Chelation Therapy (for Kentucky Only)

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➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Kentucky.

Coverage Rationale

Chelation for heavy metal toxicity and overload conditions (e.g., iron, copper, lead, aluminum) is proven and medically necessary.

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Chelation therapy for treating any chronic, progressive diseases associated with non-overload conditions
- Chelation therapy for treating mercury "toxicity" from dental amalgam fillings

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0470	Injection, dimercaprol, per 100 mg
J0600	Injection, edetate calcium disodium, up to 1,000 mg
J0895	Injection, deferoxamine mesylate, 500 mg
J3490	Unclassified drugs
J3520	Edetate disodium, per 150 mg
J8499	Prescription drug, oral, nonchemotherapeutic, NOS
M0300	IV chelation therapy (chemical endarterectomy)
S9355	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

Description of Services

Chelation therapy can provide substantial clinical benefit for conditions where heavy metal overload has been accurately diagnosed. The diagnostic workup must consider the individual's history, an appropriate choice of testing methods, and the use of accurate and specific reference values. Chelation therapy is an established treatment for removing metal toxins from the body. This involves administering naturally occurring or chemically designed molecules to bind and excrete a specific toxin in the body. The medication, route, method, and site of administration of the chelating agent vary depending on the agent used, toxicity level, and other clinical indications. Heavy metal toxicity, most often treated with chelation therapy, includes that caused by iron, copper, lead, aluminum, and mercury.

Non-Overload Conditions

Chelation therapy has been proposed as a treatment for various non-overload conditions where acute or chronic heavy metal toxicity has not been demonstrated and in which the removal of heavy metal ions is hypothesized to reduce oxidative damage caused by the production of hydroxyl radicals. However, the possible mechanism of chelators as therapeutic agents for non-overload conditions has yet to be fully understood. Chelation has been investigated as a treatment of numerous non-overload conditions including, but not limited to, cardiovascular disease (CVD), rheumatoid arthritis (RA), cancer, and diabetes.

Mercury "Toxicity" From Dental Amalgam Fillings

Chelation therapy has been proposed to treat metal toxicity from dental amalgam fillings, but it has not been shown that mercury amalgams cause harm to individuals with dental fillings, except in rare cases of allergy.

Clinical Evidence

Chelation Therapy for Heavy Metal Toxicity and Overload Conditions (e.g., Iron, Copper, Lead, Aluminum)

Through a systematic review, Lee et al. (2024) explored iron-chelation therapy (ICT) compliance and the relationship between compliance with health outcomes and health-related quality of life (HRQoL) for individuals with thalassemia. Of 4917 studies, 20 publications were included. The ICT compliance rate ranges from 20.93 to 75.3%. It also varied per agent, ranging from 48.84 to 85.1% for deferoxamine (DFO), 87.2-92.2% for deferiprone (DFP), and 90-100% for deferasirox (DFX). The majority of studies (n = 10/11, 90.91%) demonstrated significantly negative correlation between compliance and serum ferritin, while numerous studies revealed poor ICT compliance linked with increased risk of liver disease (n = 4/7, 57.14%) and cardiac disease (n = 6/8, 75%), endocrinologic morbidity (n = 4/5, 90%), and lower HRQoL (n = 4/6, 66.67%). The limitations of the review included multiple confounding factors, such as the age and sex of participants, as well as the frequency of blood transfusions, which may contribute to variations in the level of compliance. The authors concluded that consistent with expectations, the review demonstrated that compliance with iron chelators maximizes the benefits of the therapy in reducing serum ferritin, iron overload complications, and HRQoL. To fully understand the influence of compliance on the most vulnerable groups, more comprehensive research with larger sample size and assessing the impact of ICT on the outcomes of interest among different age groups is required.

In 2023, Salem et al. systematically reviewed the literature to assess the evidence regarding combined DFP and DFX outcomes in individuals with iron-overload. The studies included dual iron chelation strategies for several diagnoses. Single-arm studies (n = 7) showed a reduction of serum ferritin, which reached statistical significance in three studies. Likewise, after chelating therapy, most studies reported a numerical decrease in liver iron concentration (LIC) and increased cardiac magnetic resonance imaging (MRI)-T2* values. Alternatively, comparative studies showed no significant difference in post-treatment serum ferritin between DFX plus DFP and DFX/DFP plus DFO. The adherence to combination therapy was good to average in nearly 66.7-100% of the participants across four studies. One study reported a poor adherence rate. The combined regimen was generally tolerable, with no reported incidence of serious adverse events (AEs) among the included studies. The limitations of the study included small sample sizes, poor quality of the included studies, limited generalizability, inadequately reported safety outcomes, and lack of newer formulations of DFX and DFP, an area of future research. The authors concluded that the DFP and DFX combination is a safe and feasible option for individuals with iron overload with a limited response to monotherapy. Those with severe iron overload showed a significant reduction in serum ferritin and LIC and a significant increase in cardiac T2* values after the combined regimen. The combined regimen had a high compliance rate and a well-tolerable safety profile.

