Policy Number	**THE802.003**
Policy Effective Date	**02/01/2025**
Policy End Date	**12/31/2025**

Lipid Apheresis

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

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

LDL apheresis **may be considered medically necessary** in individuals with heterozygous familial hypercholesterolemia who have failed diet therapy and maximum tolerated combination drug therapy **(see NOTE)** AND who meet 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 ≥ 300 mg/dL;
- Functional hypercholesterolemic heterozygotes with LDL ≥ 200 mg/dL **AND** documented coronary artery disease **(see NOTE).**

LDL apheresis **is considered experimental, investigational and/or unproven** for all other uses, including, but not limited to nonfamilial hypercholesterolemia.

Therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion **is considered experimental, investigational and/or unproven** for all indications, including but not limited to acute coronary syndrome.

NOTE: For definitions of maximum tolerated drug therapy and documented coronary artery disease, see Description section.

Policy Guidelines

None.

Description

The 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.

Hyperlipidemia
A dominantly inherited disorder, FH results from a variant 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.

A scientific statement from American Heart Association for the treatment of heterozygous FH has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing LDL-C by at least 50%, usually with a statin. (1) This treatment can be followed by achieving an LDL-C of less than 100 mg/dL (absent coronary artery disease [CAD] or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors). The following approach for pharmacotherapy is suggested:

- High-intensity statin therapy to target >50% LDL-C reduction, such as rosuvastatin or atorvastatin.
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding ezetimibe.

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

Documented CAD includes 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.

Homozygous familial hypercholesterolemia (HoFH) is a rare, inherited disorder that causes extremely high levels of cholesterol and a significant risk of early cardiovascular disease and death. Due to the total lack of functioning LDL receptors, serum levels of LDL-C are almost always >500 mg/dL. (2) 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.

Treatment

Using a process similar to kidney dialysis, blood is withdrawn from a vein via a catheter and processed to remove LDL-C particles. Normal blood products are returned via another catheter. LDL-C levels will decrease approximately 50% but will rise between apheresis sessions, so they are necessary approximately weekly or every other week. The procedure is effective and well tolerated though time-consuming and only available in 50-60 sites in the U.S. (2)

The frequency of LDL apheresis varies, but typically averages once every 2 weeks to obtain an interapheresis level of LDL-C at less than 120 mg/dL. Apheresis can lower LDL-C levels by 80% acutely & 30% chronically (weekly or biweekly). (3) Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

A number of different systems are currently available for lipoprotein apheresis (Table 1). Some methods utilize plasma (immunoadsorption, filtration, dextran sulfate [Liposorber], HELP) while others utilize whole blood (DALI and dextran sulfate [Liposorber D]). In the United States, HELP precipitation and dextran sulfate adsorption (Liposorber) are approved by the FDA. (4)

Table 1. Lipoprotein Apheresis Systems

HELP: Heparin-induced extracorporal LDL precipitation	Based on the precipitation of apolipoprotein B containing lipoproteins in acidic conditions by forming complexes with other proteins
DALI: Direct adsorption of lipoproteins	Positively charged apolipoprotein B binds to negatively charged polyacrylate anions
Liposorber: Dextran sulfate	Positively charged apolipoprotein B binds to negatively charged dextran sulfate

MONET: Lipid filtration	Series of filters eliminate lipoproteins based on size
TheraSorb: Apolipoprotein B antibodies	Plasma is passed through columns containing apolipoprotein B antibodies that bind lipoproteins
Lipopac: Apoprotein (a) antibodies (this is only used for research purposes)	Plasma is passed through columns containing apoprotein (a) antibodies that bind Lp(a)

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 the FDA through the premarket approval process for use to "acutely remove LDL-C from the plasma of high-risk patient populations for whom diet has been ineffective or not tolerated."

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

In 2013, the Liposorber LA-15® System was approved for additional indications through the humanitarian device exemption (5) process for the treatment of pediatric patients with nephrotic syndrome associated 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 m^2, or
- The patient is post renal transplantation."

