

If a conflict arises between a Clinical Payment and Coding Policy and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. "Plan documents" include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. Blue Cross and Blue Shield of New Mexico may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSNM has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing Editor, American Medical Association, Current Procedural Terminology, CPT® Assistant, Healthcare Common Procedure Coding System, ICD-10 CM and PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare and Medicaid Services National Correct Coding Initiative Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Diagnostic Testing of Iron Homeostasis and Metabolism

Policy Number: CPCPLAB008

Version 1.0

Approval Date: January 23, 2025

Plan Effective Date: April 15, 2025

Description

The Plan has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

1. Measurement of serum ferritin levels **may be reimbursable** in **any** of the following situations:
 - a. For the evaluation of an individual with abnormal hemoglobin and/or hematocrit levels.
 - 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 **may be reimbursable** in **any** 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, **is not reimbursable**.
4. Serum hepcidin testing, including immunoassays, **is not reimbursable**.
5. The use of GlycA testing to measure or monitor transferrin or other glycosylated proteins **is not reimbursable**.

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

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.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
82728, 83540, 83550, 84466, 84999, 0024U, 0251U

References:

- Abioye, A. I., Aboud, S., Premji, Z., Etheredge, A. J., Gunaratna, N. S., Sudfeld, C. R., Noor, R. A., Hertzmark, E., Spiegelman, D., Duggan, C., & Fawzi, W. (2019). Hemoglobin and hepcidin have good validity and utility for diagnosing iron deficiency anemia among pregnant women. *Eur J Clin Nutr.* <https://doi.org/10.1038/s41430-019-0512-z>
- Ahmad, S., Moriconi, F., Naz, N., Sultan, S., Sheikh, N., Ramadori, G., & Malik, I. A. (2013). Ferritin L and Ferritin H are differentially located within hepatic and extra hepatic organs under physiological and acute phase conditions. *Int J Clin Exp Pathol*, 6(4), 622-629.
- Alfrey, C. P. (1978). Serum ferritin assay. *CRC Crit Rev Clin Lab Sci*, 9(3), 179-208. <https://doi.org/10.3109/10408367809150919>
- Anderson, C. P., Shen, M., Eisenstein, R. S., & Leibold, E. A. (2012). Mammalian iron metabolism and its control by iron regulatory proteins. *Biochim Biophys Acta*, 1823(9), 1468-1483. <https://doi.org/10.1016/j.bbamcr.2012.05.010>
- Arber, C. E., Li, A., Houlden, H., & Wray, S. (2016). Review: Insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation: unifying theories. *Neuropathol Appl Neurobiol*, 42(3), 220-241. <https://doi.org/10.1111/nan.12242>
- Arosio, P., & Levi, S. (2010). Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. *Biochim Biophys Acta*, 1800(8), 783-792. <https://doi.org/10.1016/j.bbagen.2010.02.005>