Through a randomized, open-label noninferiority study (2022), Kwiatkowski et al. assessed the efficacy and safety of DFP in those individuals with sickle cell disease (SCD) or other anemias receiving chronic transfusion therapy. 228 participants were randomized to receive either oral DFP (n = 152) or subcutaneous DFO (n = 76). The primary endpoint was changed

from baseline at 12 months in LIC, assessed by R2* MRI. Noninferiority of DFP was also shown for both cardiac T2* MRI and serum ferritin. The rates of overall AEs, treatment-related AEs, serious AEs, and AEs leading to withdrawal did not differ significantly between the groups. AEs related to DFP treatment included abdominal pain (17.1%), vomiting (14.5%), pyrexia (9.2%), increased alanine transferase (9.2%), and aspartate transferase levels (9.2%), neutropenia (2.6%), and agranulocytosis (0.7%). The study's limitations are related to both agents. For example, DFO must be administered parenterally over 8 to 12 hours per day, which imposes a significant treatment burden for individuals and their caregivers and can impede adherence. DFX is taken orally as tablets or granules, which provides convenience; however, the drug has been associated with hepatic, gastrointestinal, and renal toxicities, which is of particular concern for those with SCD who may have pre-existing renal impairment. The authors concluded that the efficacy and safety profiles of DFP were acceptable and consistent with those seen in individuals with TDT.

In 2022, Yang et al. conducted a systematic review and meta-analysis to analyze further ICT's therapeutic potential in lower-risk individuals with myelodysplastic syndrome (MDS). The primary outcome was survival, which was reported as median overall survival (OS) or adjusted hazard ratio (aHR) between the ICT and non-ICT groups. Secondary outcomes included MDS progression rate, acute myeloid leukemia (AML) progression rate, and incidence of cardiac injury. The exploration results demonstrated that the median OS for individuals receiving ICT was consistently longer than the non-ICT group across the nine studies reporting it. The meta-analysis of observational studies showed that ICT was associated with a lower mortality risk. Five studies indicated a decreased risk, while two indicated an increased risk of AML progression with ICT. Two studies showed a smaller percentage of deaths caused by AML progression, while three studies showed a larger percentage with ICT. In five studies, ICT decreased the risk of cardiac injury. Overall, the study demonstrated that the ICT results provide mortality benefits in those with iron overload and low- or intermediate-risk MDS in addition to other suggested benefits, including a decreased rate of AML progression and organ dysfunction. However, this observation should be balanced against the cost, complexity, and complications of ICT and our inability to discern the relative efficacy of different types of ICT (DFO, DFP, and DFX) on clinically important outcomes. Based on the available literature, the authors suggest that ICT be considered in those with low- and intermediate-risk MDS.

In a 2020 multicenter, randomized, double-blind, placebo-controlled trial (TELESTO), Angelucci et al. evaluated event-free survival (EFS) and safety of ICT for individuals with low intermediate one-risk MDS. The primary endpoint was EFS, defined as the time from the date of randomization to the first documented nonfatal event (related to cardiac or liver dysfunction and transformation to acute myeloid leukemia) or death, whichever occurred first. The trial results demonstrated a median time on treatment was 1.6 years in the DFX group and 1.0 years in the placebo group. Median EFS was prolonged by approximately 1 year with DFX versus placebo. It was reported that AEs occurred in 97.3% of DFX recipients and 90.8% of placebo recipients. Exposure-adjusted incidence rates of AEs in the DFX group versus placebo recipients, respectively, were 24.7 versus 23.9 for diarrhea, 21.8 versus 18.7 for pyrexia, 16.7 versus 22.7 for upper respiratory tract infection, and 15.9 versus 0.9 for increased serum creatinine concentration. The limitations of the trial included the protocol being amended from a phase 3 to a phase 2 study, with a reduced target sample size from 630 to 210 participants. There was differential follow-up between treatment groups. The authors concluded that the findings supported ICT in iron-overloaded people with low- to intermediate-1-risk MDS, with longer EFS than placebo and a clinically manageable safety profile. Therefore, ICT may be considered in these individuals.

