PHARMACY COVERAGE GUIDELINE

LIPID LOWERING THERAPIES:
JUXTAPID® (lomitapide) oral
PRALUENT™ (alirocumab) subcutaneous injection
REPATHA™ (evolocumab) subcutaneous injection

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

PRALUENT (alirocumab) subcutaneous injection
REPATHA (evolocumab) subcutaneous injection

- **Criteria for initial therapy:** Praluent (alirocumab) and Repatha (evolocumab) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. **ONE** of the following:
     a. **For Praluent (alirocumab)** Individual has a confirmed diagnosis of **ONE** of the following:
        i. Adult (18 years of age or older) with established cardiovascular disease (see Definitions section)

ii. Adult (18 years of age or older) with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) (see Definitions section)
Adult (18 years of age or older) with homozygous familial hypercholesterolemia (HoFH) (see Definitions section)
iii. Pediatric individual aged 8 years or older with HeFH

b. **For Repatha (evolocumab)** Individual has a confirmed diagnosis of **ONE** of the following:
i. Adult (18 years of age or older) with established cardiovascular disease (see Definitions section)
ii. Adult (18 years of age or older) with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) (see Definitions section)
iii. Individual 10 years of age or older with heterozygous familial hypercholesterolemia [HeFH] (see Definitions section)
iv. An individual 10 years of age or older with homozygous familial hypercholesterolemia (HoFH) (see Definitions section)

2. **ONE** of the following:
a. Individual has documented failure (after 3-months of use), contraindication per FDA label, or statin related rhabdomyolysis to maximally tolerable dose of a moderate or high intensity "statin"

b. Individual has skeletal muscle intolerance (myalgia, myositis, or myopathy) after **TWO** trials of maximally tolerable dose of a moderate or high intensity "statin"

3. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. Individual is counselled or is currently on and is adherent with exercise and diet

5. Individual is counselled or is currently on and is adherent with smoking cessation (see Description section for smoking cessation products)

6. No evidence of combination therapy with Juxtapid (lomitapide), or other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, or antilipemic small interfering ribonucleic acid (siRNA) agent Leqvio (inclisiran)

Initial approval duration: 6 months, renewal request must show LDL-C has reached therapeutic goal for approval

- **Criteria for continuation of coverage (renewal request):** Praluent (alirocumab) and Repatha (evolocumab) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual has reached LDL-C goal on therapy (renewal must show LDL-C has reached therapeutic goal) with LDL-C goals defined as **ONE** of the following:
a. Known baseline: LDL-C decreased by 50%
b. Unknown baseline and individual has cardiovascular disease: LDL-C < 70 mg/dL
c. Unknown baseline and individual does not have cardiovascular disease: LDL-C < 100 mg/dL

2. Individual has been adherent with the medication, and is adherent with ezetimibe and statin (if tolerated) therapy, diet, exercise, and smoking cessation (counselled or uses medication)

3. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Hypersensitivity reaction that requires hospitalization
    b. Hypersensitivity vasculitis
    c. Angioedema

5. No evidence of combination therapy with Juxtapid (lomitapide), or other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, or antilipemic small interfering ribonucleic acid (siRNA) agent Leqvio (inclisiran)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

JUXTAPID (lomitapide)

- **Criteria for initial therapy:** Juxtapid (lomitapide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or Endocrinologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **homozygous familial hypercholesterolemia** (HoFH) by **ONE** of the following:
    a. Genetic testing confirming 2 mutated alleles at LDL receptor, apoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene locus
    b. An untreated LDL cholesterol > 400 mg/dL or treated LDL cholesterol > 300 mg/dL with **either** of the following:
        i. Cutaneous or tendonous xanthoma before age of 10 years
        ii. Untreated LDL cholesterol levels consistent with heterozygous familial hypercholesterolemia in **both** parents (i.e., greater than 190 mg/dL)

4. Individual has documented failure (after at least a 3-month trial), contraindication per FDA label, intolerance, or is not a candidate for Praluent (alirocumab) or Repatha (evolocumab) based on FDA label for age

