Anthem

Clinical UM Guideline

Subject: Serum Iron Testing
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Description

This document addresses laboratory testing for iron levels. Iron studies can include serum testing of ferritin, iron, and either iron binding capacity or transferrin. These tests are used in the differential diagnosis of iron deficiency, anemia, and iron overload.

Clinical Indications

Medically Necessary:

Serum iron testing is considered **medically necessary** for any of the following indications:

1. Evaluation of suspected iron deficiency in individuals who meet any of the following criteria:
    a. Abnormal blood counts consistent with iron deficiency including, but not limited to, the following:
        i. decreased mean corpuscular volume (MCV); **or**
        ii. decreased hemoglobin/hematocrit when the MCV is low or normal; **or**
        iii. increased red cell distribution width (RDW) and low or normal MCV; **or**
    b. Evidence of acute or chronic blood loss including, but not limited to, the following:
        i. gastrointestinal blood loss; **or**
        ii. hematuria; **or**
        iii. menorrhagia; **or**
    c. Anemia associated with abnormal appetite, malnutrition, or malabsorption; **or**
    d. Malignancy, chronic inflammation or infection associated with iron deficiency; **or**
    e. A lack of response to iron replacement therapy; **or**
    f. Symptoms or clinical findings associated with iron deficiency; **or**
2. Evaluation of suspected iron overload in individuals who meet any of the following criteria:
    a. Diagnosis of a condition associated with iron overload; **or**
    b. Symptoms or clinical findings associated with iron overload; **or**
3. Evaluation of toxic effects of iron and other metals after exposure or for metabolic causes **or**
4. Evaluation of iron status following treatment for other nutritional deficiency anemias such as vitamin B12 or folate deficiency; **or**
5. Monitoring treatment response following iron replacement therapy or treatment with erythropoiesis-stimulating agents.

Not Medically Necessary:

Serum iron testing is considered **not medically necessary** when the above criteria are not met, and for all other indications, including but not limited to the following:

1. Screening of individuals in the absence of signs, symptoms, or medical history suggestive of iron dysregulation **or**
2. During acute inflammation or infection where the results will not impact or direct treatment or disease management; **or**
3. After a normal serum ferritin level has been documented, monitoring iron status in the absence of signs or symptoms of iron imbalance.

Concurrent assessment of transferrin and TIBC is considered **not medically necessary** for any indication.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
82728	Ferritin
83540	Iron
83550	Iron binding capacity
84466	Transferrin

ICD-10 Diagnosis	
A01.00-A02.9	Typhoid fever, other Salmonella infections
A04.0-A04.9	Other bacterial intestinal infections
A06.0-A09	Amebiasis, other protozoal, viral and other/unspecified intestinal diseases/infections
A15.0	Tuberculosis of lung
A18.01-A18.89	Tuberculosis of other organs
B15.0-B19.9	Viral hepatitis
B20	Human Immunodeficiency virus (HIV) disease
B25.1	Cytomegalovirus hepatitis
B52.0	Plasmodium malariae malaria with nephropathy
C00.0-C96.9	Malignant neoplasms
D00.00-D09.9	In situ neoplasms

D10.0-D36.9	Benign neoplasms, except benign neuroendocrine tumors
D37.01-D48.9	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndrome
D49.0-D49.9	Neoplasms of unspecified behavior
D50.0-D53.9	Nutritional anemias
D56.0-D57.819	Thalassemia, sickle-cell disorders
D62-D64.9	Acute posthemorrhagic anemia, anemia in diseases classified elsewhere, other anemia
D65-D69.9	Coagulation defects, purpura and other hemorrhagic conditions
D75.838-D75.839	Thrombocytosis
E08.00-E13.9	Diabetes mellitus
E23.0-E23.1	Hypopituitarism
E23.6	Other disorders of pituitary gland
E24.1	Nelson's syndrome
E28.310-E28.39	Primary ovarian failure
E29.1	Testicular hypofunction
E40-E46	Malnutrition
E61.1	Iron deficiency
E64.0	Sequelae of protein-calorie malnutrition
E75.26	Sulfatase deficiency
E79.0	Hyperuricemia without signs of inflammatory arthritis and tophaceous disease
E80.0-E80.29	Porphyria
E83.10-E83.19	Disorders of iron metabolism
E88.02	Plasminogen deficiency
E89.3	Postprocedural hypopituitarism
F45.8	Other somatoform disorders
F50.00-F50.9	Eating disorders
F98.21-F98.29	Other feeding disorders of infancy and childhood
F98.3	Pica of infancy and childhood
I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease
I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I27.83	Eisenmenger's syndrome
I42.0-I43	Cardiomyopathy, cardiomyopathy in diseases classified elsewhere
I44.0-I49.9	Atrioventricular and left bundle-branch block, other conduction disorders, cardiac arrest, paroxysmal tachycardia, atrial fibrillation, other cardiac arrhythmias
I50.1-I50.9	Heart failure
K22.6	Gastro-esophageal laceration-hemorrhage syndrome
K22.81-K22.89	Other specified diseases of esophagus
K25.0-K28.9	Gastric, duodenal, peptic, gastrojejunal ulcer
K29.00-K31.9	Gastritis and duodenitis, functional dyspepsia, other diseases of stomach and duodenum
K50.00-K52.839	Noninfective enteritis and colitis
K55.011-K55.33	Other diseases of intestines
K56.699	Other intestinal obstruction unspecified as to partial versus complete obstruction
K57.00-K57.93	Diverticular disease of intestine
K62.5	Hemorrhage of anus and rectum
K63.5	Polyp of colon
K63.81	Dieulafoy lesion of intestine
K70.0-K77	Diseases of the liver
K90.0-K90.9	Intestinal malabsorption
K91.2	Postsurgical malabsorption, not elsewhere classified
K92.0-K92.2	Hematemesis, melana, gastrointestinal hemorrhage, unspecified
K94.20-K94.29	Gastrostomy complications
L28.0-L28.2	Lichen simplex chronicus and prurigo
L29.0-L29.9	Pruritis
L57.3	Poikiloderma of Civatte
L63.0-L66.9	Alopecia, other nonscarring hair loss
L80	Vitiligo
L81.0-L81.9	Other disorders of pigmentation
L98.1	Factitial dermatitis
M07.60-M07.69	Enteropathic arthropathies
M12.80-M12.9	Other specific arthropathies, not elsewhere classified
M13.0-M13.179	Other arthritis
M14.80	Arthropathies in other specified diseases classified elsewhere, unspecific site
M1A.10X0-M1A.19X1	Lead-induced chronic gout
M25.50-M25.59	Pain in joint
M79.641-M79.646	Pain in hand and fingers
M84.750A-M84.759S	Nontraumatic fracture, not elsewhere classified
M97.01XA-M97.9XXS	Periprosthetic fracture around internal prosthetic joint
N02.0-N02.B9	Recurrent and persistent hematuria
N04.0-N04.A	Nephrotic syndrome
N08	Glomerular disorders in diseases classified elsewhere
N18.1-N18.9	Chronic kidney disease
N19	Unspecified kidney failure
N50.0	Atrophy of testis
N89.7	Hematocolpos
N91.0-N93.9	Absent/scanty/rare menstruation, excessive/frequent/irregular menstruation, other abnormal uterine and vaginal bleeding
N95.0	Postmenopausal bleeding
N99.116	Postprocedural urethral stricture, male, overlapping sites