Maggio et al. (2020) conducted a multicenter, randomized, open-label, non-inferiority, phase 3 trial to show the non-inferiority of DFP versus DFX. Participants were randomly assigned 1:1 to receive orally administered daily DFP or DFX administered as dispersible tablets, with dose adjustment for 12 months, stratified by age (< 10 years and ≥ 10 years) and balanced by country. The primary efficacy endpoint was based on predefined success criteria for changes in serum ferritin concentration and cardiac MRI T2-star to show non-inferiority of DFP versus DFX in the per-protocol population, defined as all randomly assigned participants who received the study drugs and had available data for both variables at baseline and after 1 year of treatment, without significant protocol violations. Non-inferiority was based on the two-sided 95% confidence interval (CI) of the difference in the proportion of those with treatment success between the two groups and was shown if the lower limit of the two-sided 95% CI was greater than -12·5%. Safety was assessed in all participants who received at least one dose of the study drug. A total of 435 participants were enrolled with 194 in the DFP group and 199 in the DFX group with 352 of 390 individuals with β-thalassemia major, 27 had SCD, five had thalassodrepanocytosis, and six had other hemoglobinopathies. Median follow-up was 379 days for DFP and 381 days for DFX. Non-inferiority of DFP versus DFX was established [treatment success in 69 (55·2%) of 125 people assigned DFP with primary composite efficacy endpoint data available at baseline and 1 year vs 80 (54·8%) of 146 assigned DFX, difference 0·4%; 95% CI -11·9 to 12·6]. No significant difference between the groups was shown in the occurrence of serious and drug-related AEs. The limitations of the study were a low number of participants, the duration of the study, less than 1 year, problems with randomization, and different methods used for liver and cardiac MRI assessments. The results showed that in pediatric individuals with transfusion-dependent hemoglobinopathies, DFP was effective and safe in inducing control of iron overload during 12 months of treatment. Considering the need for more chelation treatments in pediatric populations, DFP offers a valuable treatment option for this age group. The authors concluded that the trial supports the use of DFP in

pediatric individuals with transfusion-dependent hemoglobinopathies based on data from the largest randomized clinical trial of ICT in these individuals. The main clinical implication of this study is that pediatric individuals might now have more than one efficacious and safe option for oral ICT.

Chelation Therapy for Non-Overload Conditions

Well-designed, published, and peer-reviewed studies do not support chelation treatment for chronic, progressive diseases such as cardiovascular disease (CVD), atherosclerosis, diabetes, cancer, Alzheimer's disease, autism spectrum disorder, or Parkinson's Disease. No quality peer-reviewed studies were identified regarding chelation therapy for the treatment of rheumatoid arthritis, apoplectic coma, chronic fatigue syndrome, chronic renal insufficiency, defective hearing, diabetic ulcer, cholelithiasis, gout, erectile dysfunction, multiple sclerosis, osteoarthritis, osteoporosis, Raynaud's disease, renal calculus, schizophrenia, scleroderma, snake venom poisoning, varicose veins, or vision disorders. There is insufficient evidence that chelation therapy is safe and effective for the removal of undesirable metabolites or toxins, nor does it positively impact clinical outcomes for different disease states.

Chelation therapy for non-overload conditions was explored through a health technology assessment performed in 2004 and updated in 2008 by Hayes. The findings were that most studies evaluating chelation therapy for non-overload were small and flawed by several methodological issues, including heterogeneous populations, nonstandard treatment regimens, insufficient follow-up, subjective outcome measures, and lack of controls or adequate blinding. The report concluded that the available studies evaluating chelation therapy for non-overload conditions were generally weak, with conflicting findings. The strongest evidence of benefit is for dexrazoxane as a cardioprotective agent in women who are undergoing anthracycline therapy for breast cancer. However, additional studies with longer follow-ups are needed to confirm this finding and evaluate dexrazoxane's impact on survival. The evidence regarding the effect of chelation therapy on other non-overload conditions is either conflicting or insufficient and does not support any conclusions regarding efficacy or clinical benefit.

Alzheimer's Disease (AD)

Increased levels of aluminum have been discovered in several brain regions of individuals with AD. Epidemiological studies have linked the concentration of aluminum in drinking water and increased disease occurrence. Some scientists have suggested that chelation therapy may promote beneficial results for individuals with AD by inhibiting the deposition of aluminum in the brain and/or preventing iron from catalyzing the formation of toxic hydroxyl radicals. Aluminum chelators may also reactivate aluminized metalloenzyme complexes for individuals with AD and permit aluminum redistribution in the brain.

Sampson et al. conducted a Cochrane systematic review to evaluate the efficacy of metal protein attenuating compounds (MPACs) for treating cognitive impairment due to AD. The primary outcome measure was cognitive function (measured by psychometric tests). Two MPAC trials were identified. One trial compared clioquinol (PBT1) with a placebo in 36 individuals, 32 having sufficient data for protocol analysis. There was no statistically significant difference in cognition as measured on the AD Assessment Scale-Cognition (ADAS-Cog) between the active treatment and placebo groups at 36 weeks, and there was no significant impact on non-cognitive symptoms or clinical global impression. In the second trial, a successor compound, PBT2, was compared with a placebo in 78 participants with mild AD. There was no significant difference in the Neuropsychological Test Battery (NTB) composite or memory between placebo and PBT2 at week 12. However, two executive function component tests of the NTB showed significant improvement over the placebo in the PBT2 250 mg group from baseline to week 12. There was no significant effect on cognition on Mini-Mental State Examination (MMSE) or ADAS-Cog scales. PBT2 did have a favorable safety profile. The authors concluded that evidence is absent as to whether clioquinol (PBT1) is safe or has any positive clinical benefit for individuals with AD and cited that further development of PBT1 has been abandoned. The second trial of PBT2 was more rigorously conducted and appeared to be safe and well tolerated for individuals with mild AD after 12 weeks. Larger trials are now required to demonstrate cognitive efficacy (2014).

