MEDICAL POLICY

POLICY TITLE	INTRAVENOUS CHELATION THERAPY
POLICY NUMBER	MP-4.005

Original Issue Date (Created):	**7/1/2002**
Most Recent Review Date (Revised):	**8/12/2019**
Effective Date:	**10/1/2019**

I. POLICY

Intravenous chelation therapy may be considered **medically necessary** in the treatment of each of the following conditions in accordance with the FDA label of the infused drug:

- Control of ventricular arrhythmias or heart block associated with digitalis toxicity (**see note**);
- Emergency treatment of hypercalcemia (**see note**);
- Extreme conditions of metal toxicity (e.g. hemochromatosis);
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to conditions such as thalassemia);
- Wilson's disease (hepatolenticular degeneration); and
- Lead poisoning

Note: FDA removed the approval for NaEDTA as chelation therapy due to safety concerns. Its use is considered **not medically necessary**.

Other applications of chelation therapy are considered **investigational**, including, but not limited to:

- Atherosclerosis/arteriosclerosis (i.e. coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease);
- Multiple sclerosis;
- Arthritis (including rheumatoid arthritis);
- Pervasive developmental disorders;

- Alzheimer's disease;
- Diabetes.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

Policy Guidelines

For control of ventricular arrhythmias or heart block associated with digitalis toxicity; and
emergency treatment of hypercalcemia, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies.

FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

Suggested toxic or normal levels of select heavy metals are listed in Table 1. Reference standards for bismuth, chromium, and manganese were not identified and are not included in Table 1.

Table 1. Toxic or Normal Concentrations of Heavy Metals (3)

Metal	**Toxic Levels (Normal Levels Where Indicated)**
Arsenic	24-h urine: ≥50 µg/L urine or 100 µg/g creatinine
Cadmium	Proteinuria and/or ≥15 µg/g creatinine
Cobalt	Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)
Copper	Normative excretion: 25 µg/24 h (urine)
Iron	Nontoxic: <300 µg/dL Severe: >500 µg/dL
Lead	**Pediatric** Symptoms or blood lead level ≥45 µg/dL (blood) CDC level of concern: 5 µg/dL(4) **Adult** Symptoms or blood lead level ≥40 µg/dL CDC level of concern: 10 µg/dL(5)
Mercury	Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L

	(urine)(6)[a]
Nickel	Excessive exposure: ≥8 µg/L (blood) Severe poisoning: ≥500 µg/L (8-h urine)
Selenium	Mild toxicity: >1 µg/L (serum) Serious toxicity: >2 µg/L
Silver	Asymptomatic workers have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)
Thallium	24-hour urine thallium >5 µg/L(7)
Zinc	Normative range: 0.6-1.1 µg/L (plasma), 10-14 µg/L (red cells)

CDC: Centers for Disease Control and Prevention

[a] 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. [45]

Cross-reference:

MP-2.304 Autism Spectrum Disorders
MP-2.312 Genetic Testing for Hereditary Hemochromatosis

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO-Refer to FEP Medical Policy Manual MP-8.01.02 Chelation Therapy for Off-Label Uses. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-po

III. DESCRIPTION/BACKGROUND

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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. Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not FDA-approved) 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 beta 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 the treatment of Alzheimer disease.

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

Regulatory Status

In 1953, calcium-ethylenediaminetetraacetic acid (EDTA; Versenate) was approved by the U.S. Food and Drug Administration (FDA) for lowering blood lead levels among both pediatric and adult patients with lead poisoning. In 1991, succimer (Chemet) was approved by FDA for the treatment of lead poisoning in pediatric patients only. FDA approved disodium-EDTA for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, 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 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 FDA.
- In 2005, deferasirox (Exjade®; Novartis) was approved by 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 program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 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 FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu™) was approved by 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 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 that 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, FDA advised that FDA-approved chelating agents would be available by prescription only.[3] There are no FDA-approved over-the-counter chelation products.

IV. RATIONALE

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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 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 (eg, 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.

V. DEFINITIONS

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HEAVY METALS refer to metals such as mercury, lead, chromium, arsenic, and cadmium, which have known toxic effects on internal organs (i.e. kidneys, brain, bone, retina).

HEMOCHROMATOSIS is a genetic disease marked by excessive absorption and accumulation of iron into the body.