In 2020, the FDA changed the preexisting Humanitarian Use Device (HUD) 2014 designation for the Plasma Delipidation System (PDS-2™ System) to a Humanitarian Device Exemption (HDE). These regulatory pathways are intended to encourage development of devices for rare diseases. The 2020 HDE is indicated "to reduce coronary artery atheroma in adult patients with homozygous FH (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for homozygous FH, including the latest medications and other device therapies approved by the FDA." (6)

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

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

LOW-DENSITY LIPOPROTEIN APHERESIS FOR HOMOZYGOUS AND HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

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

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

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Most reviews have not incorporated the evidence gained from newer therapies such as antisense inhibitors of apolipoprotein B synthesis (e.g., mipomersen), microsomal transfer protein inhibitors (e.g., lomitapide), and PCSK9 inhibitors (e.g., alirocumab, evolocumab), which have been shown to reduce 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.

Systematic Reviews
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. (8) None were 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. Longer-term outcomes showed that LDL may gradually increase after LDL apheresis and could be back to pretreatment levels within 2 to 4 weeks. Five studies followed patients for 1 to 5 years; at the extended follow-ups, reductions after LDL apheresis ranged from 22% to 36%, demonstrating that the effects of the procedure may not last.

Marginal effectiveness of statins in reducing low-density lipoprotein cholesterol (LDL-C) is the reason why extracorporeal removal of LDL-C by lipoprotein apheresis (LA) is recommended at the earliest possible age. Lurirink et al. (2019) noted that it is unknown to what extent LA effectively reduces the burden of CVD in children with HoFH. (9) Therefore, researchers systemically reviewed the literature on the efficacy and safety of LA in children with HoFH. Researchers searched literature using Embase Classic and Embase on studies that evaluated LA in patients with HoFH aged <19 years and reported on at least one of the following outcome measures: cholesterol levels, xanthoma, CVD, or surrogate outcome markers for CVD. Adverse events were also reported on. Seventy-six studies on 209 patients were selected, 45 of these were case series and 31 were case reports. Mean LDL-C reduction per session was 63% and 71% for nonselective and selective modes of LA, respectively. HDL-C levels were best preserved with selective LA. Xanthomata regressed or disappeared in 83% of patients during LA treatment, surrogate parameters of CVD remained stable in most patients. Of 123 patients, 24 experienced a CVD event of whom 10 had experienced a CVD before LA onset. Six patients died at follow-up. Reported side effects were overall minor. Researchers concluded that LA seems to be a safe therapy and substantially reduces LDL-C and xanthomata in children with HoFH but state the efficacy with respect to CVD protection as compared with only pharmacologic and dietary treatment remains unclear.

Registry Data

Where available, lipoprotein apheresis (LA) is the mainstay of rapid and aggressive intervention to prevent death due to coronary heart disease and/or atherosclerosis. In 2018, A-HIT1 registry was conducted by Kayikcioglu et al. with the aim of providing insight to the real-life management of HoFH patients undergoing LA in Turkey, where LA procedures are fully reimbursed and widely available. (10) Participating centers provided patient information, including family history, treatment patterns and relevant laboratory values, via a standard questionnaire. The study evaluated 88 patients (mean age: 27 ± 11 years, 41 women) in 19 centers. All patients were receiving regular LA with a clinical diagnosis of HoFH. Mean age at first symptom disease was 10 ± 10 years, and at diagnosis it was 12 ± 11 years; 74.7% were diagnosed before age 15 years; and only 31% before the age of 7. First referral of most patients was to pediatricians. Early onset coronary artery disease was present in 57.8% of patients. Mean age at first LA was 21 ± 12 years. Only 11 (12.5%) patients were undergoing LA weekly. Mean frequency of apheresis sessions was 19 ± 13 days. For the last four LA sessions, LDL-C levels reached the target in only in 5.7% of patients. Investigators determined that the diagnosis of HoFH is delayed, and LDL targets are not reached. Researchers report that LA frequencies are not optimal, and urgent attention is needed to support the survival of patients with HoFH.

