherosclerotic plaque to confirm the subject does or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque. The non-invasive cardiovascular evaluation can be a procedure selected from the group consisting of cardiovascular computed tomography (CT) imaging, an exercise stress test, a pharmacologic stress test, myocardial perfusion imaging, stress echocardiography, and cardiovascular magnetic resonance imaging.

In yet another embodiment, the methods further comprise selectively administering a composition comprising an effective amount of a therapeutic agent to a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to treat the subject, wherein the therapeutic agent is selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, PCSK9 inhibitor, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin.

In one aspect, there is provided use of a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin in the manufacture of a medicament for treating atherosclerotic coronary artery disease or coronary atherosclerotic plaque in a subject that has been identified by the method of any one of claims 1-3 as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque.

For subjects identified as having ASCAD or as having a coronary atherosclerotic plaque, the methods may further comprise selecting a treatment plan for a subject. For example, the methods may further comprise selecting a treatment plan for a subject, which comprises selectively administering a composition comprising an effective amount of a therapeutic agent, and/or performing a non-invasive cardiovascular evaluation, which comprises, for example, performing a procedure selected from the group consisting of cardiovascular computed tomography (CT) imaging, an exercise stress test, a pharmacologic stress test, myocardial perfusion imaging, stress echocardiography, and cardiovascular magnetic resonance imaging. The treatment plan can comprise prescribing to the subject therapeutic lifestyle changes to improve cardiovascular health.

In some embodiments, the level of each analyte is measured using mass spectrometry (MS) analysis. The MS analysis method can be liquid chromatography-tandem mass spectrometry (UPLC-MS/MS), chromatography-mass spectrometry (GC-MS), or nuclear magnetic resonance (NMR).

In some embodiment, the methods disclosed herein further comprise selecting a subject identified as having ASCAD or as having a coronary atherosclerotic plaque for treatment. In some embodiments, the treatment comprises selectively administering a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, PCSK9 inhibitors, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin to a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to treat the subject. In some embodiments, the treatment comprises performing a non-invasive cardiovascular evaluation on a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to confirm whether the subject does or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque. In some embodiments, the treatment plan comprises prescribing therapeutic lifestyle changes to improve cardiovascular health.

The disclosure also provides a kit for evaluating a human subject for having ASCAD or as having a coronary atherosclerotic plaque. The kits include reagents suitable for determining levels of a plurality of analytes in a test sample (.e.g., reagents suitable for determining levels of the metabolomic biomarkers disclosed herein); optionally one or more control samples comprising predetermined levels of the same analytes, wherein comparison of the levels of the analytes in a test sample with levels in the control samples identifies a subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque; and instructions for use of the kit in the method described herein.

In one aspect, there is provided a kit for evaluating a human subject for having atherosclerotic coronary artery disease (ASCAD) or as having a coronary atherosclerotic plaque, the kit comprising:

reagents suitable for determining levels of a plurality of analytes in a test sample, wherein the plurality of analytes comprise:

(i) a panel of biomarkers comprising valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose;

(ii) a panel of biomarkers comprising acisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide;

(iii) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose;

(iv) a panel of biomarkers comprising glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE;

(v) a panel of biomarkers comprising o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate;

(vi) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate);

(vii) a panel of biomarkers comprising N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated);

(viii) a panel of biomarkers comprising N.acetylglycine and 3.ethylphenylsulfate;

(viv) a panel of biomarkers comprising serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate;

(x) a panel of biomarkers comprising acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate;

(xi) a panel of biomarkers comprising N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate and salicylate;

(xii) a panel of biomarkers comprising asparagine, taurine, acisoga, 1.oleoylglycerol (18:1), cholesterol, 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid and propionylglycine (C3);

optionally one or more control samples comprising predetermined levels of the same analytes, wherein comparison of the levels of the analytes in a test sample with levels in the control samples identifies a subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque; and

instructions for use of the kit in the method of the disclosure.

As used herein, the term "biological sample" or "sample" refers to a sample obtained or derived from a subject. By way of example, the sample may be selected from the group consisting of body fluids, blood, whole blood, plasma, serum, mucus secretions, urine or saliva. In some embodiments the sample is, or comprises a blood

artery disease or as having a coronary atherosclerotic plaque. Preferably, the clinical record is stored in a computer readable medium.

A summary of the relevant analysis models described herein are provided below:

a. Atherosclerosis in Native CAD - A^{nCAD}
    i. Significant in Fasting & Non-Fasting Combined - A_{FNF}^{nCAD}
    ii. Independently Significant in Fasting and Non-Fasting - A_{IFNF}^{nCAD}
    iii. Significant in Fasting - A_{F}^{nCAD}
b. Atherosclerosis in All CAD (including revascularization) - A^{aCAD}
    i. Significant in Fasting & Non-Fasting Combined - A_{FNF}^{aCAD}
    ii. Independently Significant in Fasting and Non-Fasting - A_{IFNF}^{aCAD}
    iii. Significant in Fasting - A_{F}^{aCAD}
c. 50% stenosis in Native CAD
    i. Significant in Fasting & Non-Fasting Combined - S_{FNF}^{nCAD}
    ii. Independently Significant in Fasting and Non-Fasting - S_{IFNF}^{nCAD}
    iii. Significant in Fasting - S_{F}^{nCAD}
d. 50% stenosis in ALL CAD (including revascularization)
    i. Significant in Fasting & Non-Fasting Combined - S_{FNF}^{aCAD}
    ii. Independently Significant in Fasting and Non-Fasting - S_{IFNF}^{aCAD}
    iii. Analytes Significant in Fasting - S_{F}^{aCAD} .

