

<b>BSC8.07</b>	<b>Lipid Apheresis</b>		
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<b>Section:</b>	8.0 Therapy	<b>Page:</b>	Page 1 of 25

## Policy Statement

- I. Low-density lipoprotein (LDL) apheresis may be considered **medically necessary** in patients with homozygous familial hypercholesterolemia (FH) as an alternative to plasmapheresis.
- II. Low-density lipoprotein apheresis may be considered **medically necessary** in patients with heterozygous familial hypercholesterolemia when **both** of the following criteria are met:
  - A. Failed diet therapy and maximum tolerated combination drug therapy\*
  - B. Meet **one** of the following U.S. Food and Drug Administration approved indications (all LDL levels represent the best achievable LDL level after a program of diet and drug therapy):
    1. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 300 mg/dL
    2. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 200 mg/dL\* AND documented coronary artery disease\*
- III. Low-density lipoprotein apheresis is considered **investigational** for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, non-arteritic acute anterior ischemic optic neuropathy, and acute coronary syndrome.
- IV. Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered **investigational** for all indications, including but not limited to acute coronary syndrome.

\*For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines section.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

A scientific statement from American Heart Association (see Supplemental Information section) for the treatment of heterozygous familial hypercholesterolemia (FH) has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing low-density lipoprotein cholesterol (LDL-C) by at least 50%, usually with a statin. This treatment can be followed by achieving an LDL-C of less than 100 mg/dL (absent coronary artery disease [CAD] or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors). The following approach for pharmacotherapy is suggested:

- High-intensity statin therapy to target >50% LDL-C reduction, such as rosuvastatin or atorvastatin
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding ezetimibe
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding a PCSK9 inhibitor or colesevelam (or other bile acid sequestrant or niacin).
- If the patient is adherent and LDL-C is above the target goal after 3 months, proceed to complex therapy combination such as a 4-drug combination plus LDL apheresis.

Documented CAD includes **any** of the following:

- A history of myocardial infarction
- Coronary artery bypass surgery
- Percutaneous transluminal coronary angioplasty or alternative revascularization procedure
- Progressive angina documented by exercise or nonexercise stress test

The frequency of LDL apheresis varies, but typically averages once every 2 weeks to obtain an interapheresis level of LDL-C at less than 120 mg/dL. Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

### Coding

Although the following CPT code is not specific to LDL apheresis, it does generally encompass LDL apheresis:

- **36516**: Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion

There is no specific CPT or HCPCS code for the disposable supplies associated with LDL apheresis. For example, dextran sulfate systems (e.g., Liposorber LA-15<sup>®</sup> System) require the use of a disposable column consisting of dextran sulfate ligands on cellulose beads.

The following HCPCS code is specific to the HELP procedure:

- **S2120**: Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

The following category III CPT code is for selective high-density lipoprotein (HDL) delipidation and plasma reinfusion:

- **0342T**: Therapeutic apheresis with selective HDL delipidation and plasma reinfusion

### Description

This use of low-density lipoprotein (LDL) apheresis has been proposed to treat various types of familial hypercholesterolemia (FH) and other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately removes LDL particles from plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

### Related Policies

- N/A

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Two LDL apheresis systems have been approved by the U.S. Food and Drug Administration (FDA) for marketing. In 1996, the Liposorber LA-15<sup>®</sup> System (Kaneka Pharma), dextran sulfate device, was approved by the FDA through the premarket approval process for use to "acutely remove LDL-C from the plasma of high-risk patient populations for whom diet has been ineffective or not tolerated."

In 1997, the HELP<sup>®</sup> System (B. Braun), a heparin-induced extracorporeal LDL precipitation, was approved by the FDA through the premarket approval process for the same indication. FDA product code: MMY.

In 2013, the Liposorber LA-15<sup>®</sup> System was approved for additional indications through the humanitarian device exemption<sup>1</sup> process for the treatment of pediatric patients with primary focal segmental glomerulosclerosis when the following conditions apply:

"Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well-tolerated, and the patient has a GFR [glomerular filtration rate]  $\geq$  60 mL/min/1.73 m<sup>2</sup> or The patient is post renal transplantation."

In 2020, the FDA changed the preexisting Humanitarian Use Device (HUD) 2014 designation for the Plasma Delipidation System (PDS-2<sup>™</sup> System) to a Humanitarian Device Exemption (HDE). These regulatory pathways are intended to encourage development of devices for rare diseases. The 2020 HDE is indicated "to reduce coronary artery atheroma in adult patients with homozygous FH who are either inadequately responsive to or intolerant of maximal therapy for homozygous FH, including the latest medications and other device therapies approved by the FDA."<sup>2</sup>

The modification to a HDE approval was due to safety considerations and limitations of the clinical evidence provided, which necessitated that the device use be limited to treatment of patients who are either inadequately responsive or intolerant of maximal therapy for homozygous FH. The Summary of Safety and Probable Benefit reports data on 6 patients with substantial occurrence of hypotension and bradycardia. Delipidation and reinfusion is limited to 7 treatments.