Luirink et al. (2020) notes that LA is considered a pivotal treatment option, but data on its efficacy, safety and optimal performance are limited. (11) Researchers therefore established an international registry on the execution and outcomes of LA in HoFH children. Investigators approached centers worldwide, involved in LA in children with hoFH for participation. The authors collected information on clinical and treatment characteristics on patients aged 0-19

years between November 2016 and November 2018. They reported on LA policies and short-term outcomes. The authors included 50 children, treated at 15 sites in the data. Median (IQR) LDL-C levels at diagnosis, on medication and on LA were 19.2 (16.2-22.1), 14.4 (10.8-16.7) mmol/L and 4.6 mmol/L, respectively. Median (IQR) time between diagnosis and start of LA was 2.8 (1.0-4.7) years. Six (12%) patients developed cardiovascular disease during that period. Most children received LA either weekly (43%) or biweekly (37%). Seven (17%) patients reached mean LDL-C levels <3.5 mmol/L, all of them treated at least weekly. Xanthomas were present in 42 (84%) patients at diagnosis and disappeared completely in 19 (45%) on LA. Side effects of LA were minor. There were significant differences in LA conduction between sites in terms of frequency, responsible medical specialties and vascular access. Reviewers concluded that LA is a safe treatment and may effectively lower LDL-C in children with HoFH. However, there is room for improvement with respect to time of onset and optimization of LA therapy in terms of frequency and execution.

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

For individuals 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 individuals with homozygous FH and 58% to 63% for individuals 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. 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

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with nonfamilial hypercholesterolemia.

Interventions

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

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

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

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

While the focus of most studies of LDL apheresis has been on FH-associated hypercholesterolemia, an RCT evaluating acute coronary syndrome and a small number of observational studies have evaluated LDL apheresis in patients with nonfamilial hyperlipoproteinemia, hypercholesterolemia, or both, usually in conjunction with cardiovascular disease (CVD).

Randomized Controlled Trials
Banerjee et al. (2020) evaluated the impact of LDL apheresis in nonfamilial hyperlipidemia acute coronary syndrome patients treated with percutaneous coronary intervention in the 2-phase Plaque Regression and Progenitor Cell Mobilization with Intensive Lipid Elimination Regimen (PREMIER) trial. (12) In PREMIER, 160 patients from 4 Veterans Affairs sites were randomly assigned to intensive lipid-lowering therapy of a single LDL apheresis procedure plus statins or standard medical therapy with statins alone within 72 hours of percutaneous coronary intervention. Results revealed the mean LDL reduction at discharge to be significantly improved in both the intensive lipid-lowering and standard medical therapy groups (53% and 17%) as compared to baseline ($p<0.0001$ for both), with sustained improvement in LDL levels at 30 days ($p<0.0001$) and 90 days ($p<0.0001$) for both groups. No significant difference in LDL levels between the study groups was observed at 30 ($p=0.10$) or 90 days ($p=0.34$). Additionally, the raw change in total plaque volume on average decreased more in the intensive lipid-

lowering group compared to the standard therapy group (-6.01 vs. -0.95 mm^3 ; difference of means, -5.06; 95% CI, -11.61 to 1.48; p=0.1286), while the percentage change in total plaque volume on average decreased by 4.81% in the intensive lipid-lowering group but increased by 2.31% in the standard therapy group, with a difference of -7.13% (95% CI, -14.59 to 0.34; p=0.0611). PREMIER was limited by its small sample size, primarily male enrollment, short follow-up, surrogate endpoint evaluation, absence of lipoprotein (a) and other inflammatory marker data, and not being powered to assess clinical outcomes.

