Description of Procedure or Service

Iron, an essential nutrient with a variety of biological uses, is tightly regulated in vivo to maintain homeostasis. Enterocytes absorb iron as Fe2+ either in its non-heme form via DMT1 (divalent metal-ion transporter-1) or in heme form presumably through receptor-mediated endocytosis. The enterocytes then release iron through ferroportin where transferrin binds it as biologically inactive Fe3+. Saturated transferrin can deliver iron to erythrocyte precursors in bone marrow where it can be incorporated into hemoglobin during erythropoiesis. Transferrin can also salvage iron released by the reticuloendothelial system and macrophages (Knutson, 2017).

All cells require iron; consequently, saturated transferrin can also bind to its receptors (Tfr1 or Tfr2). The bound Tfr undergoes receptor-mediated endocytosis followed by export of divalent iron for cellular use (Byrne, Krishnamurthy, & Wessling-Resnick, 2013). Intracellularly, iron is stored within the central cavity of the protein ferritin, a large spherical protein that can store up to 4500 iron atoms per protein. Ferritin has ferroxidase activity required for iron uptake and storage. In conjunction with transferrin and the transferrin receptor, ferritin is an acute phase reactant that responds to oxidative stress and inflammation (Camaschella & Schrier, 2017). Moreover, Tfr1 and Tfr2 upon activation by transferrin can initiate signaling cascades required for hepcidin expression (Roetto, Mezzanotte, & Pellegrino, 2018). Hepcidin, a small peptide hormone, acts as a modulator of serum iron concentrations by binding to ferroportin, the only iron exporter, ultimately resulting in the degradation of ferroportin, thereby resulting in an intracellular accumulation of iron (Pietrangelo, 2015).

Please note that carbohydrate-deficient transferrin is out of the scope of this policy.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for measurement of serum ferritin levels when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.
When measurement of serum ferritin levels is covered

Reimbursement for measurement of serum ferritin levels is allowed in any of the following situations:

- In the evaluation of an individual with abnormal hemoglobin and/or hematocrit levels.
- In the evaluation and monitoring of iron overload disorders.
- In individuals with symptoms of hemochromatosis (See Note 1).
- In individuals with first degree relatives with confirmed hereditary hemochromatosis (HH).
- In the evaluation of individuals with liver disease.
- In the evaluation and monitoring of patients with chronic kidney disease who are being considered for, or are receiving treatment for, anemia at a frequency of every 1 to 3 months.
- In the evaluation of hemophagocytic lymphohistiocytosis (HLH) and Still’s Disease.
- For individuals on iron therapy, at a frequency of every 1 to 3 months.
- In males with secondary hypogonadism.

Reimbursement for serum transferrin saturation (using serum iron and serum iron binding capacity measurements) is allowed in the following:

- For the evaluation of iron overload in individuals with symptoms of hemochromatosis (See Note 1).
- For the evaluation of iron overload in individuals with first-degree relatives with confirmed hereditary hemochromatosis (HH).
- For the evaluation of iron deficiency anemia.

When measurement of serum ferritin levels is not covered

1. Reimbursement is not allowed for the use of ferritin or transferrin measurement, including transferrin saturation, as a screening test in asymptomatic patients

2. Serum hepcidin testing, including immunoassays, is considered investigational.

3. The use of GlycA testing to measure or monitor transferrin or other glycosylated proteins is considered investigational.

NOTE 1: Symptoms of hemochromatosis, according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health include the following (NIDDK, 2014):

- Joint pain
- Fatigue
- Unexplained weight loss
- Abnormal bronze or gray skin color
- Abdominal pain
- Loss of sex drive

Policy Guidelines

Iron is an essential nutrient, necessary for fundamental metabolic processes as the central component in the catalytic sites of numerous essential enzymes and multiprotein complexes (Hentze, Muckenthaler, & Andrews, 2004; Zhang, Ghosh, & Rouault, 2014), including mitochondrial respiratory chain complexes and oxygen binding proteins (Wallace, 2016). However, iron is also potentially toxic due to its redox reactivity and resultant generation of
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damaging free radicals (Finazzi & Arosio, 2014). Tight regulation of iron metabolism to maintain adequate iron levels is achieved by the interaction of a number of iron metabolism related proteins (Zhang et al., 2014) and hemostatic modulation of iron absorption, utilization and recycling (Hentze, Muckenthaler, Galy, & Camaschella, 2010).