THALASSEMIA refers to a group of hereditary anemias occurring in populations bordering the Mediterranean and in Southeast Asia.

WILSON'S DISEASE is a hereditary syndrome, which permits accumulation of copper in various organs (i.e., brain, liver, kidney, and cornea).

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the

applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational for all indications:

HCPCS Code	Description
M0300	IV chelation therapy (chemical endarterectomy)

NaEDTA is considered not medically necessary as FDA has removed approval for its use with chelation therapy; therefore, not covered:

HCPCS Code	Description
J3520	Edetate disodium, per 150 mg

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Covered when medically necessary:

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
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

ICD-10 CM Diagnosis Codes	Description
D56.0	Alpha thalassemia
D56.1	Beta thalassemia
D56.2	Delta-beta thalassemia
D56.3	Thalassemia minor
D56.4	Hereditary persistence of fetal hemoglobin [HPFH]
D56.5	Hemoglobin E-beta thalassemia
D56.8	Other thalassemias
D56.9	Thalassemia, unspecified
E83.00	Disorder of copper metabolism, unspecified
E83.01	Wilson's disease
E83.09	Other disorders of copper metabolism
E83.10	Disorder of iron metabolism, unspecified
E83.110	Hereditary hemochromatosis
E83.111	Hemochromatosis due to repeated red blood cell transfusions
E83.118	Other hemochromatosis
E83.119	Hemochromatosis, unspecified
E83.19	Other disorders of iron metabolism
E83.52	Hypercalcemia
I45.9	Conduction disorder, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.1	Supraventricular tachycardia
I47.2	Ventricular tachycardia
I49.01	Ventricular fibrillation
I49.02	Ventricular flutter
I49.2	Junctional premature depolarization

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I49.3	Ventricular premature depolarization
I49.40	Unspecified premature depolarization
I49.49	Other premature depolarization
T45.4X1A	Poisoning by iron and its compounds, accidental (unintentional), initial encounter
T45.4X1D	Poisoning by iron and its compounds, accidental (unintentional), subsequent encounter
T45.4X2A	Poisoning by iron and its compounds, intentional self-harm, initial encounter
T45.4X2D	Poisoning by iron and its compounds, intentional self-harm, subsequent encounter
T45.4X3A	Poisoning by iron and its compounds, assault, initial encounter
T45.4X3D	Poisoning by iron and its compounds, assault, subsequent encounter
T45.4X4A	Poisoning by iron and its compounds, undetermined, initial encounter
T45.4X4D	Poisoning by iron and its compounds, undetermined, subsequent encounter
T46.0X1A	Poisoning by cardiac-stimulant glycosides and drugs of similar action, accidental (unintentional), initial encounter
T46.0X1D	Poisoning by cardiac-stimulant glycosides and drugs of similar action, accidental (unintentional), subsequent encounter
T46.0X2A	Poisoning by cardiac-stimulant glycosides and drugs of similar action, intentional self-harm, initial encounter
T46.0X2D	Poisoning by cardiac-stimulant glycosides and drugs of similar action, intentional self-harm, subsequent encounter
T46.0X3A	Poisoning by cardiac-stimulant glycosides and drugs of similar action, assault, initial encounter
T46.0X3D	Poisoning by cardiac-stimulant glycosides and drugs of similar action, assault, subsequent encounter
T46.0X4A	Poisoning by cardiac-stimulant glycosides and drugs of similar action, undetermined, initial encounter
T46.0X4D	Poisoning by cardiac-stimulant glycosides and drugs of similar action, undetermined, subsequent encounter
T56.0X1A	Toxic effect of lead and its compounds, accidental (unintentional), initial encounter
T56.0X1D	Toxic effect of lead and its compounds, accidental (unintentional), subsequent encounter
T56.0X2A	Toxic effect of lead and its compounds, intentional self-harm, initial encounter
T56.0X2D	Toxic effect of lead and its compounds, intentional self-harm, subsequent encounter
T56.0X3A	Toxic effect of lead and its compounds, assault, initial encounter
T56.0X3D	Toxic effect of lead and its compounds, assault, subsequent encounter
T56.0X4A	Toxic effect of lead and its compounds, undetermined, initial encounter
T56.0X4D	Toxic effect of lead and its compounds, undetermined, subsequent encounter
T56.1X1A	Toxic effect of mercury and its compounds, accidental (unintentional), initial encounter
T56.1X1D	Toxic effect of mercury and its compounds, accidental (unintentional), subsequent encounter
T56.1X1S	Toxic effect of mercury and its compounds, accidental (unintentional), sequela