The section headings used herein are for organizational purposes only and are not to be construed as limiting the described subject matter in any way. When definitions of terms in incorporated references appear to differ from the definitions provided in the present teachings, the definition provided in the present teachings shall control. It will be appreciated that there is an implied "about" prior to metrics such as temperatures, concentrations, and times discussed in the present teachings, such that slight and insubstantial deviations are within the scope of the present teachings herein. In this application, the use of the singular includes the plural unless specifically stated otherwise. Also, the use of "comprise," "comprises," "comprising," "contain," "contains," "containing," "include," "includes," and "including" are not intended to be limiting. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure. The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the

article. By way of example, "an element" means one element or more than one element.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is a graph demonstrating a box plot of Diamond Forrester Score by clinical group.

Figure 2 is a graph demonstrating a ROC curve for Diamond Forrester Score and Native CAD (AUC = 0.5; Threshold = inf; Sensitivity = 0; Specificity = 1; Accuracy = 0.57).

Figure 3 is a graph demonstrating a box plot of Morise Score by clinical group.

Figure 4 is a graph demonstrating a ROC curve for Morise Score of Native CAD (AUC = 0.58; Threshold = 20; Sensitivity = 0.04; Specificity = 0.98; Accuracy = 0.58).

Figure 5 is a graph demonstrating a ROC curve for the Clinical Model of Native CAD (AUC = 0.79; Threshold = 0.5; Sensitivity = 0.49; Specificity = 0.9; Accuracy = 0.73).

Figure 6 is a series of graphs that provide Partial Dependence Plots for the eleven clinical variables for Clinical Model of Native CAD.

Figure 7 is a graph demonstrating a ROC curve for the Metabolomic Model of Native CAD (AUC = 0.78; Threshold = 0.39; Sensitivity = 0.82; Specificity = 0.64; Accuracy = 0.72).

What is claimed is:

1. A method for evaluating a human subject for having atherosclerotic coronary artery disease (ASCAD) or as having a coronary atherosclerotic plaque, the method comprising:

measuring the levels of each analyte within a panel of analyte biomarkers in a biological sample that has been obtained from a subject, wherein the panel of analyte biomarkers is selected from the group consisting of:

(i) a panel of biomarkers comprising valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose;

(ii) a panel of biomarkers comprising acisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide;

(iii) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose;

(iv) a panel of biomarkers comprising glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE;

(v) a panel of biomarkers comprising o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate;

(vi) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate);

(vii) a panel of biomarkers comprising N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated);

(viii) a panel of biomarkers comprising N.acetylglycine and 3.ethylphenylsulfate;

(viv) a panel of biomarkers comprising serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate;

(x) a panel of biomarkers comprising acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate;

(xi) a panel of biomarkers comprising N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate and salicylate;

(xii) a panel of biomarkers comprising asparagine, taurine, acisoga, 1.oleoylglycerol (18:1), cholesterol, 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid and propionylglycine (C3);

comparing the measured levels of the analytes in the biological sample with one or more reference samples, wherein the references are representative of matched human subjects; and

identifying the subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque if measured levels of the analytes in the biological sample are increased or decreased relative to the amounts of the analytes in the reference samples.

2. The method of claim 1, further comprising instructing a healthcare professional to complete a non-invasive cardiovascular evaluation on a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to confirm the subject has or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque, optionally wherein performing a non-invasive cardiovascular evaluation comprises performing a procedure selected from the group consisting of cardiovascular computed tomography (CT) imaging, an exercise stress test, a pharmacologic stress test, myocardial perfusion imaging, stress echocardiography, and cardiovascular magnetic resonance imaging.

3. The method of claim 1, further comprising performing a non-invasive cardiovascular evaluation on a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to confirm the subject does or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque, optionally wherein performing a non-invasive cardiovascular evaluation comprises performing a procedure selected from the group consisting of cardiovascular computed tomography (CT) imaging, an exercise stress test, a pharmacologic stress test, myocardial perfusion imaging, stress echocardiography, and cardiovascular magnetic resonance imaging.

4. The method of any one of claims 1 to 3, further comprising selectively administering a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors,

niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin to a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to treat the subject.

5. The method of any one of claims 1 to 4, further comprising selecting a treatment plan for a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to treat the subject, optionally wherein the treatment plan comprises selectively administering a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin, and optionally wherein the treatment plan comprises prescribing therapeutic lifestyle changes.

6. The method of any one of claims 1 to 5, wherein the levels are measured using mass spectrometry (MS) analysis, optionally wherein the MS analysis comprises liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) or gas chromatography-mass spectrometry (GC-MS).