5. Individual is currently on and is adherent with other lipid lowering treatment (e.g., high intensity or best tolerated dose statin, ezetimibe, other)

6. Individual is counselled or is currently on and is adherent with exercise and diet

7. Individual is counselled or is currently on and is adherent with smoking cessation (see Description section for smoking cessation products)

8. Individual is currently on and is adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

9. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Negative pregnancy test, in females of reproductive potential
    b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin per REMS [Note: This is waved if it is verified that Provider, Patient, and Pharmacy are enrolled in the REMS]

10. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

11. There are **NO** FDA-label contraindications such as:
    a. Pregnancy
    b. Simultaneous use of moderate or strong CYP3A4 inhibitors (see Definitions section)
    c. Moderate or severe hepatic impairment (Child-Pugh Class B or C)
    d. Active liver disease including unexplained persistent abnormal liver function tests

12. Individual **does not have any** of the following:
    a. Hereditary problems of galactose intolerance
    b. Lapp lactase deficiency
    c. Glucose-galactose malabsorption

13. Individual does not have hypercholesterolemia due to other causes including heterozygous familial hypercholesterolemia [HeFH]

14. Will not be used with Praluent (alirocumab), Repatha (evolocumab), or Leqvio (inclisiran)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Juxtapid (lomitapide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or Endocrinologist

2. Individual's condition has responded while on therapy with response defined as individual achieved and maintains at least a 50% in LDL-C from baseline

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has been adherent with other lipid lowering therapy (e.g., high intensity or best tolerated dose statin, ezetimibe, other)

6. Individual is counselled or is currently on and is adherent with exercise and diet

7. Individual is counselled or is currently on and is adherent with smoking cessation (see Description section for smoking cessation products)

8. Individual has been adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

9. Individual does not have hypercholesterolemia due to other causes including heterozygous familial hypercholesterolemia [HeFH]

10. Will not be used with Praluent (alirocumab) or Repatha (evolocumab) or Leqvio (inclisiran)

11. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Liver toxicity
        ii. Hepatic steatosis
        iii. Cirrhosis

12. There is no evidence of simultaneous use of moderate or strong CYP3A4 inhibitors (see Definitions section)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

LIPID LOWERING THERAPIES

Description:

Praluent (alirocumab) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The effect of Praluent (alirocumab) on cardiovascular morbidity and mortality has not been determined.

Repatha (evolocumab) is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease; as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C; and it is indicated as an adjunct to diet and other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. The effect of Repatha on cardiovascular morbidity and mortality has not been determined.

Praluent (alirocumab) and Repatha (evolocumab) are human monoclonal antibodies (IgG1 & IgG2 isotypies respectively) that inhibit PCSK9. PCSK9 is the enzyme responsible for removing LDLR from the hepatocyte surface. PCSK9 promotes the degradation of hepatic LDLR, which limits the ability of the liver to bind and remove LDL-C from the blood. Inhibition of PCSK9 increases the number of available LDLR, allowing for additional capacity to remove LDL-C from the bloodstream, leading to lowering of LDL-C levels.

Juxtapid (lomitapide) is a microsomal triglyceride transfer protein (MTP) inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with HoFH. Juxtapid (lomitapide) directly binds and inhibits MTP. Juxtapid (lomitapide) prevents the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. The result is inhibition of the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

The safety and effectiveness of Juxtapid (lomitapide) have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH. The effect of Juxtapid (lomitapide) on cardiovascular morbidity and mortality has not been determined. Safety and effectiveness in pediatric patients have not established. Juxtapid (lomitapide) is only available through a restricted program called JUXTAPID REMS PROGRAM. They are only available from certified pharmacies that are enrolled in the program. Providers must be enrolled in the program in order to prescribe Juxtapid (lomitapide).

