Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration [FDA]) are considered investigational, including, but not limited to any of the following conditions:

- Alzheimer disease
- Arthritis (includes rheumatoid arthritis)
- Atherosclerosis (e.g., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
- Autism
- Diabetes
- Multiple sclerosis

Policy Guidelines

A number of indications for chelation therapy have received U.S. Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care for any of the following indications:

- Extreme conditions of metal toxicity
- Treatment of chronic iron overload due to either of the following:
  - Blood transfusions (transfusional hemosiderosis)
  - Non-transfusion-dependent thalassemia
- Wilson disease (hepatolenticular degeneration)
- Lead poisoning
- Control of ventricular arrhythmias or heart block associated with digitalis toxicity
- Emergency treatment of hypercalcemia

**Note:** For the last 2 bullet points, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. The FDA removed the approval for disodium-ethylenediaminetetraacetic acid (NaEDTA) as chelation therapy due to safety concerns and recommended that other chelators be used. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia. Lacking the FDA approval, NaEDTA [HCPCS code J3520 (Edetate disodium, per 150mg)] is not a covered benefit.

Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1.

**Coding**

There are no specific CPT codes for the performance of chelation intravenous infusion or injection. The following CPT codes may be used in conjunction with the associated chelation agent:

- **96365**: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- **96366**: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
- **96374**: Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

The following HCPCS codes are specific to chelation therapy:

- **M0300**: IV chelation therapy (chemical endarterectomy)
Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the U.S. Food and Drug Administration. Instead, it addresses off-label indications, including Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

Description

Chelation therapy, home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

The following are the most common J codes (chelation agent) that may be billed in conjunction with the above CPT or HCPCS codes:
- **J0470**: Injection, dimercaprol, per 100 mg
- **J0600**: Injection, edetate calcium disodium, up to 1,000 mg
- **J0895**: Injection, deferoxamine mesylate, 500 mg

Related Policies

- N/A

Benefit Application

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

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

Regulatory Status

In 1953, EDTA (Versenate) was approved by the FDA for lowering blood lead levels among both pediatric and adult patients with lead poisoning. In 1991, succimer (Chemet) was approved by the FDA for the treatment of lead poisoning in pediatric patients only. The FDA approved disodium-EDTA for use in selected patients with hypercalcemia and use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, the FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.2

Several iron-chelating agents are FDA-approved:
- In 1968, deferoxamine (Desferal®; Novartis) was approved by the FDA for subcutaneous, intramuscular, or intravenous injections to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved by the FDA.
- In 2005, deferasirox (Exjade®; Novartis) was approved by the FDA, is available as a tablet for oral suspension, and is indicated for the treatment of chronic iron overload due to blood transfusions in patients ages 2 years and older. Under the accelerated approval

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program, the FDA expanded the indications for deferasirox in 2013 to include treatment of patients aged 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia syndromes and specific liver iron concentration and serum ferritin levels. A generic version of deferasirox tablet for oral suspension has also been approved by the FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu™) was approved by the FDA. All formulations of deferasirox carry a black box warning because it may cause serious and fatal renal toxicity and failure, hepatic toxicity and failure, and gastrointestinal hemorrhage. As a result, treatment with deferasirox requires close patient monitoring, including laboratory tests of renal and hepatic function.

- In 2011, the iron chelator deferiprone (Ferriprox®) was approved by the FDA for treatment of patients with transfusional overload due to thalassemia syndromes when another chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox® carries a black box warning because it can cause agranulocytosis, which can lead to serious infections and death. As a result, absolute neutrophil count should be monitored before and during treatment.

In a June 2014 warning to consumers, the FDA advised that FDA-approved chelating agents would be available by prescription only. There are no FDA-approved over-the-counter chelation products.

### Rationale

#### Background

Chelation therapy is an established treatment for the removal of metal toxins by converting them to a chemically inert form that can be excreted in the urine. Chelation therapy comprises intravenous or oral administration of chelating agents that remove metal ions such as lead, aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body (see Appendix Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not approved by the U.S. Food and Drug Administration (FDA) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning. (Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.1)

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer disease, which is associated with the disequilibrium of cerebral metals. Unlike traditional systemic chelators that bind and remove metals from tissues systemically, MPACs have subtle effects on metal homeostasis and abnormal metal interactions. In animal models of Alzheimer disease, they promote the solubilization and clearance of β-amyloid by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. MPACs, therefore, interrupt 2 putative pathogenic processes of Alzheimer disease. However, no MPACs have received FDA approval for treating Alzheimer disease.