7. The method of any one of claims 1 to 6, wherein the CAD comprises atherosclerosis, optionally wherein the subject presents with symptoms of atherosclerotic CAD comprising chest pain, angina, angina equivalent, dyspnea, or dyspnea on exertion, and optionally wherein the subject has no previous history of coronary artery disease.

8. The method of any one of claims 1 to 7, wherein the biological sample is a blood sample, a serum sample or a plasma sample.

9. The method of any one of claims 1 to 8, wherein the subject presents with risk factors associated with coronary artery disease selected from the group consisting of male gender, hypertension, dyslipidemia, diabetes, and a family history of coronary artery disease.

10. The method of any one of claims 1 to 9, wherein the reference sample is one that has been obtained from at least one individual not suffering from a cardiovascular disease, or wherein the reference sample comprises predetermined, statistically significant reference analyte levels.

11. The method of any one of claims 1 to 10, further comprising modifying the subject's clinical record to identify the subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque, optionally wherein the clinical record is stored in a computer readable medium.

12. The method of any one of claims 1 to 11, further comprising selecting a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque for treatment, wherein the treatment comprises selectively administering a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants,

anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin to a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to treat the subject.

13. The method of any one of claims 1 to 11, further comprising selecting a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque for treatment, wherein the treatment comprises performing a non-invasive cardiovascular evaluation on a subject identified as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque to confirm the subject does or does not have atherosclerotic coronary artery disease or a coronary atherosclerotic plaque.

14. The method of claim 5, wherein the treatment plan comprises performing a non-invasive cardiovascular evaluation comprises performing a procedure selected from the group consisting of cardiovascular computed tomography (CT) imaging, an exercise stress test, a pharmacologic stress test, myocardial perfusion imaging, stress echocardiography, and cardiovascular magnetic resonance imaging, optionally wherein the comparing step includes analysis of the subjects age and/or gender.

15. A kit for evaluating a human subject for having atherosclerotic coronary artery disease (ASCAD) or as having a coronary atherosclerotic plaque, the kit comprising:

reagents suitable for determining levels of a plurality of analytes in a test sample, wherein the plurality of analytes comprise:

(i) a panel of biomarkers comprising valylleucine, glutamate, acisoga, urate, glucuronate, fucose, butyrylcarnitine (C4) and mannose;

(ii) a panel of biomarkers comprising acisoga, o.cresol.sulfate, threonate and cysteine.glutathione.disulfide;

(iii) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, valylleucine, xylitol, 2.hydroxyhippurate (salicylurate), glycylphenylalanine, serylleucine and fucose;

(iv) a panel of biomarkers comprising glutamate, acisoga, valylleucine, mannose, glucuronate, urate, valerylcarnitine (C5) and 12.HETE;

(v) a panel of biomarkers comprising o.cresol.sulfate, acisoga, cysteine.glutathione.disulfide, glucose, 1.nonadecanoylglycerophosphocholine (19:0) and threonate;

(vi) a panel of biomarkers comprising N.acetylphenylalanine, N.acetylleucine, glycylphenylalanine, valylleucine, xylitol, 12.HETE and 2.hydroxyhippurate (salicylurate);

(vii) a panel of biomarkers comprising N.acetylthreonine, tigloylglycine, glycerate, valerylcarnitine (C5), threonate, 2.hydroxyhippurate (salicylurate), salicylate and tartronate (hydroxymalonated);

(viii) a panel of biomarkers comprising N.acetylglycine and 3.ethylphenylsulfate;

(viv) a panel of biomarkers comprising serotonin (5HT), N.acetylputrescine, leucylleucine, propionylglycine (C3), cholate, glycocholenate.sulfate, asparagine and 3.ethylphenylsulfate;

(x) a panel of biomarkers comprising acisoga, mannose, valerylcarnitine (C5), 1.linoleoyl.GPE (18.2), glycoursodeoxycholate, threonate, 2.hydroxyhippurate (salicylurate) and salicylate;

(xi) a panel of biomarkers comprising N.acetylglycine, threonate, 2.hydroxyhippurate (salicylurate), 3.ethylphenylsulfate and salicylate;

(xii) a panel of biomarkers comprising asparagine, taurine, acisoga, 1.oleoylglycerol (18:1), cholesterol, 2.hydroxyhippurate (salicylurate), 6.oxopiperidine.2.carboxylic.acid and propionylglycine (C3);

optionally one or more control samples comprising predetermined levels of the same analytes, wherein comparison of the levels of the analytes in a test sample with levels in the control samples identifies a subject as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque; and

instructions for use of the kit in the method of any of claims 1 to 14.

16. Use of a composition comprising an effective amount of a therapeutic agent selected from the group consisting of a statin, cholesterol absorption inhibitors, niacin-derivatives, omega-3-fatty acid compounds, bile acid sequestrants, anti-platelet agents, aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digitalis, hydralazine and nitrates, warfarin and aspirin in the manufacture of a medicament for treating atherosclerotic coronary artery disease or coronary atherosclerotic plaque in a subject that has been identified by the method of any one of claims 1-3 as having atherosclerotic coronary artery disease or as having a coronary atherosclerotic plaque.