Lipid Apheresis

Policy Number: 8.02.04                                      Last Review: 4/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for low-density lipid apheresis when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
LDL apheresis may be considered medically necessary in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

LDL apheresis may be considered medically necessary in patients with heterozygous familial hypercholesterolemia who have failed diet therapy and maximum tolerated combination drug therapy AND meet the following FDA-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 ≥ 300 mg/dL, or
2. Functional hypercholesterolemic heterozygotes with LDL ≥ 200 mg/dL AND documented coronary artery disease. a

When Policy Topic is not covered
LDL apheresis is considered investigational for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, 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 all indications, including but not limited to acute coronary syndrome.

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

Considerations
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 a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or alternative revascularization procedure, or progressive angina documented by exercise or non-exercise stress test.

Because LDL apheresis represents a chronic, lifelong therapy, Plans may consider requiring precertification or prior approval to ensure that the patient meets the patient selection criteria.

Frequency of LDL apheresis varies, but typically averages about 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.

### Description of Procedure or Service

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<th>Comparators</th>
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| Individuals:  
- With homozygous familial hypercholesterolemia unable to achieve target LDL-C with maximally tolerated pharmacotherapy | Interventions of interest are:  
- Low-density lipoprotein apheresis | Comparators of interest are:  
- Medical management with lipid-lowering medications  
- Plasmapheresis | Relevant outcomes include:  
- Overall survival  
- Disease-specific survival  
- Change in disease status  
- Morbid events  
- Treatment-related morbidity |
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<td>With acute coronary syndrome</td>
<td>Selective high-density lipoprotein delipidation and plasma reinfusion</td>
<td>Medical management with lipid-lowering medications</td>
<td>Overall survival, Disease-specific survival, Change in disease status, Morbid events, Treatment-related morbidity</td>
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This use of lipid apheresis has been proposed as a treatment for various types of familial hypercholesterolemia (FH), other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately remove low-density lipoprotein (LDL) particles from the plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.
**Familial Hypercholesterolemia**
For individuals with homozygous FH and unable to achieve target LDL cholesterol (LDL-C) with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and a systematic review. The relevant outcomes are overall survival (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 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. The 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. 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 retrospective and prospective nonrandomized cohort studies. The 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 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. The 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 two RCTs. The 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 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. The 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 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. The 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. The 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 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. The 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. The 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 (eg, 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.

**Background**

**Hyperlipidemia**

A dominantly inherited disorder, familial hypercholesterolemia 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 low-density lipoprotein cholesterol levels that are approximately 2 to 3 times levels considered acceptable (ie, >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 familial hypercholesterolemia may or may not respond adequately to lipid-lowering drugs.

Homoygous hypercholesterolemia is rare, occurring in only in 1 in 1 million subjects. Due to the total lack of functioning LDL receptors, serum levels of low-density lipoprotein cholesterol 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 familial hypercholesterolemia 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**

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 low-density lipoprotein.
The apheresis procedure is designed to isolate plasma. The LDLs are then selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation, 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 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**

Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion removes plasma from the body, 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.

**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® System (Kaneka Pharma), dextran sulfate device, was approved by 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® System (B. Braun), a heparin-induced extracorporeal LDL precipitation, was approved by FDA through the premarket approval process for the same indication. FDA product code: MMY.

In 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.”

No devices have been approved by FDA specifically for HDL delipidation. The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences) was tested in clinical studies, but the company ceased business operations in 2012.
Rationale
This evidence review was created in July 1999 and updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 20, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

There are ethical limitations in the conduct of long-term RCTs that measure hard endpoints such as cardiovascular outcomes and mortality in patients with familial hypercholesterolemia (FH).

Low-Density Lipoprotein Apheresis for homozygous and heterozygous Familial Hypercholesterolemia
Most reviews have not incorporated the evidence gained from newer therapies such as antisense inhibitors of apolipoprotein B synthesis (eg, mipomersen), microsomal transfer protein inhibitors (eg, lomitapide), and PCSK9 inhibitors (eg, alirocumab, evolocumab), which have been shown to reduce low-density lipoprotein cholesterol (LDL-C) levels in patients with homozygous and heterozygous FH. 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.