Several studies have suggested improving cognitive function or biomarkers for individuals treated with clioquinol or DFO (Crapper Mclachlan, 1991; Regland, 2001; Ritchie, 2003). However, these studies were small, only two were placebo-controlled, and none were double-blind, and therefore no conclusions regarding the clinical efficacy of chelation therapy for AD can be made based on these studies.

Autism Spectrum Disorder (ASD)

A Cochrane systematic evidence review found no clinical trial evidence to suggest that pharmaceutical chelation is an effective intervention for ASD. One study was found, which was conducted in two phases. During Phase 1, 77 children with ASD were randomly assigned to receive seven days of glutathione lotion or placebo lotion, followed by three days of oral dimercaptosuccinic acid (DMSA). A total of 49 children found to be high excreters of heavy metals during Phase 1

continued to Phase 2 and received three days of oral DMSA or a placebo followed by 11 days off, with the cycle repeated up to six times. The second phase assessed the effectiveness of multiple doses of oral DMSA compared with placebo in children who were high excreters of heavy metals and received a 3-day course of oral DMSA. Overall, no evidence suggests that multiple rounds of oral DMSA influenced ASD symptoms. The authors concluded that given prior reports of serious AEs such as hypocalcemia, renal impairment, and reported death, the risks of using chelation for ASD currently outweigh the proven benefits. In their opinion, evidence that supports a causal link between heavy metals and autism must be identified, and methods that ensure the safety of participants are imperative before further trials are conducted (James et al., 2015).

Cardiovascular Disease

Chelation therapy has been proposed to treat coronary artery disease (CAD), based partly on the hypothesis that chelation could remove atherosclerotic calcium deposits or provide an antioxidant benefit.

In 2024, Lamas et al. conducted a double-masked, placebo-controlled, multicenter trial at 88 sites on Edetate Disodium-based chelation for individuals with a previous MI and diabetes. Participants in the trial were 50 years or older, had diabetes, and experienced an MI at least 6 weeks before recruitment. The eligible participants were randomly assigned to 40 weekly infusions of an ethylene diamine tetra-acetic acid (EDTA)-based chelation solution or matching placebo and to twice daily oral, high-dose multivitamin and mineral supplements or matching placebo for 60 months. The authors compared the effect of EDTA-based chelation and placebo infusion on CVD events and the impact of high doses of oral multivitamins and minerals with oral placebo. The main endpoint sought was the composite of all causes of mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina. The median follow-up was 48 months. The primary comparisons were made from participants who received at least one assigned infusion. The trial results demonstrated that of the 959 participants (27% females, 78% White, 10% Black, and 20% Hispanic), 483 received at least one chelation infusion and 476 at least one placebo infusion. A primary endpoint event occurred in 172 participants (35.6%) in the chelation group and 170 (35.7%) in the placebo group. The 5-year primary event cumulative incidence rates were 45.8% for the chelation group and 46.5% for the placebo group. CV death, MI, or stroke events occurred in 89 participants (18.4%) in the chelation group and 94 (19.7%) in the placebo group. Death from any cause occurred in 84 participants (17.4%) in the chelation group and 84 (17.6%) in the placebo group. Chelation reduced median blood lead levels from 9.03 µg/L at baseline to 3.46 µg/L at infusion 40 ($p < .001$). Corresponding levels in the placebo group were 9.3 µg/L and 8.7 µg/L, respectively. The limitations of the trial include the primary analyses being restricted to a modified intention-to-treat population, treatment adherence being imperfect, 122 participants were lost to follow-up or withdrew consent, and the therapeutic target of EDTA, population levels of blood lead decreased between the initial study and the present study, possibly reducing the therapeutic efficacy of EDTA. The authors concluded that despite effectively decreasing blood lead levels, EDTA chelation was not effective in reducing cardiovascular events in stable individuals with CAD who have diabetes and a history of MI.