- Auerbach, M., Staffa, S. J., & Brugnara, C. (2021). Using Reticulocyte Hemoglobin Equivalent as a Marker for Iron Deficiency and Responsiveness to Iron Therapy. *Mayo Clin Proc*, 96(6), 1510-1519. <https://doi.org/10.1016/j.mayocp.2020.10.042>
- Bell, S., Rigas, A. S., Magnusson, M. K., Ferkingstad, E., Allara, E., Bjornsdottir, G., Ramond, A., Sørensen, E., Halldorsson, G. H., Paul, D. S., Burgdorf, K. S., Eggertsson, H. P., Howson, J. M. M., Thørner, L. W., Kristmundsdottir, S., Astle, W. J., Erikstrup, C., Sigurdsson, J. K., Vuckovic, D., . . . Stefansson, K. (2021). A genome-wide meta-analysis yields 46 new loci associating with biomarkers of iron homeostasis. *Commun Biol*, 4(1), 156. <https://doi.org/10.1038/s42003-020-01575-z>
- Bohlius, J., Bohlke, K., Castelli, R., Djulbegovic, B., Lustberg, M. B., Martino, M., Mountzios, G., Peswani, N., Porter, L., Tanaka, T. N., Trifirò, G., Yang, H., & Lazo-Langner, A. (2019). Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. *Journal of Clinical Oncology*, 37(15), 1336-1351. <https://doi.org/10.1200/jco.18.02142>
- Brandtner, A., Tymoszek, P., Nairz, M., Lehner, G. F., Fritsche, G., Vales, A., Falkner, A., Schennach, H., Theurl, I., Joannidis, M., Weiss, G., & Pfeifhofer-Obermair, C. (2020). Linkage of alterations in systemic iron homeostasis to patients' outcome in sepsis: a prospective study. *J Intensive Care*, 8, 76. <https://doi.org/10.1186/s40560-020-00495-8>
- Bresgen, N., & Eckl, P. M. (2015). Oxidative stress and the homeodynamics of iron metabolism. *Biomolecules*, 5(2), 808-847. <https://doi.org/10.3390/biom5020808>
- Byrne, S. L., Krishnamurthy, D., & Wessling-Resnick, M. (2013). Pharmacology of iron transport. *Annu Rev Pharmacol Toxicol*, 53, 17-36. <https://doi.org/10.1146/annurev-pharmtox-010611-134648>
- Cabantchik, Z. I. (2014). Labile iron in cells and body fluids: physiology, pathology, and pharmacology. *Front Pharmacol*, 5, 45. <https://doi.org/10.3389/fphar.2014.00045>
- Camaschella, C. (2015). Iron-Deficiency Anemia. *N Engl J Med*, 373(5), 485-486. <https://doi.org/10.1056/NEJMc1507104>
- Camaschella, C., & Weiss, G. (2024, 05/29/2024). *Regulation of iron balance*. Wolters Kluwer. <https://www.uptodate.com/contents/regulation-of-iron-balance>
- Campanella, A., Rovelli, E., Santambrogio, P., Cozzi, A., Taroni, F., & Levi, S. (2009). Mitochondrial ferritin limits oxidative damage regulating mitochondrial iron availability: hypothesis for a protective role in Friedreich ataxia. *Hum Mol Genet*, 18(1), 1-11. <https://doi.org/10.1093/hmg/ddn308>
- Chen, M., Liu, J., & Wright, B. (2019). A sensitive and cost-effective HPLC/MS/MS (MRM) method for the clinical measurement of serum hepcidin. *Rapid Commun Mass Spectrom*. <https://doi.org/10.1002/rcm.8644>
- Cohen, L. A., Gutierrez, L., Weiss, A., Leichtmann-Bardoogo, Y., Zhang, D. L., Crooks, D. R., Sougrat, R., Morgenstern, A., Galy, B., Hentze, M. W., Lazaro, F. J., Rouault, T. A., & Meyron-Holtz, E. G. (2010). Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. *Blood*, 116(9), 1574-1584. <https://doi.org/10.1182/blood-2009-11-253815>
- Costa Matos, L., Batista, P., Monteiro, N., Ribeiro, J., Cipriano, M. A., Henriques, P., Girao, F., & Carvalho, A. (2013). Iron stores assessment in alcoholic liver disease.