Iron homeostasis is a complex process where the small peptide hormone hepcidin plays a major role by binding the sole mammalian iron exporter, ferroportin (FPN1), leading to FPN1 degradation by lysosomes. Hepcidin production is sensitive to extracellular iron concentrations by way of HFE and the transferrin receptors (TfR). The HFE protein has been shown to interact with both TfR1 and TfR2, initiating the BMP-SMAD signaling pathway upon transferrin binding. This signaling cascade ultimately increases expression of the HAMP gene that encodes for hepcidin (Pietrangelo, 2015; Vujić, 2014).

Ferritins are a highly conserved family of proteins that detoxify and store iron that is not needed for immediate use as less reactive ferricydrite (Hentze et al., 2004) protecting the cell, but maintaining iron readily available for metabolic demand (Finazzi & Arosio, 2014). Mammalian ferritins are heteropolymers made up of tissue specific combinations of 24 isoferritins (Theil, 2013) including H-ferritin (heavy/heart, ~21kDa), and L-ferritin (light/liver, ~19kDa) which form a spherical structure and facilitate the dynamic storage of iron (Finazzi & Arosio, 2014; Liu & Theil, 2005). The levels and composition of ferritin are regulated by oxidative stress at the transcriptional level (Arosio & Levi, 2010; Bresgen & Eckl, 2015), and by iron responsive proteins (IRP) at the post-transcriptional level (Anderson, Shen, Eisenstein, & Leibold, 2012). Some tissues express a mitochondrial specific ferritin which further protects these mitochondria from oxidative damage (Campanella et al., 2009; Paul, Manz, Torti, & Torti, 2017).

Iron is released as needed from ferritin (Linder, 2013) by ferritinophagy, the targeting of ferritin for degradation in lysosomes by the cargo protein nuclear receptor coactivator 4 (NCOA4) (Mancias, Wang, Gygi, Harper, & Kimmelman, 2014) and transported back to the cytosol by divalent metal transporter 1 (DMT1) (La et al., 2018). The iron is then available as part of the labile iron pool (Cabantchik, 2014; Kruszewski, 2003). Degradation of ferritin and resultant accumulation of lethal reactive oxygen species been recognized as a distinct iron dependent type of regulated cell death, ferroptosis (Hou et al., 2016; Xie et al., 2016).

Ferritin can routinely be detected in serum (Alfrey, 1978) as a result of secretion from macrophages (Cohen et al., 2010) or release during cell death and lysis (Kell & Pretorius, 2014). Serum ferritin is mostly made up of L subunits, contains relatively little iron, and is partially glycosylated (Santambrogio, Cozzi, Levi, & Arosio, 1987; Wang, Knoovich, Coffman, Torti, & Torti, 2010). In healthy adults, levels of serum ferritin generally reflect overall iron storage (Costa Matos et al., 2013; Enko et al., 2015; Finch et al., 1986; Jacobs, Miller, Worwood, Beamish, & Wardrop, 1972; Wang et al., 2010; Zanella et al., 1989), closely correlating with the “gold standards” of measuring iron stores in bone marrow or liver biopsy (Peng & Uprichard, 2017).

However, serum ferritin is increased in the acute phase response to infection and tissue injury (Dignass, Farrag, & Stein, 2018; Feelders et al., 1998). Given iron is important to all living organisms, the immune system has developed mechanisms for iron sequestration to prevent iron utilization by invading pathogens and tumors (Wang et al., 2010) as a part of the response to inflammation. Increased levels of serum ferritin during acute phase response, therefore, do not correlate with iron availability or stores, but rather are a general indicator of inflammation (Kell & Pretorius, 2014), making assessment of iron status in the presence of inflammation more complex (Dignass et al., 2018; Knoovich, Storey, Coffman, Torti, & Torti, 2009; Munoz, Gomez-Ramirez, et al., 2017). Additionally, the two subunits of ferritin have been reported to differentially locate during periods of inflammation (Ahmad et al., 2013), potentially complicating use as an inflammatory diagnostic tool.
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Misregulated ferroptosis has been implicated in neurotoxicity, neurodegenerative diseases, acute renal failure, drug-induced hepatotoxicity, hepatic and heart ischemia/reperfusion injury, and T-cell immunity (Xie et al., 2016).

