Diagnostic Testing of Iron Homeostasis & Metabolism

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I. Policy Description

Iron, an essential nutrient with a variety of biological uses, is tightly regulated *in vivo* to maintain homeostasis. Enterocytes absorb iron as Fe^{2+} 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 Fe^{3+}. Saturated transferrin delivers iron to erythrocyte precursors in bone marrow where it is incorporated into hemoglobin during erythropoiesis. Transferrin may also salvage iron released by the reticuloendothelial system and macrophages.[1]

All cells require iron; consequently, saturated transferrin can also bind to its receptors (TfR1 or TfR2). The bound transferrin receptor (TfR) undergoes receptor-mediated endocytosis followed by export of divalent iron for cellular use.[2] 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 TfR, ferritin is an acute phase reactant that responds to oxidative stress and inflammation.[3] Moreover, TfR1 and TfR2, upon activation by transferrin, can initiate signaling cascades required for hepcidin expression.[4] Hepcidin, a small peptide hormone, acts as a modulator of serum iron concentrations by binding to ferroportin, the only iron exporter; ultimately, this results in the degradation of ferroportin and an intracellular accumulation of iron.[5]

Terms such as male and female are used when necessary to refer to sex assigned at birth. Please note that carbohydrate-deficient transferrin is out of scope for this policy.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) Measurement of serum ferritin levels (no more than one test per month unless otherwise specified) **MEETS COVERAGE CRITERIA** in **any** of the following situations:
   a) For individuals with anemia.
   b) Once every three weeks for individuals with an iron overload disorder.
   c) For individuals with symptoms of hemochromatosis (see Note 1).

d) For individuals with first-degree relatives (see Note 2) with confirmed hereditary hemochromatosis (HH).

e) For the evaluation of individuals with liver disease.

f) For the evaluation of hemophagocytic lymphohistiocytosis (HLH) and Still Disease.

g) In males with secondary hypogonadism.

h) For individuals who have chronic kidney disease:

i) One test every three months if the individual is not receiving dialysis.

ii) One test every month if the individual is receiving dialysis.

i) For individuals on iron therapy.

j) For individuals with restless legs syndrome or periodic limb movement disorder.

2) Measurement of serum transferrin saturation **MEETS COVERAGE CRITERIA** in **any** of the following:

a) For the evaluation of iron overload in individuals with symptoms of hemochromatosis (see Note 1).

b) For the evaluation of iron overload in individuals with first-degree relatives (see Note 2) with confirmed hereditary hemochromatosis (HH).

c) For the evaluation of iron deficiency anemia.

d) For individuals with restless legs syndrome or periodic limb movement disorder.

3) For all other situations not addressed above, measurement of ferritin or transferrin levels, including transferrin saturation, **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

4) Serum hepcidin testing, including immunoassays, **DOES NOT MEET COVERAGE CRITERIA**.

5) The use of GlycA testing to measure or monitor transferrin or other glycosylated proteins **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Symptoms of hemochromatosis (iron overload):[6]

- Fatigue
- Arrhythmias
- Joint pain
- Low libido or erectile dysfunction
- Pain in the knuckles of the index and middle fingers (sometimes called "iron fist")
- Skin darkening (a gray or bronze tint)
- Unexplained weight loss

- Upper abdominal pain

Note 2: First-degree relatives include parents, full siblings, and children of the individual.

III. Table of Terminology

Term	Definition
25(OH) vitamin D	25-hydroxy-vitamin D
AAFP	American Academy of Family Physicians
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
BMP-SMAD	Bone morphogenetic protein-Smad
BPAN	Beta-propeller protein-associated neurodegeneration
BRINDA	Biomarkers reflecting the inflammation and nutritional determinants of anemia
TM	Beta thalassemia major
CBC	Complete blood cell count
CHF	Congestive heart failure
CKD	Chronic kidney disease
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CLSI-C62A	Clinical and Laboratory Standards Institute-C62A
CMS	Centers for Medicare and Medicaid Services
CRP	C-reactive protein
CVs	Coefficients-of-variation
DMT1	Divalent metal-ion transporter-1
DUOX2	*Dual oxidase 2*
ECCO	European Crohn’s and Colitis Organisation
ELISA	Enzyme-linked immunosorbent assay
ESAs	Erythropoiesis-stimulating agents
F5	*Coagulation factor V*
Fe2+	Ferrous ion
Fe3+	Ferric ion
FBC	Full blood count
FDA	Food and Drug Administration
FTH	Ferritin H
FTL	Ferritin L
FTL1	Ferritin light polypeptide 1
GDF-15	Growth differentiation factor 15
GlycA	Glycoprotein acetylation
GPX4	Glutathione peroxidase 4
GRE	Gradient recalled echo
GSH	Glutathione
HAMP	*Hepcidin antimicrobial peptide*