In 2022, Ravalli et al. systematically reviewed literature related to chelation therapy for individuals with CVD to examine the effect of repeated EDTA on clinical outcomes. Of the 24 studies investigated, predetermined outcomes such as mortality, disease severity, plasma biomarkers of disease chronicity, and quality of life for individuals with preexistent CVD who utilized EDTA chelation treatments were included. In total, 17 studies, including one RCT, found improvement in individuals' outcomes following EDTA treatment. The most significant improvement was uncovered in the studies that included individuals with a high prevalence of diabetes and/or severe occlusive artery disease. The meta-analysis conducted demonstrated a gain of 0.08 (95% CI, 0.06-0.09) from baseline from four studies reporting ankle-brachial index. Limitations in the available studies included the small number of RCTs, lack of reported clinical outcomes in several studies, differing infusion regimens, small sample sizes, and limited follow-up data. The authors concluded that this present systematic review of past studies suggests a signal of benefit for individuals with atherosclerotic disease, particularly those with diabetes. Future clinical research on EDTA chelation for individuals with diabetes and PAD must include a mechanical component that could clarify if chelation therapy signifies a benefit for this population subgroup, contributing to precision environmental medicine [Lamas et al. (2013) and Knudtson et al. (2002) are included in this systematic review].

In 2022, Lamas et al. conducted a trial to assess the rationale and design of chelation therapy 2 (TACT2) through a randomized, 2x2 factorial, double-masked, placebo-controlled, multicenter clinical trial testing 40 weekly infusions of a multi-component edetate disodium (disodium ethylenediamine tetra-acetic acid, or Na2EDTA)-based chelation solution and twice daily oral, high-dose multivitamin and mineral supplements in those with diabetes and a prior myocardial infarction (MI). The subjects from the TSCT2 were followed for 2.5 to 5 years. The primary endpoint assessed was the composite of the time to first occurrence of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina. One perceived weakness of the initial TACT, when presented in 2012 and published in 2013, was the virtual absence of any underlying accepted hypothesis presented to support the unexpectedly positive results of the trial.

The authors concluded that TACT2 may provide definitive evidence of the benefit of edetate disodium-based chelation on cardiovascular outcomes, as well as the clinical importance of longitudinal changes in toxic metal levels of participants.

Cochrane systematic review of evidence published initially in 2002 was completed by Villarruz-Sulit et al. (2020) to assess the effects of EDTA chelation therapy versus placebo or no treatment on clinical outcomes among people with atherosclerotic cardiovascular disease (ASCVD). The review included five RCTs of EDTA chelation therapy versus placebo or no treatment, with 1,993 randomized participants. The number of participants in each study varied widely (from 10 to 1708 participants), but all studies compared EDTA chelation to a placebo. The risk of bias for the included studies was generally moderate to low, but one had a high risk of bias because the study investigators broke their randomization code halfway through the study and rolled the placebo participants over to active treatment. The main outcome measures included all-cause or cause-specific mortality, non-fatal cardiovascular events, direct or indirect measurement of disease severity, and subjective measures of improvement or AEs. Two studies with participants with CAD reported no evidence of a significant difference in all-cause mortality between chelation therapy and placebo [risk ratio (RR) 0.97, 95% CI 0.73 to 1.28; 1792 participants; low certainty]. One study with participants with CAD reported no evidence of a significant difference in coronary heart disease deaths between chelation therapy and placebo (RR 1.02, 95% CI 0.70 to 1.48; 1708 participants; very low certainty). Two studies with participants with CAD reported no evidence of a significant difference in MI (RR 0.81, 95% CI 0.57 to 1.14; 1792 participants; moderate certainty), angina (RR 0.95, 95% CI 0.55 to 1.67; 1792 participants; very low certainty), or coronary revascularization (RR 0.46, 95% CI 0.07 to 3.25; 1792 participants). Two studies [one of the participants with CAD and one of the participants with peripheral vascular disease (PVD) reported no evidence of a significant difference in stroke (RR 0.88, 95% CI 0.40 to 1.92; 1867 participants; low certainty)]. Ankle-brachial pressure index (ABPI, also known as ankle-brachial index) was measured in three studies, all including participants with PVD; two studies found no evidence of a significant difference in the treatment groups after three months of treatment [mean difference (MD) 0.02, 95% CI-0.03 to 0.06; 181 participants; low-certainty]. A third study reported an improvement in ABPI in the EDTA chelation group, but this study was at elevated risk of bias. Meta-analysis of maximum and pain-free walking distances three months after treatment included participants with PVD and showed no evidence of a significant difference between the treatment groups (MD-31.46, 95%CI-87.63 to 24.71; 165 participants; two studies; low-certainty). Quality of life outcomes was reported by two studies that included participants with CAD; however, the authors were unable to pool the data due to different methods of reporting and varied criteria. No major differences between the treatment groups were reported – none of the included studies reported on vascular deaths. Overall, there was no evidence of major or minor AEs associated with EDTA chelation treatment. The authors concluded that there is currently insufficient evidence to determine the effectiveness or ineffectiveness of chelation therapy in improving the clinical outcomes of people with ASCVD. The authors stated that while these results should guide further research, there still is insufficient evidence to support the routine use of chelation therapy for individuals post-MI. The publication by Knudtson et al. (2002) previously included in this policy is included in this systematic review.