MTP plays a key role in the assembly and release of apo B-containing lipoproteins, including LDL-C, and inhibition of this protein significantly lowers associated plasma lipid levels. It is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Normal concentrations and function of MTP in the liver and intestine are necessary for the proper assembly and secretion of apo B-containing lipoproteins from the liver and chylomicrons from the intestine. Inhibition of MTP leads directly to decreases in circulating levels of apo B-containing lipoproteins, including LDL-C.

Under normal physiological conditions, LDL-C is removed from the blood when it binds to an LDL receptor (LDLR) on the hepatocyte surface. Each LDLR binds a single LDL-C particle and is internalized into the hepatocyte. The LDL-C separates from the receptor and the unoccupied receptors are returned to the cell surface for reuse. At the same time, the lipoprotein is degraded, and the released cholesterol is stored in the cell and used for a variety of cellular activities such as production of bile acids and very low-density lipoproteins. The level of hepatic LDLR is controlled at the transcriptional level by proprotein convertase subtilisin kexin type 9 (PCSK9). Following its secretion, PCSK9 binds to LDLR and blocks the cholesterol-removal process by metabolizing the LDLR and

breaking it up, effectively making it impossible for the LDLR to return to the surface of the cell and remove more cholesterol.

Hypercholesterolemia:

- Hypercholesterolemia is a major risk factor for ASCVD, which may result in one or more of the following: acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, revascularization procedures, stroke or transient ischemic attack, and peripheral arterial disease that is atherosclerotic in origin
- It usually results from nutritional factors such as a diet high in saturated fats combined with an underlying polygenic predisposition or it may be caused solely by a genetic disorder or a combination of other factors
    - Other risk factors include older age, early menopause in women, and family history of the condition

Familial hypercholesterolemia (FH):

- FH is an autosomal-dominant genetic disorder, is classified as heterozygous (inherited from one parent) or homozygous (inherited from both parents).
- Characterized by very high LDL-C levels requiring aggressive lipid-lowering in order to prevent cardiovascular disease
- FH may be caused by mutations in any of several genes affecting receptor-mediated uptake of LDL-C, including the genes for the LDLR, the LDL receptor ligand (apolipoprotein B100, APOB), and PCSK9
- Most people with FH have inherited a single mutation from one parent in either of these genes
- A loss of function mutation in the LDLR gene results in absent or grossly malfunctioning LDLR and reduced uptake and clearance of circulating LDL-C by the liver
- Due to absence or abnormality in the LDLR, the liver is unable to internalize LDL-C particles, leading to elevation in serum LDL-C levels
    - Hepatic synthesis of cholesterol is not suppressed because LDL-C is not internalized by the hepatocytes
    - This leads to higher cholesterol production by the liver, despite already high levels of circulating cholesterol
    - As a result, circulating cholesterol levels increase dramatically
- The elevated serum levels of LDL-C increase an LDL-C receptor-independent cholesterol uptake pathway in non-hepatic cells
    - This scavenger pathway allows cholesterol uptake by monocytes and macrophages, leading to foam cell formation, plaque deposition in the endothelium of coronary arteries, and premature coronary heart disease

FH forms:

- There are two forms of FH: HeFH and HoFH
- HeFH is more common than HoFH, while HoFH is more severe
- HeFH is estimated to occur in 1:300 to 1:500 individuals in the United States and Europe, while HoFH occurs in 1:1,000,000
- Patients with HeFH can present with total cholesterol in the range of 350-550 mg/dL, while patients with HoFH can have total cholesterol in the range of 650-1000 mg/dL
- In all forms of FH, the phenotype is characterized by a high LDL-C level from birth, relatively normal high-density lipoprotein (HDL-C) and triglycerides, and early-onset coronary heart disease
- Findings of FH on physical examination may include arcus corneae (a white ring around the cornea), xanthelasma (sharply demarcated yellowish deposits of fat underneath the skin), and tendon or tuberous xanthomas

Management:

