

(80102)

<b>Medical Benefit</b>		<b>Effective Date:</b> 01/01/16	<b>Next Review Date:</b> 11/20
<b>Preauthorization</b>	No	<b>Review Dates:</b> 02/07, 01/08, 11/08, 09/09, 05/10, 05/11, 05/12, 05/13, 07/13, 05/14, 11/14, 11/15, 11/16, 11/17, 11/18, 11/19	

**Preauthorization is not required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With Alzheimer disease</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Chelation therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard medical care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With cardiovascular disease</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Chelation therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard medical care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With autism spectrum disorder</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Chelation therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard medical care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With diabetes</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Chelation therapy</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard medical care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>

Populations	Interventions	Comparators	Outcomes
Individuals: • With multiple sclerosis	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With arthritis	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

## DESCRIPTION

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.

## 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 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 randomized controlled trial (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 randomized controlled trials 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.

## POLICY

Off-label applications of chelation therapy (see Policy Guidelines for uses approved by the Food and Drug Administration) are considered **investigational** including but not limited to:

- Alzheimer disease
- atherosclerosis (e.g., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
- autism

- diabetes
- multiple sclerosis
- arthritis (includes rheumatoid arthritis).

## POLICY GUIDELINES

A number of indications for which chelation therapy have received FDA approval, and for which chelation therapy is considered standard of care treatment, include:

- extreme conditions of metal toxicity
- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to 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.

For the last two bullet points, 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. NaEDTA 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.

Table 1. Toxic or Normal Concentrations of Heavy Metals<sup>40</sup>

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24-h urine: $\geq 50$ $\mu\text{g/L}$ urine or 100 $\mu\text{g/g}$ creatinine
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or $\geq 15$ $\mu\text{g/g}$ creatinine
Chromium	No clear reference standard
Cobalt	Normative excretion: 0.1-1.2 $\mu\text{g/L}$ (serum), 0.1-2.2 $\mu\text{g/L}$ (urine)
Copper	Normative excretion: 25 $\mu\text{g}/24$ h (urine)
Iron	<ul style="list-style-type: none"> <li>• Nontoxic: <math>&lt; 300</math> <math>\mu\text{g/dL}</math></li> <li>• Severe: <math>&gt; 500</math> <math>\mu\text{g/dL}</math></li> </ul>
Lead	<p><b>Pediatric</b></p> <ul style="list-style-type: none"> <li>• Symptoms or blood lead level <math>\geq 45</math> <math>\mu\text{g/dL}</math> (blood)</li> <li>• CDC level of concern: 5 <math>\mu\text{g/dL}</math><sup>40</sup></li> </ul> <p><b>Adult</b></p> <ul style="list-style-type: none"> <li>• Symptoms or blood lead level <math>\geq 70</math> <math>\mu\text{g/dL}</math></li> <li>• CDC level of concern: 10 <math>\mu\text{g/dL}</math><sup>41</sup></li> </ul>
Manganese	No clear reference standard
Mercury	Background exposure normative limits: 1 – 8 $\mu\text{g/L}$ (whole blood); 4 - 5 $\mu\text{g/L}$ (urine) <sup>42,a</sup>
Nickel	<ul style="list-style-type: none"> <li>• Excessive exposure: <math>\geq 8</math> <math>\mu\text{g/L}</math> (blood)</li> <li>• Severe poisoning: <math>\geq 500</math> <math>\mu\text{g/L}</math> (8-h urine)</li> </ul>
Selenium	<ul style="list-style-type: none"> <li>• Mild toxicity: <math>&gt; 1</math> <math>\text{mg/L}</math> (serum)</li> <li>• Serious toxicity: <math>&gt; 2</math> <math>\text{mg/L}</math></li> </ul>
Silver	Asymptomatic workers have mean levels of 11 $\mu\text{g/L}$ (serum) and 2.6 $\mu\text{g/L}$ (spot urine)
Thallium	24-hour urine thallium $> 5$ $\mu\text{g/L}$ <sup>43</sup>

Metal	Toxic Levels (Normal Levels Where Indicated)
Zinc	Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

Adapted from Adal (2018).<sup>44</sup>

CDC: Centers for Disease Control and Prevention

<sup>a</sup> 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.<sup>45</sup>

## 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 Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not approved by the 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.<sup>1</sup>)

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 two 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.