## Rationale

### Background

#### Hyperlipidemia

A dominantly inherited disorder, familial hypercholesterolemia (FH) results from a variant in the gene that encodes for the specific cell surface receptor responsible for low-density lipoprotein (LDL) uptake by the cells. The heterozygous form affects about 1 in 500 people. The number of LDL receptors is halved in this condition, resulting in serum LDL cholesterol levels that are approximately 2 to 3 times levels considered acceptable (i.e., > 300 mg/dL). Affected male patients typically develop coronary heart disease (CHD) in their thirties and forties, while women develop the disease in their fifties. Depending on the patient, heterozygous FH may or may not respond adequately to lipid-lowering drugs.

Homozygous hypercholesterolemia is rare, occurring in only 1 in 1 million subjects. Due to the total lack of functioning LDL receptors, serum levels of LDL cholesterol may be elevated 6-fold (> 500 mg/dL). Homozygotes may develop severe aortic stenosis and CHD by 20 years of age. These patients typically do not adequately respond to drug or diet modification therapies. In the past, patients with homozygous FH may have been treated with plasma exchange, but the advent of LDL apheresis provides a more targeted approach by permitting selective removal of LDL from plasma.

## Treatment

### Low-Density Lipoprotein

Low-density lipoprotein apheresis (also referred to as lipid apheresis) involves the extracorporeal removal of apolipoprotein B (apo B)-containing lipoproteins, including LDL, lipoprotein(a), and very low-density lipoprotein.

The apheresis procedure is designed to isolate plasma. The LDLs are then selectively removed from the plasma by immunoabsorption, heparin-induced extracorporeal LDL precipitation, dextran sulfate adsorption, or double-filtration plasmapheresis of lipoprotein. In immuno-adsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL, because apo B is the protein moiety of LDL. In heparin-induced extracorporeal LDL precipitation, LDL and other particles containing apo B are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apo B to dextran sulfate particles bound to cellulose. High-density lipoprotein (HDL) delipidation and plasma reinfusion removes plasma from the body, processed through a delipidation device, and then returns it to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major  $\alpha$ -HDL to pre- $\beta$ -like HDL, a form of HDL that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden. The plasma with pre- $\beta$ -like HDL is then reinfused into the patient.

### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### Low-Density Lipoprotein Apheresis for Homozygous and Heterozygous Familial Hypercholesterolemia

#### Clinical Context and Therapy Purpose

The purpose of low-density lipoprotein (LDL) apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical management with lipid-lowering medications or plasmapheresis, in patients with homozygous or heterozygous familial hypercholesterolemia (FH) unable to achieve target low-density lipoprotein cholesterol (LDL-C) with maximally tolerated pharmacotherapy.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with homozygous or heterozygous FH unable to achieve target LDL-C with maximally tolerated pharmacotherapy?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest are individuals with homozygous or heterozygous FH unable to achieve target LDL-C with maximally tolerated pharmacotherapy.

### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with homozygous or heterozygous FH are actively managed by primary care physicians, endocrinologists, and cardiologists in an outpatient clinical setting. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### ***Comparators***

Comparators of interest include medical management with lipid-lowering medications and plasmapheresis.

Patients with homozygous or heterozygous FH are actively managed by primary care physicians, endocrinologists, and cardiologists in an outpatient clinical setting.

### ***Outcomes***

The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, morbid events, and treatment-related morbidity.

These conditions are chronic, and patients are followed throughout their lives.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Most reviews have not incorporated the evidence gained from newer therapies such as antisense inhibitors of apolipoprotein B synthesis (e.g., mipomersen), microsomal transfer protein inhibitors (e.g., lomitapide), and PCSK9 inhibitors (e.g., alirocumab, evolocumab), which have been shown to reduce LDL-C levels in patients with homozygous and heterozygous FH. Randomized controlled trials comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels.

### **Review of Evidence**

#### **Systematic Reviews**

Wang et al (2016) published a systematic review of LDL apheresis that included 15 studies in patients with homozygous and heterozygous FH.<sup>3</sup> None was a RCT. Seven studies assessed patients with homozygous and heterozygous FH separately, while the remaining made no such distinction. Studies reported a range of mean acute LDL-C reductions after apheresis of 57% to 75% for patients with

homozygous FH and of 58% to 63% for patients with heterozygous FH. Longer-term outcomes showed that LDL may gradually increase after LDL apheresis and could be back to pretreatment levels within 2 to 4 weeks. Five studies followed patients for 1 to 5 years. At the extended follow-ups, reductions after LDL apheresis ranged from 22% to 36%, demonstrating that the effects of the procedure may not last.

### **Section Summary: Low-Density Lipoprotein Apheresis for Homozygous and Heterozygous Familial Hypocholesterolemia**

For patients with homozygous or heterozygous FH, no RCTs have compared LDL apheresis alone with drug therapy alone, no intervention, usual care, or apheresis plus drug therapy. Studies have reported reductions in LDL-C levels after apheresis in the mean range of 57% to 75% for patients with homozygous FH and 58% to 63% for patients with heterozygous FH. Currently, direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trial comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and are unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels.<sup>4,5</sup>

### **Low-Density Lipoprotein Apheresis for Nonfamilial Hypercholesterolemia**

#### **Clinical Context and Therapy Purpose**

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical management with lipid-lowering medications, in patients with nonfamilial hypercholesterolemia.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with nonfamilial hypercholesterolemia?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest are individuals with nonfamilial hypercholesterolemia.

#### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with nonfamilial hypercholesterolemia are actively managed by primary care physicians, endocrinologists, and cardiologists in an outpatient clinical setting. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

#### ***Comparators***

Comparators of interest include medical management with lipid-lowering medications.

Patients with nonfamilial hypercholesterolemia are actively managed by primary care physicians, endocrinologists, and cardiologists in an outpatient clinical setting.

#### ***Outcomes***

The general outcomes of interest are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity.

This condition is chronic, and patients are followed throughout their lives.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

While the focus of most studies of LDL apheresis has been on FH-associated hypercholesterolemia, a smaller number of observational studies have evaluated LDL apheresis in patients with lipoprotein(a) [Lp(a)]-hyperlipoproteinemia, hypercholesterolemia, or both, usually in conjunction with cardiovascular disease.

## Review of Evidence

### Observational Studies

Leebmann et al (2013) reported on a prospective observational multicenter study of 170 patients treated with LDL apheresis for Lp(a)-hyperlipoproteinemia and progressive cardiovascular disease despite receiving maximally tolerated lipid-lowering treatment.<sup>6</sup> During the 2-year treatment period with LDL apheresis, the authors reported a significant decrease in cardiovascular disease events compared with the 2-year period before treatment with LDL apheresis.

Heigl et al (2015) reported on a retrospective observational study of 118 consecutive patients treated at a single apheresis center with LDL apheresis for severe hypercholesterolemia or isolated Lp(a)-hyperlipoproteinemia with progressive cardiovascular disease.<sup>7</sup> Most patients (n = 111 [94%]) had hypercholesterolemia; 83 (70.3%) had Lp(a)-hyperlipoproteinemia, but isolated Lp(a)-hyperlipoproteinemia was the indication for LDL apheresis only in 35 (29.7%) patients. All patients were receiving maximally tolerated lipid-lowering medication and individually optimized cardiac medications before and during apheresis treatment, although specifics about the lipid-lowering regimens used and reasons for treatment intolerance were not provided. Compared with the time between patients' first cardiovascular event and first LDL apheresis (mean = 6.4 years), the average annual per-patient major adverse cardiac event rate decreased from 0.35 to 0.07 (a 79.7% reduction; p<0.001) while patients were receiving chronic lipid apheresis treatment (mean duration of treatment = 6.4 years). The mean total LDL-C reduction was 32.1% from the pre-lipid apheresis period to steady state during lipid apheresis, while the mean total Lp(a) reduction was 56.4%. During 36,745 lipid apheresis treatments, there were unexpected adverse events in 1.1% of patients, vascular problems in 2.1%, and technical problems in 0.08%. Heigl et al (2015) provided additional details about the study procedures and outcomes.<sup>8</sup>

### Section Summary: Low-Density Lipoprotein Apheresis for Nonfamilial Hypercholesterolemia

For patients with hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia without FH, non-randomized studies have reported improvements in lipid levels pretreatment and posttreatment. In patient populations that are well-characterized regarding previous treatments, lipid levels, and comorbidities, randomized trials are necessary to demonstrate improvements in health outcomes.

### Low-Density Lipoprotein Apheresis for Nephrotic Syndrome

#### Clinical Context and Therapy Purpose

Altered lipid metabolism is a prominent abnormality in patients with nephrotic syndrome, which is defined as the presence of proteinuria and hypoalbuminemia at 3.5 g/d or higher. Nephrotic syndrome may arise due to primary nephropathic and systemic diseases, with specific underlying disease prevalence varying by patient age.

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as blood pressure and cholesterol-lowering medications,

diuretics, anticoagulants, and immune system–suppressing medications, in patients with treatment-resistant nephrotic syndrome.<sup>9</sup>

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with treatment-resistant nephrotic syndrome?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest are individuals with treatment-resistant nephrotic syndrome.

### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with nephrotic syndrome are actively managed by nephrologists in an outpatient clinical setting.

### ***Comparators***

Comparators of interest include medical management with blood pressure and cholesterol-lowering medications, diuretics, anticoagulants, and immune system–suppressing medications.

Patients with nephrotic syndrome are actively managed by nephrologists in an outpatient clinical setting. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Based on the available literature, patients with nephrotic syndrome should be followed for at least 2 years after completion of treatments.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Prospective Cohorts**

Two prospective single-cohort studies have shown improvements in nephrotic syndrome with LDL apheresis. Muso et al (1999) developed an apheresis treatment protocol in 24 patients with focal segmental glomerulosclerosis and nephrotic syndrome and 1 patient with minimal change nephrotic syndrome.<sup>10</sup> Results showed rapid improvements of hyperlipidemia levels and a high incidence of remission at relatively short intervals posttreatment. Hattori et al (2003) reported remission of nephrotic syndrome in 7 of 11 patients with steroid- and cyclosporine-resistant primary focal segmental glomerulosclerosis after initiating prednisone therapy with LDL apheresis.<sup>11</sup>