- Scand J Gastroenterol*, 48(6), 712-718.
<https://doi.org/10.3109/00365521.2013.781217>
- da Silva, W. R., Silveira, L., Jr., & Fernandes, A. B. (2019). Diagnosing sickle cell disease and iron deficiency anemia in human blood by Raman spectroscopy. *Lasers Med Sci*. <https://doi.org/10.1007/s10103-019-02887-1>
- Dahlfors, G., Stal, P., Hansson, E. C., Barany, P., Sisowath, C., Onelov, L., Nelson, D., Eggertsen, G., Marmur, J., & Beshara, S. (2015). Validation of a competitive ELISA assay for the quantification of human serum hepcidin. *Scand J Clin Lab Invest*, 75(8), 652-658.
- DeLoughery, T. G. (2017). Iron Deficiency Anemia. *Med Clin North Am*, 101(2), 319-332. <https://doi.org/10.1016/j.mcna.2016.09.004>
- Dignass, A., Farrag, K., & Stein, J. (2018). Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions. *Int J Chronic Dis*, 2018, 9394060. <https://doi.org/10.1155/2018/9394060>
- Dignass, A., Gasche, C., Bettenworth, D., Birgegård, G., Danese, S., Gisbert, J. P., Gomollon, F., Iqbal, T., Katsanos, K., Koutroubakis, I., Magro, F., Savoye, G., Stein, J., Vavricka, S., the European, C. s., & Colitis, O. (2015). European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. *Journal of Crohn's and Colitis*, 9(3), 211-222. <https://doi.org/10.1093/ecco-jcc/jju009>
- Emmenegger, U., Frey, U., Reimers, A., Fux, C., Semela, D., Cottagnoud, P., Spaeth, P. J., & Neftel, K. A. (2001). Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. *Am J Hematol*, 68(1), 4-10. <https://www.ncbi.nlm.nih.gov/pubmed/11559930>
- Enko, D., Wagner, H., Kriegshauser, G., Kimbacher, C., Stolba, R., & Halwachs-Baumann, G. (2015). Assessment of human iron status: A cross-sectional study comparing the clinical utility of different laboratory biomarkers and definitions of iron deficiency in daily practice. *Clin Biochem*, 48(13-14), 891-896. <https://doi.org/10.1016/j.clinbiochem.2015.05.008>
- Evensen, K. J., Swaak, T. J., & Nossent, J. C. (2007). Increased ferritin response in adult Still's disease: specificity and relationship to outcome. *Scand J Rheumatol*, 36(2), 107-110. <https://doi.org/10.1080/03009740600958504>
- Finazzi, D., & Arosio, P. (2014). Biology of ferritin in mammals: an update on iron storage, oxidative damage and neurodegeneration. *Arch Toxicol*, 88(10), 1787-1802. <https://doi.org/10.1007/s00204-014-1329-0>
- Finch, C. A., Bellotti, V., Stray, S., Lipschitz, D. A., Cook, J. D., Pippard, M. J., & Huebers, H. A. (1986). Plasma ferritin determination as a diagnostic tool. *West J Med*, 145(5), 657-663. <https://www.ncbi.nlm.nih.gov/pubmed/3541387>
- Fleming, R. E., & Ponka, P. (2012). Iron overload in human disease. *N Engl J Med*, 366(4), 348-359. <https://doi.org/10.1056/NEJMra1004967>
- Ganz, T. (2013). Systemic iron homeostasis. *Physiol Rev*, 93(4), 1721-1741. <https://doi.org/10.1152/physrev.00008.2013>
- Ganz, T., & Nemeth, E. (2009). Iron sequestration and anemia of inflammation. *Semin Hematol*, 46(4), 387-393. <https://doi.org/10.1053/j.seminhematol.2009.06.001>
- Garcia-Casal, M. N., Pasricha, S. R., Martinez, R. X., Lopez-Perez, L., & Peña-Rosas, J. P. (2021). Serum or plasma ferritin concentration as an index of iron deficiency and overload. *Cochrane Database Syst Rev*, 5(5), Cd011817. <https://doi.org/10.1002/14651858.CD011817.pub2>