## 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 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, FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used.<sup>2</sup>

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 two years and older. Under the accelerated approval program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients age ten years and older with chronic iron overload due to nontransfusion-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, 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, FDA advised that FDA-approved chelating agents would be available by prescription only.<sup>3</sup> There are no FDA-approved over-the-counter chelation products.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Centers for Disease Control and Prevention. Deaths associated with hypocalcemia from chelation therapy-- Texas, Pennsylvania, and Oregon, 2003-2005. MMWR Morb Mortal Wkly Rep. Mar 03 2006;55(8):204-207. PMID 16511441
2. Food and Drug Administration. Hospira, Inc., et al.; Withdrawal of Approval of One New Drug Application and Two Abbreviated New Drug Application. Federal Register. 2008;73(113):33440-33441. PMID
3. U.S. Food and Drug Administration. FDA warns consumers about potential health risks from using Thorne Research's Captomer products. 2014 June 12; [http://www.fda.gov/Drugs/DrugSafety/ucm400977.htm?source=govdelivery&utm\\_medium=email&utm\\_source=govdelivery](http://www.fda.gov/Drugs/DrugSafety/ucm400977.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery). Accessed January 23, 2018.
4. Sampson E, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's disease. Cochrane Database Syst Rev. Jan 23 2008(1):CD005380. PMID 18254079
5. Ritchie CW, Bush AI, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch Neurol. Dec 2003;60(12):1685-1691. PMID 14676042
6. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's dementia. Cochrane Database Syst Rev. May 16 2012;5(5):CD005380. PMID 22592705
7. Lannfelt L, Blennow K, Zetterberg H, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomized, placebo-controlled trial. Lancet Neurol. Sep 2008;7(9):779-786. PMID 18672400

8. Villarruz MV, Dans A, Tan F. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev*. Jan 2002(4):CD002785. PMID 12519577
9. Knudtson ML, Wyse DG, Galbraith PD, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. *Jama*. Jan 23-30 2002;287(4):481-486. PMID 11798370
10. Anderson TJ, Hubacek J, Wyse DG, et al. Effect of chelation therapy on endothelial function in patients with coronary artery disease: PATCH substudy. *J Am Coll Cardiol*. Feb 5 2003;41(3):420-425. PMID 12575969
11. Guldager B, Jelnes R, Jorgensen SJ, et al. EDTA treatment of intermittent claudication--a double-blind, placebo-controlled study. *J Intern Med*. Mar 1992;231(3):261-267. PMID 1556523
12. van Rij AM, Solomon C, Packer SG, et al. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. *Circulation*. Sep 1994;90(3):1194-1199. PMID 8087928
13. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. *Jama*. Mar 27 2013;309(12):1241-1250. PMID 23532240
14. Mark DB, Anstrom KJ, Clapp-Channing NE, et al. Quality-of-life outcomes with a disodium EDTA chelation regimen for coronary disease: results from the trial to assess chelation therapy randomized trial. *Circ Cardiovasc Qual Outcomes*. Jul 2014;7(4):508-516. PMID 24987051
15. Lamas GA, Boineau R, Goertz C, et al. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: The factorial group results of the Trial to Assess Chelation Therapy. *Am Heart J*. Jul 2014;168(1):37-44 e35. PMID 24952858
16. Nissen SE. Concerns about reliability in the Trial to Assess Chelation Therapy (TACT) [editorial]. *Jama*. Mar 27 2013;309(12):1293-1294. PMID 23532246
17. 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
18. Bernard S, Enayati A, Redwood L, et al. Autism: a novel form of mercury poisoning. *Med Hypotheses*. Apr 2001;56(4):462-471. PMID 11339848
19. Nelson KB, Bauman ML. Thimerosal and autism? *Pediatrics*. Mar 2003;111(3):674-679. PMID 12612255
20. Ng DK, Chan CH, Soo MT, et al. Low-level chronic mercury exposure in children and adolescents: meta-analysis. *Pediatr Int*. Feb 2007;49(1):80-87. PMID 17250511
21. Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. *Ann Clin Psychiatry*. Oct-Dec 2009;21(4):213-236. PMID 19917212
22. Cooper GJ, Young AA, Gamble GD, et al. A copper(II)-selective chelator ameliorates left-ventricular hypertrophy in type 2 diabetic patients: a randomised placebo-controlled study. *Diabetologia*. Apr 2009;52(4):715-722. PMID 19172243
23. Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes*. Jan 2014;7(1):15-24. PMID 24254885
24. Chen KH, Lin JL, Lin-Tan DT, et al. Effect of chelation therapy on progressive diabetic nephropathy in patients with type 2 diabetes and high-normal body lead burdens. *Am J Kidney Dis*. Oct 2012;60(4):530-538. PMID 22721929
25. U.S. Department of Labor, Occupational Health and Safety Administration. Safety and Health Regulations for Construction: Substance Data Sheet for Occupational Exposure to Lead. 1993; [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10642](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10642). Accessed January 23, 2018.
26. Weinreb O, Mandel S, Youdim MB, et al. Targeting dysregulation of brain iron homeostasis in Parkinson's disease by iron chelators. *Free Radic Biol Med*. Sep 2013;62:52-64. PMID 23376471
27. Grolez G, Moreau C, Sablonniere B, et al. Ceruloplasmin activity and iron chelation treatment of patients with Parkinson's disease. *BMC Neurol*. May 6 2015;15:74. PMID 25943368