Observational Studies

Leebmann et al. (2013) reported on a prospective observational multicenter study of 170 patients treated with LDL apheresis for Lp(a)-hyperlipoproteinemia and progressive CVD despite receiving maximally tolerated lipid-lowering treatment. (13) During the 2-year treatment period with LDL apheresis, the authors reported a significant decrease in cardiovascular 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. (14) 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%. Heigl et al. (2015) provided additional details about the study procedures and outcomes. (15)

In 2022, Safarova et al. reported the results of lipoprotein apheresis for 10 plus years on carotid intima medial thickness (CIMT) in 10 patients with severe hypercholesterolemia. (16) Pretreatment LDL cholesterol was 214 mg/dL and 40% of the patients had an Lp(a) >60 mg/dL. As expected, LDL cholesterol and Lp(a) levels decreased over 70% immediately after apheresis. The percentage of patients with CIMT above their "vascular age" decreased from 80% to 30% over the treatment course and the estimated annual rate of change in mean common CIMT was minus 4 µm/year.

Section Summary: LDL Apheresis for Non-FH Hypercholesterolemia

For individuals with hypercholesterolemia and/or hyperlipoproteinemia without FH, a small RCT and observational studies have reported improvements in lipid levels pre- and posttreatment. In patient populations that are well-characterized regarding previous treatments, lipid levels,

and comorbidities, large, randomized trials are necessary to demonstrate improvements in health outcomes.

HIGH-DENSITY LIPOPROTEIN DELIPIDATION AND PLASMA REINFUSION FOR ACUTE CORONARY SYNDROME

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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

Randomized Controlled Trials

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. (17) 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 mm^3 [SD=36.75] in the delipidated group vs 2.80 mm^3 [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 are 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, registry data, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. 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 an 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, registry data, and systematic reviews. Relevant outcomes are overall survival, 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, 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 an improvement in the net health outcome.

Nonfamilial Hypercholesterolemia

For individuals with non-FH who receive LDL apheresis, the evidence includes an RCT evaluating acute coronary syndrome and a small number of observational studies that have evaluated LDL apheresis in individuals with nonfamilial hyperlipoproteinemia, hypercholesterolemia, or both, usually in conjunction with cardiovascular disease (CVD). 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 that the technology results in an improvement in the net health outcome.

Acute Coronary Syndrome

For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes a single RCT. Relevant outcomes are overall survival, disease-specific survival, change in 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 that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)

In 2021, NICE updated its guidance on familial hypercholesterolemia (FH):

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

- 1.3.3.2 – "In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist center on a case-by-case basis and data recorded in an appropriate registry." (18)

American Society for Apheresis (ASFA)

In 2023, the ASFA updated guidelines on the use of apheresis for 7 conditions (see Table 2). (19)

Table 2. Guidelines on Use of Low-Density Lipoprotein Apheresis

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

[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] Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Category II: Disorders for which apheresis is accepted as second-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Category III: Optimum role not established. Decision-making should be individualized.

American Heart Association (AHA)

In 2015 (updated in 2019), the AHA issued a scientific statement on the treatment of heterozygous FH indicating that high-risk adults should be treated with available pharmacotherapy with an initial goal of reducing LDL-C by at least 50%, and treatment should be intensified based on response. (1, 20)

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

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

European Atherosclerosis Society

In 2023, The European Atherosclerosis Society released a consensus statement with clinical guidance for homozygous familial hypercholesterolaemia. They state “Lipoprotein apheresis is foundational in children and adults with HoFH, adjunctive to other lipid-lowering therapy… Treatment should be started as soon as possible… Registry data provide strong evidence for the efficacy and clinical benefit of LA in adults, with resolution of clinical manifestations such as xanthomas and no major safety concerns to date. Rebound effects are slower in HoFH than in HeFH (up to 30 days) with an average LDL-C reduction of 55%, as well as over 50% reduction in Lp(a) concentration. The frequency or requirement for apheresis may be reduced with novel therapies such as lomitapide and evinacumab.” (21)