HEIRS	Hemochromatosis and iron overload screening
HFE	*Homeostatic iron regulator*
HH	Hereditary hemochromatosis
HLH	Hemophagocytic lymphohistiocytosis
HPLC/MS/MS	High-performance liquid chromatography/tandem mass spectrometry
hsCRP	High-sensitivity C-reactive protein
IBD	Inflammatory bowel disease
ICCAMS	International Consensus Conference on Anemia Management in Surgical Patients
ID	Iron deficiency
IDA	Iron deficiency anemia
IL-6	Interleukin-6
IRP	Iron responsive proteins
ISN	International Society of Nephrology
KDIGO	Kidney Disease: Improving Global Outcomes
LC-MS/MS	Light chromatography with tandem mass spectroscopy
LDTs	Laboratory-developed tests
LPI	Labile plasma iron
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MPAN	Mitochondrial membrane protein-associated neurodegeneration
MRI	Magnetic resonance imaging
NBIA	Neurodegeneration with brain iron accumulation
NCOA4	Nuclear receptor coactivator 4
NF	Neuroferritinopathy
NICU	Neonatal intensive care unit
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NKF-KDOQI	The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
NMR	Nuclear magnetic resonance
NTBI	Non-transferrin-bound iron
PKAN	Pantothenate kinase-associated neurodegeneration
RBC	Red blood cell
RET-He	Reticulocyte hemoglobin equivalent
RDW	Red cell distribution width
RLS	Restless Leg Syndrome
ROS	Reactive oxygen species
SCD	Sickle cell disease
SF	Serum ferritin
SLC11A2	*Solute carrier family 11 member 2*
SLE	Systemic lupus erythematosus
SOFA	Severity of organ failure
SWI	Susceptibility weighted imaging
TfR	Transferrin receptor
TfR1	Transferrin receptor 1

TfR2	Transferrin receptor 2
TfS/TSAT	Transferrin saturation
TMPRSS6	*Transmembrane protease, serine 6*
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

IV. Scientific Background

Iron is necessary for fundamental metabolic processes and acts as the central component in the catalytic sites of numerous essential enzymes and multiprotein complexes, such as mitochondrial respiratory chain complexes and oxygen binding proteins.[7,8] Tight regulation of iron metabolism for maintaining adequate iron levels is achieved by the interaction of a number of iron metabolism-related proteins as well as the hemostatic modulation of iron absorption, utilization, and recycling.[8,9] This strict regulation is pertinent due to the potential toxicity of iron from its redox reactivity and the resultant generation of damaging free radicals.[10]

Several mechanisms in the body regulate the dietary absorption of iron and its concentration in other areas, such as plasma and extracellular milieu; this process is known as systemic iron homeostasis.[11] Iron homeostasis is a complex process where the small peptide hormone hepcidin plays a major role by binding the sole mammalian iron exporter, ferroportin. This leads to ferroportin degradation of lysosomes. Furthermore, hepcidin production is sensitive to extracellular iron concentrations by way of the human homeostatic iron regulator (HFE) protein and the TfRs. 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.[5,12]

Ferritins are a highly conserved family of proteins that detoxify and store excess iron as less reactive ferrihydrite.[7] This intracellular iron storage mechanism allows the cell to maintain and utilize spare iron based on changes in metabolic demand.[10] Mammalian ferritins are heteropolymers comprised of tissue-specific combinations of 24 subunits. These subunits consist of two types: Ferritin L (FTL) and Ferritin H (FTH); a spherical structure is formed from these subunits, facilitating the dynamic storage of iron.[10,13] The levels and composition of ferritin are regulated by oxidative stress at the transcriptional level,[14,15] and by iron responsive proteins (IRP) at the post-transcriptional level.[16] Several tissues express a mitochondria-specific ferritin protein that further protect these mitochondria from oxidative damage.[17,18]

Iron is released as needed from ferritin by ferritinophagy, the targeting of ferritin for degradation by lysosomes; this process requires cargo protein nuclear receptor coactivator 4 (NCOA4), as NCOA4-deficient cells cannot degrade ferritin correctly.[19] After release, the iron is transported back to the cytosol by divalent metal transporter 1 (DMT1).[20] This process allows the iron to become available as part of the labile iron pool.[21,22]

Degradation of ferritin and resultant accumulation of lethal reactive oxygen species (ROS) has been recognized as a distinct iron-dependent type of regulated, non-apoptotic cell death known as ferroptosis.[23,24] Dysregulated ferroptosis has been implicated in neurotoxicity, neurodegenerative diseases, acute renal failure, drug-induced hepatotoxicity, hepatic and heart ischemia/reperfusion injury, and T-cell immunity.[24] Abnormal ferroptosis has also been recently found to play a role in drug treatment, particularly in decitabine treatment of myelodysplastic syndrome (MDS). The drug-induced

ROS release decreases glutathione (GSH) and glutathione peroxidase 4 (GPX4), features characteristic of this unique cell death process.[25]

Ferritin can routinely be detected in serum as a result of secretion from macrophages or release during cell death and lysis.[26-28] Serum ferritin (SF) is primarily composed of L subunits, contains relatively little iron, and is partially glycosylated.[29,30] Causes of elevated SF levels include, but are not limited to, acute or chronic inflammation, chronic alcohol consumption, liver disease, renal failure, metabolic syndrome, or malignancy rather than iron overload.[31] In healthy adults, levels of SF generally reflect overall iron storage.[29,32-36] This closely correlates with the "gold standards" of measuring iron stores in bone marrow or liver biopsy.[37]

Given that iron is an essential component for many metabolic processes, the immune system has developed mechanisms for iron sequestration as part of the inflammatory response in order to prevent invading pathogens and tumors from utilizing iron.[29] Hence, increased levels of SF during the immune system-based acute phase response do not necessarily correlate with iron availability or stores, but rather are a general indicator of inflammation.[38] This becomes a critical issue when assessing iron deficiency (ID), as elevations in SF during inflammation can mask the presence of ID.[39] However, this makes the assessment of iron status in the presence of inflammation more complex.[38,40,41] Additionally, the two subunits of ferritin (FTL and FTH) have been reported to differentially locate during periods of inflammation; this complicates the use of these subunits as an inflammatory diagnostic tool.[42] In analyzing data from the Biomarkers Reflecting the Inflammation and Nutritional Determinants of Anemia (BRINDA) project, Suchdev, et al. (2017) identified that all their examined indicators of iron status (SF, serum TfR, total body iron) were affected by inflammation, and suggested utilizing C-reactive protein (CRP), a measure of acute inflammation, and α1-acid glycoprotein, a measure of chronic inflammation, in addition to iron indicators to better account for the full range and severity of inflammation.