Chelation therapy also has been considered as a treatment for other indications, including atherosclerosis and autism spectrum disorder. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

#### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and a 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.

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To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 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. The following is a summary of the key literature to date.

Chelation therapy is an established treatment for metal toxicity and transfusional hemosiderosis. These uses are not discussed herein. Literature searches have focused on the use of chelation therapy for off-label conditions including, but not limited to, Alzheimer disease, atherosclerosis, autism spectrum disorder, diabetes, multiple sclerosis (MS), and arthritis.

**Alzheimer Disease**

**Clinical Context and Test Purpose**

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the U.S. Food and Drug Administration (FDA).

The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, MS, and arthritis, improve the net health outcome?

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

**Patients**
The population of interest includes patients with Alzheimer disease.

**Interventions**
The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

**Comparators**
The comparator of interest is standard medical care without chelation therapy.

**Outcomes**
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

A Cochrane review (2008) evaluated metal protein attenuating compounds for treating Alzheimer disease. Reviewers identified a placebo-controlled randomized trial. This study by Ritchie et al. (2003) assessed patients treated with PBT1, a metal protein attenuating compound also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier. The FDA withdrew clioquinol for oral use from the market in 1970 because of its association with subacute myelo-optic neuropathy. Ritchie et al (2013) administered oral clioquinol to 16 Alzheimer disease patients in doses increasing to 375 mg twice daily and compared this group with 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer Disease Assessment Scale—Cognitive. One patient in the treatment group developed impaired
visual acuity and color vision during weeks 31 to 36 of treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. The update of this Cochrane review (2012) included trials through December 2011. Only the Lannfelt et al. (2008) trial (discussed next) was identified.

Further study of PBT1 was abandoned in favor of a successor compound, PBT2. Lannfelt et al (2008) completed a double-blind, placebo-controlled randomized trial of 78 Alzheimer disease patients who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29). There was no statistically significant difference in Alzheimer Disease Assessment Scale-Cognitive or Mini-Mental Status Examination scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis, transient ischemic event) were reported in the placebo arm.

Section Summary: Alzheimer Disease
There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published RCTs did not find that chelation was superior to placebo for improving health outcomes.

Cardiovascular Disease
Clinical Context and Test Purpose
Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the FDA.

The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, MS, and arthritis, improve the net health outcome?

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

Patients
The population of interest includes patients with cardiovascular disease.

Interventions
The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

Comparators
The comparator of interest is standard medical care without chelation therapy.

Outcomes
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Atherosclerosis
Villaruz et al. (2002) published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease. Five placebo-controlled randomized trials were identified, none of which reported mortality, nonfatal events, or cerebrovascular events. Four (n=250 patients) of the 5 studies found no significant benefit of EDTA chelation therapy on reported outcomes, including direct or indirect measures of disease severity and subjective measures of improvement. The fifth study (N=10 patients) was stopped early due to benefit, but relevant outcome data were unavailable. Cochrane reviewers found that the evidence was insufficient to support conclusions about the
efficacy of chelation therapy for treating atherosclerosis. Additional RCTs reporting health outcomes like mortality and cerebrovascular events were suggested.

Among published RCTs, Knudtson et al. (2002) randomized 84 patients with coronary artery disease and a positive treadmill test to EDTA chelation therapy or placebo. Treatment was administered for 3 hours twice weekly for 15 weeks and then monthly for 3 months. Outcome measures included a change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the 2 groups. Another double-blind, placebo-controlled randomized trial (2003) of EDTA chelation showed no difference between groups in short- or long-term improvement in vasomotor response. Two small RCTs from the 1990s also reported no benefit of chelation therapy as a treatment for peripheral arterial disease.

Section Summary: Atherosclerosis
Several RCTs of chelation therapy for treating atherosclerosis generally have reported on intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs reporting health outcomes would be needed to establish treatment efficacy.