- Gerday, E., Brereton, J. B., Bahr, T. M., Elmont, J. O., Fullmer, S., Middleton, B. A., Ward, D. M., Ohls, R. K., & Christensen, R. D. (2020). Urinary ferritin; a potential noninvasive way to screen NICU patients for iron deficiency. *J Perinatol*. <https://doi.org/10.1038/s41372-020-0746-6>
- Gozzelino, R., & Arosio, P. (2016). Iron Homeostasis in Health and Disease. *Int J Mol Sci*, 17(1). <https://doi.org/10.3390/ijms17010130>
- Hayflick, S. J., Kurian, M. A., & Hogarth, P. (2018). Neurodegeneration with brain iron accumulation. *Handb Clin Neurol*, 147, 293-305. <https://doi.org/10.1016/b978-0-444-63233-3.00019-1>
- Hentze, M. W., Muckenthaler, M. U., & Andrews, N. C. (2004). Balancing acts: molecular control of mammalian iron metabolism. *Cell*, 117(3), 285-297. [https://doi.org/10.1016/S0092-8674\(04\)00343-5](https://doi.org/10.1016/S0092-8674(04)00343-5)
- Hentze, M. W., Muckenthaler, M. U., Galy, B., & Camaschella, C. (2010). Two to tango: regulation of Mammalian iron metabolism. *Cell*, 142(1), 24-38. <https://doi.org/10.1016/j.cell.2010.06.028>
- Hogarth, P., Kurian, M. A., Gregory, A., Csanyi, B., Zagustin, T., Kmiec, T., Wood, P., Klucken, A., Scalise, N., Sofia, F., Klopstock, T., Zorzi, G., Nardocci, N., & Hayflick, S. J. (2017). Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). *Mol Genet Metab*, 120(3), 278-287. <https://doi.org/10.1016/j.ymgme.2016.11.004>
- Hou, W., Xie, Y., Song, X., Sun, X., Lotze, M. T., Zeh, H. J., 3rd, Kang, R., & Tang, D. (2016). Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy*, 12(8), 1425-1428. <https://doi.org/10.1080/15548627.2016.1187366>
- Ismail, N. A., Habib, S. A., Talaat, A. A., Mostafa, N. O., & Elghoroury, E. A. (2019). The Relation between Serum Hcpidin, Ferritin, Hcpidin: Ferritin Ratio, Hydroxyurea and Splenectomy in Children with beta-Thalassemia. *Open Access Maced J Med Sci*, 7(15), 2434-2439. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6814476/>
- Jacobs, A., Miller, F., Worwood, M., Beamish, M. R., & Wardrop, C. A. (1972). Ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *Br Med J*, 4(5834), 206-208. <https://www.ncbi.nlm.nih.gov/pubmed/5082548>
- Jones, K. S., Meadows, S. R., Chamberlain, K., Parkington, D. A., Collins, D., Page, P., & Koulman, A. (2021). Delayed Processing of Chilled Whole Blood for 24 Hours Does Not Affect the Concentration of the Majority of Micronutrient Status Biomarkers. *J Nutr*. <https://doi.org/10.1093/jn/nxab267>
- Karlsson, T. (2017). Evaluation of a competitive hepcidin ELISA assay in the differential diagnosis of iron deficiency anaemia with concurrent inflammation and anaemia of inflammation in elderly patients. *J Inflamm (Lond)*, 14, 21. <https://doi.org/10.1186/s12950-017-0166-3>
- Kassebaum, N. J., Jasrasaria, R., Naghavi, M., Wulf, S. K., Johns, N., Lozano, R., Regan, M., Weatherall, D., Chou, D. P., Eisele, T. P., Flaxman, S. R., Pullan, R. L., Brooker, S. J., & Murray, C. J. (2014). A systematic analysis of global anemia burden from 1990 to 2010. *Blood*, 123(5), 615-624. <https://doi.org/10.1182/blood-2013-06-508325>
- KDIGO. (2012). KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl*, 2(4), 279-335. <https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf>

- 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. <https://doi.org/10.1039/c3mt00347g>
- Keogh, M. J., Morris, C. M., & Chinnery, P. F. (2013). Neuroferritinopathy. *Int Rev Neurobiol*, 110, 91-123. <https://doi.org/10.1016/b978-0-12-410502-7.00006-5>
- Kliger, A. S., Foley, R. N., Goldfarb, D. S., Goldstein, S. L., Johansen, K., Singh, A., & Szczech, L. (2013). KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *American Journal of Kidney Diseases*, 62(5), 849-859. <https://doi.org/10.1053/j.ajkd.2013.06.008>
- Knovich, M. A., Storey, J. A., Coffman, L. G., Torti, S. V., & Torti, F. M. (2009). Ferritin for the clinician. *Blood Rev*, 23(3), 95-104. <https://doi.org/10.1016/j.blre.2008.08.001>
- Knutson, M. D. (2017). Iron transport proteins: Gateways of cellular and systemic iron homeostasis. *J Biol Chem*, 292(31), 12735-12743. <https://doi.org/10.1074/jbc.R117.786632>
- Ko, C. W., Siddique, S. M., Patel, A., Harris, A., Sultan, S., Altayar, O., & Falck-Ytter, Y. (2020). AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia. *Gastroenterology*, 159(3), 1085-1094. <https://doi.org/10.1053/j.gastro.2020.06.046>
- Koperdanova, M., & Cullis, J. O. (2015). Interpreting raised serum ferritin levels. *BMJ*, 351, h3692. <https://doi.org/10.1136/bmj.h3692>
- Kroot, J. J., Tjalsma, H., Fleming, R. E., & Swinkels, D. W. (2011). Hepcidin in human iron disorders: diagnostic implications. *Clin Chem*, 57(12), 1650-1669. <https://doi.org/10.1373/clinchem.2009.140053>
- Kruszewski, M. (2003). Labile iron pool: the main determinant of cellular response to oxidative stress. *Mutat Res*, 531(1-2), 81-92. <https://www.ncbi.nlm.nih.gov/pubmed/14637247>
- Kumar, N., Rizek, P., & Jog, M. (2016). Neuroferritinopathy: Pathophysiology, Presentation, Differential Diagnoses and Management. *Tremor Other Hyperkinet Mov (N Y)*, 6, 355. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4795517/>
- Kuwata, T., Okada, Y., Yamamoto, T., Sato, D., Fujiwara, K., Fukumura, T., & Ikeguchi, M. (2019). Structure, Function, Folding, and Aggregation of a Neuroferritinopathy-Related Ferritin Variant. *Biochemistry*, 58(18), 2318-2325. <https://doi.org/10.1021/acs.biochem.8b01068>
- Kwiatek-Majkusiak, J., Geremek, M., Koziorowski, D., Tomasiuk, R., Szlufik, S., & Friedman, A. (2020). Serum levels of hepcidin and interleukin 6 in Parkinson's disease. *Acta Neurobiol Exp (Wars)*, 80(3), 297-304.
- Kwo, P. Y., Cohen, S. M., & Lim, J. K. (2017). ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*, 112(1), 18-35. <https://doi.org/10.1038/ajg.2016.517>
- La, A., Nguyen, T., Tran, K., Sauble, E., Tu, D., Gonzalez, A., Kidane, T. Z., Soriano, C., Morgan, J., Doan, M., Tran, K., Wang, C. Y., Knutson, M. D., & Linder, M. C. (2018). Mobilization of iron from ferritin: new steps and details. *Metallomics*, 10(1), 154-168. <https://doi.org/10.1039/c7mt00284j>
- Lanier, J. B., Park, J. J., & Callahan, R. C. (2018). Anemia in Older Adults. *Am Fam Physician*, 98(7), 437-442. <https://www.aafp.org/afp/2018/1001/p437.html>