- Medications currently approved for the treatment of hypercholesterolemia have been extensively studied, and many have long safety and efficacy track records
- Patients with hypercholesterolemia are typically treated with statin therapy
    - Statins have been shown to reduce cardiovascular events and mortality
- However, many patients are not able to achieve LDL goals on statin therapy alone
- Other options that can be used with or without statin therapy include Zetia (ezetimibe), fibrates, niacin, and bile acid sequestrants
- LDL apheresis is considered a standard of care in patients with HoFH, but may not be feasible due to patient access or tolerability
    - Other options for HoFH include Juxtapid (lomitapide), and Repatha (evolocumab)
        - Are typically used in patients who are not adequately controlled with or cannot receive LDL apheresis

Statin adverse effects:

- Approximately 3-10% of patients on statins may develop intolerance to the statin used
- Intolerance is defined as an inability to take a statin because of muscle symptoms or elevated creatine kinase
    - Individuals may present with muscle weakness, aches, cramps, or flu-like symptoms
    - Other effects, such as, headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and/or arthritis, may also contribute to a patient's inability to take them
- Less than 1% of patients on statin therapy developed serious side-effects such as myopathy, myositis, or rhabdomyolysis
- Risk factors for statin intolerance and of developing muscle-related symptoms include, female gender, advanced age, patients with significant comorbidities (such as liver failure, kidney failure, or thyroid disease), family history of myopathy, and statin dose
- In many cases it occurs after patients are co-administered an interacting medication (such as azole antifungals, cimetidine, clarithromycin, erythromycin, or cyclosporine)
- Some patients will respond favorably to lowering the statin dose or switching to another statin or administering statins in an unconventional (eccentric) schedule such as every other day, every second day, every third day, or even weekly instead of daily
- Studies have shown that 92% of patients can tolerate a second statin and 72.5% can successfully tolerate a third agent
- Use of long-acting statins weekly instead of daily resulted in 74% of patients able to tolerate continued statin use
- However, some patients cannot achieve optimal lowering of LDL-C despite these dose modifications or use of an alternative statin

  The risk of developing statin associated muscle symptoms (SAMS) is not identical across all statins
    - Studies have suggested that the risk of developing SAMS is highest with simvastatin, atorvastatin, and lovastatin
    - The risk of myopathy has been suggested to be lowest with pravastatin and fluvastatin, possibly because they are more hydrophilic and, as a result, have less muscle penetration

Smoking cessation products:

- Nicotine gum
- Nicotine lozenge
- Nicotine nasal spray

- Nicotine oral inhaler
- Nicotine transdermal patch
- Varenicline tablet
- Bupropion (smoking deterrent) extended-release tablet

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Risk Evaluation and Mitigation Strategies (REMS):

Use of Juxtapid is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

The goal of the Juxtapid REMS program is to mitigate the risk of hepatotoxicity associated with the use of Juxtapid

Homozygous familial hypercholesterolemia:

Loss of function mutations in both alleles of the LDLR gene

Heterozygous familial hypercholesterolemia:

Loss of function mutation in one allele of the LDLR gene

Hyperlipidemia:

Abnormal elevation of any or all lipids or lipoproteins

Types:

Primary hyperlipidemia:

Hyperlipidemia that is the result of a genetic cause such as a mutation in a receptor protein
The management of the risk factors for atherosclerotic cardiovascular disease (CVD), of which elevated low density lipoprotein cholesterol (LDL-C) is one, is called primary prevention if this process is done in someone who has not previously experienced an atherosclerotic vascular event

Secondary hyperlipidemia:

Hyperlipidemia that is the result of another underlying disorder such as diabetes, drugs, hypothyroidism, etc.