Myocardial Infarction
Lamas et al. (2013) published results of the multicenter, 2 × 2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT). TACT included 1708 patients, ages 50 years or older, who had a history of myocardial infarction at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Patients also received oral high-dose vitamin plus mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. The primary endpoint was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years. The threshold for statistical significance was adjusted for multiple interim analyses to a p-value of 0.036. A total of 361 (43%) patients in the chelation group and 464 (57%) patients in the placebo group discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary endpoint was 33% (95% confidence interval [CI], 29% to 37%) in the chelation group and 39% (95% CI, 35% to 42%) in the control group, a statistically significant difference (p=0.035). The most common individual clinical endpoint was coronary revascularization, which occurred in 130 (16%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=0.08). The next most frequent endpoint was death, which occurred in 87 (10%) patients in the chelation group and 93 (11%) patients in the placebo group (p=0.64). No individual component of the primary outcome differed statistically between groups; however, the trial was not powered to detect differences in individual components. Four severe adverse events definitely or possibly related to study therapy occurred, 2 each in the treatment and control groups, including 1 death in each. Quality of life outcomes (reported in 2014) did not differ between groups at 2-year follow-up.

Another 2014 follow-up publication reported results for the 4 treatment groups in the 2 × 2 factorial design (double-active group [disodium-EDTA infusions with oral high-dose vitamins; n=421 patients], active infusions with placebo vitamins [n=418 patients], placebo infusions with active vitamins [n=432 patients], double placebo [n=437 patients]). The proportions of patients who discontinued treatment withdrew consent, or were lost to follow-up per treatment group were not reported. Five-year Kaplan-Meier estimates for the primary composite endpoint were 32%, 34%, 37%, and 40%, respectively. The reduction in primary endpoint by double-active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74; 95% CI, 0.57 to 0.95). In 633 patients with diabetes (=36% of each treatment group), the primary endpoint reduction in the double-active group compared with the double placebo group was more pronounced (HR=0.49; 95% CI, 0.33 to 0.75).

The trial was limited by the high number of withdrawals, with differential withdrawals between groups. The primary endpoint included components of varying clinical significance, and the
largest difference between groups was for revascularization events. The primary endpoint barely met the significance threshold; if more patients had remained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the original (2013) publication, 60% of patients were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in the selection of a population not generalizable to that seen in general clinical care.\textsuperscript{15} Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings.\textsuperscript{16} This secondary analysis had the same limitations as the parent study previously described (i.e., high and differential withdrawal, heterogeneous composite endpoint). Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

**Section Summary: Myocardial Infarction**

One RCT with limitations, including high dropout rate with differential dropout between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes. However, this trial was not of high-quality and, therefore, results might have been biased. More high-quality trials are needed to corroborate whether chelation therapy improves outcomes in patients with prior myocardial infarction.

**Autism Spectrum Disorder**

**Clinical Context and Test Purpose**

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the FDA.

The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, MS, and arthritis, improve the net health outcome?

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

**Patients**

The population of interest includes patients with autism spectrum disorder.

**Interventions**

The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

**Comparators**

The comparator of interest is standard medical care without chelation therapy.

**Outcomes**

The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Based on symptoms similarities between mercury poisoning and autism spectrum disorder, Bernard et al (2001) hypothesized a link between environmental mercury and autism.\textsuperscript{17} This theory was rejected by Nelson and Bauman (2003), who found that many characteristics of mercury poisoning, such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children.\textsuperscript{18} A meta-analysis by Ng et al. (2007) concluded that there was no association between mercury poisoning and autism.\textsuperscript{19}
Rossignol (2009) published a systematic review of novel and emerging treatments for autism and identified no controlled studies. Rossignol (2009) stated that case series had suggested a potential role for chelation in treating some autistic people with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

**Section Summary: Autism Spectrum Disorder**
There is a lack of controlled studies on how chelation therapy affects health outcomes in patients with autism.

**Diabetes**

**Clinical Context and Test Purpose**
Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the FDA.

The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, MS, and arthritis, improve the net health outcome?

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

**Patients**
The population of interest includes patients with diabetes.

**Interventions**
The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

**Comparators**
The comparator of interest is standard medical care without chelation therapy.

**Outcomes**
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

**Cardiovascular Disease in Patients With Diabetes**
A trial by Cooper et al. (2009) in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes. Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area in the active treatment group (-10.6 g/m²) than in the placebo group -0.1 g/m²; p=0.01). The trial was limited by small sample size and high dropout rate.