Extremely elevated SF, in excess of five times the upper limit of normal,[43] can indicate adult-onset Still disease. Still disease is a systemic inflammatory disorder that is characterized by fever, arthritis, and rash.[40,44] More extremely elevated SF (above 10,000 ug/L), especially in the context of autoimmune disorders, such as Still disease and systemic lupus erythematosus (SLE), and viral infections, indicates the possibility of hemophagocytic syndrome,[45] which involves the phagocytosis of red blood cells by macrophages,[40] along with a final common pathway of elevated triglycerides, ferritin, pancytopenia, and highly fatal multiple organ failure.[46]

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, iron is released by ferroportin, allowing hepcidin levels to remain low; if iron overload is detected, hepcidin is activated to sequester the excess iron.[47] Unregulated activity of hepcidin can therefore result in hypoferremia due to iron sequestration.[48] Interleukin-6 (IL-6), an inflammatory cytokine, stimulates hepcidin to decrease erythropoiesis due to a lack of bioavailable iron for hemoglobin.[49]

No physiological process is present in the body to excrete excess iron, leaving individuals susceptible to developing iron overload. Iron overload may 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.[29] Excess iron may be a symptom or complication of a hereditary disease, such as HH, an autosomal recessive disorder that causes an enhancement in the intestinal absorption of excess iron.[50] Too much iron in the body can lead to a plethora of problems, including

arthritis, skin pigmentation, hypogonadism, cardiomyopathy, and diabetes. The majority of individuals with HH contain mutant hemochromatosis (*HFE*) genotypes, including homozygosity for p.Cys282Tyr or p.Cys282Tyr, and compound heterozygosity for p.His63Asp; based on these results, it is suggested that genetic testing be performed for these mutations in all patients with primary iron overload and an idiopathic increase in transferrin saturation (TSAT) and/or SF values.[50]

Another genetic disorder characterized by excess iron accumulation is known as neuroferritinopathy (NF). NF was first discovered in 2001 and is a movement disorder identified by excess iron in specific areas of the brain.[51] NF is the only known autosomal dominant genetic disease of neurodegeneration caused by mutations in the ferritin light polypeptide 1 (*FTL1*) gene.[52,53] The modification causes mutant L-chain ferritins that negatively alter ferritin function and stability.[54,55] Several conditions indicative of NF include brain iron accumulation (NBIA) disorder alongside pantothenate kinase-associated neurodegeneration (PKAN), phospholipase A_2-associated neurodegeneration, mitochondrial membrane protein-associated neurodegeneration (MPAN), and beta-propeller protein-associated neurodegeneration (BPAN).[56] NBIAs are typically characterized by dystonia, Parkinsonism, spasticity, and iron accumulation within the basal ganglia. Depending on the NBIA subtype, the condition may also exhibit hyperphosphorylated tau, axonal swelling, and Lewy body formation.[57] NF is typically considered as a diagnosis in patients exhibiting movement disorders, decreased SF, variable phenotypes, negative genetic testing for common movement disorders such as Huntington disease, and imaging showing potential iron deposits in the brain.[52]

Iron overload can also be caused by increased intake or absorption, transfusions given for anemia not caused by iron deficiency or blood loss, ineffective erythropoiesis, liver disease, and other rare sources of excess iron, such as individuals with chronic kidney disease who are receiving intravenous iron infusions. Red blood cell transfusions for hereditary anemias, such as thalassemia, sickle cell disease, myelodysplastic syndrome, or inherited bone marrow failure syndromes like pyruvate kinase deficiency are the most frequent causes of increased iron intake. Less common contributors include overuse of iron supplements or iron-containing medications, such as hemin. Increased iron absorption is seen in HH due to biallelic HFE C282Y conditions with ineffective erythropoiesis, such as thalassemia and sideroblastic anemias. Liver disease, including alcoholic liver disease and chronic hepatitis, can also increase iron absorption. Uncommon causes include gestational alloimmune liver disease and rare genetic variants that affect iron absorption or distribution. Red blood cell disorders that can lead to iron overload include thalassemias, pyruvate kinase deficiency, congenital dyserythropoietic anemia, some sideroblastic anemias, and hereditary stomatocytosis or xerocytosis.[58]

Iron deficiency (ID), referring to a reduced amount of iron stores, is usually an acquired disorder that affects over one billion people worldwide.[59,60] Inadequate iron intake is often due to poverty, malnutrition, dietary restriction, and malabsorption; additional causes include menstrual periods, gastrointestinal bleeding, and chronic blood loss.[61-63] SF analysis is the most efficient test for a diagnosis of ID.[63] In children, ID is most commonly caused by insufficient dietary iron intake when compared to a child's rapid growth rate, as well as gastrointestinal issues due to cow's milk.[64]

It has been reported that more than one in three pregnant individuals present with iron deficiency anemia worldwide.[65] Anemia in pregnant individuals could affect the fetus' intrauterine growth and may cause neurodevelopmental impairment.[66] Maternal anemia in early pregnancy is associated with an increased risk of autism spectrum disorder, attention-deficit/hyperactivity disorder, and intellectual disability.[67] Efficient vitamin and mineral supplementation are vital during pregnancy for the health of both the mother and of the fetus; however, certain supplements may be more helpful than others. It

has been suggested that in pregnant women, intravenous iron administration may be a more effective treatment option than oral iron administration.[65]