O09.A0-O09.A3	Supervision of pregnancy with history of molar pregnancy
O11.4-O11.5	Pre-existing hypertension with pre-eclampsia, complicating childbirth or puerperium
O90.81	Anemia of the puerperium
O99.011-O99.03	Anemia complicating pregnancy, childbirth and the puerperium
O99.891-O99.893	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium
P50.0-P57.9	Hemorrhagic disorders of newborn, hemolytic disease of newborn
Q85.00-Q85.09	Neurofibromatosis (nonmalignant)
R00.1	Bradycardia, unspecified
R11.10-R11.2	Vomiting, nausea with vomiting
R63.8	Other symptoms and signs concerning food and fluid intake
R64	Cachexia
R71.0-R71.8	Abnormality of red blood cells
R74.01-R74.9	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
R78.71-R78.79	Finding of abnormal level of heavy metals in blood
R78.89	Finding of other specified substances, not normally found in blood
R79.0-R79.9	Other abnormal findings of blood chemistry
T40.411A-T40.415S	Poisoning by, adverse effect of fentanyl or fentanyl analogs
T40.421A-T40.425S	Poisoning by, adverse effect of tramadol
T40.491A-T40.495S	Poisoning by, adverse effect of other synthetic narcotics
T43.641A-T43.644S	Poisoning by ecstasy
T45.4X1A-T45.4X4S	Poisoning by iron and its compounds
T50.911A-T50.915S	Poisoning by, adverse effect of multiple unspecified drugs, medicaments and biological substances
T56.0X1A-T56.0X4S	Toxic effect of lead and its compounds
T80.89XA	Other complications following infusion, transfusion and therapeutic injection, initial encounter
T80.910A-T80.919S	Hemolytic transfusion reaction, unspecified incompatibility
T80.92XA	Unspecified transfusion reaction, initial encounter
T86.00-T86.09	Complications of bone marrow transplant
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z31.7	Encounter for procreative management and counseling for gestational carrier
Z49.31-Z49.32	Encounter for adequacy testing for dialysis
Z83.430-Z83.438	Family history of other disorder of lipoprotein metabolism and other lipidemias
Z84.82	Family history of sudden infant death syndrome
Z86.2	Personal history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Z86.39	Personal history of other endocrine, nutritional and metabolic disease
Z95.0-Z95.9	Presence of cardiac and vascular implants and grafts
Z96.60	Presence of unspecified orthopedic joint implant
Z98.870-Z98.871	Personal history of in utero procedure
Z98.890-Z98.891	Other specified postprocedural states

When services are Not Medically Necessary:
For the procedure codes listed above for all other diagnoses not listed.

Discussion/General Information

Reference standard indices of iron deficiency and iron overload, which include bone marrow iron content and liver iron content assessments, are generally invasive, unpleasant, and have the potential for associated risks. Alternatively, serum iron testing has been proposed as an alternative strategy for screening, diagnosis, and monitoring of conditions associated with iron deficiency and iron overload.

