

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Repatha Prior Authorization Policy

- Repatha® (evolocumab subcutaneous injection – Amgen)

REVIEW DATE: 05/08/2024

OVERVIEW

Repatha, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:¹

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
- **Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH])**, in adults as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies to reduce LDL-C.
- **HeFH, in pediatric patients ≥ 10 years of age**, as an adjunct to diet and other LDL-C lowering therapies.
- **Homozygous familial hypercholesterolemia (HoFH), in patients ≥ 10 years of age**, as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) to reduce LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years of age.¹ Another PCSK9 inhibitor that is available is Praluent® (alirocumab subcutaneous injection).² Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.³

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.⁴⁻¹⁰ For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Ezetimibe is usually the next therapy added.

- The **American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Role of Non-Statins Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.⁴ For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL (or non-high-density lipoprotein cholesterol [HDL-C] < 85 mg/dL) with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).
- The **American Heart Association (AHA)/ACC guidelines on the management of blood cholesterol** (updated 2018) defines patients with ASCVD as those with an acute coronary

05/08/2024

© 2024. All Rights Reserved.

This document is confidential and proprietary. Unauthorized use and distribution are prohibited.

syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.^{5,6} Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.^{5,6} Additionally, reviews have recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.¹²⁻¹⁵

- The **American Diabetes Association Standards of Care for Diabetes** discuss CV disease and risk management (2024).⁸ For patients with diabetes who are 40 to 75 years of age at higher CV risk (including those with one or more ASCVD risk factors), it is recommended to use high-intensity statin therapy to reduce LDL-C by $\geq 50\%$ of baseline and to target an LDL-C of < 70 mg/dL. Also, for patients with diabetes who are 40 to 75 years of age at higher CV risk, especially those with multiple ASCVD risk factors and an LDL-C ≥ 70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to a maximum tolerated statin.
- Guidelines for **Chronic Coronary Disease from the AHA and ACC** (along with other organizations) [2023] state in such patients who are judged to be at very high risk and on maximally tolerated statin therapy and with an LDL-C ≥ 70 mg/dL, ezetimibe can be beneficial to further reduce the risk of a major adverse coronary event.⁹ Patients with chronic coronary disease who are considered to be at very high risk who have an LDL-C ≥ 70 mg/dL who are receiving maximally tolerated statins and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of a major adverse coronary event.
- The **European Atherosclerosis Society Consensus Statement on HoFH** (2023), states that HoFH should be suspected if untreated LDL-C levels are > 400 mg/dL.⁷ Other suggestions of HoFH involve cutaneous or tendon xanthomas before 10 years of age and/or untreated elevated LDL-C levels consistent with HeFH in both parents. Of note, in the digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH. Lipid-lowering therapy should be initiated with high-intensity statin therapy and ezetimibe. A PCSK9 inhibitor can be added as well. If the patient does not achieve LDL-C goals, other agents can be added (e.g., Juxtapid® [lomitapide capsules], Evkeeza® [evinacumab-dgnb intravenous infusion]). Lipoprotein apheresis may also be considered. The goal is to reduce LDL-C to < 115 mg/dL in children and adolescents, < 70 mg/dL in adults if no major ASCVD risk factors are present, and < 55 mg/dL if patients have ASCVD or major ASCVD risk factors.
- A **Scientific Statement from the AHA on Familial Hypercholesterolemia** (2015),¹⁰ as well as other information,¹¹ provide additional guidance on diagnosing familial hypercholesterolemia (e.g., HoFH, HeFH). For HeFH, Dutch Lipid Network criteria scoring is used, as well as the Simon Broome criteria.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Repatha. All approvals are provided for the duration noted below. Only a patient who has previously met initial therapy criteria for Repatha for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Repatha, or is restarting Repatha, initial criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Repatha is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Established Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL the following (i, ii, and iii):