International Atherosclerosis Society

The International Atherosclerosis Society published guidance for implementing best practice in the care of familial hypercholesterolaemia in 2023. (22) They state “Lipoprotein apheresis is a safe and effective means of treating patients with HoFH on a lifelong basis, especially in combination with statins and ezetimibe. Apheresis units should participate in a national or international network of similar centres to share educational, clinical and research experience and to establish and consolidate a comprehensive clinical quality registry of patients receiving treatment.” The Society published clinical recommendations on the treatment of FH by LA. (Table 3)

Table 3. Clinical Recommendations On The Treatment of FH by Lipoprotein Apheresis

Clinical Recommendations	Class	Level
1. LA should be undertaken, if feasible, in children (aged ≥3 years and <8 years) and adults with HoFH who do not achieve guideline-recommended LDL-cholesterol goals, despite maximally tolerated, combination drug therapy	1	A
2. LA should be undertaken in adults with phenotypic HeFH and progressive ASCVD who do not achieve LDL-cholesterol goals despite combined treatment with a high-potency statin, ezetimibe and a PCSK9 inhibitor, especially those with a Lp(a) concentration ≥125 nmol/l (≥60 mg/dl)	1	B
3. Vascular access for lipoprotein apheresis should initially be via peripheral veins, but an arteriovenous fistula may be needed if peripheral venous access becomes impossible, which may be particularly relevant to children. Central venous catheters are not recommended except in an emergency or as a temporary measure	1	B
4. Onefold to twofold plasma volumes (body weight in kg × 0.045 l) or blood volumes [plasma volume/ (1 − hematocrit)] should be treated weekly or fortnightly in a specialized setting (a lipid clinic, nephrology unit or blood transfusion centre). Plasma exchange requires a smaller extracorporeal blood volume than LA and is recommended as an alternative in children with a body weight <30 kg	1	A
5. All diet and drug therapy to lower LDL-cholesterol concentrations should be continued during treatment with LA, and comprehensive psychosocial support should be offered to all patients receiving LA	1	A

6. Routine full blood counts should be monitored regularly, and iron supplementation initiated if iron-deficiency anemia develops in patients with FH receiving long-term LA	1	A
7. Angiotensin-converting enzyme inhibitors should not be used in patients undergoing LA based on apolipoprotein B adsorption, and angiotensin-receptor blocking agents should be substituted	1	A
8. Patients receiving anticoagulants, such as warfarin, will require dose adjustment or discontinuation several days before an apheresis procedure that uses intravenous heparin, but antiplatelet therapy should be maintained. Direct oral anticoagulants (such as apixaban, dabigatran or rivaroxaban) need only be stopped on the day of apheresis because of their shorter half-life	1	B
9. The cholesterol-lowering efficacy of LA should be monitored by measuring acute reductions in LDL-cholesterol and Lp(a) concentrations (ideally 65–70%) and by calculating the interval mean (C_{mean}) between consecutive procedures, using the Kroon formula: $C_{mean} = C_{min} + k(C_{max} - C_{min})$, for which C_{max} is the pre-procedure value and C_{min} is the post-procedure value. Values for k are 0.65 for LDL-cholesterol in patients with HoFH and 0.71 for LDL-cholesterol in patients with HeFH receiving statin therapy and undergoing LA at fortnightly intervals. Comparison of interval means with the recommended LDL-cholesterol goals for patients with HoFH should be used to adjust the volume of blood or plasma to be treated and/or the frequency of LA procedures as necessary	1	B
10. Because the rate of rebound of plasma Lp(a) levels after LA is similar to that of plasma LDL-cholesterol levels in patients with HeFH, a value for k of 0.71 in the Kroon formula should be considered appropriate when estimating the interval (intercycle) mean concentration of lipoprotein(a); this value may be used to adjust the LA regimen to achieve a therapeutic goal of <90 nmol/l (<43 mg/dl) in patients with elevated Lp(a) concentrations	2	B
11. In children and adults with HoFH and aortic root or coronary artery disease, the effect of LA on disease progression should be monitored at least annually by echocardiography or coronary angiography, respectively. The latter procedure is also applicable to patients with HeFH with coronary disease and should be performed as and when indicated	1	B
12. Adjunctive therapy with a PCSK9 inhibitor, either evolocumab or alirocumab, should be attempted in all patients with FH before starting or while receiving LA. These therapies will be effective mainly in patients with HeFH and often may replace LA. Injected therapeutic agents should be administered soon after, but not immediately before, a LA procedure	1	B
13. Adjunctive therapy with lomitapide or evinacumab should be considered in patients with HoFH, particularly in those with progressive ASCVD, who do not reach guideline-recommended LDL-cholesterol goals while receiving LA combined with statin, ezetimibe and a PCSK9 inhibitor. This adjunctive therapy increases LDL-cholesterol lowering and may reduce the frequency of LA and, if tolerated, sometimes replaces it	2	B