Analytical Validity

Low SF (<30ug/L) is a sensitive and specific indicator for ID.[38] However, a normal SF level can be misleading in the context of inflammation.[37] Dignass, et al. (2018) published recommendations which stated that the standard ID level is <30 μg/L and that "A serum ferritin threshold of <100 μg/L or TSAT < 20% can be considered diagnostic for iron deficiency in congestive heart failure (CHF), chronic kidney disease (CKD), and inflammatory bowel disease (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."[38]

Biomarker glycoprotein acetylation (GlycA) has been associated with chronic inflammation and utilizes nuclear magnetic resonance (NMR) to measure the serum or plasma concentration of the *N*-acetyl methyl functional groups of *N*-acetylglucosamine glycans associated with inflammation; these include transferrin, haptoglobin, α_1-acid glycoprotein, α_1-antitrypsin, and α_1-antichymotrypsin.[68] According to Otvos, et al. (2015) the 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; therefore, a linear least squares deconvolution determination must be performed. In doing so, Otvos, et al. (2015) have shown that GlycA has lower imprecision and variability than high-sensitivity 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."[69] Consequently, the GlycA test cannot be used to accurately determine concentration of individual proteins, including transferrin.

Dahlfors, et al. (2015) measured serum hepcidin in more than 400 patients using a competitive ELISA assay; several types of patients were included in this study including those with liver disorders and iron disorders, as well as healthy individuals. The researchers note that this ELISA assay has a good correlation with light chromatography with tandem mass spectroscopy (LC-MS/MS) (r=0.89), but it does cross-react with forms of hepcidin (hepcidin-20 and -22) that are not associated with iron disorder biomarkers.[70] Another study by Karlsson (2017) compared the ELISA hepcidin assay to the use of ferritin, CRP, and IL-6 to differentiate ID 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). It was concluded that "Hepcidin shows a strong positive correlation with ferritin, and also correlates positively with C-reactive protein in this patient population."[71] Recently, Chen, et al. (2019) have developed a high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method, in accordance to CLSI-C62A guidelines, to measure serum hepcidin levels. This method has intra- and inter-day coefficients-of-variation (CVs) of <3% and <6%, respectively, with relative error rates ≤1.2% and ≤4.4% at ambient temperature and 4˚C, respectively. The authors also report that the relative error rate after three cycles of freeze-thaw (-70˚C) is ≤1.8%.[72]

da Silva, et al. (2019) has shown that both iron deficiency anemia (IDA) and sickle cell disease (SCD) can be detected in whole human blood samples via Raman spectroscopy; this study detected both IDA and SCD, when compared to healthy subject controls, with a sensitivity of 93.8% and a specificity of 95.7%. These results were based on detailed spectra analysis methods such as partial least squares and principal component analysis.[73]

Gerday, et al. (2020) measured urinary ferritin in neonatal intensive care unit (NICU) patients, and found that in those neonates at risk for iron deficiency (n=49), "a corrected urine ferritin < 12 ng/mL had a sensitivity of 82% (95% CI, 67-93%) and a specificity of 100% (CI, 66-100%) for detecting iron-limited erythropoiesis, with a positive predictive value of 100% (CI, 89-100%)." Though iron deficiency can be confirmed via serum iron, transferrin, SF, among other tests, the volume of blood and costs associated with these tests necessitate a non-invasive and accurate alternative for diagnosing iron deficiency.[74]

Jones, et al. (2021) investigated the effect of delayed processing on measuring 25 micronutrients and select clinical biomarkers, including iron (ferritin), in human blood samples. Blood from 16 healthy participants was collected and processed within either two hours or 24 hours. The concentration difference between the two process delays was compared. All analytes had a four percent or lower change in concentration between the two delays. There was no significant effect of delayed processing on ferritin. The authors concluded that "in blood collected from adult participants, delayed processing of chilled, whole blood for 24 hours did not materially affect the measured concentrations of the majority of micronutrient and selected clinical biomarkers."[75]

Bell, et al. (2021) performed a meta-analysis to study genes associated with iron homeostasis. Data about blood levels of ferritin, total iron binding capacity, iron saturation, and transferrin saturation was used from three genome-wide association studies from Iceland, the UK, and Demark. The authors identified 56 loci with variants associated with one or more of the biomarkers, 46 of which are novel variants. Specifically, "variants at *DUOX2*, *F5*, *SLC11A2* and *TMPRSS6* associate with iron deficiency anemia, while variants at *TF*, *HFE*, *TFR2* and *TMPRSS6* associate with iron overload."[76]

Clinical Utility and Validity

Dysregulated iron metabolism has been implicated in a variety of pathophysiological conditions from mild ID to anemia, iron overload, inflammation, infection, cancer, and cardiovascular and neurodegenerative diseases.[77] 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.[31,40,78] According to the Hemochromatosis and Iron Overload Screening (HEIRS) study,[79] ferritin levels above 200 ng/mL (449 pmol/L) in women or 300 ng/mL (674 pmol/L) in men with no signs of inflammatory disease warrant additional testing. Therapeutic phlebotomy is indicated in patients with hemochromatosis who have high TSAT and SF levels of more than 1000 ng/mL (2247 pmol/L). Therapeutic phlebotomy is also recommended in patients who do not have anemia.[78,80,81] Saeed, et al. (2015) used a receiver operating characteristic curve to evaluate the value of ferritin >500 ng/mL for diagnosing hemophagocytic lymphohistiocytosis (HLH) in 344 consecutive patients and found that the optimal maximum SF level for the diagnosis of HLH was 3951 ng/mL.