Patients with cardiovascular disease (CVD) are at high risk for future CVD events. Therapy to reduce the risk of subsequent events in such patients is referred to as secondary prevention. Secondary prevention interventions are aimed at known modifiable risk factors for CVD events such as smoking, hypertension, diabetes, and elevated levels of low density lipoprotein cholesterol (LDL-C). LDL-C lowering has been shown in large clinical trials to reduce the risk of CVD events and, in some populations, to reduce all-cause mortality

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Clinical atherosclerotic cardiovascular disease (ASCVD) defined as:

1. LDL > 100 mg/dL (within the last 30 days)
2. LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite high- or moderate-intensity statin therapy
3. One or more of the following clinical situations
   - Acute coronary syndrome
   - History of or diagnosis of myocardial infarction
   - Stable or unstable angina
   - Coronary or other arterial revascularization (such as percutaneous coronary intervention or coronary bypass graft surgery)
   - Diagnosis of non-hemorrhagic stroke or transient ischemic attack
   - Symptomatic Peripheral arterial disease (PAD) presumed to be of atherosclerotic origin), as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease
   - Clinically significant coronary heart disease diagnosed by invasive or noninvasive tests (e.g., coronary angioplasty, stress test using treadmill, stress echocardiography, or nuclear imaging)

Heterozygous familial hypercholesterolemia (HeFH) defined as ONE of the following:

1. World Health Organization/Dutch Lipid Network Criteria score > 8
2. Simon-Broome Register Diagnostic Criteria of Definite HeFH

Homozygous familial hypercholesterolemia (HoFH) defined by ONE of the following:

1. Genetic confirmation of **two** mutant alleles at the LDL receptor, ApoB, PCSK9, or ARH adaptor protein 1/LDLRAP1
2. An untreated LDL-C > 400mg/dl (or treated LDL-C > 300 mg/dl) with **EITHER**:
   a. Cutaneous or tendon xanthoma before age 10
   b. Documented evidence of HeFH in **both** biologic parents

ASCVD Pooled Cohort Risk Assessment:

The Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group, an arm of the ACC/AHA Cardiovascular Risk Guidelines, to identify appropriate candidates for statin therapy based on elevated cardiovascular risk

The purpose of the Pooled Cohort Equations is to estimate the risk of ASCVD within a 10-year period among patients who have never had one of these events in the past

The Pooled Cohort Equations were developed and validated among Caucasian and African American men and women who did not have clinical ASCVD. There are inadequate data in other racial groups, such as Hispanics, Asians, and American-Indian populations. Given the lack of data, current guidelines suggest to use the "Caucasian" race to estimate 10-year ASCVD risk with the knowledge that further research is needed to stratify these patients' risk. Compared to Caucasians, the risk of ASCVD is generally lower among Hispanic and Asian populations and generally higher among American-Indian populations.
The 2013 ACC/AHA guidelines recommend either a high-intensity or moderate-intensity statin regimen in patients who have an elevated ASCVD risk (≥ 7.5%) for primary prevention of cardiovascular disease

Framingham Risk Score (FRS):

A validated means of predicting cardiovascular disease (CVD) risk in asymptomatic patients
It is used to determine lipid-lowering therapy for primary prevention
A 10-year risk score is expressed as a percentage

Risk is considered:
Low if the FRS < 10%
Moderate if the FRS is 10-19%
High if the FRS ≥ 20%

Diagnosis of Heterozygous familial hypercholesterolemia (HeFH):

World Health Organization Criteria / Dutch Lipid Network Criteria:

		Score
Family history	First degree relative with known premature CAD &/or vascular disease (men < 55 y, woman < 60 y)	1
	First degree relative with known LDL-C > 95th percentile by age and gender	1
	First degree relative with tendon xanthomata &/or arcus cornealis	2
	Children < 18 y with LDL-C > 95th percentile by age and gender	2
Clinical history	Patient has premature CAD (male before age 55, female before age 60)	2
	Patient has premature cerebral/peripheral vascular disease (male before age 55, female before age 60)	1
Physical exam	Tendon xanthomata	6
	Arcus cornealis age < 45 y	4
LDL-C	> 330 mg/dL (> 8.5 mmol/L)	8
	250-329 mg/dL (6.5-8.4 mmol/L)	5
	190-249 mg/dL (5.0-6.4 mmol/L)	3
	155-189 mg/dL (4.0-4.9 mmol/L)	1
Genetic test	Mutation in LDLR, ApoB, or PCSK9 gene	8
Definite FH		Score > 8
Probable FH		Score 6-8
Possible FH		Score 3-5
Unlikely FH		Score < 3
First degree relative: blood relative – parents, full siblings, children Second degree relative: blood relative – grandparents, grandchildren, aunts, uncles, nephews, nieces, half siblings Third degree relative: blood relative – first cousins, great-grandparents, great grandchildren		