Muso et al (2015) reported on the short-term results of a prospective single-cohort study of LDL apheresis for drug-resistant nephrotic syndrome.<sup>12</sup> Over 2 years, the study enrolled 58 patients with nephrotic syndrome resistant to primary medication (usually full-dose steroids or saturated cyclosporine A for at least 4 weeks) who were considered candidates for LDL apheresis. The 58 patients underwent 64 episodes of LDL apheresis, of which 17 episodes were excluded from analysis due to missing urinary protein data or the need to estimate urinary protein data (14 episodes), resolution of proteinuria before LDL apheresis (7 episodes), and treatment with LDL apheresis less than 4 weeks after the primary medication (2 episodes). Short-term clinical data for the 47 episodes in 44 patients were analyzed. Resolution of nephrotic syndrome occurred in 25 (53.1%) episodes. Muso et al (2015) also published updated results reporting that, of the 44 subjects followed for 2 years, 21 (47.7%) showed remission based on a urinary protein level less than 1.0 g/d.<sup>13</sup>

### **Section Summary: Low-Density Lipoprotein Apheresis for Nephrotic Syndrome**

Small nonrandomized studies using variable schedules of LDL apheresis with short-term follow-up have reported that apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies, with concurrent controls and longer-term follow-up, are necessary to determine whether outcomes are improved for the use of LDL apheresis in nephrotic syndrome.

### **Low-Density Lipoprotein Apheresis for Other Indications**

#### **Sudden Sensorineural Hearing Loss**

#### **Clinical Context and Therapy Purpose**

The purpose of LDL and fibrinogen apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as systemic steroids or other measures dictated by the etiology (if known), in patients with sudden sensorineural hearing loss.

The question addressed in this evidence review is: Does the use of LDL and fibrinogen apheresis improve the net health outcome in individuals with sudden sensorineural hearing loss?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest are individuals with sudden sensorineural hearing loss.

#### ***Interventions***

The therapy being considered is LDL and fibrinogen apheresis. Low-density lipoprotein and fibrinogen apheresis isolates plasma fibrinogen and serum LDL and discriminately removes them, leaving other factors intact, allowing the filtrated plasma to be returned to the patient. Patients with sudden sensorineural hearing loss are actively managed by otolaryngologists in an outpatient clinical setting. Low-density lipoprotein and fibrinogen apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

#### ***Comparators***

Comparators of interest include systemic steroids or other medical treatment based upon the etiology of the sudden sensorineural hearing loss, if known.

Patients with sudden sensorineural hearing loss are actively managed by otolaryngologists in an outpatient clinical setting.

#### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Little literature is available to determine appropriate follow-up; however, treatment success would be determined within approximately 2-10 days following treatment.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### Review of Evidence

#### Randomized Controlled Trials

Sückfull et al (2002) reported on the results of a RCT using LDL apheresis to treat sudden sensorineural hearing loss, which is an acute, mostly unilateral, inner ear disorder of unknown etiology.<sup>14</sup> This RCT allocated 201 patients to single fibrinogen plus LDL apheresis or standard treatment (prednisolone, hydroxyethyl starch, and pentoxifylline). The primary outcome was the recovery of hearing as measured by pure-tone audiometry 48 hours after treatment began. There were no statistically significant differences in the improvements of pure-tone thresholds between patients who received the apheresis and those who received a standard regimen (difference = 7.7; 95% confidence interval [CI], -8.2 to 23.6). Bianchin et al (2010) reported on the results of a RCT in which 132 patients were randomized to standard treatment of glycerol and dexamethasone plus a single heparin-induced extracorporeal LDL precipitation apheresis or standard treatment only.<sup>15</sup> An a priori primary endpoint, power calculations, and a statistical plan to control for type I error for multiple comparisons were not reported. The proportion of patients achieving hearing recovery was significantly higher in patients receiving heparin-induced extra-corporeal LDL precipitation apheresis plus standard treatment than in those receiving standard care alone after day 1 (75% vs. 42%) and day 10 (76% vs. 45%) of treatment, respectively. Further evaluation and replications of these findings are required because of conflicting reports.

#### Diabetic Foot Ulcers

##### Clinical Context and Therapy Purpose

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as infection control and, in some cases, amputation, in patients with severe diabetic foot ulcerations.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with severe diabetic foot ulcerations?

The following PICO was used to select literature to inform this review.

##### *Populations*

The relevant population of interest are individuals with severe diabetic foot ulcerations.

##### *Interventions*

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with severe diabetic foot ulcerations are actively managed by endocrinologists in an outpatient clinical setting; a wound care or vascular specialist may also treat diabetic foot ulcers. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### ***Comparators***

Comparators of interest include standard of care measures, such as infection control and, in some cases, amputation.

Patients with severe diabetic foot ulcerations are actively managed by endocrinologists in an outpatient clinical setting; a wound care or vascular specialist may also treat diabetic foot ulcers.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, morbid events, and treatment-related morbidity.