14. When lomitapide or evinacumab is first selected in preference to LA, adjunctive use of LA should be considered in all patients with HoFH who do not reach guideline-recommended LDL-cholesterol goals	2	B

FH: familial hypercholesterolemia; LA: Lipoprotein Apheresis; LDL: low-density lipoprotein; HoFH: homozygous FH; HeFH: heterozygous FH; ASCVD: atherosclerotic cardiovascular disease; kg: kilogram; Lp(a): lipoprotein(a).

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 4.

Table 4. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05181969	Long-term Characterization of Lipoprotein Apheresis Technologies for Individual Device Adaption (LOLIDA) (LOLIDA)	500	Dec 2024 (recruiting)
Unpublished			
NCT04088799	Effect of LDL-Apheresis on Cardiovascular and Renal Outcomes in Focal Segmental Glomerulosclerosis (FSGS)	10	June 2023
NCT02791802	Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes	1000	Dec 2022 (unknown status)

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36516, 0342T
HCPCS Codes	S2120

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement from the American Heart Association. Circulation. Dec 01 2015; 132(22):2167-2192. PMID 26510694
2. National Organization for Rare Disorders. Homozygous Familial Hypercholesterolemia. July 2024. Available at: <https://rarediseases.org> (accessed October 2, 2024).
3. Ison HE, Clarke SL, Knowles JW. Familial Hypercholesterolemia. 2014 Jan 2 [Updated 2022 Jul 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: <https://www.ncbi.nlm.nih.gov> (accessed November 18, 2024).
4. Feingold KR. Lipoprotein Apheresis. February 19, 2023. In: Endotext [Internet], Feingold KR, et al. (Eds), South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID 28402616
5. Food and Drug Administration. Summary of Safety and Probable Benefit (SSPB): LDL Apheresis System (HDE number H120005). 2013. Available at: <https://www.accessdata.fda.gov> (accessed March 5, 2024).
6. HDL Therapeutics. Operator's manual and instructions for use. Plasma Delipidation System (PDS-2 System). Available at: <https://www.accessdata.fda.gov> (accessed March 5, 2024).
7. Food and Drug Administration. Summary of Safety and Probable Benefit (SSPB): High Density Lipoprotein Plasma Delipidation System (HDE number H190001). 2020. Available at: <https://www.accessdata.fda.gov> (accessed March 5, 2024).
8. Wang A, Richhariya A, Gandra SR, et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. J Am Heart Assoc. Jul 06 2016; 5(7):e003294. PMID 27385428
9. Luirink I, Determeijer J, Hutten B, et al. Efficacy and safety of lipoprotein apheresis in children with homozygous familial hypercholesterolemia: A systematic review. J Clin Lipidol. 2019; 13(1):31-39. PMID 30553758
10. Kayikcioglu M, Tokgozoglu L, Yilmaz M, et al. A nation-wide survey of patients with homozygous familial hypercholesterolemia phenotype undergoing LDL-apheresis in Turkey (A-HIT 1 registry). Atherosclerosis. Mar 2018; 270:42-48. PMID 29407887
11. Luirink I, Hutten B, Greber-Platzer S, et al. Practice of lipoprotein apheresis and short-term efficacy in children with homozygous familial hypercholesterolemia: Data from an international registry. Atherosclerosis. April 2020; 299:24-31.
12. Banerjee S, Luo P, Reda DJ, et al. Plaque Regression and Endothelial Progenitor Cell Mobilization With Intensive Lipid Elimination Regimen (PREMIER). Circ Cardiovasc Interv. Aug 2020; 13(8):e008933. PMID 32791950
13. Leebmann J, Roeseler E, Julius U, et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. Circulation. Dec 17 2013; 128(24):2567-2576. PMID 24056686
14. Heigl F, Hettich R, Lotz N, et al. Clinical benefit of long-term lipoprotein apheresis in patients with severe hypercholesterolemia or Lp(a)-hyperlipoproteinemia with progressive cardiovascular disease. Clin Res Cardiol Suppl. Apr 2015; 10:8-13. PMID 25672934
15. Heigl F, Hettich R, Lotz N, et al. Efficacy, safety, and tolerability of long-term lipoprotein apheresis in patients with LDL- or Lp(a) hyperlipoproteinemia: Findings gathered from more