- Lehn, A., Boyle, R., Brown, H., Airey, C., & Mellick, G. (2012). Neuroferritinopathy. *Parkinsonism & Related Disorders*.
<https://www.sciencedirect.com/science/article/abs/pii/S1353802012002593>
- Lewkowicz, A. K., & Tuuli, M. G. (2019). Iron-deficiency anaemia in pregnancy: the role of hepcidin. *Lancet Glob Health*, 7(11), e1476-e1477.
[https://doi.org/10.1016/s2214-109x\(19\)30414-0](https://doi.org/10.1016/s2214-109x(19)30414-0)
- Liu, X., & Theil, E. C. (2005). Ferritins: dynamic management of biological iron and oxygen chemistry. *Acc Chem Res*, 38(3), 167-175.
<https://doi.org/10.1021/ar0302336>
- Lv, Q., Niu, H., Yue, L., Liu, J., Yang, L., Liu, C., Jiang, H., Dong, S., Shao, Z., Xing, L., & Wang, H. (2020). Abnormal Ferroptosis in Myelodysplastic Syndrome. *Front Oncol*, 10, 1656. <https://doi.org/10.3389/fonc.2020.01656>
- Madore, F., White, C. T., Foley, R. N., Barrett, B. J., Moist, L. M., Klarenbach, S. W., Culleton, B. F., Tonelli, M., & Manns, B. J. (2008). Clinical practice guidelines for assessment and management of iron deficiency. *Kidney Int Suppl*(110), S7-s11.
<https://doi.org/10.1038/ki.2008.269>
- Mancias, J. D., Wang, X., Gygi, S. P., Harper, J. W., & Kimmelman, A. C. (2014). Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature*, 509(7498), 105-109. <https://doi.org/10.1038/nature13148>
- Marell, P. S., Blohowiak, S. E., Evans, M. D., Georgieff, M. K., Kling, P. J., & Tran, P. V. (2019). Cord Blood-Derived Exosomal CNTN2 and BDNF: Potential Molecular Markers for Brain Health of Neonates at Risk for Iron Deficiency. *Nutrients*, 11(10). <https://doi.org/10.3390/nu11102478>
- McLaren, C. E., Barton, J. C., Adams, P. C., Harris, E. L., Acton, R. T., Press, N., Reboussin, D. M., McLaren, G. D., Sholinsky, P., Walker, A. P., Gordeuk, V. R., Leiendecker-Foster, C., Dawkins, F. W., Eckfeldt, J. H., Mellen, B. G., Speechley, M., Thomson, E., Hemochromatosis, & Iron Overload Study Research, I. (2003). Hemochromatosis and Iron Overload Screening (HEIRS) study design for an evaluation of 100,000 primary care-based adults. *Am J Med Sci*, 325(2), 53-62.
<https://www.ncbi.nlm.nih.gov/pubmed/12589228>
- McNally, J. R., Mehlenbacher, M. R., Luscieti, S., Smith, G. L., Reutovich, A. A., Maura, P., Arosio, P., & Bou-Abdallah, F. (2019). Mutant L-chain ferritins that cause neuroferritinopathy alter ferritin functionality and iron permeability. *Metallomics*, 11(10), 1635-1647. <https://doi.org/10.1039/c9mt00154a>
- Mei, Z., Addo, O. Y., Jefferds, M. E., Sharma, A. J., Flores-Ayala, R. C., & Brittenham, G. M. (2021). Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study. *Lancet Haematol*, 8(8), e572-e582. [https://doi.org/10.1016/s2352-3026\(21\)00168-x](https://doi.org/10.1016/s2352-3026(21)00168-x)
- Miller, J. L. (2013). Iron deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med*, 3(7). <https://doi.org/10.1101/cshperspect.a011866>
- Muñoz, M., Acheson, A. G., Auerbach, M., Besser, M., Habler, O., Kehlet, H., Liunbruno, G. M., Lasocki, S., Meybohm, P., Rao Baikady, R., Richards, T., Shander, A., So-Osman, C., Spahn, D. R., & Klein, A. A. (2017). International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia*, 72(2), 233-247. <https://doi.org/10.1111/anae.13773>
- Muñoz, M., Gomez-Ramirez, S., Besser, M., Pavia, J., Gomollon, F., Liunbruno, G. M., Bhandari, S., Cladellas, M., Shander, A., & Auerbach, M. (2017). Current