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ICD-10 CM Diagnosis Codes	Description
T56.1X2A	Toxic effect of mercury and its compounds, intentional self-harm, initial encounter
T56.1X2D	Toxic effect of mercury and its compounds, intentional self-harm, subsequent encounter
T56.1X3A	Toxic effect of mercury and its compounds, assault, initial encounter
T56.1X3D	Toxic effect of mercury and its compounds, assault, subsequent encounter
T56.1X4A	Toxic effect of mercury and its compounds, undetermined, initial encounter
T56.1X4D	Toxic effect of mercury and its compounds, undetermined, subsequent encounter
T56.3X1A	Toxic effect of cadmium and its compounds, accidental (unintentional), initial encounter
T56.3X1D	Toxic effect of cadmium and its compounds, accidental (unintentional), subsequent encounter
T56.3X2A	Toxic effect of cadmium and its compounds, intentional self-harm, initial encounter
T56.3X2D	Toxic effect of cadmium and its compounds, intentional self-harm, subsequent encounter
T56.3X3A	Toxic effect of cadmium and its compounds, assault, initial encounter
T56.3X3D	Toxic effect of cadmium and its compounds, assault, subsequent encounter
T56.3X4A	Toxic effect of cadmium and its compounds, undetermined, initial encounter
T56.3X4D	Toxic effect of cadmium and its compounds, undetermined, subsequent encounter
T56.4X1A	Toxic effect of copper and its compounds, accidental (unintentional), initial encounter
T56.4X1D	Toxic effect of copper and its compounds, accidental (unintentional), subsequent encounter
T56.4X2A	Toxic effect of copper and its compounds, intentional self-harm, initial encounter
T56.4X2D	Toxic effect of copper and its compounds, intentional self-harm, subsequent encounter
T56.4X3A	Toxic effect of copper and its compounds, assault, initial encounter
T56.4X3D	Toxic effect of copper and its compounds, assault, subsequent encounter
T56.4X4A	Toxic effect of copper and its compounds, undetermined, initial encounter
T56.4X4D	Toxic effect of copper and its compounds, undetermined, subsequent encounter
T56.5X1A	Toxic effect of zinc and its compounds, accidental (unintentional), initial encounter
T56.5X1D	Toxic effect of zinc and its compounds, accidental (unintentional), subsequent encounter
T56.5X2A	Toxic effect of zinc and its compounds, intentional self-harm, initial encounter
T56.5X2D	Toxic effect of zinc and its compounds, intentional self-harm, subsequent encounter
T56.5X3A	Toxic effect of zinc and its compounds, assault, initial encounter
T56.5X3D	Toxic effect of zinc and its compounds, assault, subsequent encounter
T56.5X4A	Toxic effect of zinc and its compounds, undetermined, initial encounter
T56.5X4D	Toxic effect of zinc and its compounds, undetermined, subsequent encounter
T56.6X1A	Toxic effect of tin and its compounds, accidental (unintentional), initial encounter
T56.6X1D	Toxic effect of tin and its compounds, accidental (unintentional), subsequent encounter
T56.6X1S	Toxic effect of tin and its compounds, accidental (unintentional), sequela
T56.6X2A	Toxic effect of tin and its compounds, intentional self-harm, initial encounter
T56.6X2D	Toxic effect of tin and its compounds, intentional self-harm, subsequent encounter
T56.6X3A	Toxic effect of tin and its compounds, assault, initial encounter