Escolar et al. (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. In this trial (also discussed above), there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes: Among 538 (31% of the trial sample) self-reported diabetic patients, those randomized to EDTA had a 39% reduced risk of the primary composite outcome (i.e., death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years) compared with placebo (HR=0.61; 95% CI, 0.45 to 0.83; p=0.02); among 1170 nondiabetic patients, risk of the primary outcome did not differ statistically between treatment groups (HR=0.96; 95% CI, 0.77 to 1.20; p=0.73). For the subsequent subgroup analysis, the definition of diabetes was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose of 126 mg/dL or more at
trial entry. Of 1708 patients in TACT, 633 (37%) had diabetes by this definition: 322 were randomized to EDTA and 311 to placebo. Compared with all other trial participants, this subgroup of diabetic patients had higher body mass index, fasting blood glucose, and prevalence of heart failure, stroke, hypertension, peripheral artery disease, and hypercholesterolemia. Within this subgroup, baseline characteristics were similar between treatment groups. With approximately 5 years of follow-up, the primary composite endpoint occurred in 25% of the EDTA group and 38% of the placebo group (adjusted HR=0.59; 99.4% CI, 0.39 to 0.88; p=0.002). In an adjusted analysis of the individual components of the primary endpoint, there were no statistically significant differences between treatment groups. Thirty-six adverse events attributable to the study drug led to trial withdrawal (16 in the EDTA group vs. 20 in the placebo group).

**Diabetic Nephropathy**

Chen et al (2012) conducted a single-blind RCT assessing the effects of chelation therapy on the progression of diabetic nephropathy in Chinese patients with high-normal lead levels.23, Fifty patients with diabetes, high-normal body lead burden (80-6000 μg), and serum creatinine of 3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 μg/dL in the treatment group and 7.1 μg/dL in the control group; baseline mean body lead burden was 151 μg in the treatment group and 142 μg in the control group. According to the U.S. Occupational and Health Safety Administration, the maximum acceptable blood lead level in adults is 40 μg/dL.24, Patients were randomized to 3 months of calcium disodium EDTA or to placebo. During 24 months of treatment follow-up, patients in the chelation group received additional chelation treatments as needed (i.e., for serum creatinine level above pretreatment levels or body lead burden >60 μg), and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate. Mean yearly rate of decrease in estimated glomerular filtration rate was 5.6 mL/min/173 m² in the chelation group and 9.2 mL/min/173 m² in the control group, a statistically significant difference (p=0.04). The secondary endpoint was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) patients in the treatment group and 17 (68%) in the control group attained the secondary endpoint, a statistically significant difference (p=0.02). There were no reported adverse events of chelation therapy during the trial.

**Section Summary: Diabetes**

Two small RCTs with limitations represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small, single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients that report health outcomes (e.g., cardiovascular events, end-stage renal disease, mortality) are needed.

**Other Potential Indications: Multiple Sclerosis and Arthritis**

**Clinical Context and Test Purpose**

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This evidence review does not address indications for chelation therapy approved by the FDA.

The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis (MS), and arthritis, improve the net health outcome?

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

**Patients**

The population of interest includes patients with MS or arthritis.
Interventions
The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

Comparators
The comparator of interest is standard medical care without chelation therapy.

Outcomes
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for other conditions (e.g., MS, arthritis) were identified. Iron chelation therapy is being investigated for Parkinson disease, and endotoxemia.

Summary of Evidence
For individuals who have Alzheimer disease, or cardiovascular disease, or autism spectrum disorder, or diabetes, or multiple sclerosis, or arthritis who receive chelation therapy, the evidence includes a small number of randomized controlled trials (RCTs) and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One RCT (the Trial to Assess Chelation Therapy) reported that chelation therapy reduced cardiovascular events in patients with previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations (e.g., high dropout rates) and, therefore, conclusions are not definitive. For other conditions, the available RCTs did not report improvements in health outcomes with chelation therapy and, as evidence, the case series are inadequate to determine efficacy. The evidence is insufficient to determine the effect of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
American College of Physicians et al.
In 2012, the American College of Physicians, American College of Cardiology Foundation, American Heart Association (AHA), and 3 other medical associations published joint clinical practice guidelines on the management of stable ischemic heart disease (IHD). The guidelines recommended that “chelation therapy should not be used with the intent of improving symptoms or reducing cardiovascular risk in patients with stable IHD. (Grade: strong recommendation; low-quality evidence).” However, citing the Trial to Assess Chelation Therapy, a 2014 focused update of these guidelines included a revised recommendation on chelation therapy, stating that the “usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable IHD.” The recommendation was upgraded from class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies).