Simon-Broome Register Diagnostic Criteria:

A	Adult: TC > 290 mg/dL (or > 7.5 mmol/L) Child < 16 y: TC > 260 mg/dL (or > 6.7 mmol/L) **OR** Adult: LDL-C > 190 mg/dL (or > 4.9 mmol/L), pre-treatment or highest on treatment Child: LDL-C > 155 mg/dL (or > 4.0 mmol/L), pre-treatment or highest on treatment
B	Tendon xanthomas in the individual or first- **OR** second-degree relative
C	DNA-based evidence of a LDLR mutation **OR** a familial defective ApoB-100 **OR** PCSK9 mutation
D	First-degree relative with an MI before age 60 **OR** Second-degree relative with an MI before age 50

E	First- or second-degree relative with TC > 290 mg/dL (or > 7.5 mmol/L) **OR** Sibling or child < 16 years of age with TC > 260 mg/dL (or > 6.7 mmol/L)
Definite FH	(A + B) or C
Possible FH	A + (D or E)

First degree relative: blood relative – parents, full siblings, children
Second degree relative: blood relative – grandparents, grandchildren, aunts, uncles, nephews, nieces, half siblings
Third degree relative: blood relative – first cousins, great-grandparents, great grandchildren

2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guideline

Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C treatment Goals

Risk Category	Risk factor*/10-year risk†	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme	• Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL • Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH • History of premature ASCVD (< 55 male, < 65 female)	< 55	< 80	< 70
Very high	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk > 20% • Diabetes or CKD 3/4 with 1 or more risk factor(s) • HeFH	< 70	< 100	< 80
High	• ≥ 2 risk factors and 10-year risk 10-20% • Diabetes or CKD 3/4 with no other risk factors	< 100	< 130	< 90
Moderate	• ≤ 2 risk factors and a 10-year risk of 10-20%	< 100	< 130	< 90
Low	• 0 risk factors	< 130	< 160	--

* Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.
† Framingham risk scoring is applied to determine 10-year risk

Four Major Statin Benefit Groups: 2013 Recommendations AHA/ACC Cholesterol Guidelines

Patient Category	Recommendation for Statin intensity
Secondary prevention	
-Clinical ASCVD	● High intensity if age ≤75 y ● Moderate intensity if age >75 y
Primary prevention	
-LDL-C ≥190 mg/dL	High-intensity statin
-Age 40-75 y LDL-C 70-189 mg/dL +DM & no clinical ASCVD	● Moderate intensity if low risk (10-y ASCVD risk <7.5%) ● High intensity if high risk (10-y ASCVD risk >7.5%)

PHARMACY COVERAGE GUIDELINE

LIPID LOWERING THERAPIES

-Age 40-75 y LDL-C 70-189 mg/dL -DM or clinical ASCVD	Moderate or high intensity (10-y ASCVD risk ≥7.5%)

Statin Treatment Categorized by Intensity Using 2013 AHA/ACC Cholesterol Guidelines			
	High Intensity	**Moderate Intensity**	**Low Intensity**
	Daily dose lowers LDL-C, on average, by about ≥ 50%	Daily dose lowers LDL-C, on average, by about 30% to < 50%	Daily dose lowers LDL-C, on average, by about < 30%
Atorvastatin	≥ 40 mg	10-40 mg	< 10 mg
Fluvastatin		80 mg	< 80 mg
Lovastatin		≥ 40 mg	< 40 mg
Pitavastatin		≥ 2 mg	< 2 mg
Pravastatin		≥ 40 mg	< 40 mg
Simvastatin	80 mg*	20 - < 80 mg	< 20 mg
Rosuvastatin	≥ 20 mg	5- < 20 mg	< 5 mg
* Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by FDA due to the increased risk of myopathy, including rhabdomyolysis.			

