Policy Statement

Low-density lipoprotein (LDL) apheresis may be considered medically necessary in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

Low-density lipoprotein (LDL) apheresis may be considered medically necessary in patients with heterozygous familial hypercholesterolemia (FH) when both of the following criteria are met:

- Failed diet therapy and maximum tolerated combination drug therapy*
- Meets 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.)
  - Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 300 mg/dL
  - Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 200 mg/dL* and documented coronary artery disease*

Low-density lipoprotein (LDL) apheresis is considered investigational for all other uses, including nonfamilial hypercholesterolemia, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy.

Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered investigational.

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

Policy Guidelines

A scientific statement from American Heart Association 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 coronary artery disease 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 non-exercise stress test
The frequency of LDL apheresis varies, but typically averages once every 2 weeks to obtain an interapheresis level of LDL cholesterol 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 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 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 low-density lipoprotein (LDL) apheresis systems have been approved by the U.S. Food and Drug Administration (FDA) for marketing. In February 1996, the Liposorber LA-15® System (Kaneka Pharma, New York, NY), 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 October 2013, the Liposorber LA-15® System was approved for additional indications through the humanitarian device exemption 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] ≥60 mL/min/1.73 m² or
- The patient is post renal transplantation.”

In September 2007, the HELP® System (B. Braun, Melsungen, Germany), a heparin-induced extracorporeal LDL precipitation, was approved by the FDA through the premarket approval process for use in the above indication. FDA product code: MMY.

No devices have been approved by the FDA specifically for high-density lipoprotein delipidation. The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences, Pleasanton, CA) was tested in clinical studies, but the company ceased business operations in 2012.

**Rationale**

**Background**

**Low-Density Lipoprotein Apheresis**

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

The apheresis procedure is designed to isolate plasma. The LDLs are then selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation (HELP), dextran sulfate adsorption, or double-filtration plasma pheresis of lipoprotein. In immunoadsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL, because apo B is the protein moiety of LDL. In HELP, 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.

Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion removes plasma from the body by apheresis, processed through a delipidation device, and then returned to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major α-HDL to pre-β-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-β-like HDL is then reinfused into the patient.

**Diseases Treated with Low-density lipoprotein (LDL) Apheresis**

Lipid apheresis is used for disorders with marked hyperlipidemia, primarily familial hypercholesterolemia (FH). A dominantly inherited disorder, FH results from a mutation in the gene that encodes for the specific cell surface receptor responsible for 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 low-density lipoprotein cholesterol (LDL-C) levels that are approximately 2 to 3 times levels considered acceptable (i.e., >300 mg/dL). Affected male patients typically develop coronary heart disease 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 in 1 in 1 million subjects. Due to the total lack of functioning LDL receptors, serum levels of LDL-C may be elevated 6-fold (>500 mg/dL). Homozygotes may develop severe aortic stenosis and coronary heart disease 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.

**Literature Review**

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Also known as surrogate outcome measures, intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

**Low-Density Lipoprotein Apheresis for homozygous and heterozygous Familial Hypercholesterolemia**

In 2008, the National Institute for Health and Care Excellence (NICE) produced a systematic review of the literature on familial hypercholesterolemia (FH) that included use of low-density lipoprotein (LDL) apheresis in its management. Although small RCTs were identified, they were not randomized to the treatment question of LDL apheresis versus other treatments but rather evaluated apheresis in each arm. Therefore studies with lower level evidence-informed reviewers' conclusions. They found that, in homozygous individuals, apheresis is relatively safe and reduces LDL, but were unable to draw definitive conclusions on newer statin agents in conjunction with, or instead of, apheresis. They could not form recommendations on the frequency of treatments. For heterozygous persons, authors concluded that there was insufficient evidence to define entry criteria for apheresis treatment and recommended this intervention only in exceptional cases. The NICE review is summarized below:

- There are no RCTs for the treatment of FH homozygous individuals. However, observational studies of FH homozygous individuals showed that treatment with LDL apheresis lowered LDL concentrations by 72% compared with use of multiple lipid-modifying maximal drug therapy.
- Pre and post studies showed that LDL apheresis treatment of individuals with FH who were primarily heterozygous and receiving lipid-lowering drugs demonstrated a total low-density lipoprotein cholesterol (LDL-C) percent decrease ranging from 34% to 81%.
- In 2 small studies of individuals with heterozygous FH receiving LDL apheresis and lipid-modifying drug treatment, symptoms of coronary artery disease improved in 4 (16%) individuals and in 3 (13%) individuals, respectively.
- The major limitation of these recommendations concerns the basis for treatment comparators: the studies compared LDL apheresis with older studies that used less well tolerated drugs or suboptimal statin doses. The current standard of care for homozygous and heterozygous FH has changed with the availability of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (Evolocumab, Alirocumab) and use of maximally tolerated statins doses.