Abioye, et al. (2019) collected data from 2,100 pregnant individuals in Tanzania to determine how capable hematologic biomarkers such as hemoglobin and hepcidin were at detecting IDA in pregnant individuals; hepcidin administration >1.6 µg/L was found to reduce the risk of anemia at delivery by an estimated 49%. This study suggests that both hemoglobin and hepcidin may be helpful in determining iron supplementation needs in "resource-limited countries."[83]

Ismail, et al. (2019) studied the role of hepcidin in children with B-thalassemia (n = 88 total). The authors measured both serum hepcidin and SF levels as well as determined the hepcidin: ferritin ratio. As expected, serum hepcidin significantly correlated with the hepcidin: ferritin ratio, but the authors reported that there was no statistically significant difference in serum hepcidin levels between splenectomized and non-splenectomized patients. Serum hepcidin levels were more elevated in

individuals with B-thalassemia, especially those with B-thalassemia major (bTM), than in control patients (21.74 ng/mL and 13.01 ng/mL, respectively). The authors conclude, "knowing that hepcidin in serum has a dynamic and multi-factorial regulation, individual evaluation of serum hepcidin and follow up, e.g. every six months could be valuable, and future therapeutic hepcidin agonists could be helpful in management of iron burden in such patient."[84]

Yuniati, et al. (2019) studied the association between maternal vitamin D, ferritin, and hemoglobin levels during the first trimester of pregnancy, and how these factors affected birthweight. Data collected from these individuals included maternal demography, bloodwork to test ferritin levels, 25(OH) vitamin D results in their first trimester, and the final birthweight of the child after delivery. A total of 203 Indonesian individuals were followed until delivery; it was determined that neither vitamin D, ferritin or hemoglobin levels significantly impacted birthweights in this study. However, the authors suggest that other unknown variables may be at play here and that nutritional supplementation during pregnancy is still important.[85]

Kwiatek-Majkusiak, et al. (2020) investigated the connection between hepcidin and chronic neuroinflammation. Serum hepcidin and IL-6 were found to be involved in the progression of Parkinson's Disease. Dysregulation in immune/inflammatory pathways, wherein levels of serum hepcidin and IL-6 would be elevated, were not only predictive of neurodegeneration, with IL-6- induced hepcidin expression in astrocytes, microglia, and epithelial cells, but also response to deep brain stimulation treatment.[86]

Brandtner, et al. (2020) found linkages between serum markers of iron metabolism and prognosis of sepsis survival. Positive correlations were found between increased serum iron and SF levels and severity of organ failure (SOFA score) and mortality. High TSAT, elevated ferritin and serum iron levels, and low transferrin concentrations were associated with decreased chances of survival as well. This indicates the utility of iron metabolism in the context of extreme systemic inflammation; from this study, it was also concluded that TSAT can be a stand-alone predictor of sepsis survival.[87]

Nalado, et al. (2020) evaluated the diagnostic validity of GDF-15 and hepcidin as biomarkers of IDA in non-dialysis CKD patients. Serum levels of GDF-15 and hepcidin were measured in 312 non-dialysis CKD patients and 184 healthy control participants in Johannesburg, South Africa. For absolute IDA diagnosis among CKD patients, GDF-15 had a predictive value of 74.02%. For functional IDA diagnosis among CKD patients, hepcidin had a predictive value of 70.1%. The authors concluded that "serum GDF-15 is a potential biomarker of absolute IDA, while hepcidin levels can predict functional IDA among CKD patients."[88]

Phillips, et al. (2021) studied how the full blood count (FBC) parameters change in older patients. FBC, mean corpuscular volume (MCV), and red cell distribution width (RDW) test results were compiled from male and female patients aged 1-100 years from the National Health Service in England. In males, the mean hemoglobin concentration increased from birth until age 20, then decreased at a steady rate from age 20 to 70, then decreased at a higher rate after age 70. In females, the mean hemoglobin concentration increased from birth until age 14, then decreased slowly from age 14 to 30, then increased again from age 30 to age 60, and then decreased after the age of 60. Overall, "hemoglobin concentrations in males and females begin to converge after age 60 and equalize by approximately 90 years." The authors concluded that FBC parameters trend throughout life, particularly "a falling hemoglobin level and rising MCV and RDW with older age."[89]

Mei, et al. (2021) performed a cross-sectional study using data from the US National Health and Nutrition Examination Survey to determine physiologically based SF concentration thresholds for iron deficiency in healthy children (12-59 months) and non-pregnant individuals (15-49 years). The study analyzed the relationship between SF and hemoglobin, and the relationship between SF and soluble transferrin receptor. The study resulted in SF concentration thresholds for iron deficiency of "about 20 µg/L for children and 25 µg/L for non-pregnant women." The authors concluded that "physiologically based thresholds for iron deficiency might be more clinically and epidemiologically relevant than those based on expert opinion."[90]

Garcia-Casal, et al. (2021) performed a meta-analysis studying the diagnostic accuracy of serum and plasma ferritin concentrations for detecting iron deficiency or overload in primary and secondary iron-loading syndromes. The authors used 72 studies, with a total of 6095 participants, that measured serum or plasma ferritin concentrations. The authors compared ferritin blood tests to iron levels in the bone marrow to diagnose iron deficiency and compared ferritin blood tests to iron levels in the liver to diagnose iron overload. The authors concluded that at a threshold of 30 µg/L, there "is low certainty evidence that blood ferritin concentration is reasonably sensitive and a very specific test for iron deficiency." Additionally, there is "very low certainty that high concentrations of ferritin provide a sensitive test for iron overload in people where this condition is suspected." The authors note that overall confidence in the studies is low because of potential bias, indirectness, and heterogenous evidence, and that there is insufficient evidence to make conclusions about using ferritin concentrations to diagnose iron deficiency or overload in asymptomatic people.[91]