Based on the limited available literature, patients with severe diabetic foot ulcerations should be followed until the infection is cleared and for several months after. However, diabetes is a chronic condition, and patients require lifelong medical management.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Case Series**

Rietzsch et al (2008) reported on data from a prospective case series of 17 patients with severe diabetic foot ulcerations treated with LDL apheresis regularly until fibrinogen levels were stabilized at 3 g/L or infection was controllable, as evidenced by alleviation of necrosis.<sup>16</sup> They hypothesized that lowering fibrinogen and possibly lowering plasma viscosity would improve perfusion to the ischemic tissue and facilitate wound healing. Patients underwent between 1 and 7 treatments and were followed for 2 to 73 months. The authors concluded that LDL apheresis might have improved wound healing and reduced the risk of lower leg amputations; however, there was no control group or formal quantitative assessments of the lesions.

#### **Peripheral Artery Disease**

##### **Clinical Context and Therapy Purpose**

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as lifestyle changes, medications, and surgery, in patients with peripheral artery disease.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with peripheral artery disease?

The following PICO was used to select literature to inform this review.

##### ***Populations***

The relevant population of interest are individuals with peripheral artery disease.

### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with peripheral artery disease are actively managed by vascular specialists and cardiologists. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### ***Comparators***

Comparators of interest include standard of care measures, such as lifestyle changes, medications, and surgery.

Patients with peripheral artery disease are actively managed by vascular specialists and cardiologists.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Available literature does not describe recommended follow-up for patients with peripheral artery disease. However, peripheral artery disease is a chronic condition and must be managed throughout the lifetime of the patient.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Case Series**

Tsuchida et al (2006) reported on data from a case series of 31 patients with peripheral artery disease (84% Fontaine symptom classification II) and an average LDL level of 197 mg/dL.<sup>17</sup> The average number of LDL apheresis treatments was 9.6. Improvement of at least 10% for symptomatic parameters (coldness, 89%; numbness, 64%; rest pain, 100%) was observed with no symptoms worsening. Using the same 10% criterion as for the symptomatic parameters, the Ankle-Brachial Index improved in 60% of limbs observed, worsened in 2%, and mean tolerated walking distance improved in 16 (70%) of 23 patients. No change was observed in any of the arterial occlusive lesions observed.

#### **Preeclampsia**

##### **Clinical Context and Therapy Purpose**

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medications to lower blood pressure, in patients with preeclampsia.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with preeclampsia?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest are individuals with preeclampsia.

### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with preeclampsia are actively managed by obstetricians. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting.

### ***Comparators***

Comparators of interest include standard of care measures, such as blood pressure–lowering medications.

Patients with preeclampsia are actively managed by obstetricians.

### ***Outcomes***

The general outcomes of interest are OS , disease-specific survival, change in disease status, morbid events, and treatment-related morbidity.

Patients with preeclampsia would be followed until the birth of the child and the mother’s return to normal blood pressure.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Case Series**

Wang et al (2006) reported on data from a prospective case series of 13 women with preeclampsia.<sup>19</sup> Of the 13, 9 underwent from 1 to 7 heparin-mediated extracorporeal LDL precipitation apheresis treatments and were reported to have experienced longer gestation by an average of 18 days (range = 3-49 days). Mortality was 1 in 9 in neonates of apheresis-treated mothers and 1 in 4 in neonates of mothers not treated with apheresis. The high risk of mortality in preeclampsia and the improved perinatal outcomes that accompany longer gestation are important reasons for the further study of LDL apheresis.

#### **Non-Arteritic Acute Anterior Ischemic Optic Neuropathy**

##### **Clinical Context and Therapy Purpose**

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, which are still being investigated and include surgical, systemic

and topical pharmacological, and intravitreal interventions, in patients with non-arteritic acute anterior ischemic optic neuropathy.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with non-arteritic acute anterior ischemic optic neuropathy?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest are individuals with non-arteritic acute anterior ischemic optic neuropathy.

### ***Interventions***

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with non-arteritic acute anterior ischemic optic neuropathy are actively managed by ophthalmologists. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### ***Comparators***

Comparators of interest include standard of care measures, which are still being investigated, such as surgical, systemic and topical pharmacological, and intravitreal interventions.

Patients with non-arteritic acute anterior ischemic optic neuropathy are actively managed by ophthalmologists.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Patients with non-arteritic acute anterior ischemic optic neuropathy would be followed until the condition is resolved.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Case Series**

Ramunni et al (2005) reported on a prospective case series of 11 patients with non-arteritic acute anterior ischemic optic neuropathy who were treated with 3 courses of LDL apheresis in conjunction with standard therapy of prednisone, salicylate, and pentoxifylline.<sup>19</sup> All patients reported improvements in visual function, but the contribution of the LDL apheresis cannot be evaluated in a nonrandomized multi-intervention cohort.

## Section Summary: Low-Density Lipoprotein Apheresis for Conditions Other Than Hypercholesterolemia

The evidence on the use of LDL apheresis for sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy consists of prospective case series. Larger randomized trials with longer follow-up are needed to determine the impact of LDL apheresis on health outcomes for these conditions.