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ICD-10 CM Diagnosis Codes	Description
T56.6X3D	Toxic effect of tin and its compounds, assault, subsequent encounter
T56.6X4A	Toxic effect of tin and its compounds, undetermined, initial encounter
T56.6X4D	Toxic effect of tin and its compounds, undetermined, subsequent encounter
T56.811A	Toxic effect of thallium, accidental (unintentional), initial encounter
T56.811D	Toxic effect of thallium, accidental (unintentional), subsequent encounter
T56.812A	Toxic effect of thallium, intentional self-harm, initial encounter
T56.812D	Toxic effect of thallium, intentional self-harm, subsequent encounter
T56.813A	Toxic effect of thallium, assault, initial encounter
T56.813D	Toxic effect of thallium, assault, subsequent encounter
T56.814A	Toxic effect of thallium, undetermined, initial encounter
T56.814D	Toxic effect of thallium, undetermined, subsequent encounter
T56.891A	Toxic effect of other metals, accidental (unintentional), initial encounter
T56.891D	Toxic effect of other metals, accidental (unintentional), subsequent encounter
T56.892A	Toxic effect of other metals, intentional self-harm, initial encounter
T56.892D	Toxic effect of other metals, intentional self-harm, subsequent encounter
T56.893A	Toxic effect of other metals, assault, initial encounter
T56.893D	Toxic effect of other metals, assault, subsequent encounter
T56.894A	Toxic effect of other metals, undetermined, initial encounter
T56.894D	Toxic effect of other metals, undetermined, subsequent encounter
T56.94XA	Toxic effect of unspecified metal, undetermined, initial encounter
T56.94XD	Toxic effect of unspecified metal, undetermined, subsequent encounter
T57.0X1A	Toxic effect of arsenic and its compounds, accidental (unintentional), initial encounter
T57.0X1D	Toxic effect of arsenic and its compounds, accidental (unintentional), subsequent encounter
T57.0X2A	Toxic effect of arsenic and its compounds, intentional self-harm, initial encounter
T57.0X2D	Toxic effect of arsenic and its compounds, intentional self-harm, subsequent encounter
T57.0X3A	Toxic effect of arsenic and its compounds, assault, initial encounter
T57.0X3D	Toxic effect of arsenic and its compounds, assault, subsequent encounter
T57.0X4A	Toxic effect of arsenic and its compounds, undetermined, initial encounter
T57.0X4D	Toxic effect of arsenic and its compounds, undetermined, subsequent encounter
T80.89XA	Other complications following infusion, transfusion and therapeutic injection, initial encounter
T80.89XD	Other complications following infusion, transfusion and therapeutic injection, subsequent encounter

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X. POLICY HISTORY

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MP 4.005	**CAC 6/24/03**
	CAC 4/26/05
	CAC 4/25/06
	CAC 3/27/07
	CAC 1/29/08
	CAC 3/31/09
	7/1/09 Cross Reference added for Pervasive Developmental Disorders
	CAC 3/30/10 Consensus review.
	CAC 7/26/11 Adopted BCBSA: Added Alzheimer's disease to conditions in investigational statement per BCBSA. Retained arteriosclerosis in investigational statement. Retained examples of specific conditions in medically necessary criteria (e.g. hemochromatosis, thalassemia).
	CAC 10/30/12 Consensus review. References updated; background revised to reflect current status of chelating agents. No changes to policy statements. FEP variation added. Codes reviewed 10/23/12
	CAC 11/26/13 Consensus review. No change to policy statements. Rationale Section added. Added Medicare variation to reference LCD L32692 Chelation Therapy
	CAC 9/30/14 Consensus review. Deleted reference to LCD L32692 and added reference to NCD 20.21 and 20.22. Added policy guidelines. Updated references and rationale. No change to policy statements.
	01/16/15 Admin code review.
	CAC 11/24/15 Consensus review. Hypoglycemia deleted from list of investigational indications. It is not reviewed in this policy. Updated rationale and references. Coding reviewed/updated.
	Admin update 1/1/17: Product variation section reformatted.
	CAC 11/29/16 Minor review. Changed title to Intravenous Chelation Therapy. Added note indicating FDA removed the approval for NaEDTA as chelation therapy due to safety concerns. Its use is considered **not medically necessary**.

POLICY TITLE	INTRAVENOUS CHELATION THERAPY
POLICY NUMBER	MP-4.005

	Added "in accordance with the FDA label of the infused drug" References and rationale updated. Coding Reviewed.
	CAC 12/19/17 Consensus. No change to policy statements. References and rationale updated.
	10/31/18 Consensus review. For clarification, the indication "treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia", the conjunction "and" was changed to "or". References reviewed. Rationale revised**.**
	Admin update 4/1/19: Coding reviewed and diagnosis codes updated.
	08/12/19 Consensus review. References and rationale reviewed. No changes to policy statements. Diagnosis Codes updated. Effective 10/1/19.

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