Auerbach, et al. (2021) performed a study to assess the accuracy of diagnosing IDA using the complete blood cell count (CBC) and reticulocyte hemoglobin equivalent (RET-He) analysis. A total of 556 patients referred to for the diagnosis and/or treatment of anemia were studied at baseline, and 150 of the participants were later studied after intravenous iron treatment. RET-He identified iron deficiency with a 68.2% sensitivity and 69.7% specificity. RET-He predicted responsiveness to intravenous iron with 84% sensitivity and 78% specificity. The authors concluded that "CBC and RET-He can identify patients with IDA, determine need for and responsiveness to intravenous iron, and reduce time for therapeutic decisions."[92]

Tahara, et al. (2022) examined the usage of RET-He as a marker of iron deficiency in patients with heart failure, as both anemia and iron deficiency are common among patients with heart failure. RET-He has been considered as a proxy due to the limitations of using serum ferritin and transferring saturation for the diagnosis of iron deficiency in the clinical setting. Namely, ferritin can be overestimated in cases of chronic inflammation, such as in the case of heart failure, and thus may be inaccurately measured for the diagnosis of iron deficiency. In this prospective study, researchers enrolled 142 patients hospitalized for decompensated heart failure, with 65% of them having iron deficiency. RET-He was directly correlated with serum iron and ferritin concentrations and TSAT for iron deficiency. They found that "there was a poor relationship between quartile of RET-He and [heart failure] hospitalization or death but increases or decreases in RET-He between admission and discharge were associated with a worse outcome." This demonstrated a potential for using RET-He for predicting improvements in iron deficiency per response to IV iron and prognosis of patients with comorbid iron deficiency and heart failure.[93]

V. Guidelines and Recommendations

Guidelines and recommendations related to the screening of anemia in certain populations are available; however, published recommendations regarding the use of ferritin as a first line test in asymptomatic individuals have not been identified.

Regarding NF, "At present, no established guidelines or specific management recommendations for patients with NF have been identified. An individualized symptomatic approach to treatment is recommended."[52] To date, the only NBIA guidelines published concerning diagnosis and management of the condition is pantothenate kinase-associated neurodegeneration (PKAN, formerly called Hallervorden-Spatz syndrome).[94]

American Gastroenterological Association (AGA)

The AGA has published its official recommendations on the gastrointestinal evaluation of IDA. It has stated:

- "In patients with anemia, the AGA recommends using a cutoff of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency. Strong recommendation, high-quality evidence. Comment: In patients with inflammatory conditions or chronic kidney disease, other laboratory tests such as C-reactive protein, transferrin saturation, or soluble transferrin saturation, may be needed in conjunction with ferritin to diagnose iron deficiency anemia."[95]

In 2024, the AGA released the AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review to provide best-practice guidance on the appropriate management of iron deficiency anemia. In the update they include the following recommendations on managing iron therapy:

- "Every-other-day oral iron may be better tolerated and has similar absorption compared to daily dosing in many patients.
- Adding vitamin C to oral iron supplementation can improve absorption.
- IV iron is recommended if a patient does not tolerate oral iron, or ferritin levels do not improve after an oral iron trial, or in conditions where oral iron absorption is likely impaired.
- Intravenous iron formulations that can replace iron deficits with 1 or 2 infusions are preferred over those that require more than 2 infusions.
- Intravenous iron therapy should be used in individuals who have undergone bariatric procedures, particularly those that are likely to disrupt normal duodenal iron absorption and have iron-deficiency anemia with no identifiable source of chronic gastrointestinal blood loss. In individuals with inflammatory bowel disease and iron-deficiency anemia, clinicians first should determine whether iron-deficiency anemia is owing to inadequate intake or absorption, or loss of iron, typically from gastrointestinal bleeding.
- Intravenous iron therapy should be given in individuals with inflammatory bowel disease, iron-deficiency anemia, and active inflammation with compromised absorption."[96]

American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)

The ASCO and ASH have published guidelines regarding the management of cancer-related anemia with erythropoiesis-stimulating agents (ESAs). It is stated that "with the exception of selected patients with MDS, ESAs should not be offered to most patients with nonchemotherapy-associated anemia. During

ESA treatment, hemoglobin may be increased to the lowest concentration needed to avoid transfusions. Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without ID. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended."[97]

American Academy of Family Physicians (AAFP)

The AAFP have recommend the following with "C" evidence ratings (consensus, disease-oriented evidence, usual practice, expert opinion, or case series):

- "A low serum ferritin level is associated with a diagnosis of iron deficiency anemia,"
- "Older patients with suspected iron deficiency anemia should undergo endoscopy to evaluate for occult gastrointestinal malignancy," and
- "Low-dose formulations of iron (15 mg of elemental iron) can be effective for treatment of suspected iron deficiency anemia and have a lower risk of adverse effects than standard preparations."[98]

Also stated is: "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."[98]

In 2021, the AAFP also published the 2020 AGA guidelines on iron deficiency anemia, reported above (please see the guidelines for the AGA).

American College of Gastroenterology (ACG)

The ACG practice guidelines regarding the evaluation of abnormal liver chemistries recommend that "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]."[99]

World Health Organization (WHO)

The WHO guideline on the use of ferritin concentrations to assess iron status in individuals and populations, published in 2020, updated the previous serum ferritin levels recommendations. The guidelines recommend cut-off serum ferritin levels for iron deficiency in infants (0-23 months) and preschool children (24-59 months) as under 12 µg/L in apparently healthy individuals and under 30 µg/L in individuals with infections or inflammation. The guidelines recommend cut-off serum ferritin levels for iron deficiency in school age children (5-12 years), adolescents (13-19 years), adults (20-59 years), and older persons (over 60 years) as under 15 µg/L in apparently healthy individuals and under 70 µg/L in individuals with infections or inflammation. The guidelines recommend cut-off serum ferritin levels for iron deficiency in apparently healthy pregnant women in their first trimester as under 15 µg/L.