than 36,000 treatments at one center in Germany. Atheroscler Suppl. May 2015; 18:154-162. PMID 25936320
16. Safarova M, Nugent A, Gorby L, et al. Effect of Lipoprotein Apheresis on Progression of Carotid Intima-Media Thickness in Patients with Severe Hypercholesterolemia. Am J Cardiol. Aug 2022; 177:22-27. PMID 35718549
17. Waksman R, Torguson R, Kent KM, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. J Am Coll Cardiol. Jun 15 2010; 55(24):2727-2735. PMID 20538165
18. National Institute for Health and Care Excellence (NICE). Familial hypercholesterolaemia: identification and management [CG71] (2021). Available at: <https://www.nice.org> (accessed March 6, 2024).
19. Connelly-Smith L, Alquist C, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023; 38:77-278.
20. McGowan M, Dehkordi SH, Moriarty P, et al. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. JAHA. 2019; 8(24):e013225. PMID 31838973
21. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical Guidance. Eur Heart J. Jul 2023; 44(25):2277-2291. PMID 37130090
22. Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. Nat Rev Cardiol. Dec 2023; 20(12):845-869. PMID 37322181

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion. 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. (26)

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.

02/01/2025	Document updated with literature review. The following change was made to Coverage: Removed specific examples from experimental, investigational and/or unproven statement on LDL apheresis with the exception of nonfamilial hypercholesterolemia; intent unchanged. Added references 2-4, 7, 9-11, 16, and 20-22. Others removed.
06/01/2023	Reviewed. No changes.
12/15/2022	Document updated with literature review. The following change was made to Coverage: Added “acute coronary syndrome” to experimental, investigational and/or unproven list for LDL apheresis. Added references 2, 21, and 25.
08/01/2021	Reviewed. No changes.
12/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 8, 20, and 21.
08/01/2019	Reviewed. No changes.
10/15/2018	Document updated with literature review. The following changes were made to Coverage: 1) Changed > to ≥ in regard to levels of functional hypercholesterolemic heterozygotes with low-density lipoprotein (LDL); 2) Added nephrotic syndrome to experimental, investigational and/or unproven list for LDL apheresis; 3) Added acute coronary syndrome as an example of an experimental, investigational, and/or unproven indication for therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion. References 20-21 added; multiple references removed.
12/01/2017	Document updated with literature review. The following conditions added to the experimental, investigational and unproven listing: nonfamilial hypercholesterolemia, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease and non–arteritic acute anterior ischemic optic neuropathy.
07/15/2016	Reviewed. No changes.
03/15/2015	Document updated with literature review. The following was added to the coverage statement: therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered experimental, investigational and/or unproven. Title changed from Low Density Lipid Apheresis.
11/15/2012	Document updated with literature review. Coverage unchanged.
08/15/2008	Revised/updated entire document. This policy is no longer scheduled for routine literature review and update
01/01/2006	Revised/updated entire document
06/01/2004	CPT/HCPCS code(s) updated
11/01/2000	New medical document