Wang et al (2016) published a systematic review of LDL apheresis that included 15 studies in patients with homozygous and heterozygous FH treated with LDL apheresis. 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 for mean LDL-C reductions after apheresis of 57% to 75% for patients with homozygous FH and of 58% to 63% for patients with heterozygous FH. No hard end points such as cardiovascular (CV) outcomes or mortality were reported.

Assessing the efficacy for a therapeutic intervention involves making a determination whether an intervention improves health outcomes compared with available alternatives. The optimal study design for this purpose is an RCT that compares the therapeutic intervention with existing alternative treatments and includes clinically relevant measures of health outcomes. However,
there are ethical limitations in the conduct of long-term RCTs that measure hard end points such as CV outcomes and mortality in patients with FH. An empirical review of multiple nonrandomized studies by Thompson (2013) showed that drastic lowering of LDL by LDL apheresis increases longevity in patients with homozygous FH and decreases CV morbidity in those with FH heterozygotes refractory to or intolerant of statins. However, most of the published guidelines and reviews have not incorporated the evidence gained from newer therapies such as antisense inhibitor of apolipoprotein B synthesis (mipomersen), inhibitor of microsomal transfer protein (lomitapide), and PCSK9 inhibitors (alirocumab, evolocumab), which have been shown to reduce LDL-C levels in patients with homozygous and heterozygous FH. Randomized controlled trials (RCTs) 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.

Section Summary: Low-Density Lipoprotein Apheresis for Homozygous and Heterozygous Familial Hypercholesterolemia

For patients with homozygous or heterozygous FH, no RCTs have compared LDL apheresis alone with no intervention, usual care, or apheresis plus drug therapy. Multiple nonrandomized studies have shown that drastically lowering LDL using lipoprotein apheresis increases longevity in homozygous FH and decreases CV morbidity in FH heterozygotes refractory to or intolerant of statins. 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 CV events. Randomized controlled trials (RCTs) 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.

Low-density lipoprotein (LDL) Apheresis for Non-FH Hyperlipidemia

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 (CVD).

Leebmann et al (2013) reported on a prospective observational multicenter study of 170 patients treated with LDL apheresis for Lp(a)-hyperlipoproteinemia and progressive CVD despite receiving maximally tolerated lipid-lowering treatment. During the 2-year treatment period with LDL apheresis, the authors reported a significant decrease in CV 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 either severe hypercholesterolemia or isolated Lp(a)-hyperlipoproteinemia with progressive CVD. 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 pre-LDL apheresis period (average, 6.8 years), while patients were receiving chronic lipid apheresis treatment (average, 6.8 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). 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%. Additional details about the study procedures and outcomes were described by Muso et al (1999).10

Section Summary: Low-density lipoprotein (LDL) Apheresis for Non-FH Hypercholesterolemia

For patients with hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia without known FH, nonrandomized studies have reported improvements in lipid levels pre- 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 (LDL) Apheresis for Nephrotic Syndrome

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.

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 in 1 patient with minimal change nephrotic syndrome.11 Results showed rapid improvements of hyperlipidemia levels and a high incidence of remission at relatively short intervals posttreatment. Hatori 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.12

In 2015, Muso et al reported on the short-term results of a prospective single-cohort study of LDL apheresis for drug-resistant nephrotic syndrome.13 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 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. Updated results were published in 2015: they reported 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.14

Section Summary: Low-density lipoprotein (LDL) Apheresis for Nephrotic Syndrome

Several 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 (LDL) Apheresis for Other Indications

There are several reports of LDL apheresis use for other indications, including sudden sensorineural hearing loss, diabetic foot ulcers, peripheral arterial disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy some of which are summarized here.