## High-Density Lipoprotein Delipidation and Plasma Reinfusion for Acute Coronary Syndrome Clinical Context and Therapy Purpose

The purpose of selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medications, coronary bypass surgery, and angioplasty and stenting, in patients with acute coronary syndrome.

The question addressed in this evidence review is: Does the use of selective HDL delipidation and plasma reinfusion improve the net health outcome in individuals with acute coronary syndrome?

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest are individuals with acute coronary syndrome.

### *Interventions*

The therapy being considered is selective HDL delipidation and plasma reinfusion. This procedure removes plasma from the body, processes it through a delipidation device, and returns the blood to the patient. This process selectively removes cholesterol from HDL and converts major  $\alpha$ -HDL to pre- $\beta$ -like HDL, which is a form of HDL that enhances cholesterol transport to the liver; it is thought to reduce atherosclerosis and burden. The plasma with pre- $\beta$ -like HDL is then reinfused into the patient.

Patients with acute coronary syndrome are often first seen by emergency room physicians then are actively managed by cardiologists in a tertiary care setting. Selective HDL delipidation and plasma reinfusion may be performed in a specialty center or a tertiary care setting.

### *Comparators*

Comparators of interest include standard of care measures, such as medications, coronary bypass surgery, and angioplasty and stenting.

Patients with acute coronary syndrome are often first seen by emergency room physicians, then are actively managed by cardiologists and/or cardiac surgeons in a tertiary care setting.

### *Outcomes*

The general outcomes of interest are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity.

Literature indicating appropriate follow-up is lacking; however, patients with acute coronary syndrome would be followed by a cardiologist until the acute episode is resolved and throughout the life of the patient.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Randomized Controlled Trials

Waksman et al (2010) reported on the results of a RCT that allocated 28 patients with acute coronary syndrome to 7 weekly therapeutic sessions of apheresis and plasma reinfusion with or without HDL delipidation.<sup>20</sup> During catheterization and up to 2 weeks after the apheresis sessions were completed, intravascular ultrasound was performed on a target vessel. Pre- $\beta$ -like HDL and  $\alpha$ -HDL levels in the plasma before and after delipidation changed from 5.6% to 79.1% and 92.8% to 20.9%, respectively. Intravascular ultrasound showed some evidence of regression in total atheroma volume in the delipidation patients, but this finding was not statistically significant (12.18 mm<sup>3</sup> in the delipidated group vs. 2.80 mm<sup>3</sup> in the control group;  $p=0.268$ ). No additional studies were identified. The trial was not powered to detect any changes in clinical events associated with the regression of atheroma volume due to the short interval of time of follow-up.

### Section Summary: High-Density Lipoprotein Delipidation and Plasma Reinfusion for Acute Coronary Syndrome

The evidence on the use of delipidated HDL plasma for acute coronary syndrome consists of a single RCT. While there were improvements in certain biochemical measures (e.g., pre- $\beta$ -like HDL and  $\alpha$ -HDL levels), there was no significant change in atheroma volume. Larger randomized trials with longer follow-up and clinically relevant outcomes are needed to determine the impact of delipidated HDL plasma on acute coronary syndrome.

## Low-Density Lipoprotein Apheresis for Acute Coronary Syndrome

### Clinical Context and Therapy Purpose

The purpose of LDL apheresis is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medications, coronary bypass surgery, and angioplasty and stenting, in patients with acute coronary syndrome.

The question addressed in this evidence review is: Does the use of LDL apheresis improve the net health outcome in individuals with acute coronary syndrome?

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest are individuals with acute coronary syndrome.

### *Interventions*

The therapy being considered is LDL apheresis. Low-density lipoprotein apheresis isolates plasma and discriminately removes LDL particles, leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Patients with acute coronary syndrome are often first seen by emergency room physicians then are actively managed by cardiologists in a tertiary care setting. Low-density lipoprotein apheresis may be performed in a specialty apheresis center or a tertiary care setting on an outpatient basis.

### *Comparators*

Comparators of interest include standard of care measures, such as medications, coronary bypass surgery, and angioplasty and stenting.

Patients with acute coronary syndrome are often first seen by emergency room physicians, then are actively managed by cardiologists and/or cardiac surgeons in a tertiary care setting.

### **Outcomes**

The general outcomes of interest are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity.

Literature indicating appropriate follow-up is lacking; however, patients with acute coronary syndrome would be followed by a cardiologist until the acute episode is resolved and throughout the life of the patient.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