Iron deficiency

The most common disorder of iron homeostasis is iron deficiency. Iron deficiency represents approximately 40% of cases of anemia in the United States (United States Preventive Services Task Force [USPSTF], 2015b). Iron deficiency can occur when there is an increased demand for iron (such as during periods of rapid growth), when there is decreased iron intake and absorption, or blood loss. In adults in resource-rich countries, dietary intake is frequently adequate. Inadequate supplies of iron can lead to a disruption in circulating hemoglobin known as iron deficiency anemia. Iron deficiency anemias can be classified as absolute or functional iron deficiencies. Absolute iron deficiency anemia results when the iron stores become so low that hemoglobin synthesis is impaired causing anemia. In functional iron deficiency, the supply of iron for erythropoiesis is inadequate despite apparently normal iron stores (Snook, 2021). In the United States during 1999 and 2000, the estimated prevalence of iron deficiency ranged from 2% to 16% with higher prevalence in children aged 1 to 2 years and in individuals subject to uterine blood loss between ages 12 to 49 years (Centers for Disease Control [CDC], 2002). Iron deficiency anemia was most common in individuals subject to uterine blood loss. Prevalence for these individuals was 4% between the ages of 20 to 49 years and 3% for those aged 50 to 69 years (CDC, 2002). Treatment involves an assessment to address underlying causes and may include diet modification, oral or intravenous iron supplementation, or transfusion of red blood cells.

Iron deficiency anemia is more common in certain groups than the general population. Increased iron demands due to blood loss during menstruation, pregnancy, and in the postpartum period as well as tissue growth during pregnancy places individuals who may become pregnant at increased risk of iron deficiency anemia (CDC, 1998). General symptoms may include pallor, weakness, dyspnea, dizziness, rapid heartbeat, headache, dry rough skin, damaged hair, and restless leg syndrome (American Society of Hematology, 2021; Aul, 1998). People with mild or moderate iron deficiency anemia may not have any signs or symptoms. Severe iron deficiency anemia may cause fatigue or tiredness, shortness of breath, or chest pain. The possibility of iron deficiency is typically explored in individuals when the cause of anemia is unclear. Abnormal blood count values may require investigation. A decreased mean corpuscular volume (MCV) is commonly associated with iron deficiency or thalassemic syndromes. A decreased hemoglobin and hematocrit when the MCV is low or normal could indicate anemia of chronic disease or inflammation, but may be seen in hypothyroidism, chronic kidney disease, iron deficiency, or vitamin B12 and folate deficiencies. An increased red cell distribution width (RDW) and a low or normal MCV could also be associated with iron deficiency anemia, blood transfusion, and vitamin B12 or folate deficiency (Society for the Advancement of Patient Blood Management, 2020). In individuals with folate and vitamin B12 deficiencies, it may be appropriate to evaluate iron status as these conditions may cause macrocytosis that masks the microcytosis caused by iron deficiency (Bilic, 2004; Hannibal, 2016).

Other situations that may require further investigation include chronic blood loss; pregnancy; individuals with atypical symptoms of malnutrition or abnormal appetite such as pica; gastrointestinal syndromes of malabsorption; anemia associated with chronic diseases such as heart failure, chronic inflammatory disorders, and in individuals with chronic kidney disease (CKD) who have anemia, or are receiving hemodialysis or an erythropoiesis-stimulating agent (ESA). Anemia of chronic disease can occur in individuals with acute or chronic immune activation. In states of increased inflammation, cytokines and cells of the reticuloendothelial system induce changes in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin, and the life span of red cells (Weiss, 2005).

Bone marrow iron content is considered the gold standard measurement for the diagnosis of iron deficiency, but is infrequently utilized and not recommended for routine testing. Serum iron testing can include an assessment of the following: iron, total iron binding capacity (TIBC), transferrin, and ferritin. The serum iron test measures circulating iron, most of which is bound to the transport protein transferrin. Serum iron is low in iron deficiency as well as in anemia of chronic disease. Serum iron can also fluctuate with iron-containing supplements and dietary intake as well as normal diurnal variation. By itself, low serum iron is not diagnostic of any condition and must be evaluated in consideration of other tests such as transferrin and ferritin (Auerbach, 2016). In iron deficiency, iron is reduced and TIBC is increased. Transferrin proteins facilitate iron uptake and transport to red blood cell precursors in the bone marrow. Levels of transferrin are elevated in iron deficiency anemia. It is not ordinarily necessary to measure both transferrin and TIBC at the same time because TIBC is an indirect measure of transferrin (Auerbach, 2016). The serum iron and the TIBC are used to calculate percent transferrin saturation (TSAT). Ferritin is a blood protein that contains iron. A low ferritin level may indicate reduced iron stores and absolute iron deficiency (Aapro, 2018, Cullis, 2018). A very low ferritin level is diagnostic of iron deficiency when present, but ferritin levels may be elevated or falsely normal in individuals with comorbidities and cannot be used independently to eliminate the possibility of iron deficiency. The TSAT is a key test in the further investigation of an unexpectedly raised serum ferritin (Cullis, 2018). Although investigating bone marrow iron stores is still considered the standard index, circulating ferritin levels are used for distinguishing between absolute and functional iron deficiency in clinical practice (Aapro, 2018).

Garcia-Casal and colleagues (2021) published a Cochrane Review evaluating the diagnostic accuracy of ferritin concentrations for detecting iron deficiency and the risk of iron overload in primary and secondary iron-loading syndromes. The review of evidence related to iron deficiency included 72 studies involving 6059 individuals. In the general, apparently healthy adult population, 3 studies reported sensitivities of 63% to 100% at the optimum cutoff for ferritin, with corresponding specificities of 92% to 98% with cutoff variations between studies. One study in healthy children reported a sensitivity of 74% and specificity of 77% and one in pregnant individuals reported a sensitivity of 88% with a specificity of 100%. However, confidence in the estimates is low due to the sparse, heterogenous data, and potential for bias. Among non-healthy adults using a fixed threshold of 30 µg/L, the pooled estimate for sensitivity was 79% (95% confidence interval [CI], 58% to 91%) and specificity was 98% (95% CI, 91% to 100%). The estimated odds ratio of 140 indicates it is a relatively highly informative test. Blood ferritin concentration appears to be reasonably sensitive and a very specific test for iron deficiency in people presenting for medical care, but the reviewers reported that the findings are based on evidence of low-certainty.