Neuroferritinopathy (NF) is classified as a neurodegeneration with brain iron accumulation (NBIA) disorder alongside pantothenate kinase-associated neurodegeneration (PKAN), phospholipase A2-associated neurodegeneration, mitochondrial membrane protein-associated neurodegeneration (MPAN), and beta-propeller protein-associated neurodegeneration (BPAN) among more rare genetic conditions (Hayflick, Kurian, & Hogarth, 2018). NBIAAs typically can be characterized by dystonia, parkinsonism, and spasticity, with iron accumulation within the basal ganglia. Depending on the NBIA subtype, the condition may also exhibit hyperphosphorylated tau, axonal swelling, and Lewy body formation (Arber, Li, Houlden, & Wray, 2016).

Hepcidin regulates serum iron levels by activating the endocytosis and proteolysis of ferroportin, the sole mammalian iron exporter. In healthy individuals, iron status is monitored by hepatocytes, which regulate hepcidin promoter activity according to iron needs. If iron levels are low, then iron is released by ferroportin and hepcidin levels remain low. If iron overload is detected, hepcidin is activated to ultimately sequester the excess iron (Ueda & Takasawa, 2018). Unregulated activity of hepcidin can, therefore, result in hypoferremia due to iron sequestration (Ganz & Nemeth, 2009). Interleukin-6 (IL-6), an inflammatory cytokine, stimulates hepcidin to ultimately decrease erythropoiesis due to a lack of bioavailable iron for hemoglobin. This “anemia of chronic inflammation (ACI) is a frequently diagnosed anemia and portends an independently increased morbidity and poor outcome associated with multiple underlying diseases (Langer & Ginzburg, 2017).”

Clinical Validity and Utility

Dysregulated iron metabolism has been implicated in a variety of pathophysiological conditions from mild iron deficiency to anemia, iron overload, inflammation, infection, cancer, cardiovascular and neurodegenerative diseases (Gozzelino & Arosio, 2016).

Iron deficiency refers to a reduced amount of iron stores, is usually acquired, and is a global health problem affecting over billion people worldwide (Camaschella, 2015). Inadequate intake due to poverty, malnutrition, dietary restriction, malabsorption and chronic blood loss are common cause of iron deficiency and resultant anemia (Kassebaum et al., 2014; Sankaran & Weiss, 2015). A low serum ferritin (<30 μg/L) is a sensitive and specific indicator for iron deficiency (Camaschella, 2015, 2017; Dignass et al., 2018; Enko et al., 2015; Ferraro, Mozzi, & Panteghini, 2012; Finch et al., 1986; Shin, Kim, Park, Suh, & Shin, 2015; Zanella et al., 1989), however a normal serum ferritin can be misleading in the context of inflammation (Peng & Uprichard, 2017). Dignass et al (2018) published recommendations which suggested “The standard threshold for iron deficiency (<30 μg/L) therefore does not apply and transferrin saturation (TSAT), a marker of iron availability, should also be assessed. A serum ferritin threshold of <100 μg/L or TSAT < 20% can be considered diagnostic for iron deficiency in CHF, CKD, and IBD. If serum ferritin is 100-300 μg/L, TSAT < 20% is required to confirm iron deficiency. Routine surveillance of serum ferritin and TSAT in these at-risk groups is advisable so that iron deficiency can be detected and managed.”

As there is no physiologic process present to excrete excess iron, iron overload can result from increased absorption, transfusion or hereditary disease. Excess iron collects within the internal organs specifically the liver and heart where it causes chronic free-radical induced injury (Wang et al., 2010). Initial signs and symptoms of iron overload are insensitive and nonspecific, so laboratory studies including ferritin are clinically useful in the identification and treatment of iron overload (Fleming & Ponka, 2012; Knovich et al., 2009; Koperdanova & Cullis, 2015). According to the HEIRS study (McLaren et al., 2003) ferritin levels above 200 ng per milliliter (449 pmol per liter) in women or 300 ng per milliliter (674 pmol per liter) in men who have no
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signs of inflammatory disease warrant additional testing. Therapeutic phlebotomy is indicated in patients with hemochromatosis who have high transferrin saturations and serum ferritin levels of more than 1000 ng per milliliter (2247 pmol per liter) and who do not have anemia (Fleming & Ponka, 2012; Salgia & Brown, 2015; van Boekhoven, van Deursen, & Swinkels, 2011). However, elevated ferritin levels are usually due to causes such as acute or chronic inflammation, chronic alcohol consumption, liver disease, renal failure, metabolic syndrome, or malignancy rather than iron overload (Koperdanova & Cullis, 2015).