Approximate Equivalent Daily Doses of Statins: LDL Lowering Data from Clinical Trials						
Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
--	40 mg	20 mg	1 mg	20 mg	--	10 mg
10 mg	80 mg	40 mg	2 mg	40 mg	--	20 mg
20 mg	--	80 mg	4 mg	**	--	40 mg
40 mg	--	--	--	--	10 mg	80 mg
80 mg	--	--	--	--	20 mg	--

FDA-label contraindications of Statins and Ezetimibe:

Statins:

Hypersensitivity to HMG-CoA reductase inhibitor (statin) or any component of the formulations
Active liver disease or unexplained persistent elevations of serum transaminases
Pregnancy (or women who may become pregnant [**fluvastatin, simvastatin**]
Breastfeeding
Co-administration of **simvastatin** with gemfibrozil or danazol
Co-administration of **pitavastatin** or **simvastatin** with cyclosporine
Co-administration of **lovastatin** or **simvastatin** with strong ***CYP3A4 inhibitors*** (e.g., clarithromycin, cobicistat-containing products, erythromycin, HIV protease inhibitors [including boceprevir and telaprevir], itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole)

Zetia (ezetimibe):

Hypersensitivity to ezetimibe or any component of the formulation
Concomitant use with a statin in patients with active hepatic disease or unexplained persistent elevations in serum transaminases
Women who are pregnant or may become pregnant
Who are breast-feeding (when used concomitantly with a statin)

Rhabdomyolysis is documented by either:

i. Increased creatinine kinase > 5 x ULN
ii. Increased CK isoenzyme, MM-subunit
iii. Increased myoglobin in blood and urine

iv. Increased serum potassium
v. Increased serum creatinine (or decreased CrCl)

The Child-Pugh classification system:

	Score: 1 point	**Score: 2 points**	**Score: 3 points**
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

Resources:

Juxtapid (lomitapide) product information, revised by Amryt Pharmaceuticals DAC 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 31, 2024.

Praluent (alirocumab) product information, revised by Regeneron pharmaceuticals, Inc 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 31, 2024.

Repatha (evolocumab) product information, revised by Amgen USA, Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 31, 2024.

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 Jul 1; 44(25): 2277–2291. Accessed July 08, 2024.

Rosenson RS, Durrington P. Familial hypercholesterolemia in adults: Overview. In: UpToDate, Freeman MW, Yeon SB (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on December 10, 2023. Accessed July 06, 2024.

Rosenson RS, Durrington P. Familial hypercholesterolemia in adults: Treatment. In: UpToDate, Freeman MW, Yeon SB (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated December 07, 2023. Accessed July 06, 2024.

de Ferranti SD. Familial hypercholesterolemia in children. In: UpToDate, Fulton DR, Armsby C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on April 02, 2024. Accessed July 06, 2024.

Pignone M, Cannon CP. Low-density lipoprotein cholesterol-lowering therapy in primary prevention of cardiovascular disease. In: UpToDate, Freeman MW, Swenson S, Yeon SB (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on June 27, 2024. Accessed July 06, 2024.

Rosenson RS, Lopez-Sendon J. Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease. In: UpToDate, Freeman MW, Cannon CP, Kaski JC, Parikh N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on June 12, 2024. Accessed July 06, 2024.

Rosenson RS, de Ferranti SD, Durrington P. Treatment of drug-resistant hypercholesterolemia. In: UpToDate, Freeman MW, Parikh N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on October 10, 2023. Accessed July 06, 2024.

Rosenson RS. Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors. In: UpToDate, Freeman MW, Yeon SB (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on April 26, 2024. Accessed July 06, 2024.