The British Society of Gastroenterology (BSG) published guidelines for the management of iron deficiency anemia in adults (Snook, 2021). Iron deficiency anemia can be caused by a range of gastrointestinal pathologies including cancer. The BSG recommends investigating gastrointestinal causes on an urgent basis in individuals with a new diagnosis of IDA without obvious explanation (evidence quality – high, consensus – 85%, statement strength – strong). The recommendations include the following statements:

- We recommend that anaemia is defined as a haemoglobin (Hb) concentration below the lower limit of normal for the relevant population and laboratory performing the test (evidence quality – medium, consensus – 100%, statement strength – strong).
- We recommend that iron deficiency should be confirmed by iron studies prior to investigation. Serum ferritin is the single most useful marker of IDA, but other blood tests (eg, transferrin saturation) can be helpful if a false-normal ferritin is suspected (evidence quality – medium, consensus – 92%, statement strength – strong).
- We recommend that patients should be monitored in the first 4 weeks for an Hb response to oral iron, and treatment should be continued for a period of around 3 months after normalisation of the Hb level, to ensure adequate repletion of the marrow iron stores (evidence quality – medium, consensus – 92%, statement strength – strong).
- After the restoration of Hb and iron stores with [iron replacement therapy] IRT, we recommend that blood count should be monitored periodically (perhaps every 6 months initially) to detect recurrent IDA (evidence quality – very low, consensus 85%, statement strength – strong).
- Confirmed IDA is uncommon in young men, but when found we recommend that it warrants the same investigation algorithm as for older people (evidence quality – moderate, consensus – 100%, statement strength – strong).
- Iron deficiency is common in the elderly, and is often multifactorial in aetiology (evidence quality – high, consensus – 100%, statement strength – strong).
- Functional iron deficiency (FID) is a common contributory factor to the anaemia associated with advanced chronic kidney disease (CKD) (evidence quality – high, consensus – 92%, statement strength – strong).
- Iron deficiency is common in chronic heart failure (CHF), and is often multifactorial (evidence quality – high, consensus – 92%, statement strength – strong).

The etiology of iron deficiency anemia could be the result of inadequate intake, poor gastrointestinal absorption, or gastrointestinal blood loss. In their guidelines on the gastrointestinal evaluation of iron deficiency anemia, the American Gastroenterological Association (AGA; Ko, 2020) recommends using a cutoff of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency, a strong recommendation based on high quality evidence. The AGA also comments that in individuals with inflammatory conditions or CKD, other laboratory tests such as C-reactive protein, TSAT, or soluble transferrin saturation, may be needed in conjunction with ferritin to diagnose iron deficiency anemia.

The American College of Obstetricians and Gynecologists (ACOG; 2021) guidelines for anemia in pregnancy recommend that all pregnant individuals should be screened for anemia with a CBC in the first trimester and again at 24 0/7 to 28 6/7 weeks of gestation. Those who meet criteria for anemia should be evaluated to determine the cause. The recommendations are based on consensus and expert opinion (Level C). The initial evaluation of pregnant individuals with mild to moderate anemia may include serum iron and ferritin levels. Iron deficiency anemia is defined by abnormal iron test values along with low hemoglobin or hematocrit levels. In individuals “without evidence of causes of anemia other than iron deficiency, it may be reasonable to empirically initiate iron therapy without first obtaining iron test results” (ACOG, 2021).

The World Health Organization (WHO; 2020) created guidelines addressing the use of indicators for assessing a population’s iron status and application of the use of ferritin concentration for monitoring and evaluating iron interventions. The guidance included the following recommendations related to the scope of this document:

- Ferritin concentration is a good marker of iron stores and should be used to diagnose iron deficiency in otherwise apparently healthy individuals (strong recommendation, low certainty of evidence).
- Ferritin concentration should not be used alone to identify risk of iron overload. Patients with elevated ferritin levels should receive clinical and laboratory evaluation to establish the underlying cause (strong recommendation, very low certainty of

evidence).
- Ferritin concentration increases in response to iron-related interventions and may be used to monitor and assess the impact of interventions on iron status (strong recommendation, moderate certainty of evidence).
- In areas of widespread infection or inflammation, serum ferritin should be assessed with concurrent measurement of two acute phase response proteins, CRP and AGP (strong recommendation, moderate certainty of evidence).
- The increase in ferritin values caused by inflammation should be accounted for in individuals and populations.

In 2019, guidelines from the British Society of Haemotology issued the following recommendations for individuals who are pregnant:

- Healthcare workers should be aware that iron deficiency is the most common cause of anemia in pregnancy and the risk of iron deficiency should be considered in all pregnant women (1B).
- Haemoglobin concentration should be routinely measured at booking and at 28 weeks' gestation (1D).
- The optimal diagnostic strategy for anaemia in pregnancy is unknown but unselected routine screening with serum ferritin outside the context of research is not currently recommended (1D).
- Serum ferritin should be measured in women with a known haemoglobinopathy to identify concomitant iron deficiency and exclude iron loading states (1D).
- Non-anaemic women at risk for iron deficiency should be identified and either started on prophylactic iron empirically or have serum ferritin checked first (1D).
- Other biomarkers of iron status are not currently recommended for screening as there is insufficient validation in pregnancy (2B).