28. van Eijk LT, Heemskerk S, van der Pluijm RW, et al. The effect of iron loading and iron chelation on the innate immune response and subclinical organ injury during human endotoxemia: a randomized trial. *Haematologica*. Mar 2014;99(3):579-587. PMID 24241495
29. Qaseem A, Fihn SD, Dallas P, et al. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. *Ann Intern Med*. Nov 20 2012;157(10):735-743. PMID 23165665
30. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. Nov 4 2014; 64(18):1929-1949. PMID 25077860
31. Snow V, Barry P, Fihn SD, et al. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. Oct 5 2004;141(7):562-567. PMID 15466774
32. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. Mar 21 2006; 113(11):e463-654. PMID 16549646
33. 2011 ACCF/AHA Focused Update of the Guideline for the Management of patients with peripheral artery disease (Updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. Nov 1 2011;124(18):2020-2045. PMID 21959305
34. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. Apr 2 2013; 127(13):1425-1443. PMID 23457117
35. Mancini GB, Gosselin G, Chow B, et al. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol*. Aug 2014;30(8):837-849. PMID 25064578
36. National Institute for Health and Care Excellence. Autism spectrum disorder in under 19s: support and management [CG170]. 2013; <https://www.nice.org.uk/guidance/cg170>. Accessed January 23, 2018.
37. National Institute for Health and Care Excellence. Autism spectrum disorder in adults: diagnosis and management [CG142]. 2016; <https://www.nice.org.uk/guidance/CG142>. Accessed January 23, 2018.
38. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for CHELATION THERAPY for Treatment of Atherosclerosis (20.21). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=86&ncdver=1&CoverageSelection=National&Keyword=Chelation+Therapy&KeywordLookUp=Title&KeywordSearchType=And&bc=gAAAACAAAAAAA%3d%3d&>. Accessed January 23, 2018.

39. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Ethylenediamine-Tetra-Acetic (EDTA) CHELATION THERAPY for Treatment of Atherosclerosis (20.22). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=146&ncdver=1&CoverageSelection=National&Keyword=Chelation+Therapy&KeywordLookup=Title&KeywordSearchType=And&bc=gAAAACAAAAAAAAA%3d%3d&>. Accessed January 23, 2018.
40. Centers for Disease Control and Prevention (CDC). What Do Parents Need to Know to Protect Their Children? 2017, May 17; [http://www.cdc.gov/nceh/lead/ACCLPP/blood\\_lead\\_levels.htm](http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm). Accessed January 23, 2018.
41. Very high blood lead levels among adults - United States, 2002-2011. MMWR Morb Mortal Wkly Rep. Nov 29 2013;62(47):967-971. PMID 24280917
42. Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury. 1999 March; <https://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf>. Accessed January 23, 2018.
43. Centers for Disease Control and Prevention (CDC). Emergency preparedness and response. Case definition: thallium. 2015 November 18; <http://emergency.cdc.gov/agent/thallium/casedef.asp>. Accessed January 23, 2018.
44. Adal A. Medscape. Heavy metal toxicity. 2018; <http://emedicine.medscape.com/article/814960-overview>. Accessed January 24, 2018.
45. Kempson IM, Lombi E. Hair analysis as a biomonitor for toxicology, disease and health status. Chem Soc Rev. Jul 2011;40(7):3915-3940. PMID 21468435