#### **Randomized Controlled Trials**

Banerjee et al (2020) evaluated the impact of LDL apheresis in nonfamilial hyperlipidemia acute coronary syndrome patients treated with percutaneous coronary intervention in the 2-phase Plaque Regression and Progenitor Cell Mobilization with Intensive Lipid Elimination Regimen (PREMIER) trial.<sup>21</sup> In PREMIER, 160 patients from 4 Veterans Affairs sites were randomly assigned to intensive lipid-lowering therapy of a single LDL apheresis procedure plus statins or standard medical therapy with statins alone within 72 hours of percutaneous coronary intervention. Results revealed the mean LDL reduction at discharge to be significantly improved in both the intensive lipid-lowering and standard medical therapy groups (53% and 17%) as compared to baseline ( $p < 0.0001$  for both), with sustained improvement in LDL levels at 30 days ( $p < 0.0001$ ) and 90 days ( $p < 0.0001$ ) for both groups. No significant difference in LDL levels between the study groups was observed at 30 ( $p = 0.10$ ) or 90 days ( $p = 0.34$ ). Additionally, the raw change in total plaque volume on average decreased more in the intensive lipid-lowering group compared to the standard therapy group ( $-6.01$  vs.  $-0.95$  mm<sup>3</sup>; difference of means,  $-5.06$ ; 95% CI,  $-11.61$  to  $1.48$ ;  $p = 0.1286$ ), while the percentage change in total plaque volume on average decreased by 4.81% in the intensive lipid-lowering group but increased by 2.31% in the standard therapy group, with a difference of  $-7.13\%$  (95% CI,  $-14.59$  to  $0.34$ ;  $p = 0.0611$ ). PREMIER was limited by its small sample size, primarily male enrollment, short follow-up, surrogate endpoint evaluation, absence of lipoprotein(a) and other inflammatory marker data, and not being powered to assess clinical outcomes.

#### **Section Summary: Low-Density Lipoprotein Apheresis for Acute Coronary Syndrome**

The evidence on the use of LDL apheresis for acute coronary syndrome consists of a single RCT. While there were improvements in the mean LDL reduction and percentage change in total plaque volume in the intensive-lipid lowering group as compared to standard therapy, no significant differences were seen. Larger randomized trials with longer follow-up and clinically relevant outcomes are needed to determine the impact of LDL apheresis on acute coronary syndrome.

### **Summary of Evidence**

#### **Familial Hypercholesterolemia**

For individuals with homozygous FH who are unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple non-

randomized prospective and retrospective small cohort studies and a systematic review. Relevant outcomes are OS disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis, with means ranging from 57% to 75%. Currently, the direct evidence does not demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trials (RCTs) comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible and are unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with heterozygous FH who are unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple non-randomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. Currently, there is no direct evidence that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trials comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible and are unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### **Nonfamilial Hypercholesterolemia**

For individuals with non-FH who receive LDL apheresis, the evidence includes multiple retrospective and prospective nonrandomized cohort studies. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pretreatment and posttreatment. Randomized trials in patient populations that are well-characterized regarding previous treatments, lipid levels, and comorbidities are necessary to demonstrate improvements in health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Nephrotic Syndrome**

For individuals with treatment-resistant nephrotic syndrome who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Using variable schedules of LDL apheresis with short-term follow-up, these studies have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer-term follow-up are necessary to determine whether outcomes are improved with the use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Other Indications**

For individuals with sudden sensorineural hearing loss who receive LDL and fibrinogen apheresis, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. One RCT compared LDL apheresis with the standard treatment of prednisolone, hydroxyethyl starch, and pentoxifylline; it reported no statistically significant differences in hearing recovery between groups. The second RCT compared the combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the addition of apheresis to standard treatment. An a priori primary endpoint, power calculations, and the statistical plan to control for type I error for multiple comparisons were not reported in the second trial. Further evaluation and

replication of these findings are required given the inconsistent reporting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with severe diabetic foot ulcerations who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity. In the case series, patients underwent from 1 to 7 treatment procedures and were followed for 2 to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations, but results were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with peripheral artery disease who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Improvements in gestation were reported but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-arteritic acute anterior ischemic optic neuropathy who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Acute Coronary Syndrome**

For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes a RCT. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (e.g., pre- $\beta$ -like HDL and  $\alpha$ -HDL levels). There were no significant changes in atheroma volume. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of delipidated HDL plasma on acute coronary syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with acute coronary syndrome who receive LDL apheresis, the evidence includes a RCT. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results revealed a nonsignificant improvement in the mean LDL reduction and percentage change in total plaque volume in the intensive-lipid lowering group (including apheresis) as compared to standard therapy with statins alone. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of LDL apheresis on acute coronary syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence (NICE) updated its guidance on familial hypercholesterolemia (FH):

1.3.3.1 "Healthcare professionals should consider offering LDL [low-density lipoprotein] apheresis for the treatment of adults and children/young people with homozygous FH. The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.

1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist center on a case-by-case basis and data recorded in an appropriate registry."<sup>22</sup>

### American Society for Apheresis

In 2019, the American Society for Apheresis updated guidelines on the use of apheresis for 7 conditions (Table 1).<sup>23</sup>

**Table 1. Guidelines on Use of Low-Density Lipoprotein Apheresis**

Recommendation	Category	Grade <sup>a</sup>
Homozygous familial hypercholesterolemia	I	1A
Heterozygous familial hypercholesterolemia	II	1A
Focal segmental glomerulosclerosis	II	2C
Lipoprotein (a) hyperlipoproteinemia	II	1B
Peripheral vascular diseases	II	1B
Phytanic acid storage disease (Refsum disease)	II	2C
Sudden sensorineural hearing loss	III <sup>b</sup>	2A

<sup>a</sup> Grade 1A: strong recommendation, high-quality evidence; grade 1B: strong recommendation, moderate-quality evidence; grade 2A: weak recommendation, high-quality evidence; grade 2C: weak recommendation, low-quality evidence.