Extremely elevated serum ferritin, in excess of five times the upper limit of normal (Evensen, Swaak, & Nossent, 2007), can indicate adult onset Still’s disease, a systemic inflammatory disorder characterized by fever, arthritis, and rash typically affecting young women (Knovich et al., 2009; Zandman-Goddard & Shoenfeld, 2007). Extremely elevated serum ferritin above 10,000 ug/L especially in the context of an autoimmune disorder such as Still’s disease, lupus, and viral infections indicate the possibility of hemophagocytic syndrome (Emmenegger et al., 2001). Phagocytosis of red blood cells by macrophages is characteristic of this disorder (Knovich et al., 2009) along with a final common pathway of elevated triglycerides, ferritin, pancytopenia ad multiple organ failure which is highly fatal (Sekigawa et al., 2001). Saeed et al (2015) used a receiver operating characteristic curve to evaluate the value of ferritin >500 ng/mL in diagnosing HLH in 344 consecutive patients and found that the optimal maximum serum ferritin level for the diagnosis of HLH was 3951 ng/mL.

The GlycA test utilizes NMR to measure the serum or plasma concentration of the N-acetyl methyl functional groups of N-acetylglucosamine glycans of glycosylated proteins associated with inflammation, including transferrin, haptoglobin, α1-acid glycoprotein, α1-antitrypsin, and α1-antichymotrypsin. Simple integration of the GlycA signal to accurately quantify concentration is not possible due to signal overlap with allylic protons of unsaturated fatty acids in the plasma or serum sample so a linear least-squares deconvolution determination must be performed. In doing so, Otvos and colleagues have shown that GlycA has lower imprecision and variability than hsCRP, cholesterol, and triglyceride testing; however, “because the GlycA signals originating from different plasma glycoproteins are not distinguishable, and the glycan on each is heterogeneous and varies dynamically, only a rough estimate can be made of how much each contributes to measured plasma GlycA concentrations (Otvos et al., 2015).” Consequently, the GlycA test cannot be used to accurately determine concentration of individual proteins, including transferrin.

A 2015 study measured serum hepcidin in more than 400 patients, including patients with liver disorders and iron disorders as well as healthy individuals, using a competitive ELISA assay. The researchers note that this ELISA assay has a good correlation with LC-MS/MS (r=0.89), but it does cross-react with forms of hepcidin (hepcidin-20 and -22) that are not associated with being biomarkers of iron disorders (Dahlfors et al., 2015). Another study compared the ELISA hepcidin assay to the use of ferritin, C-reactive protein, and IL-6 to differentiate iron deficiency anemia and anemia of inflammation in elder patients. Even though the study was small (n=30), they measured a sensitivity and specificity of the hepcidin assay of 100% and 67%, respectively, as compared to the lower sensitivity but higher specificity of ferritin (91% and 83%, respectively). They conclude, “Hepcidin shows a strong positive correlation with ferritin, and also correlates positively with C-reactive protein in this patient population (Karlsson, 2017).”

State and Federal Regulations, as applicable
A search of the FDA Devices databases on 09/13/2018 for “ferritin” yielded 122 records of approved products.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not
approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Policy Statement(s)
Guidelines and Recommendations
While there are guidelines and recommendations related to screening for anemia in certain populations, none of them recommend use of ferritin as a first-line test in asymptomatic individuals. Use of ferritin is recommended as a follow-up to abnormal hemoglobin or hematocrit screening results. Concerning neuroferritinopathy (NF), “At present, there are no established guidelines or specific management recommendations for patients with NF. An individualized symptomatic approach to treatment is recommended (Kumar, Rizek, & Jog, 2016).” To date, the only NBIA to have guidelines published concerning diagnosis and management of the condition is pantothenate kinase-associated neurodegeneration (PKAN, formerly called Hallervorden-Spatz syndrome) (Hogarth et al., 2017).

Kidney Disease Improving Global Outcomes (KDIGO, 2012)
In the 2012 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease publication, they recommend as part of an initial evaluation of anemia for all CKD patients, regardless of age or stage of degree progression, a complete blood count, an absolute reticulocyte count, serum ferritin, serum TSAT, serum vitamin B₁₂, and serum folate levels. Moreover, for patients undergoing ESA therapy, “including the decision to start or continue iron therapy”, both TSAT and ferritin should be tested at least every 3 months. TSAT and ferritin should be tested “more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted.”