- i. Patient is ≥ 18 years of age; AND
- ii. Patient has had ONE of the following conditions or diagnoses (a, b, c, d, e, or f):
 - a) A previous myocardial infarction or a history of an acute coronary syndrome; OR
 - b) Angina (stable or unstable); OR
 - c) A past of stroke or transient ischemic attack; OR
 - d) Coronary artery disease; OR
 - e) Peripheral arterial disease; OR
 - f) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets ONE of the following (a or b):

- a) Patient meets BOTH of the following [(1) and (2)]:
 - (1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
 - (2) Low-density lipoprotein cholesterol level after this treatment remains ≥ 55 mg/dL; OR
- b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
 - (1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
 - (2) Patient meets ALL of the following [(a), (b), and (c)]:
 - (a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
 - (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
 - (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products), the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Repatha. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review

under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

2. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

- i.** Patient is ≥ 10 years of age; AND
- ii.** Patient meets ONE of the following (a, b, or c):
 - a)** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
 - b)** Patient has phenotypic confirmation of heterozygous familial hypercholesterolemia; OR
Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.
 - c)** Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting ONE of the following diagnostic criteria thresholds [(1) or (2)]:
 - (1)** Prescriber confirms that the Dutch Lipid Network criteria score was > 5 ; OR
 - (2)** Prescriber confirms that Simon Broome criteria met the threshold for “definite” or “possible (or probable)” familial hypercholesterolemia; AND

iii. Patient meets ONE of the following (a or b):

- a)** Patient meets BOTH of the following [(1) and (2)]:
 - (1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
 - (2)** Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR
- b)** Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
 - (1)** Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [$a \geq 0.5$ mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
 - (2)** Patient meets ALL of the following [(a), (b), and (c)]:
 - (a)** Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
 - (b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
 - (c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products), the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Repatha. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received

approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

3. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 10 years of age; AND

ii. Patient meets ONE of the following (a, b, or c):

a) Patient has phenotypic confirmation of homozygous familial hypercholesterolemia; OR
Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 400 mg/dL AND meets ONE of the following [(1) or (2)]:

Note: Untreated refers to therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; OR

Note: An example of familial hypercholesterolemia is an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

b) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets ONE of the following [(1) or (2)]:

Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), or Juxtapid (lomitapide capsules).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

(2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; AND

Note: An example of familial hypercholesterolemia is an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets ONE of the following (a or b):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has tried ONE high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [$a \geq 0.5$ mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Repatha. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

4. **Primary Hyperlipidemia.*** Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with established cardiovascular disease, heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; OR

b) Patient has diabetes; AND

iii. Patient meets ONE of the following (a or b):

a) Patient meets ALL of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal),

along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [$a \geq 0.5$ mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products), the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Repatha. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

Note:

* A patient may have a diagnosis that pertains to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have established cardiovascular disease, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Repatha is not recommended in the following situations:

1. **Concurrent use of Repatha with Praluent (alirocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection).** Praluent is another PCSK9 inhibitor and should not be used with Repatha.² Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Repatha.³
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Repatha® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; September 2021.
2. Praluent® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; March 2024.
3. Leqvio® subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2022;80(14):1366-1418.

5. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-S45.
6. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082-e1143.
7. Cuchel M, Raal FJ, Hegele RA, et al. 2023 update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44:2277-2291.
8. American Diabetes Association Professional Practice Committee. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218.
9. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2023;82(9):833-955.
10. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.
11. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2012;23:282-289.
12. Hect HS, Cronin P, Blaha M, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Thorac Imaging*. 2017;32(5):W54-S66.
13. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72(4):434-447.
14. Razavi AC, Agatston AS, Shaw LJ, et al. Evolving role of calcium density in coronary artery calcium scoring and atherosclerotic cardiovascular disease risk. *JACC Cardiovas Imaging*. 2022;15:1648-1662.
15. Lehker A, Mukherjee D. Coronary calcium risk score and cardiovascular risk. *Curr Vasc Pharmacol*. 2021;19(3):280-284.

APPENDIX A

Simon Broome Register Diagnostic Criteria.^{10,11}

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.^{10,11}

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.