The American Academy of Pediatrics (AAP; Hagan, 2017) issued guidelines that include recommendations on iron supplementation and screening for anemia. Their recommendations include universal screening for anemia in infants at age 12 months. For children at other ages, selective screening for anemia based on an assessment of risk during routine health examinations is recommended. Starting in adolescence, the AAP recommends screening all nonpregnant individuals who are subject to uterine blood loss for anemia every 5 to 10 years, throughout the years they have the potential to become pregnant, during routine health examinations. They also recommend annual screening for anemia in individuals subject to uterine blood loss with other known risk factors for iron deficiency that include extensive menstrual or other blood loss, low iron intake, or a previous diagnosis of iron deficiency anemia. Screening includes an assessment of hemoglobin. Specific testing for serum iron concentrations is not addressed in the guidelines. They include the following statement:

> Screening for anemia has limited accuracy for iron deficiency. Treatment for iron deficiency anemia shows improvement in iron deficiency but not necessarily in developmental outcomes. Evidence suggests some harm caused by increased incidence of iron poisoning when iron-containing medications are kept in the home. No high-quality studies were found regarding screening adolescents for anemia.
>
> Because iron deficiency is associated with many and sometimes subtle detrimental effects, the AAP recommends iron supplementation or fortification in infants. They also recommend that all infants at age 12 months be screened for anemia by determining hemoglobin concentration.

The United States Preventive Services Task Force (USPSTF) has issued separate guidance addressing iron deficiency anemia in young children (ages 6 to 24 months) and individuals who are pregnant (2015a; 2015b). In both groups, the USPSTF determined that evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia with a Grade I recommendation. The guidelines included the following statement regarding individuals who are pregnant:

> The primary screening test for anemia is to measure serum hemoglobin or hematocrit levels. However, given the hemodilution and physiologic anemia that normally occurs during pregnancy, using hemoglobin or hematocrit measurement alone to determine iron deficiency status can be imprecise, and its sensitivity and specificity for detecting iron deficiency anemia in pregnant women are unknown. Serum ferritin, which is often used to measure iron status, may have limited use during pregnancy because its concentration often decreases in late pregnancy despite adequate iron stores in the bone marrow. Also, serum ferritin is an acute phase reactant, which means its levels increase during periods of inflammation.

The CDC (1998) has developed guidelines for iron deficiency screening to detect deficiency at earlier stages and prevent serious complications of iron deficiency anemia in at-risk populations. According to the guidelines, secondary prevention for iron deficiency involves screening for, diagnosing, and treating iron-deficiency anemia. The CDC indicates that the cost, feasibility, and variability of measurements other than hemoglobin and hematocrit currently preclude their use for screening. Screening recommendations for infants ages 0 to 12 months and preschool children ages 1 to 5 years include the following:

> Secondary Prevention Universal Screening
>
> - In populations of infants and preschool children at high risk for iron-deficiency anemia (e.g., children from low-income families, children eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children [WIC], migrant children, or recently arrived refugee children), screen all children for anemia between ages 9 and 12 months, 6 months later, and annually from ages 2 to 5 years.
>
> Selective Screening
>
> - In populations of infants and preschool children not at high risk for iron-deficiency anemia, screen only those children who have known risk factors for the condition. These children are described in the next three bulleted items.
> - Consider anemia screening before age 6 months for preterm infants and low-birthweight infants who are not fed iron-fortified infant formula.
> - Annually assess children aged 2-5 years for risk factors for iron-deficiency anemia (e.g., low-iron diet, limited access to food because of poverty or neglect, or special healthcare needs). Screen these children if they have any of these risk factors.
> - At ages 9-12 months and 6 months later (at ages 15-18 months), assess infants and young children for risk factors for anemia. Screen the following children:
>   - Preterm or low-birthweight infants
>   - Infants fed a diet of non-iron-fortified infant formula for greater than 2 months
>   - Infants introduced to cow's milk before age 12 months
>   - Breast-fed infants who do not consume a diet adequate in iron after age 6 months (i.e., who receive insufficient iron from supplementary foods)
>   - Children who consume greater than 24 oz daily of cow's milk
>   - Children who have special health-care needs (e.g., children who use medications that interfere with iron absorption and children who have chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery).

The CDC (1998) recommends the following for diagnosis and treatment for infants and preschool aged children:

- Check a positive anemia screening result by performing a repeat hemoglobin (Hb) concentration or hematocrit (Hct) test. If the tests agree and the child is not ill, a presumptive diagnosis of iron-deficiency anemia can be made and treatment begun.
- Repeat anemia screening in 4 weeks. An increase in Hb concentration of greater than or equal to 1 g/dL or in Hct of greater than or equal to 3% confirms the diagnosis of iron-deficiency anemia. If iron-deficiency anemia is confirmed, reinforce dietary counseling, continue iron treatment for 2 more months, then recheck Hb concentration or Hct. Reassess Hb concentration or Hct approximately 6 months after successful treatment is completed.
- If after 4 weeks the anemia does not respond to iron treatment despite compliance with the iron supplementation regimen and the absence of acute illness, further evaluate the anemia by using other laboratory tests, including MCV, RDW, and serum ferritin concentration. For example, a serum ferritin concentration of less than or equal to 15 ug/L confirms iron deficiency, and a concentration of greater than 15 ug/L suggests that iron deficiency is not the cause of the anemia.