The guidelines recommend cut-off serum ferritin levels for risk of iron overload in school age children (5-12 years), adolescents (13-19 years), adults (20-59 years), and older persons (over 60 years) as over 150 µg/L in apparently healthy individuals females, over 200 µg/L in apparently healthy males, and over 500 µg/L in individuals with infections or inflammation.[100]

International Consensus Guideline for Clinical Management of Pantothenate Kinase-Associated Neurodegeneration (PKAN)

An international group released guidelines concerning the clinical management of the NBIA condition PKAN in 2017. Although no specific recommendation is directly given regarding measurement of iron, Hogarth, et al. (2017) state, "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 hyperintense signal."[94]

International Consensus Statement on the Peri-operative Management of Anemia and Iron Deficiency

An expert workshop, including several experienced researchers and clinicians, was conducted to develop guidance for the diagnosis and management of anemia in surgical patients. A series of best-practice and evidence-based statements to advise on patient care with respect to anemia have been published via this workshop. It was stated that serum ferritin measurement is the most sensitive and specific test used for the identification of absolute iron deficiency.[101]

International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS)

The ICCAMS recommends the following for the diagnosis of anemia:

- All patients with anemia should be evaluated for the cause of anemia—wherever possible, early enough preoperatively to enable sufficient time for treatment to be successful.
- It is important to identify iron deficiency, including in patients with anemia of inflammation (or anemia of chronic disease).
- Patients with IDA should be evaluated for the cause of the iron deficiency, whereas patients with anemia and normal iron studies should be evaluated for coexisting causes of anemia (ie, renal disease, primary hematologic disease, and nutrition deficiency).
- Evaluation for iron deficiency should include iron studies (serum iron, total iron binding capacity, transferrin saturation (TSAT), serum ferritin); if available, reticulocyte Hb content and/or serum hepcidin should be considered in inflammatory states.

The most important criteria for defining absolute iron deficiency were ferritin <30 ng/mL and/or TSAT <20%; ferritin <100 ng/mL may define iron deficiency in inflammatory states. If available, either a reticulocyte Hb <29 pg or a serum hepcidin level <20 µg/L also suggest the presence of iron deficiency in inflammatory states.[102]

European Crohn's and Colitis Organisation (ECCO)

The ECCO guidelines published in 2015 concerning iron deficiency and anemia in IBD with an EL 5-recommendation 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."[103] Also mentioned in the section concerning the workup for anemia

with an EL-4 recommendation is that anemia workups "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."[103]

Regarding the management of iron deficiency in patients with IBD, ECCO explains that "In patients with IBD the usage of ferritin is complicated by the fact that it is an acute phase protein and can increase in the setting of inflammation," but "if serum ferritin is below the lower cutoff, iron deficiency can be diagnosed, but if ferritin is normal, iron deficiency cannot be excluded in patients with IBD." Consequently, "the 2015 ECCO guidelines therefore recommend a serum ferritin 30 µg/liter as a cutoff in patients with clinical, endoscopical and biochemical remission. In patients with active inflammation a serum ferritin 100 µg/liter may still be consistent with iron deficiency."[104]

More recent ECCO guidance and position statements (2021–2024) reaffirm these recommendations and provide practical monitoring details for IBD patients stating, "anaemia parameters should be evaluated every 6–12 months in patients in remission or with mild disease activity; patients with active disease should be monitored at least every 3 months." Following iron deficiency treatment ECCO recommends that "haemoglobin and ferritin should be monitored every 3–6 months for at least a year after deficiency restoration and every 6–12 months thereafter." ECCO continues to note that a ferritin <30 µg/L indicates iron deficiency in remission, whereas ferritin up to ~100 µg/L may still be consistent with deficiency in the setting of active inflammation.[105]

The United States Preventive Services Task Force (USPSTF)

The USPSTF states that "the current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in pregnant [individuals] to prevent adverse maternal health and birth outcomes; the current evidence is insufficient to assess the balance of benefits and harms of routine iron supplementation for pregnant [individuals] to prevent adverse maternal health and birth outcomes; the current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in children ages 6 to 24 months."[106,107] All recommendations have been given a grade I.

In 2024, USPSTF released an updated recommendation reconfirming that the current evidence is insufficient to assess the benefits and harms of screening for iron deficiency or iron deficiency anemia in asymptomatic pregnant adolescents or adults. They also continue to support routine iron supplementation in asymptomatic pregnant people. The report found that supplementation does improve hemoglobin and ferritin levels, but that improvements in clinical outcomes have not been clearly established.[108]

American Society of Hematology (ASH)

In the ASH "Guidelines for Quantifying Iron Overload", it is stated that "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, the guidelines also state that "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 one 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."[109] Within the conclusion of the paper, the author notes that "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."[109]

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)

The NFK-KDOQI published guidelines in 2012. In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) group reviewed these guidelines in a separate publication. Based on the suggestions made by the KDOQI, the 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."[110]

Further, the KDOQI stated that ferritin testing along with TSAT as part of the evaluation of iron status in individuals with CKD who are being treated for anemia is recommended. Also, in agreement with KDIGO, the KDOQI recommend testing prior to initiation of treatment, once per month during initial treatment, and at least every three months after a stable hemoglobin level is reached.