- misconceptions in diagnosis and management of iron deficiency. *Blood Transfus*, 15(5), 422-437. <https://doi.org/10.2450/2017.0113-17>
- Nalado, A. M., Olorunfemi, G., Dix-Peek, T., Dickens, C., Khambule, L., Snyman, T., Paget, G., Mahlangu, J., Duarte, R., George, J., & Naicker, S. (2020). Hcpidin and GDF-15 are potential biomarkers of iron deficiency anaemia in chronic kidney disease patients in South Africa. *BMC Nephrol*, 21(1), 415. <https://doi.org/10.1186/s12882-020-02046-7>
- NIDDK. (2020, January 2020). *Hemochromatosis*. National Institutes of Health (NIH). <https://www.niddk.nih.gov/health-information/liver-disease/hemochromatosis>
- Niepel, D., Klag, T., Malek, N. P., & Wehkamp, J. (2018). Practical guidance for the management of iron deficiency in patients with inflammatory bowel disease. *Therap Adv Gastroenterol*, 11, 1756284818769074. <https://doi.org/10.1177/1756284818769074>
- Otvos, J. D., Shalaurova, I., Wolak-Dinsmore, J., Connelly, M. A., Mackey, R. H., Stein, J. H., & Tracy, R. P. (2015). GlycA: A Composite Nuclear Magnetic Resonance Biomarker of Systemic Inflammation. *Clin Chem*, 61(5), 714-723. <https://doi.org/10.1373/clinchem.2014.232918>
- Ozdemir, N. (2015). Iron deficiency anemia from diagnosis to treatment in children. *Turk Pediatri Ars*, 50(1), 11-19. <https://doi.org/10.5152/tpa.2015.2337>
- Paul, B. T., Manz, D. H., Torti, F. M., & Torti, S. V. (2017). Mitochondria and Iron: current questions. *Expert Rev Hematol*, 10(1), 65-79. <https://doi.org/10.1080/17474086.2016.1268047>
- Peng, Y. Y., & Uprichard, J. (2017). Ferritin and iron studies in anaemia and chronic disease. *Ann Clin Biochem*, 54(1), 43-48. <https://doi.org/10.1177/0004563216675185>
- Phillips, R., Wood, H., Weaving, G., & Chevassut, T. (2021). Changes in full blood count parameters with age and sex: results of a survey of almost 900 000 patient samples from primary care. *Br J Haematol*, 192(4), e102-e105. <https://doi.org/10.1111/bjh.17290>
- Pietrangelo, A. (2015). Genetics, Genetic Testing, and Management of Hemochromatosis: 15 Years Since Hcpidin. *Gastroenterology*, 149(5), 1240-1251.e1244. <https://doi.org/10.1053/j.gastro.2015.06.045>
- Ritchie, S. C., Wurtz, P., Nath, A. P., Abraham, G., Havulinna, A. S., Fearnley, L. G., Sarin, A. P., Kangas, A. J., Soininen, P., Aalto, K., Seppala, I., Raitoharju, E., Salmi, M., Maksimow, M., Mannisto, S., Kahonen, M., Juonala, M., Ripatti, S., Lehtimaki, T., . . . Inouye, M. (2015). The Biomarker GlycA Is Associated with Chronic Inflammation and Predicts Long-Term Risk of Severe Infection. *Cell Syst*, 1(4), 293-301. <https://doi.org/10.1016/j.cels.2015.09.007>
- Roetto, A., Mezzanotte, M., & Pellegrino, R. M. (2018). The Functional Versatility of Transferrin Receptor 2 and Its Therapeutic Value. *Pharmaceuticals (Basel)*, 11(4). <https://doi.org/10.3390/ph11040115>
- Saeed, H., Woods, R. R., Lester, J., Herzig, R., Gul, Z., & Monohan, G. (2015). Evaluating the optimal serum ferritin level to identify hemophagocytic lymphohistiocytosis in the critical care setting. *Int J Hematol*, 102(2), 195-199. <https://doi.org/10.1007/s12185-015-1813-1>
- Salgia, R. J., & Brown, K. (2015). Diagnosis and management of hereditary hemochromatosis. *Clin Liver Dis*, 19(1), 187-198. <https://doi.org/10.1016/j.cld.2014.09.011>