Among persons 5 to less than 12 years of age and individuals age 12 to less than 18 years who are not subject to uterine blood loss, the CDC recommends that “only those who have a history of iron-deficiency anemia, special health-care needs, or low iron intake should be screened for anemia” (CDC, 1998). Among individuals subject to uterine blood loss age 12 and older the CDC recommends the following:

> Secondary Prevention Screening

- Starting in adolescence, screen all nonpregnant women for anemia every 5-10 years throughout their childbearing years during routine health examinations.
- Annually screen for anemia women having risk factors for iron deficiency (e.g., extensive menstrual or other blood loss, low iron intake, or a previous diagnosis of iron deficiency anemia).

> Diagnosis and Treatment

- Confirm a positive anemia screening result by performing a repeat Hb concentration or Hct test. If the adolescent girl or woman is not ill, a presumptive diagnosis of iron-deficiency anemia can be made and treatment begun.
- If after 4 weeks the anemia does not respond to iron treatment despite compliance with iron supplementation regimen and the absence of acute illness, further evaluate the anemia by using other laboratory tests, including MCV, RDW, and serum ferritin concentration.

For individuals who are pregnant and postpartum the CDC recommends:

> Secondary Prevention Screening

- Screen for anemia at the first prenatal care visit.

> Diagnosis and Treatment

- Confirm a positive anemia screening result by performing a repeat Hb concentration or Hct test. If the pregnant woman is not ill, a presumptive diagnosis of iron-deficiency anemia can be made and treatment begun.
- If after 4 weeks the anemia does not respond to iron treatment (the woman remains anemic for her stage of pregnancy and Hb concentration does not increase by 1 g/dL or Hct by 3%) despite compliance with an iron supplementation regimen and the absence of acute illness, further evaluate the anemia by using other tests, including MCV, RDW, and serum ferritin concentration.

> Postpartum Women
> Women at risk for anemia at 4-6 weeks postpartum should be screened for anemia by using a Hb concentration or Hct test…Risk factors include anemia continued through the third trimester, excessive blood loss during delivery, and a multiple birth. Treatment and follow-up for iron deficiency anemia in postpartum women are the same as for nonpregnant women.

For individuals who are not subject to uterine blood loss, including those who have experienced menopause, age greater than or equal to 18 years, the CDC states the following:

> No routine screening for iron deficiency is recommended for men or postmenopausal women. Iron deficiency or anemia detected during routine medical examinations should be fully evaluated for its cause.

The Institute of Medicine (IOM; Earl, 1993) published guidance on the prevention, detection, and management of iron deficiency anemia among children and individuals that may become pregnant. The IOM recommends measuring hemoglobin and hematocrit levels to screen for anemia and suspected iron deficiency. However, they warn that this method may fail to recognize mild degrees of iron deficiency due to the overlap in values between normal and iron deficient individuals. Screening of infants who are breastfed or not receiving iron-fortified formula should occur at age 9 months or no later than age 3 months in preterm infants. If there is an infection or there has been an infection within the 2 weeks prior to screening, it should be delayed. Routine screening is not recommended for children over age 24 months, in the absence of anemia during a prior screening. Children at mid-youth may need to be screened in the presence of risk factors for iron deficiency anemia which may include abuse and resource limited conditions. The guidelines recommend that all individuals who may become pregnant should be screened for anemia between 15 and 25 years of age and every 5 to 10 years if there are no risk factors for anemia. More frequent screening is recommended for individuals with risk factors that include high parity, frequent blood donation, high menstrual blood loss, previous diagnosis of iron deficiency anemia, and resource-limited conditions. For individuals who are pregnant, the IOM recommends screening for anemia at the first prenatal visit and at the second-trimester visit by evaluating hemoglobin and ferritin concentrations.

Medical society guidelines make a distinction between evaluating individuals suspected to have iron deficiency anemia, evaluating asymptomatic individuals considered to be at increased risk, and individuals who are asymptomatic and not at increased risk of iron deficiency anemia. Universal screening of asymptomatic individuals who are not at risk of iron deficiency anemia is not recommended. Recommendations for initial screening typically include an evaluation of hemoglobin and hematocrit with a subsequent assessment of iron studies except in cases of known higher risk or suspicion of iron deficiency.

Iron Deficiency Anemia in Chronic Diseases

The cause of iron deficiency in chronic diseases can be multifactorial. Contributing factors may include malabsorption, malnutrition, GI blood loss, and the presence of a chronic inflammatory state. Impaired erythropoietic activity and disturbed iron homeostasis can be consequences of increased release of inflammatory cytokines due to chronic conditions such as underlying cancer or toxicity of cancer therapy, congestive heart failure, and CKD (Aapro, 2018; Snook, 2021).

Iron deficiency and anemia are considered common in individuals with heart failure. The European Society of Cardiology recommends that all individuals with heart failure are regularly screened for anemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT (McDonagh, 2021).

Anemia and iron deficiency can be common complications in individuals with solid tumors or hematologic malignancies, particularly those treated with chemotherapeutic agents. Iron replacement may be used to improve hemoglobin response and reduce red blood cell transfusions in individuals with chemotherapy associated anemia receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, TIBC, transferrin saturation, or ferritin levels is recommended by the European Society of Medical Oncology and American Society of Oncology/American Society of Hematology (Aapro, 2018; Bohlius, 2019)

Among individuals with CKD, functional iron deficiency is related in part to the administration of ESA or anemia of chronic disease. Assessment of iron status is performed to determine if iron deficiency is causing or contributing to anemia, guide the use of iron therapy to achieve or maintain target hemoglobin levels, and avoid complications associated with iron overload. Measurement of serum iron, TIBC, ferritin, and TSAT are commonly used to assess iron status in this population.