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) (Klim et al., 2013)
The National Kidney Foundation’s KDOQI guidelines state, “KDIGO continued to recommend the use of serum ferritin concentration and transferrin saturation (TSAT) to define iron stores and iron availability. For all their imperfections, these metrics remain our best routinely-available tools to assess iron status and manage iron supplementation. In the absence of superior, cost-effective, and easily applicable alternatives, this approach seems reasonable.” They recommend use of ferritin testing along with TSAT as part of the evaluation of iron status in individuals with chronic kidney disease who are being treated for anemia. In agreement with KDIGO, they recommend testing prior to initiation of treatment, once per month during initial treatment, and at least every 3 months after a stable hemoglobin level is reached.

American Academy of Family Physicians (AAFP) (Lanier, Park, & Callahan, 2018)
A key recommendation for practice in the AAFP (with a “C” evidence rating or “consensus, disease-oriented evidence, usual practice, expert opinion, or case series”), they recommend “a low serum ferritin level is associated with a diagnosis of iron deficiency anemia.” They also state, “Patients with an elevated serum ferritin level or macrocytic anemia should be evaluated for underlying conditions, including vitamin B₁₂ or folate deficiency, myelodysplastic syndrome, and malignancy (Lanier et al., 2018).”

The Endocrine Society (Bhasin et al., 2018)
In the 2018 guidelines on hypogonadism, they state, “In men deemed to have secondary hypogonadism, additional diagnostic evaluations may be needed to exclude hyperprolactinemia, head trauma, iron overload syndromes, hypothalamic or pituitary tumors, and other infiltrative or destructive hypothalamic–pituitary diseases, as well as genetic disorders associated with gonadotropin deficiency. Measuring serum prolactin and iron saturation and/or serum ferritin can help determine the presence of hyperprolactinemia and iron overload syndromes, respectively.”
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In their practice guideline on the evaluation of abnormal liver chemistries, ACG recommends, “All patients with abnormal liver chemistries in the absence of acute hepatitis should undergo testing for hereditary hemochromatosis with an iron level, transferrin saturation, and serum ferritin” [Strong recommendation, very low level of evidence] (Kwo et al., 2017).

American Society of Hematology (ASH) (Wood, 2014)
In the ASH Guidelines for Quantifying Iron Overload, they state, “Despite improved availability of advanced imaging techniques, serum ferritin remains the mostly commonly used metric to monitor iron chelation therapy and remains the sole metric in many countries. Serum ferritin measurements are inexpensive and generally correlate with both total body iron stores and clinical outcomes... Given interpatient and temporal variability of serum ferritin values, serum ferritin is best checked frequently (every 3-6 weeks) so that running averages can be calculated; this corrects for many of the transient fluctuations related to inflammation and liver damage.” Regarding the use of transferrin, “Iron that is bound to transferrin is not redox active, nor does it produce extrahepatic iron overload. However, once transferrin saturations exceed 85%, non-transferrin-bound iron (NTBI) species begin to circulate, creating a risk for endocrine and cardiac iron accumulation. A subset of NTBI can catalyze Fenton reactions and is known as labile plasma iron (LPI). Therefore, transferrin saturation, NTBI, and LPI are potentially attractive serum markers for iron toxicity risk. Transferrin saturation is widely available, but values cannot be interpreted if iron chelator is present in the bloodstream, so patients have to be instructed to withhold iron chelation for at least 1 day before measurement... Although some studies link elevated LPI to cardiac iron accumulation, large validation studies are lacking. Therefore, to date, these metrics remain important and interesting research tools, but are not suitable for routine monitoring.” Within the conclusion of the paper, the author concludes, “Serum markers of somatic stores (ferritin and transferrin saturation) are useful surrogates for total iron stores and extrahepatic risk, respectively. However, they cannot replace LIC or cardiac T2* assessment for monitoring chelator efficacy or stratifying end organ risk (Wood, 2014).”

International Society of Nephrology (ISN) (Madore et al., 2008)
The most recent guidelines from the ISN, released in 2008, states that for CKD patients “who require iron and/or ESA therapy, measurement of serum ferritin and transferrin saturation every 1-3 months is reasonable, depending upon the clinical status of the patient, the hemoglobin response to iron supplementation, the ESA dose, and recent iron status test results. In stable patients with mild anemia (hemoglobin >110 g/l) who are not receiving iron or ESA therapy, assessment of iron status could be performed less frequently, potentially on a yearly basis.”