The Cochrane review above included a study by Lamas et al. (2012) that described a pivotal clinical trial, the TACT, in detail. The use of chelation therapy in lieu of established therapies, the lack of adequate prior research to verify its effectiveness and clinical utility, and the overall impact of CAD prompted the National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) to sponsor this large-scale clinical study. The 5-year study was a multicenter, double-blind, randomized efficacy trial from 2002 to 2011 to determine whether EDTA chelation therapy and high-dose oral vitamin and mineral therapy offered clinical, quality of life, and economic benefits for individuals with a prior MI. The participants (n = 1708) were randomized to receive 40 infusions of a 500-mL chelation solution or a placebo infusion, with a second randomization to an oral vitamin and mineral regimen or an oral placebo. Following the infusion phase of the trial, participants were contacted quarterly by telephone, had annual clinic visits, and were seen at the end of the trial or at the 5-year follow-up, whichever occurred first.

A study in the Cochrane review by Escolar et al. (2014) used results of the TACT clinical trial to perform an initial subgroup analysis which showed a greater effect of EDTA treatment among participants with a self-reported history of diabetes. Further examination of the data for individuals with diabetes demonstrated a 41% overall reduction in the risk of any cardiovascular event; a 40% reduction in risk of cardiovascular mortality, non-fatal stroke, or non-fatal MI; a 52% reduction in recurrent heart attacks; and a 43% reduction in death from any cause. In contrast, EDTA treatment was of no significant benefit in the subgroup of 1,045 participants who did not have diabetes. The authors note that the results of this analysis support the initiation of clinical trials for individuals with diabetes and vascular disease to replicate these findings and to define the mechanisms of benefit. However, it was also concluded that there is not enough evidence to support the routine use of chelation therapy for this.

In additional analyses of the TACT study, in 2020, Lewis et al. examined the effect of edetate disodium chelation therapy as a function of MI location and diabetes. Chelation therapy was associated with a lower risk of the primary endpoint for 674 individuals' post-MI (HR 0.63, 95% CI 0.47-0.86, p = 0.003) for individuals with anterior MI. For post-non-anterior MI individuals totaling 1034 participants, chelation therapy was not associated with a lower risk of the primary endpoints (HR

0.96, 95% CI 0.77-1.20, p = 0.702) (p-for-interaction = 0.032). However, the point estimates of each part of the primary endpoint favored chelation therapy. The differing treatment effect for individuals with post-anterior vs. non-anterior MI was consistent among those with or without diabetes and remained significant after adjusting other prognostic variables (p < 0.01). There were several limitations to this analysis. First, the individuals with anterior MI had a lower overall event rate than non-anterior MI and no difference in the distribution of congestive heart failure or revascularization at baseline. The anterior MI cohort also included significant differences compared to the non-anterior MI cohort, including higher HDL concentrations, lower blood pressure, and lower rates of former smokers, which may have contributed to the results. There are no quantities of metals or coronary artery calcium at baseline or throughout follow-up to allow mechanistic assessments of the influence of edetate disodium infusions and for the association of the degree of responsiveness to results reached. The authors concluded that Edetate disodium-based infusions, compared to placebo, independently reduced the risk of adverse cardiovascular events among stable individuals with prior anterior MI. However, the authors state that the current results must be considered exploratory and hypothesis-generating. These post hoc findings should be taken with caution and studies specific to individuals with anterior MI should be conducted to confirm these findings.

Chronic Kidney Disease (CKD)

In 2025, Murillo et al. conducted an open-label, randomized study to investigate the impact of iron chelation on telomere length, oxidative stress, and ferritin levels in those undergoing hemodialysis. The study was conducted with a control group of individuals undergoing hemodialysis who will receive deferasirox treatment for iron chelation for six months. The results of the study demonstrated that significant differences were observed in serum ferritin levels and TBARS (thiobarbituric acid reactive substances). Telomere length had a significant increase after chelation. The serum deferasirox concentration at zero time at 48h was maintained within a 2.67-23.78mmol/L range. The authors concluded that iron chelation in individuals undergoing hemodialysis significantly reduces ferritin and TBARS, increasing telomere length. Deferasirox proves to be beneficial for those with iron overload undergoing hemodialysis. The clinical significance of the findings on patient-centered outcomes is unclear.