Kidney Disease Improving Global Outcomes (KDIGO)

In the *2012 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease* publication, a complete blood count, absolute reticulocyte count, serum ferritin, serum TSAT, serum vitamin $B_{12,}$ and serum folate levels are recommended as part of an initial evaluation of anemia for all CKD patients, regardless of age or stage of degree progression. 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 three 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."[111]

In the updated 2024 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease, KDIGO continues to recommend TSAT with ferritin as the primary approach to assessing iron status and guiding iron therapy in CKD patients. For patients treated with iron, they state: "it is reasonable to test hemoglobin, ferritin, and TSAT every 3 months for those not receiving dialysis" and monthly for those receiving hemodialysis. They further advise withholding iron if ferritin is ≥700 ng/mL or TSAT ≥40%.[112]

International Society of Nephrology (ISN)

The most recent guidelines from the ISN, released in 2008, state 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."[113]

American Academy of Sleep Medicine (AASM)

The AASM has published clinical practice guidelines on the treatment of restless legs syndrome (RLS) and periodic limb movement disorder. The AASM included a good practice statement noting that "in all patients with clinically significant RLS, clinicians should regularly test serum iron studies including ferritin and transferrin saturation (calculated from iron and total iron binding capacity). The test should ideally be administered in the morning avoiding all iron-containing supplements and foods at least 24 hours prior to blood draw. Consensus guidelines, which have not been empirically tested, suggest that supplementation of iron in adults with RLS should be instituted with oral or IV iron if serum ferritin ≤ 75 ng/mL or transferrin saturation < 20%, and only with IV iron if serum ferritin is between 75 ng/mL and 100 ng/mL." The guideline also recommends iron treatment, either intravenous or oral over no iron treatment for adults with RLS, adults with end-stage renal disease, and children with RLS.[114]

Government of British Columbia

The Government of British Columbia published a guideline on the diagnosis and management of iron deficiency. In it, they note that ferritin is the test of choice for the diagnosis of iron deficiency and that serum iron, iron binding capacity, and transferrin saturation/fraction saturation are not routinely useful for investigating iron deficiency anemia. They recommend that oral iron supplements should be prescribed as a first line therapy for individuals with iron deficiency.

The Government of British Columbia also provides the following steps for monitoring response to oral iron:

1. "The frequency of subsequent monitoring depends upon the severity of the anemia, the underlying cause of the iron deficiency, and the clinical impact on the patient. Reassess patients with moderate to severe anemia by testing CBC as early as 2–4 weeks. Hemoglobin should increase by 10-20 g/L by 4 weeks. It may take up to 6 months to replenish iron stores.
2. Hemoglobin will correct within 2 to 4 months if appropriate iron dosages are taken as prescribed and underlying cause of iron deficiency is corrected.
3. Continue iron therapy an additional 4 to 6 months (adults) after correction of anemia to replenish the iron stores.23 Ferritin should be re-checked 3 to 6 months after normalization of hemoglobin in anemic patients, or after initiation of iron supplementation in non-anemic patients. Target normal ferritin >100 µg/L.
4. If ferritin and hemoglobin are not responding as anticipated, consider adherence, ongoing bleeding, malabsorption, or alternate diagnosis.
5. If the patient's clinical status is compromised by moderate to severe anemia, consider blood transfusion. Once the patient is stable, iron replacement can commence."[115]

VI. Applicable State and Federal Regulations

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
82728	Ferritin
83540	Iron
83550	Iron binding capacity
84466	Transferrin
0024U	Glycosylated acute phase proteins (GlycA), nuclear magnetic resonance spectroscopy, quantitative Proprietary test: GlycA Lab/Manufacturer: Laboratory Corporation of America
0251U	Hepcidin-25, enzyme-linked immunosorbent assay (ELISA), serum or plasma Proprietary test: Intrinsic Hepcidin IDx™ Test Lab/Manufacturer: IntrinsicDx

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
05/23/2022	Updated background, guidelines, and evidence-based scientific references. Client requested variance: Removal of Coverage Criteria 4 and code 84999 Added CPT code 0251U
04/04/2023	Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity:

	CC1, 2, and 3 all edited for clarity and consistency Addition of new Note 2 to define first-degree relative "Note 2: First degree relative include parents, full siblings, and children of the individual." Committee approved 04/04/2023
02/12/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee approved 02/12/2024
02/06/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency: Removed "(using serum iron and serum iron binding capacity measurements)" from CC2. Now reads: "2) Measurement of serum transferrin saturation MEETS COVERAGE CRITERIA in any of the following:" Edited CC3 to clarify that testing outside of conditions addressed above is not allowed, including the testing of asymptomatic individuals (individuals should be symptomatic for indications provided in criteria, not just symptomatic in general). Now reads: "3) For all other situations not addressed above, measurement of ferritin or transferrin levels, including transferrin saturation, DOES NOT MEET COVERAGE CRITERIA." Committee approved: 02/06/2025
02/11/2026	Client requested to remove prior variance: Add CC4, "Serum hepcidin testing, including immunoassays, DOES NOT MEET COVERAGE CRITERIA." Committee Approved: 02/11/2026
06/17/2026	CAB Review Q1 2026: Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1, added "(no more than one test per month unless otherwise specified)" CC1a edited for clarity CC1b edit for clarity and to add a frequency, now reads: "b) Once every three weeks for individuals with an iron overload disorder." CC1.h. edited to include frequencies for CKD dependent on if the individual is or isn't receiving hemodialysis, now reads: "h) For individuals who have chronic kidney disease: i) One test every three months if the individual is not receiving dialysis. ii) One test every month if the individual is receiving dialysis." CC1.h.ii. becomes its own subcriterion, CC1.i. New CC1.j.: "j) For individuals with restless legs syndrome or periodic limb movement disorder." New CC2.d.: "d) For individuals with restless legs syndrome or periodic limb movement disorder." Updated Note 1 to align with symptoms of hemochromatosis (iron overload) from Cleveland Clinic, expands to allow arrhythmias, erectile dysfunction, and pain the knuckles, provides specificity in the region of abdominal pain. Committee Approved: 06/17/2026