<sup>b</sup> Optimum role not established.

### American Heart Association

In 2015, the American Heart Association issued a scientific statement on the treatment of heterozygous FH indicating that high-risk adults should be treated with available pharmacotherapy with an initial goal of reducing low-density lipoprotein cholesterol (LDL-C) by at least 50%, usually with a statin, and treatment should be intensified based on the response.<sup>24</sup> It also stated that there are no data to inform pediatric treatment goals, whether to target an LDL-C level of less than 100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline.

For homozygous FH, the American Heart Association has recommended that lipid apheresis should be considered by 5 years of age or earlier in exceptional circumstances and should be used after maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The LDL-C selection criteria for lipid apheresis include a reduction in LDL-C of less than 50% by other treatments and residual severe LDL-C elevation of more than 300 mg/dL or more than 200 mg/dL with prevalent cardiovascular disease.

No guidelines on therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion were identified.

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

Not applicable.

**Medicare National Coverage**

National Coverage Decision 110.14 on apheresis lists the indications for which apheresis is a covered benefit in cellular and immune-complex mediated disorders. There is no determination for hypercholesterolemia or LDL apheresis.<sup>25</sup>

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02791802	Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes	1000	Aug 2021
NCT04088799	Effect of LDL-Apheresis on Cardiovascular and Renal Outcomes in Focal Segmental Glomerulosclerosis (FSGS)	10	Dec 2022

NCT: national clinical trial.

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## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Type of familial hypercholesterolemia (i.e., homozygous or heterozygous)
  - Documented failed trial of diet and maximum drug therapy (including names of drugs and duration of treatment)
  - Laboratory report(s) for low-density lipoprotein levels

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion
	36516	Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion
HCPCS	S2120	Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/09/1999	BCBSA Medical Policy adoption
06/01/2001	Policy reviewed. Policy statement unchanged
10/01/2010	Policy Revision with title change from Lipid Apheresis in the Treatment of Patients with Severe, Refractory Hypercholesterolemia
04/04/2014	Policy revision with position change
07/31/2015	Coding Update
01/01/2017	Policy title change from Low-Density Lipid Apheresis Policy revision without position change
07/01/2017	Policy revision without position change
02/01/2018	Coding update
07/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. Policy statement and literature updated.
07/01/2022	New custom policy. No change to policy statement.
06/01/2023	Annual review. No change to policy statement.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Lipid Apheresis BSC8.07</b></p> <p><b>Policy Statement:</b></p> <ol style="list-style-type: none"> <li>I. Low-density lipoprotein (LDL) apheresis may be considered <b>medically necessary</b> in patients with homozygous familial hypercholesterolemia (FH) as an alternative to plasmapheresis.</li>   <li>II. Low-density lipoprotein apheresis may be considered <b>medically necessary</b> in patients with heterozygous familial hypercholesterolemia when <b>both</b> of the following criteria are met:                     <ol style="list-style-type: none"> <li>A. Failed diet therapy and maximum tolerated combination drug therapy*</li> <li>B. Meet <b>one</b> of the following U.S. Food and Drug Administration approved indications (all LDL levels represent the best achievable LDL level after a program of diet and drug therapy):                             <ol style="list-style-type: none"> <li>1. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 300 mg/dL</li> <li>2. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 200 mg/dL* AND documented coronary artery disease*</li> </ol> </li> </ol> </li>   <li>III. Low-density lipoprotein apheresis is considered <b>investigational</b> for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, non-arteritic acute anterior ischemic optic neuropathy, and acute coronary syndrome.</li>   <li>IV. Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered <b>investigational</b> for all indications, including but not limited to acute coronary syndrome.</li> </ol> <p>*For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines section.</p>	<p><b>Lipid Apheresis BSC8.07</b></p> <p><b>Policy Statement:</b></p> <ol style="list-style-type: none"> <li>I. Low-density lipoprotein (LDL) apheresis may be considered <b>medically necessary</b> in patients with homozygous familial hypercholesterolemia (FH) as an alternative to plasmapheresis.</li>   <li>II. Low-density lipoprotein apheresis may be considered <b>medically necessary</b> in patients with heterozygous familial hypercholesterolemia when <b>both</b> of the following criteria are met:                     <ol style="list-style-type: none"> <li>A. Failed diet therapy and maximum tolerated combination drug therapy*</li> <li>B. Meet <b>one</b> of the following U.S. Food and Drug Administration approved indications (all LDL levels represent the best achievable LDL level after a program of diet and drug therapy):                             <ol style="list-style-type: none"> <li>1. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 300 mg/dL</li> <li>2. Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 200 mg/dL* AND documented coronary artery disease*</li> </ol> </li> </ol> </li>   <li>III. Low-density lipoprotein apheresis is considered <b>investigational</b> for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, non-arteritic acute anterior ischemic optic neuropathy, and acute coronary syndrome.</li>   <li>IV. Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered <b>investigational</b> for all indications, including but not limited to acute coronary syndrome.</li> </ol> <p>*For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines section.</p>