Parkinson's Disease (PD)

Martin-Bastida et al. (2017) performed a randomized, double-blind, placebo-controlled trial to investigate whether iron chelator, DFP, is well tolerated and able to chelate iron from various brain regions and improve PD symptomology. The study included 22 participants (12 males and 10 females, aged 50-75 years) with early-stage PD, a disease duration of fewer than five years. The individuals with PD were recruited between April 4, 2012, and March 27, 2013, and randomly selected to receive a placebo or 20 or 30 mg/kg/day DFP (80 mg/mL DFP solution or excipient matched placebo provided by ApoPharma Inc., Toronto, ON, Canada) which was divided into two daily oral doses, morning and evening, and administered for six months. Participants were evaluated for PD severity, cognitive function, depression rating, and quality of life. Iron concentrations were assessed in the substantia nigra (SNc), dentate and caudate nucleus, red nucleus, putamen, and globus pallidus by T2 MRI at baseline and after three and six months of treatment. DFP therapy was well tolerated and was associated with a reduced dentate and caudate nucleus iron content compared to placebo. Reductions in the iron content of the SNc occurred in only three individuals, with no changes being detected in the putamen or globus pallidus. Although 30 mg/kg DFP-treated individuals showed a trend for improvement in Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores and quality of life, this did not reach significance. Cognitive function and mood were not adversely affected by DFP therapy. The authors concluded that short-term DFP therapy for individuals with PD is safe and associated with decreased iron-specific brain regions. A small sample size renders these non-statistically significant findings largely inconclusive. The findings of this study need to be confirmed by more extensive well-designed studies assessing patient-centered outcomes.

Mercury "Toxicity" From Dental Amalgam (DA) Fillings

DAs have been investigated as a cause of increased blood levels of mercury, potentially associated with several diseases and disorders. While no studies were identified that addressed chelation directly therapy for mercury "toxicity" from amalgam fillings, high-quality indirect evidence supports the lack of such toxicity. RCTs have concluded that mercury amalgams used in dental restorations cause no harm (Shenker et al., 2008; Bellinger et al., 2006; DeRouen et al., 2006).

In a 2020 systematic review, meta-analysis, and trial of sequential analysis of randomized controlled trials, Patini et al. aimed to definitively evaluate the possible effects of exposure to mercury in adults and children with and without DA fillings by measuring the mercury concentration in various biological fluids. The primary outcome measures were the Hg concentration in biological fluids (e.g., urine, hair, blood, and saliva) to assess their reliability as biomarkers of Hg exposure. The meta-analysis results were concluded from data gathered from 859 individuals but group difference were not significant (p = 0.12). The trial sequential analysis (TSA) confirmed the evidence revealed that it was due to the lack of statistical power since the required information size threshold was not reached. The lack of longer RCTs for assessing various types of adverse effects linked to using DA was a limiting factor in the review. The authors concluded that the

existing evidence reveals insufficient data to support the hypothesis that restorations with DA can cause nephrotoxicity when compared with the composite resins' restorations.

Golding et al. (2016) evaluated the extent to which DA may contribute to total blood mercury (TBHg) levels of pregnant women in a single geographic region in the UK. The authors reviewed the laboratory assay results for total mercury levels in whole blood samples of 4,484 pregnant women and concluded that the number of DA fillings is responsible for at least 6.47% of the participants' TBHg level. For perspective, in an earlier publication, the authors noted that 8.75% of the TBHg level was shown to be attributable to seafood consumption in the same study population. The number of amalgams in the participants' mouths at the start of pregnancy accounted for most of the variance in dental variability. The authors noted that the measures of DA exposure were at risk of recall bias as they were dependent on the responses to a retrospective questionnaire completed two years after the study child's delivery. The questions asked in the questionnaire regarding dental care received before and during the pregnancies were inserted in the middle of the questionnaire without reference to any outcome to minimize bias. Another disadvantage to the study noted by the authors was that the timing of the blood draw in relation to the timing of any dental work was not known. The authors concluded that DA contributes a comparable amount of variance in TBHg to seafood consumption in this population and that there is no evidence to date that fetal exposures to mercury from maternal DAs cause adverse effects on a developing child.

Clinical Practice Guidelines

American Academy of Family Physicians (AAFP)

In its clinical policy on chelation therapy, the AAFP states that it is appropriate for cases of heavy metal intoxication when diagnosed using validated testing in appropriate biological samples. The use of chelation therapy for other problems remains investigational and should not be recommended (2018; reviewed 2024).

American Academy of Pediatrics (AAP) Council on Environmental Health

As part of the "Choosing Wisely" initiative, in 2021, the AAP released five things' physicians and patients should question regarding environmental health and autism. The AAP Council on Environmental Health recommends against ordering 'chelation challenge' urinary analyses for children with suspected lead poisoning. The 'chelation challenge' was formerly used to assess whether a child had a significant body burden of lead, or "lead poisoning," and whether formal chelation would result in significant lead clearance. Evidence suggests that the chelation challenge has no better prognostic value than the standard blood lead level. Further, there is some evidence that the chelation challenge may be potentially dangerous. In summary, the chelation challenge has no clinical utility in treating childhood lead poisoning today (Mackara., 2021).