- Sankaran, V. G., & Weiss, M. J. (2015). Anemia: progress in molecular mechanisms and therapies. *Nat Med*, 21(3), 221-230. <https://doi.org/10.1038/nm.3814>
- Santambrogio, P., Cozzi, A., Levi, S., & Arosio, P. (1987). Human serum ferritin G-peptide is recognized by anti-L ferritin subunit antibodies and concanavalin-A. *Br J Haematol*, 65(2), 235-237. <https://www.ncbi.nlm.nih.gov/pubmed/3828232>
- Santos, P. C., Krieger, J. E., & Pereira, A. C. (2012). Molecular diagnostic and pathogenesis of hereditary hemochromatosis. *Int J Mol Sci*, 13(2), 1497-1511. <https://doi.org/10.3390/ijms13021497>
- Sekigawa, I., Suzuki, J., Nawata, M., Ikeda, K., Koike, M., Iida, N., Hashimoto, H., & Oshimi, K. (2001). Hemophagocytosis in autoimmune disease. *Clin Exp Rheumatol*, 19(3), 333-338. <https://www.ncbi.nlm.nih.gov/pubmed/11407091>
- Shander, A., Corwin, H. L., Meier, J., Auerbach, M., Bisbe, E., Blitz, J., Erhard, J., Faraoni, D., Farmer, S. L., Frank, S. M., Girelli, D., Hall, T., Hardy, J. F., Hofmann, A., Lee, C. K., Leung, T. W., Ozawa, S., Sathar, J., Spahn, D. R., . . . Muñoz, M. (2023). Recommendations From the International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS). *Ann Surg*, 277(4), 581-590. <https://doi.org/10.1097/sla.0000000000005721>
- Siu, A. L. (2015a). Screening for Iron Deficiency Anemia and Iron Supplementation in Pregnant Women to Improve Maternal Health and Birth Outcomes: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*, 163(7), 529-536. <https://doi.org/10.7326/m15-1707>
- Siu, A. L. (2015b). Screening for Iron Deficiency Anemia in Young Children: USPSTF Recommendation Statement. *Pediatrics*, 136(4), 746-752. <https://doi.org/10.1542/peds.2015-2567>
- Suchdev, P. S., Williams, A. M., Mei, Z., Flores-Ayala, R., Pasricha, S. R., Rogers, L. M., & Namaste, S. M. (2017). Assessment of iron status in settings of inflammation: challenges and potential approaches. *Am J Clin Nutr*, 106(Suppl 6), 1626s-1633s. <https://doi.org/10.3945/ajcn.117.155937>
- Tahara, S., Naito, Y., Okuno, K., Yasumura, S., Horimatsu, T., Ohno, J., Sunayama, I., Matsumoto, Y., Manabe, E., Masai, K., Azuma, K., Nishimura, K., Min, K. D., Goda, A., Asakura, M., & Ishihara, M. (2022). Clinical utility of reticulocyte hemoglobin equivalent in patients with heart failure. *Sci Rep*, 12(1), 13978. <https://doi.org/10.1038/s41598-022-18192-x>
- Ueda, N., & Takasawa, K. (2018). Impact of Inflammation on Ferritin, Hepcidin and the Management of Iron Deficiency Anemia in Chronic Kidney Disease. *Nutrients*, 10(9). <https://doi.org/10.3390/nu10091173>
- van Bokhoven, M. A., van Deursen, C. T., & Swinkels, D. W. (2011). Diagnosis and management of hereditary haemochromatosis. *BMJ*, 342, c7251. <https://doi.org/10.1136/bmj.c7251>
- Vujić, M. (2014). Molecular basis of HFE-hemochromatosis. *Front Pharmacol*, 5. <https://doi.org/10.3389/fphar.2014.00042>
- Wang, W., Knovich, M. A., Coffman, L. G., Torti, F. M., & Torti, S. V. (2010). Serum ferritin: Past, present and future. *Biochim Biophys Acta*, 1800(8), 760-769. <https://doi.org/10.1016/j.bbagen.2010.03.011>
- WHO. (2020). WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. <https://www.who.int/publications/i/item/9789240000124>