In 2004, the American College of Physician’s clinical practice guidelines stated that chelation “should not be used to prevent myocardial infarction or death or to reduce symptoms in patients with symptomatic chronic stable angina. (Level of evidence B: Based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries).”
American College of Cardiology et al.
In 2005, the American College of Cardiology, American Heart Association (AHA), and other medical societies stated that chelation “is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses).” In 2013, the American College of Cardiology Foundation and AHA compiled previous American College of Cardiology/AHA and American College of Cardiology Foundation/AHA recommendations issued in 2005 and 2011 on the management of peripheral artery disease. The recommendation against chelation therapy remained unchanged.

Canadian Cardiovascular Society
In 2014, the evidence-based, consensus guidelines from the Canadian Cardiovascular Society included a conditional recommendation (based on moderate-quality evidence) that chelation therapy should not be used to attempt to improve angina or exercise tolerance in patients with stable IHD.

National Institute for Health and Care Excellence
In 2013, the National Institute for Health and Care Excellence issued guidance reports on autism in children and young people, and autism in adults which was updated in 2016. Both documents specifically recommended against the use of chelation therapy for the management of autism.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid have issued 2 national coverage determinations on chelation therapy relevant to this evidence review. Section 20.21 states: “The application of chelation therapy using ethylenediamine-tetra-acetic acid (EDTA) for the treatment and prevention of atherosclerosis is controversial. There is no widely accepted rationale to explain the beneficial effects attributed to this therapy. Its safety is questioned and its clinical effectiveness has never been established by well designed, controlled clinical trials. It is not widely accepted and practiced by American physicians. EDTA chelation therapy for atherosclerosis is considered experimental. For these reasons, EDTA chelation therapy for the treatment or prevention of atherosclerosis is not covered.

Some practitioners refer to this therapy as chemoendarterectomy and may also show a diagnosis other than atherosclerosis, such as arteriosclerosis or calcinosis. Claims employing such variant terms should also be denied under this section.”

Section 20.22 states: “The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA [Food and Drug Administration] as an approved use is not covered. Any such use of EDTA is considered experimental.”

These national coverage determinations are long-standing; effective dates of these versions have not been posted.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.
### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT02655315</td>
<td>Conservative Iron Chelation as a Disease-modifying Strategy in Parkinson's Disease European Multicentre, Parallel-group, Placebo-controlled, Randomized Clinical Trial of Deferiprone</td>
<td>338</td>
<td>Feb 2021</td>
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<tr>
<td>NCT02733185</td>
<td>Trial to Assess Chelation Therapy 2</td>
<td>1200</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
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<td>NCT02367248a</td>
<td>Safety and Effectiveness Study of Deferoxamine and Xingnaojing Injection in Intracerebral Hemorrhage</td>
<td>180</td>
<td>Dec 2016 (unknown; last update posted 05/18/2015)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

### Appendix

Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1.

**Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals**

<table>
<thead>
<tr>
<th>Metal</th>
<th>Toxic Levels (Normal Levels Where Indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>24-h urine: ≥50 μg/L urine or 100 μg/g creatinine</td>
</tr>
<tr>
<td>Bismuth</td>
<td>No clear reference standard</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Proteinuria and/or ≥15 μg/g creatinine</td>
</tr>
<tr>
<td>Chromium</td>
<td>No clear reference standard</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Normative excretion: 0.1-1.2 μg/L (serum), 0.1-2.2 μg/L (urine)</td>
</tr>
<tr>
<td>Copper</td>
<td>Normative excretion: 25 μg/24 h (urine)</td>
</tr>
<tr>
<td>Iron</td>
<td>• Nontoxic: &lt;300 μg/dL</td>
</tr>
<tr>
<td></td>
<td>• Severe: &gt;500 μg/dL</td>
</tr>
<tr>
<td>Lead</td>
<td><strong>Pediatric</strong></td>
</tr>
<tr>
<td></td>
<td>• Symptoms or blood lead level ≥45 μg/dL (blood)</td>
</tr>
<tr>
<td></td>
<td>• CDC level of concern: 5 μg/dL</td>
</tr>
<tr>
<td></td>
<td><strong>Adult</strong></td>
</tr>
<tr>
<td></td>
<td>• Symptoms or blood lead level ≥70 μg/dL</td>
</tr>
<tr>
<td></td>
<td>• CDC level of concern: 10 μg/dL</td>
</tr>
<tr>
<td>Manganese</td>
<td>No clear reference standard</td>
</tr>
<tr>
<td>Mercury</td>
<td>Background exposure normative limits: 1-8 μg/L (whole blood); 4-5 μg/L (urine)41,a</td>
</tr>
<tr>
<td>Nickel</td>
<td>• Excessive exposure: ≥8 μg/L (blood)</td>
</tr>
<tr>
<td></td>
<td>• Severe poisoning: ≥500 μg/L (8-h urine)</td>
</tr>
<tr>
<td>Selenium</td>
<td>• Mild toxicity: &gt;1 mg/L (serum)</td>
</tr>
<tr>
<td></td>
<td>• Serious toxicity: &gt;2 mg/L</td>
</tr>
<tr>
<td>Silver</td>
<td>Asymptomatic workers have mean levels of 11 μg/L (serum) and 2.6 μg/L (spot urine)</td>
</tr>
<tr>
<td>Thallium</td>
<td>24-hour urine thallium &gt;5 μg/L</td>
</tr>
<tr>
<td>Zinc</td>
<td>Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)</td>
</tr>
</tbody>
</table>

Adapted from Adal (2018).43,

CDC: Centers for Disease Control and Prevention.

* Hair analysis is useful to assess mercury exposure in epidemiologic studies. However, hair analysis in individual patients must be interpreted with consideration of the patient’s history, signs, and symptoms, and possible alternative explanations.

Measurement of blood and urine mercury levels can exclude exogenous contamination; therefore, blood or urine mercury levels may be more robust measures of exposure in individual patients. [Kempson IM, Lombi E. Hair analysis as a biomonitor.... 40(7):3915-3940. PMID 21468435]
References

15. Nissen SE. Concerns about reliability in the Trial to Assess Chelation Therapy (TACT) [editorial]. JAMA. Mar 27 2013;309(12):1293-1294. PMID 23532246
16. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: When evidence conflicts with beliefs [editorial]. Am Heart J. Jul 2014;168(1):4-5. PMID 24952853


**Documentation for Clinical Review**

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

- History and physical and/or consultation notes including:
  - Reason treatment required
  - Treatment plan (including drug, method, number of treatments)

**Post Service**

- Chelation therapy progress notes
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)</td>
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<tr>
<td></td>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
<tr>
<td></td>
<td>J0470</td>
<td>Injection, dimercaprol, per 100 mg</td>
</tr>
<tr>
<td></td>
<td>J0600</td>
<td>Injection, edetate calcium disodium, up to 1,000 mg</td>
</tr>
<tr>
<td></td>
<td>J0895</td>
<td>Injection, deferoxamine mesylate, 500 mg</td>
</tr>
<tr>
<td></td>
<td>J3520</td>
<td>Edetate disodium, per 150 mg</td>
</tr>
<tr>
<td></td>
<td>M0300</td>
<td>IV chelation therapy (chemical endarterectomy)</td>
</tr>
<tr>
<td></td>
<td>S9355</td>
<td>Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>02/14/1973</td>
<td>New Policy Adoption</td>
</tr>
<tr>
<td>12/14/2005</td>
<td>Policy Review Policy clarification, rationale added, coding update</td>
</tr>
<tr>
<td>06/26/2009</td>
<td>Policy Revision</td>
</tr>
<tr>
<td>01/11/2013</td>
<td>Policy revision with position change</td>
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<tr>
<td>03/28/2014</td>
<td>Policy revision with position change</td>
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<tr>
<td>07/31/2015</td>
<td>Coding update</td>
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<tr>
<td>06/01/2016</td>
<td>Policy title change from Chelation Therapy</td>
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<td>Policy revision without position change</td>
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<tr>
<td>05/01/2017</td>
<td>Policy revision without position change</td>
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<tr>
<td>04/01/2018</td>
<td>Policy revision without position change</td>
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<tr>
<td>05/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

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