The Renal Association (Mikhail, 2017) published clinical practice guidelines on anemia of CKD. The guidance indicates that initial laboratory evaluation for anemia should include tests to determine iron status (Grade 1B). These tests include percentage of hypochromic red blood cells (CHr), but only if processing of blood sample is possible within 6 hours, reticulocyte hemoglobin count (Ret-Hb), or equivalent tests. If testing for CHr or Ret-Hb is not feasible or the person has thalassemia or thalassemia trait, it is preferable to test ferritin and TSAT together because the combination provides an important insight into erythropoiesis, iron storage, and iron availability to bone marrow. Serum ferritin is considered the only available blood marker to assess iron stores and should also be obtained at the initial evaluation. It is recommended that iron status is monitored every 1 to 3 months in individuals receiving intravenous iron therapy to avoid toxicity (Grade 2B).

Clinical practice guidelines for anemia in individuals with CKD were published by the Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group (2012). The guidelines indicate that individuals with CKD and anemia should have a complete blood count, absolute reticulocyte count, serum ferritin, TSAT, vitamin B12, and folate levels measured at the initial evaluation of anemia. The recommendation was supported by a review from the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (Kliger, 2013). Ongoing assessment of hemoglobin, TSAT, and ferritin is considered necessary to monitor response to therapy. Evaluation of iron status, TSAT and ferritin, is recommended at least every 3 months during ESA therapy and for decision making regarding iron therapy. Testing iron status more frequently is recommended with ESA dose modifications, to monitor response to intravenously delivered iron therapy, when there is blood loss, and in other circumstances where iron stores may become depleted. These recommendations are not graded and based on limited evidence with few RCTs.

Guidelines from the International Society of Nephrology (Madore, 2008) recommend assessing iron status as part of the initial evaluation of anemia in all individuals with CKD. Frequency of iron testing is adapted to the individual's condition. In individuals who require iron or ESA therapy, measurement of serum ferritin and TSAT every 1 to 3 months is considered reasonable. The frequency of follow-up evaluation is dependent an individual's clinical status, hemoglobin response to iron supplementation, the ESA dose, and the results of recent iron studies. Evaluation would occur less frequently in stable individuals with mild anemia who are not receiving iron supplementation or ESA therapy, or more frequently during acute management.

Iron Overload

An excess of iron, iron overload, is a potentially serious problem with nonspecific and often gradual symptom development. Left untreated, individuals are at risk of life-threatening organ toxicity. Increased iron levels can be caused by red blood cell transfusions, excesses in iron supplementation, increases in iron absorption due hereditary hemochromatosis, ineffective erythropoiesis such as occurs in thalassemia, sickle cell anemia, and liver disease. Chronic alcohol consumption has also been associated with increased hepatic iron stores from increased intestinal iron absorption (Costa Matos, 2013). Iron overload syndromes are divided into three groups: inherited causes, various causes of secondary iron overload, and a small miscellaneous group. Typical findings in individuals with suspected iron overload may include a family history of hereditary hemochromatosis, multiple red blood cell transfusions, and unexplained organ damage (such as liver or heart damage) with its associated symptoms. Screening is recommended in symptomatic individuals and those considered to be at risk for iron overload based on medical history.

Hereditary hemochromatosis is defined as an inherited iron overload disorder characterized by excessive absorption of iron due to deficiency of hepcidin. Although it is seen worldwide, it is one of the most commonly identified genetic disorders in populations of northern European origin. Approximately 85% to 90% have a homozygous C282Y mutation in the HFE gene (Bacon, 2011). A smaller proportion (2% to 4%) have C282Y/H63D compound heterozygosity.

The measurement of liver iron concentration is regarded as the best predictor of total body iron, but the procedure is invasive and associated with risks. The two most useful serum measurements to evaluate iron overload are serum ferritin and TSAT, both of which are elevated in iron overload (Bacon, 2011). The measurement of TSAT is commonly used as an index of iron status. The test is especially useful in screening for hereditary hemochromatosis though not as useful in cases of overload caused by blood transfusions (Jensen, 2004). Serum ferritin has been shown to be a useful, non-invasive tool for monitoring iron status in situations of overload. However, serum ferritin is an acute phase reactant, increasing with inflammatory processes, infection, and chronic diseases. These etiologies should be investigated in individuals with elevated serum ferritin values suspected to have iron overload (Jensen, 2004). Serum ferritin levels have an additional value as a predictor of advanced fibrosis and cirrhosis in confirmed cases of hereditary hemochromatosis (Beaton, 2002; Guyader, 1998; Morrison, 2003).

Garcia-Casal and colleagues (2021) published a Cochrane Review evaluating the diagnostic accuracy of ferritin concentrations for detecting iron deficiency and the risk of iron overload in primary and secondary iron-loading syndromes. The review included 36 studies involving 1927 participants for iron overload. All studies concerned non-healthy populations, and none were specifically focused on infants, children, or individuals who are pregnant. The investigators found ferritin to have a specificity of 65% with a sensitivity of 80%. The estimated odds ratio was 8. The evidence indicates there is a low certainty that high concentrations of ferritin provide a sensitive test for iron overload in people where this condition is suspected.