- Wieggersma, A. M., Dalman, C., Lee, B. K., Karlsson, H., & Gardner, R. M. (2019). Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. *JAMA Psychiatry*, 76(12), 1-12. <https://doi.org/10.1001/jamapsychiatry.2019.2309>
- Wood, J. C. (2014). Guidelines for quantifying iron overload. *Hematology Am Soc Hematol Educ Program*, 2014(1), 210-215. <https://doi.org/10.1182/asheducation-2014.1.210>
- Xie, Y., Hou, W., Song, X., Yu, Y., Huang, J., Sun, X., Kang, R., & Tang, D. (2016). Ferroptosis: process and function. *Cell Death Differ*, 23(3), 369-379. <https://doi.org/10.1038/cdd.2015.158>
- Yuniati, T., Judistiani, R. T. D., Natalia, Y. A., Irianti, S., Madjid, T. H., Ghozali, M., Sribudiani, Y., Indrati, A. R., Abdulah, R., & Setiabudiawan, B. (2019). First trimester maternal vitamin D, ferritin, hemoglobin level and their associations with neonatal birthweight: Result from cohort study on vitamin D status and its impact during pregnancy and childhood in Indonesia. *J Neonatal Perinatal Med*. <https://doi.org/10.3233/npm-180043>
- Zandman-Goddard, G., & Shoenfeld, Y. (2007). Ferritin in autoimmune diseases. *Autoimmun Rev*, 6(7), 457-463. <https://doi.org/10.1016/j.autrev.2007.01.016>
- Zanella, A., Gridelli, L., Berzuini, A., Colotti, M. T., Mozzi, F., Milani, S., & Sirchia, G. (1989). Sensitivity and predictive value of serum ferritin and free erythrocyte protoporphyrin for iron deficiency. *J Lab Clin Med*, 113(1), 73-78. <https://www.ncbi.nlm.nih.gov/pubmed/2909654>
- Zhang, D. L., Ghosh, M. C., & Rouault, T. A. (2014). The physiological functions of iron regulatory proteins in iron homeostasis - an update. *Front Pharmacol*, 5. <https://doi.org/10.3389/fphar.2014.00124>

Policy Update History:

Approval Date	Effective Date; Summary of Changes
01/23/2025	04/15/2025; Document updated with literature review. The following changes were made to Reimbursement Information: Removed “using serum iron and serum iron binding capacity measurements)” from #2; edited #3 to clarify that testing outside of conditions mentioned is not allowed. Now states: For all other situations not addressed above, measurement of ferritin or transferrin levels, including transferrin saturation, is not reimbursable. References revised.
03/15/2024	Document updated with literature review. Reimbursement Information unchanged. References revised; some added.
06/15/2023	Document updated with literature review. Reimbursement information revised for clarity. References revised; some added, others removed.
11/1/2022	New policy