European Crohn’s and Colitis Organisation (ECCO) (Dignass et al., 2015)
In the 2015 ECCO guideline concerning iron deficiency and anemia in inflammatory bowel diseases (IBD) with an EL-5 recommendation they state, “For laboratory screening, complete blood count, serum ferritin, and C-reactive protein [CRP] should be used. For patients in remission or mild disease, measurements should be performed every 6 to 12 months. In outpatients with active disease such measurements should be performed at least every 3 months.” Within the section concerning the workup for anemia, with an EL-4 recommendation they state, “Anaemia workup should be initiated if the hemoglobin is below normal. The minimum workup includes red blood cell indices such as red cell distribution width [RDW] and mean corpuscular volume [MCV], reticulocyte count, differential blood cell count, serum ferritin, transferrin saturation [TfS], and CRP concentration. More extensive workup includes serum concentrations of vitamin B, folic acid, haptoglobin, the percentage of hypochromic red cells, reticulocyte hemoglobin, lactate dehydrogenase, soluble transferrin receptor, creatinine, and urea (Dignass et al., 2015).”

International consensus guideline for clinical management of pantothenate kinase-associated neurodegeneration (PKAN) (Hogarth et al., 2017)
An international group released guidelines concerning the clinical management of the NBIA condition PKAN. Although no specific recommendation is directly given regarding measurement
of iron, the group states, “The role that iron plays in PKAN pathogenesis is still unclear because iron dyshomeostasis is a secondary phenomenon in this disorder. Nevertheless, high iron levels develop in globus pallidus and probably contribute to cell and tissue damage. The utility of iron chelators has been limited by systemic iron depletion. Newer agents more readily cross the blood-brain barrier yet have a lower affinity for iron, thereby minimizing systemic iron loss.” Concerning diagnosis of PKAN, “People suspected to have PKAN based on clinical features should undergo brain MRI using iron sensitive sequences such as SWI, GRE, T2* as a first line diagnostic investigation to identify the characteristic changes. The MRI abnormality, called the ‘eye-of-the-tiger’ sign, is observed on T2-weighted imaging and consists of hypointense signal in the globus pallidus surrounding a region of hypointense signal.”

International consensus statement on the peri-operative management of anemia and iron deficiency by Munoz et al (2017)

An expert workshop, including a number of experienced researchers and clinicians, was conducted to develop a guidance for the diagnosis and management of anemia in surgical patients. They have developed a series of best-practice and evidence-based statements to advise on patient care with respect to anemia. Their statements included serum ferritin measurement as the most sensitive and specific test used for the identification of absolute iron deficiency (Munoz, Acheson, et al., 2017).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 82728, 84466, 84999, 0024U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Kell, D. B., & Pretorius, E. (2014). Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics, 6(4), 748-773. doi:10.1039/c3mt00347g


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Avalon review 12/2018.

Specialty Matched Consultant Advisory Panel review 02/2020

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>1/1/19</td>
<td>New policy developed. BCBSNC will provide coverage for measurement of serum ferritin levels when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review. Policy noticed 1/1/2019 for effective date 4/1/2019. (mco)</td>
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<tr>
<td>4/16/19</td>
<td>Policy renamed from Ferritin to Diagnostic Testing of Iron Homeostasis and Metabolism. Description and Policy Guidelines sections updated. Added the following statements to the coverage criteria: Specifically added serum ferritin testing for symptomatic patients of hereditary hemochromatosis (HH), first-degree relatives of patients with diagnosed HH, or males with secondary hypogonadism, Added CC (from old HH policy) that serum transferrin saturation (i.e. TSAT) in patients with symptomatic hemochromatosis or first-degree relatives with diagnosed HH, Added “transferrin” so that CC reads that serum ferritin or transferrin in general screening for anemia, Added CC that serum hepcidin testing, including immunoassays for hepcidin, is investigational, Added CC that GlycA testing is investigational (since there is a PLA code for this testing). Added CPT Codes 84466, 84999, and PLA Code 0024U to the Billing/Coding section. References revised to include new references from the Avalon review. (an)</td>
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<td>10/29/19</td>
<td>Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)</td>
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<td>02/11/20</td>
<td>Reviewed by Avalon 4th Quarter CAB. No changes to policy. (eel)</td>
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<tr>
<td>03/10/20</td>
<td>Specialty Matched Consultant Advisory Panel 02/19/2020. No changes to policy. (eel)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.