

## PRIOR AUTHORIZATION POLICY

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

- Praluent® (alirocumab subcutaneous injection – Regeneron)

**REVIEW DATE:** 04/26/2023; selected revision 01/17/2024

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### OVERVIEW

Praluent, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:<sup>1</sup>

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization.
- **Primary hyperlipidemia** (including **heterozygous familial hypercholesterolemia [HeFH]**), in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).
- **Homozygous familial hypercholesterolemia (HoFH)**, in adults as an adjunct to other LDL-C lowering therapies, to reduce LDL-C.

The safety and efficacy of Praluent in children have not been established.<sup>1</sup> Repatha® (evolocumab subcutaneous injection) is another PCSK9 inhibitor.<sup>2</sup> Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.<sup>3</sup>

### Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.<sup>4-10</sup> 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  $\geq 50\%$ . Ezetimibe is usually the next therapy added.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.<sup>4</sup> 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  $\geq 50\%$  LDL-C reduction and an LDL-C  $< 55$  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  $\geq 190$  mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is  $\geq 1,000$  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  $\geq 50\%$  LDL-C reduction (and LDL-C threshold  $< 70$  mg/dL).
- The **American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.<sup>5,6</sup> 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.<sup>5,6</sup> Additionally, guidelines and reviews have

recognized that patients with an elevated coronary artery calcium or calcification score (e.g.,  $\geq 300$  Agatston units) are at an increased risk of CV events.<sup>8,11-14</sup>

- The **National Lipid Association** published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).<sup>9</sup> Genetic testing can identify HoFH and HeFH in some cases. Also, HeFH can be diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria. Patients with an untreated LDL-C  $\geq 190$  mg/dL suggest familial hypercholesterolemia. Statins are the initial treatment for all adults with familial hypercholesterolemia, usually at high-potency doses. Ezetimibe can also be added. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels  $\leq 100$  mg/dL are recommended.
- The **2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society** states the diagnosis of HoFH is made based on genetic or clinical criteria.<sup>15</sup> A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the low density lipoprotein receptor, apolipoprotein B, PCSK9, or low-density lipoprotein receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C  $> 500$  mg/dL, or a treated LDL-C  $\geq 300$  mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents. Other clinical manifestations of HoFH include arcus cornea or xanthelasma. Initial therapy for HoFH is high-intensity statins.<sup>15</sup> Other guidelines note that ezetimibe and PCSK9 inhibitors can be added for patients with HoFH if further reductions are needed; Juxtapid<sup>®</sup> (lomitapide capsules) and Evkeeza<sup>®</sup> (evinacumab-dgnb intravenous infusion) can be considered.<sup>4</sup>

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Praluent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and monitoring, approval requires Praluent to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Praluent 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 Praluent, or is restarting Praluent, initial criteria must be met.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

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

### FDA-Approved Indications

1. **Atherosclerotic 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 of the following (i, ii, iii, and iv):
    - i. Patient is  $\geq 18$  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  $\geq$  40 mg daily; rosuvastatin  $\geq$  20 mg daily [as a single-entity or as a combination product]) for  $\geq$  8 continuous weeks; AND
    - (2) Low-density lipoprotein cholesterol level after this treatment remains  $\geq$  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); AND  
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.
- iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR
- B) Patient Currently Receiving Praluent. Approve if according to the prescribing physician, 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 Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.
2. **Heterozygous Familial Hypercholesterolemia (HeFH).**\* Approve for 1 year if the patient meets ONE the following (A or B):
- A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):
    - i. Patient is  $\geq$  18 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) level  $\geq 190$  mg/dL (prior to treatment with antihyperlipidemic agents); OR
  - b) Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR
  - c) Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds [(1) or (2)]:
    - (1) Prescribing physician confirms that the Dutch Lipid Network criteria score was  $> 5$ ; OR
    - (2) Prescribing physician confirms that Simone 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  $\geq 40$  mg daily; rosuvastatin  $\geq 20$  mg daily [as a single-entity or as a combination product]) for  $\geq 8$  continuous weeks; AND
    - (2) Low-density lipoprotein cholesterol level after this treatment remains  $\geq 70$  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); AND  
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.
- iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR
- B) Patient Currently Receiving Praluent.** Approve if according to the prescribing physician, 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 Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, 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, iii, and iv):

- i.** Patient is  $\geq 18$  years of age; AND
- ii.** Patient meets one of the following (a, b, or c):
  - a)** Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; OR
  - b)** Patient has an untreated low-density lipoprotein (LDL-C) level  $> 500$  mg/dL AND meets one of the following [(1) or (2)]:
    - Note: Untreated refers to prior 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)** Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR
      - Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level  $\geq 190$  mg/dL and/or an untreated total cholesterol level  $> 250$  mg/dL.
  - c)** Patient has a treated LDL-C level  $\geq 300$  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., Repatha [evolocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), and 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)** Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND
      - Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C  $\geq 190$  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  $\geq 40$  mg daily; rosuvastatin  $\geq 20$  mg daily [as a single-entity or as a combination product]) for  $\geq 8$  continuous weeks; AND
    - (2)** LDL-C level after this treatment remains  $\geq 70$  mg/dL; OR
  - b)** Patient has been determined to be statin intolerant by meeting one of the following criteria [(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); AND

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

- iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

- B) Patient Currently Receiving Praluent. Approve if according to the prescribing physician, 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 Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, 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 atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) 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, iii, and iv):

- i. Patient is  $\geq 18$  years of age; AND
- ii. Patient has a coronary artery calcium or calcification score  $\geq 300$  Agatston units; 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  $\geq 40$  mg daily; rosuvastatin  $\geq 20$  mg daily [as a single-entity or as a combination product]); AND
    - (2) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for  $\geq 8$  continuous weeks; AND
    - (3) LDL-C level after this treatment regimen remains  $\geq 100$  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); AND

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

- iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

- B) Patient Currently Receiving Praluent. According to the prescribing physician, 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 Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.

**Note:**

\* A patient may have diagnoses that pertain 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 had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Praluent is not recommended in the following situations:

1. **Concurrent use of Praluent with Repatha (evolocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection).** Repatha is another PCSK9 inhibitor and should not be used with Praluent.<sup>2</sup> Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Praluent.<sup>3</sup>
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. Praluent® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; April 2021.
2. Repatha® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; September 2021.
3. Leqvio® subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; December 2021.
4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin 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. Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2020;105(12):3613-3682.

8. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-full report. *J Clin Lipidol.* 2015;9:129-169.
9. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipidol.* 2011;5:S1-S8.
10. Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an Expert Panel of the National Lipid Association. *J Clin Lipid.* 2017;11:880-890.
11. 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.
12. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol.* 2018;72(4):434-447.
13. Razavi AC, Agatston AS, Shaw LJ, et al. Evolving role of calcium density in coronary artery calcium scoring and atherosclerotic cardiovascular disease risk. *J Am Coll Cardiol Img.* 2022;15:1648-1662.
14. Lehker A, Mukherjee D. Coronary calcium risk score and cardiovascular risk. *Curr Vasc Pharmacol.* 2021;19(3):280-284.
15. Cuchel M, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J.* 2014;35:2146-2157.
16. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol.* 2012;23:282-289.
17. 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.



**APPENDIX A.**

**Simon Broome Register Diagnostic Criteria.<sup>16</sup>**

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.<sup>17</sup>**

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.