Sudden Sensorineural Hearing Loss

Sückfull et al (2002) reported on the results of an RCT using of LDL apheresis to treat sudden sensorineural hearing loss, which is an acute, mostly unilateral, inner ear disorder of unknown etiology.15 This RCT allocated 201 to single fibrinogen plus LDL apheresis or standard treatment (prednisolone, hydroxyethyl starch, and pentoxyfylline). 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 pure-tone thresholds between patients who received apheresis and those who received standard regimen (difference, 7.7; 95% CI, -8.2 to 23.6). Bianchin et al (2010) reported on the results of an RCT in which 132 patients were randomized to standard treatment of glycerol and dexamethasone plus a single HELP apheresis or standard treatment only. An a priori primary end point, 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 HELP apheresis plus standard treatment that in those receiving standard of care alone after day 1 (75% vs 42%) and day 10 of treatment (76% vs 45%), respectively. Further evaluation and replications of these findings are required because of conflicting reports.

**Diabetic Foot Ulcers**
Rietzsch et al (2008) reported 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. 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. 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**
Tsuchida et al (2006) reported 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. 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 symptom 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**
Wang et al (2006) reported data from a prospective case series of 13 women with preeclampsia. Of the 13, 9 underwent from 1 to 7 heparin-mediated extracorporeal LDL precipitation (HELP) 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**
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. 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 (LDL) 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

Waksman et al (2010) reported the results of an RCT that allocated 28 patients with acute coronary syndrome to 7 weekly therapeutic sessions of apheresis and plasma reinfusion with or without high-density lipoprotein (HDL) delipidation. During catheterization and up to 2 weeks after the apheresis sessions were completed, intravascular ultrasound was performed on a target vessel. Pre-β-like HDL and α-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 was not statistically significant (12.18 mm³ [SD=36.75] in the delipidated group vs 2.80 mm³ [SD=21.25] 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-β-like HDL and α-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.

Summary of Evidence
Familial Hypercholesterolemia

For individuals with homozygous familial hypercholesterolemia (FH) and unable to achieve target low-density lipoprotein cholesterol (LDL-C) with maximally tolerated pharmacotherapy who receive low-density lipoprotein (LDL) apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and 1 systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastically lowering LDL by lipoprotein apheresis increases longevity in homozygous FH. Studies have reported reductions in LDL-C levels after apheresis, ranging in mean 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 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 a meaningful improvement in the net health outcome.

For individuals with heterozygous FH and unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastically lowering LDL using LDL apheresis decreases cardiovascular morbidity in FH heterozygotes refractory to or intolerant of statins. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. 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 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 a meaningful improvement in the net health outcome.
Nonfamilial Hypercholesterolemia
For individuals with non-FH who receive LDL apheresis, the evidence includes multiple nonrandomized cohort studies, both retrospective and prospective. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pre- 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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 end point, 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 the effects of the technology on health outcomes.

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, ultimately, results were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are overall survival, 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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

**Acute Coronary Syndrome**
For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are overall mortality, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (e.g., pre-β-like HDL and α-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 the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**National Institute for Health and Care Excellence**
The National Institute for Health and Care Excellence’s 2016 guidance on familial hypercholesterolemia (FH) states the following:

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.”

**European Atherosclerosis Society**
In 2014, the European Atherosclerosis Society (EAS) issued guidelines on the management of homozygous FH, which made the following recommendations on use of low-density lipoprotein (LDL) apheresis:

“This Consensus Panel recommends that lipoprotein apheresis be considered in patients with HoFH [homozygous familial hypercholesterolemia]. Treatment should be started as soon as possible, ideally by age 5 and not later than 8 years.”

In 2013, EAS issued a consensus statement on the management of heterozygous FH: “This Consensus Panel recommends that lipoprotein apheresis be considered in patients with treatment resistant HeFH [heterozygous familial hypercholesterolemia].”

**International FH Foundation**
In 2015, the International FH Foundation published integrated guidelines on treatment for FH, which made the following recommendations about the use of lipoprotein apheresis (see Table 1).
Table 1. Guidelines on Use of Lipoprotein Apheresis

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
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<tr>
<td>Lipoprotein Apheresis should be considered in all patients with homozygous or compound heterozygous FH (i.e., homozygous FH phenotype) and carried out in a dedicated centre with the relevant expertise.</td>
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<tr>
<td>Lipoprotein Apheresis should be considered in patients with heterozygous FH with CHD who cannot achieve LDL-cholesterol targets despite maximal drug therapy or because they cannot tolerate statins.</td>
<td>2A</td>
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<tr>
<td>Lipoprotein Apheresis should be considered in children with homozygous FH by the age of five and no later than eight years.</td>
<td>2A</td>
</tr>
<tr>
<td>Diet and drug therapy to lower LDL cholesterol should be continued during treatment with LA.</td>
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CHD: FH: Familial Hypercholesterolemia; LA: Lipoprotein Apheresis; LDL: Low-Density Lipoprotein.