American College of Cardiology (ACC)/American Heart Association Task Force on Practice Guidelines (AHA)/American Association for Thoracic Surgery (AATS)/Preventative Cardiovascular Nurses Association (PCNA)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS)

The ACC/AHA/AATS/PCNA/SCAI/STS concluded that although disodium EDTA is approved by the U.S. Food and Drug Administration for specific indications, such as iron overload and lead poisoning, it is not approved for use in preventing or treating CVD. Accordingly, the group finds that the usefulness of chelation therapy in cardiac disease is highly questionable (Fihn et al., 2014).

American College of Medical Toxicology (ACMT)

A position statement released by the American College of Medical Toxicology on September 26, 2013, concluded that chelation is not recommended for any condition other than documented metal intoxication, which has been diagnosed using validated tests in appropriate biological samples. Chelation does not improve objective outcomes in autism, CVD, or neurodegenerative conditions like Alzheimer's. Chelating drugs may have significant side effects, including dehydration, hypocalcemia, kidney injury, liver enzyme elevations, hypotension, allergic reactions, and essential mineral deficiencies, even when used for appropriately diagnosed metal intoxication. Inappropriate chelation, which may cost hundreds to thousands of dollars, risks these harms, as well as neurodevelopmental toxicity, teratogenicity, and death (released 2013 and 2015; last reviewed 2021).

American College of Physicians (ACP)

The American College of Physicians, American College of Cardiology Foundation, American Heart Association, and three other medical associations published joint clinical practice guidelines on managing stable ischemic heart disease (IHD). The guidelines recommended that "chelation therapy should not be used to improve symptoms or reduce cardiovascular risk for individuals with stable ischemic heart disease" (Qaseem et al., 2012).

In 2004, the American College of Physician's clinical practice guidelines said that chelation "should not be used to prevent MI or death or to reduce symptoms for individuals with symptomatic chronic stable angina." (Snow et al. 2004).

American Heart Association (AHA)

The "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease" offers an update to and combines new evidence since the "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" and the corresponding "2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease." This guideline provides an evidenced-based and patient-centered approach to management of patients with chronic coronary disease, considering social determinants of health and incorporating the principles of shared decision-making and team-based care. The guideline states that EDTA is presently not approved by the FDA for preventing or treating CVD (Virani et al., 2023).

Canadian Cardiovascular Society

The evidence-based, consensus guidelines (2014) 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 for individuals with stable ischemic heart disease (IHD) (Mancini et al., 2014).

National Institute for Health and Care Excellence (NICE)

A NICE guideline on autism does not recommend using chelation to manage core symptoms of autism in adults (2012; updated 2021).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Chelation therapy, using FDA-approved chelating agents, is approved when used for metal poisoning or iron overload treatment. Use is limited to FDA-approved indications for each chelation agent, as referenced in a generally recognized drug compendium (e.g., American Hospital Formulary Services Drug Information® or DrugDex® System). Additional information is available at: http://www.accessdata.fda.gov/scripts/Cder/ob/default.cfm. (Accessed January 30, 2025)

The FDA issued updated recommendations concerning DA and potential risks to certain high-risk individuals that may be associated with mercury-containing fillings. In 2020 the FDA released a statement saying that certain groups may be at risk for potential harmful health effects; the agency recommends that certain high-risk groups avoid getting DA when possible and appropriate. These groups that may be at a greater risk for potential harmful health effects include:

- Pregnant women and their developing fetuses
- Women who are planning to become pregnant
- Nursing women and their newborns and infants
- Children, especially those younger than six years of age
- People with pre-existing neurological diseases such as multiple sclerosis, Alzheimer's disease, or Parkinson's disease
- People with impaired kidney function; and
- People with known heightened sensitivity (allergy) to mercury or other components of DA

Additional information is available at: https://www.fda.gov/news-events/press-announcements/fda-issues-recommendations-certain-high-risk-groups-regarding-mercury-containing-dental-amalgam. (Accessed January 30, 2025)

In 2019 the FDA warned against several companies that have made improper claims about their products' intended use as a treatment or cure for autism or autism-related symptoms. The FDA states that FDA-approved chelating agents are approved for specific uses that do not include the treatment or cure of autism, such as the treatment of lead poisoning and iron overload and are available by prescription only. Additional information is available at: https://www.fda.gov/consumers/consumer-updates/be-aware-potentially-dangerous-products-and-therapies-claim-treat-autism. (Accessed January 30, 2025)

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Policy History/Revision Information

Date	Summary of Changes
09/01/2025	**Title Change** • Previously titled *Chelation Therapy for Non-Overload Conditions (for Kentucky Only)* **Coverage Rationale** • Replaced language indicating “chelation for heavy metal toxicity and overload conditions (e.g., iron, copper, lead, aluminum) is proven and medically necessary *and not addressed in this policy*” with “chelation for heavy metal toxicity and overload conditions (e.g., iron, copper, lead, aluminum) is proven and medically necessary”

Date	Summary of Changes
	Supporting Information • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS016.KY.05

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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