The American College of Gastroenterology (ACG; Kowdley, 2019) issued guidelines on the management of hereditary hemochromatosis. The ACG recommends screening for hereditary hemochromatosis in individuals with family members, particularly first-degree relatives, diagnosed with hereditary hemochromatosis (conditional recommendation, very low quality of evidence). Screening in the general population is not recommended. Though not an official recommendation on iron studies related to the assessment of iron overload, the ACG guidelines include the following:

> The initial approach to the evaluation of patients with suspected iron overload disorders includes measurement of serum iron level, TS [transferrin saturation], SF [serum ferritin], and unsaturated iron-binding capacity (UIBC). TS is the preferred initial screening test, and fasting is not required to accurately determine TS. A TS of greater than 45% identifies 97.9%–100% of C282Y homozygotes, although a small proportion of patients with HH [hereditary hemochromatosis] such as younger individuals at an earlier stage may have TS of < 45%. Iron overload may also be

present with an elevated SF level and a normal TS level, particularly in non–HFE-related iron overload.

The British Society of Haematology (BSH) published guidelines on the investigation of raised serum ferritin (Cullis, 2018). Serum ferritin may be elevated in individuals with true iron overload, but it is recommended to investigate reactive causes of raised ferritin levels such as disease, malignancy, inflammatory, or metabolic disorders as they are more common (Grade 1B). In individuals with an incidental finding of elevated serum ferritin, a full blood count, a repeat serum ferritin, and TSAT should be included in the first line investigations (Grade 1C). In individuals with a moderately elevated serum ferritin level (<1000 µg/l) and normal TSAT, it may be reasonable to repeat assessment after 3 to 6 months (Grade 2C).

The American Association for the Study of Liver Diseases (AASDL; Bacon, 2011) published guidelines on the diagnosis and management of hereditary hemochromatosis. The AASDL recommends that individuals with abnormal iron studies should be evaluated as individuals with hemochromatosis, even in the absence of symptoms (Grade A). They also recommend evaluation for hemochromatosis in all individuals with evidence of liver disease (Grade 1B). Diagnostic evaluation using serum iron markers is recommended for high-risk individuals with a family history of hereditary hemochromatosis or suspected organ involvement (Grade 1B). In individuals with suggestive symptoms, physical findings, or family history of hereditary hemochromatosis, assessment should include a combination of TSAT and ferritin (Grade 1B). If TSAT is < 45% and ferritin is normal, no further evaluation is needed. In individuals with a TSAT ≥ 45% and/or elevated ferritin, further investigation is recommended. Screening by simultaneously performing iron studies and HFE mutation analysis in first-degree relatives of individuals with HFE-related hereditary hemochromatosis is recommended to detect early disease and prevent complications (Grade 1A). Individuals with hemochromatosis and iron overload are recommended to undergo therapeutic phlebotomy weekly, as tolerated (Grade 1A). Therapeutic phlebotomy is recommended in non-HFE iron overload in individuals with hepatic iron concentrations (Grade 1B). It is recommended that individuals with end-organ damage due to iron overload also undergo regular phlebotomy (Grade 1A). The target levels of phlebotomy for both groups of individuals should be a ferritin level of 50 to 100 µg/L (Grade 1B). The frequency of serum ferritin analysis varies by individual, but should be performed every 10 to 12 phlebotomies (approximately every 3 months) in the initial stages of treatment. As the target range of 50 to 100 µg/L is approached, testing may be repeated more frequently to avoid the development of overt iron deficiency. Frequency of phlebotomy varies by tolerance in each individual and frequency of serum ferritin analysis varies with it. General population screening in those with average risk for hereditary hemochromatosis is not recommended (Grade 1B).

The European Association for the Study of the Liver (EASL; 2010) published guidelines for HFE-associated hemochromatosis. The guidelines recommend that individuals with suspected iron overload have fasting measurements of TSAT and serum ferritin (Grade 1B). HFE testing (genetic testing) should be performed only on those with increased TSAT (Grade 1A). It is recommended that individuals from liver clinics are screened by measuring fasting TSAT and serum ferritin (Grade 1C) and offered HFE testing if TSAT is increased (Grade 1B). Diagnosis of HFE hemochromatosis requires evidence of increased iron stores and should not be based on C282Y homozygosity alone (Grade 1B). The EASL recommends treating individuals with HFE hemochromatosis and evidence of excess iron with phlebotomy (1C). The guidance indicates that data is lacking on an optimal treatment regimen and target serum iron indices. The goal of treatment is to prevent re-accumulation of iron once depletion has been achieved. Standard practice is to maintain serum ferritin between 50 to 100 µg/L which is typically achieved after 3 to 6 months of venesection. Some individuals may be offered ceasing of venesection with monitoring of serum ferritin then restarting a short program when serum ferritin reaches the upper limit of the normal range. Individuals with a C282Y homozygotic mutation and the absence of evidence for iron overload could be monitored annually and treatment instituted when serum ferritin rises above normal (Grade 2C).

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Index

Ferritin
Iron
TIBC
Total Iron Binding Capacity
Transferrin

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. References section updated. Updated Coding section to consolidate diagnosis ranges, added ICD-10-CM codes D75.838-D75.839.
	09/27/2023	Updated Coding section with 10/01/2023 ICD-10-CM changes; added N02.B9 to end of range.
Reviewed	02/16/2023	MPTAC review. References section updated. Coding section updated with Z95.812 and removed Z95.818.
	04/21/2022	Corrected typographical errors in diagnosis codes in the Coding section.
New	02/17/2022	MPTAC review. Initial document development.

guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.