

Reimbursement Policy

Diagnostic Testing of Iron Homeostasis and 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 (Knutson, 2017).

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 (Byrne et al., 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 TfR, ferritin is an acute phase reactant that responds to oxidative stress and inflammation (Camaschella & Weiss, 2024). Moreover, TfR1 and TfR2, upon activation by transferrin, can initiate signaling cascades required for hepcidin expression (Roetto et al., 2018). 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 (Pietrangelo, 2015).

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. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) Measurement of serum ferritin levels **MEETS COVERAGE CRITERIA** in **any** of the following situations:
 - a) For the evaluation of an individual with abnormal hemoglobin and/or hematocrit levels.

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- b) For the evaluation and monitoring of iron overload disorders.
- 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) At a frequency of every 1 to 3 months:
 - i) For the evaluation and monitoring of patients with chronic kidney disease who are receiving or being considered for receiving treatment for anemia.
 - ii) For individuals on iron therapy.
- 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.
- 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.**

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NOTES:

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, 2020):

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

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

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82728	Ferritin
83540	Iron
83550	Iron binding capacity
84466	Transferrin
84999	Unlisted chemistry procedure

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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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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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