American Society for Apheresis

In 2013, the American Society for Apheresis issued guidelines on the use of apheresis for 78 conditions (see Table 2).

Table 2. Guidelines on Use of Apheresis

<table>
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<tr>
<th>Guideline</th>
<th>Category</th>
<th>Gradea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein apheresis for homozygous FH is considered first-line treatment</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Heterozygous FH is considered appropriate as a second-line treatment</td>
<td>II</td>
<td>1A</td>
</tr>
<tr>
<td>Lipoprotein (a) hyperlipoproteinemia</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Peripheral vascular diseases</td>
<td>IIIb</td>
<td>2C</td>
</tr>
<tr>
<td>Phytanic acid storage disease (Refsum disease)</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td>Sudden sensorineural hearing loss</td>
<td>IIIb</td>
<td>2A</td>
</tr>
</tbody>
</table>

FH: familial hypercholesterolemia.

a 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.
b Optimum role not established.

American Heart Association

A 2006 scientific statement from American Heart Association (AHA) on the treatment of heterozygous 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, and treatment should be intensified based on response. 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 patients, lipid-lowering therapy, usually statins, should be instituted at diagnosis and as early as possible. Among the 2 currently available proprotein convertase subtilisin/kexin type 9 inhibitors in the United States, only alirocumab has been approved for homozygous FH patients, in whom it has been shown that the addition of alirocumab to standard treatment (statins and ezetimibe but not lipid apheresis) reduces LDL-C by an additional 31%. AHA 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.

Ministry of Health of Ontario

In 2007, the Ministry of Health of Ontario published an evidence-based analysis of the available literature for the period from January 1998 to May 2007. For homozygous FH patients, there was a strong recommendation based on low- to very low quality evidence that the benefits of LDL apheresis outweigh risks and burdens. In contrast, there was a weak recommendation based on low- to very low quality evidence favoring apheresis for heterozygous people. For the small
number of heterozygous people intolerant to lipid-lowering medications or unable to reach lipid level targets on maximal diet and medication, LDL apheresis was indicated to be likely as beneficial and less likely to have fewer adverse effects as plasmapheresis.

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 APHERESIS (therapeutic pheresis) 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.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 3.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01967355</td>
<td>Prolongation of Pregnancy in Preeclampsia by Therapeutic Lipid Apheresis</td>
<td>15</td>
<td>Jun 2017</td>
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<tr>
<td>NCT01518205</td>
<td>HELP-Apheresis in Diabetic Ischemic Foot Treatment (H.A.D.I.F): an RC Trial</td>
<td>132</td>
<td>Dec 2017</td>
</tr>
<tr>
<td></td>
<td>to Evaluate the Effect of LDL-apheresis on the Recovery of Diabetic Ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in Patients With Peripheral Vasculopathy Not Susceptible to Revascularization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02791802</td>
<td>Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes</td>
<td>1000</td>
<td>Feb 2021</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial.

**References**


### Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Type of familial hypercholesterolemia (i.e., homozygous or heterozygous)
  - Documented failed trial of diet and drug therapy
  - 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 benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0342T</td>
<td>Therapeutic apheresis with selective HDL delipidation and plasma reinfusion</td>
</tr>
<tr>
<td></td>
<td>36516</td>
<td>Therapeutic apheresis, with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion <em>(Code revision effective 1/1/2018)</em></td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2120</td>
<td>Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>6A550Z3</td>
<td>Pheresis of Plasma, Single</td>
</tr>
<tr>
<td></td>
<td>6A551Z3</td>
<td>Pheresis of Plasma, Multiple</td>
</tr>
</tbody>
</table>
### Type | Code | Description
--- | --- | ---
ICD-10 Diagnosis | All Diagnoses |  

#### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/09/1999</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2001</td>
<td>Policy reviewed. Policy statement unchanged</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/01/2010</td>
<td>Policy Revision with title change from Lipid Apheresis in the Treatment of Patients with Severe, Refractory Hypercholesterolemia</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/04/2014</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/31/2015</td>
<td>Coding Update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>01/01/2017</td>
<td>Policy title change from Low-Density Lipid Apheresis Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

#### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
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.