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 an 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 endpoints such as cardiovascular outcomes or mortality were reported.

**Section Summary: LDL Apheresis for Homozygous and Heterozygous Familial Hypercholesterolemia**
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. 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. 

**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.

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. During the two-year treatment period with LDL apheresis, the authors reported a significant decrease in cardiovascular disease events compared with the two-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. 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 36745 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 in Heigl et al (2015).6

Section Summary: LDL Apheresis for Non-FH Hypercholesterolemia
For patients with hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia without 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.

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 1 patient with minimal change nephrotic syndrome.7 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.8

Muso et al (2015) reported on the short-term results of a prospective single-cohort study of LDL apheresis for drug-resistant nephrotic syndrome.9 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 also published by Muso et al (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.10

Section Summary: 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.

**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. This RCT allocated 201 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 pure-tone thresholds between patients who received apheresis and those who received standard regimen (difference, 7.7; 95% confidence interval, -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 heparin-induced extracorporeal LDL precipitation apheresis or standard treatment only. 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 extracorporeal LDL precipitation apheresis plus standard treatment that in those receiving standard of 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**

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. 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 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. 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 on 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 apheresis treatments and were reported to have experienced longer gestation by an average of 18 days (range, 3-49 days). Mortality was one in nine in neonates of apheresis-treated mothers and one in four 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: 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 on 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 HDL delipidation. During catheterization and up to two 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 finding was not statistically significant (12.18 mm³ in the delipidated group vs 2.80 mm³ 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: HDL 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 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 and a systematic review. The relevant outcomes are overall survival (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. 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. The 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. 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 retrospective and prospective nonrandomized cohort studies. The 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 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. The 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 two RCTs. The 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 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. The 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 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. The 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. The 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 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. The 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 HDL delipidation and plasma reinfusion, the evidence includes an RCT. The 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 (eg, 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 (2017) guidance on familial hypercholesterolemia (FH) has stated 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.”

**American Society for Apheresis**
The American Society for Apheresis (2016) issued guidelines on the use of apheresis for 7 conditions (see Table 1).

**Table 1. Guidelines on Use of Apheresis**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category</th>
<th>Grade&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein apheresis for homozygous familial hypercholesterolemia</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td>II</td>
<td>1A</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Lipoprotein (a) hyperlipoproteinemia</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Peripheral vascular diseases</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Phytanic acid storage disease (Refsum disease)</td>
<td>II&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2C</td>
</tr>
<tr>
<td>Sudden sensorineural hearing loss</td>
<td>III&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2A</td>
</tr>
</tbody>
</table>

<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**
A scientific statement from American Heart Association (2015) on the treatment of heterozygous FH has indicated 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. 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 five 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.20

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></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


**Billing Coding/Physician Documentation Information**

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

**36516** Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion

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

**ICD-10 Codes**

**E78.00** Pure hypercholesterolemia, unspecified

**E78.01** Familial hypercholesterolemia

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

4/1/05 New policy.
4/1/06 No policy statement changes.
4/1/07 No policy statement changes.
4/1/08 No policy statement changes.
Policy statement clarified that other uses, e.g., use in preeclampsia, are considered investigational (previously considered not medically necessary)

No policy statement changes.

No policy statement changes.

No policy statement changes.

No policy statement changes.

Added policy statement indicating therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is investigational; title changed to Lipid Apheresis. Added CPT 0342T.

No policy statement changes.

No policy statement changes.

“No 6-month trial” removed from the second medically necessary policy statement. Additional specific examples added to the LDL apheresis investigational for other uses statement. The Policy Guidelines section was revised by deleting the statement “Maximum tolerated drug therapy is defined as a trial of drugs from at least 2 separate classes of hypolipidemic agents such as bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, or niacin/nicotinic acids.”

No policy statement changes.

Policy statement on high density lipoprotein apheresis was clarified.

No policy statement changes.