MEDICAL POLICY
For use with the UnitedHealthcare Laboratory Benefit Management Program, administered by BeaconLBS

SERUM IRON STUDIES

Policy Number: CMP - 007
Effective Date: January 1, 2018

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BACKGROUND

Dietary iron is absorbed in the small intestine via the transporter divalent metal transporter 1, moved across the intestinal surface by ferroportin (as regulated by a liver hormone, hepcidin), and delivered to the tissues by the carrier protein, transferrin. Tissue iron is then used in cellular metabolic processes or incorporated into hemoglobin for developing red blood cells, whose synthesis in the bone marrow is regulated by erythropoietin, produced mainly by the kidneys as regulated by tissue oxygen levels. As red blood cells turnover, iron is phagocytosed by macrophages before its release into the bloodstream. Due to the complexity of iron metabolism, there are a myriad of clinical abnormalities that can result in iron deficiency or iron overload from any number of different molecular perturbations of iron metabolism.

Iron deficiency occurs in settings of increased demand, low iron stores and increased blood loss. During childhood growth and during pregnancy, there is a demand for more iron. In situations of malabsorption, such
as gluten enteropathy, supply may not keep up with demand. In the setting of gastrointestinal pathology, occult bleeding can result in iron deficiency and iron deficiency anemia. Patients suffering from iron deficiency often present with fatigue or pallor but less common manifestations include alopecia and pruritis. Following major surgery the patient may have iron deficient erythropoietin for months or years if adequate iron replacement has not been given. High doses of supplemental iron may cause the serum iron to be elevated. Serum iron may also be altered in acute and chronic inflammatory and neoplastic conditions.

Iron overload from increased absorption occurs in hereditary conditions classified as primary hemochromatosis, including hereditary hemochromatosis, African hemochromatosis and juvenile hemochromatosis. Secondary hemochromatosis can be caused by other genetic disorders of iron metabolism or erythropoiesis. These conditions include atransferrinemia, aceruloplasminemia, X-linked hereditary sideroblastic anemia, thalassemia major, congenital dyserythropoietic anemia, and disorders of red blood cell metabolism, including pyruvate kinase deficiency and glucose-6-phosphate dehydrogenase deficiency. Systemic illnesses such as liver disease lead to iron overload. Iatrogenic causes of iron overload include parenteral iron therapy, hemodialysis, and transfusions. Exposure to occupational fumes and accidental ingestion of iron supplements (generally in the pediatric population) can also lead to iron poisoning. Patients with iron overload can present with nausea, vomiting, fatigue, cardiac dysfunction, diabetes mellitus, hyperpigmentation, and signs of liver pathology.

Serum iron studies measure not only serum iron (SI) but also serum ferritin (SF) and total iron-binding capacity (TIBC). Transferrin saturation (TSAT) can be calculated from SI and TIBC. Serum iron reflects the amount of iron in blood. It can be transiently increased due to meat ingestion or iron supplementation. Serum ferritin is an iron-binding protein that reflects total body iron and is generally more clinically significant. Nonetheless, it is an acute phase reactant that is elevated by inflammation and malignancy; interpretation of SF must be correlated with clinical history. Total iron-binding capacity reflects the ability of transferrin to bind iron. Transferrin saturation is a calculated percentage derived from SI/TIBC X 100. Serum iron studies are best interpreted as a unit and in the context of the patient’s clinical history, other hematologic indices such as CBC results, and various clinical algorithms.

Serum iron studies are used to diagnose iron deficiency and iron overload. In iron deficiency, hemoglobin levels are not the first laboratory abnormality, and SF is an earlier indicator. The patient progresses from storage iron depletion, to early functional iron depletion to established functional iron deficiency (iron deficiency anemia). In storage iron depletion, SF levels will be decreased (assuming the absence of clinical factors causing the production of acute phase reactants). In early functional iron deficiency, hemoglobin values remain within normal limits but SI declines. Hemoglobin levels do not fall until functional iron deficiency is established. Iron studies may be appropriate in patients after treatment for other nutritional deficiency anemias, such as folate and vitamin B12, because iron deficiency may not be revealed until such a nutritional deficiency is treated.

Characteristic increases and decreases of serum iron studies guide clinicians in the workup of anemia to distinguish between iron deficiency anemia and anemia of chronic disease. In iron deficiency anemia, SI and SF decrease and TIBC increases. In contrast, in anemia of chronic disease, TIBC is slightly increased, serum iron is normal to decreased and SF is normal to increased.

Despite the fact that bone marrow biopsy with iron staining is the gold standard for the diagnosis of iron depletion, a low SF has a high specificity for the condition and is more readily measured. Only two other conditions, hypothyroidism and ascorbate deficiency, cause a decrease in SF. In end-stage kidney disease
dialysis patients, SF is less reliable because these patients generally have inflammatory conditions and ferritin is an acute phase reactant that increases in inflammatory states, even in the face of iron deficiency. Transferrin saturation is a better indicator of functional iron deficiency in these patients.

Serum ferritin is also the key serum assay for diagnosing iron overload even though liver biopsy is considered the gold standard for iron quantification in this setting. Aside from its use in the diagnosis of iron overload, SF is also used to monitor iron in phlebotomy therapy. In patients with hemochromatosis, SF is measured at regular intervals to establish an end point for iron depletion.

Once a diagnosis of either iron deficiency or iron overload is made, clinicians must establish the etiology of the laboratory abnormalities to determine the appropriate therapy. Depending on the clinical scenario, this workup can ultimately include medical procedures such as colonoscopy for detection of colon cancer or hemoglobin electrophoresis for the diagnosis of a hemoglobinopathy. Ferritin, iron and either iron binding capacity or transferrin are useful in the differential diagnosis of iron deficiency, anemia, and for iron overload conditions. The following presentations are examples that may support the use of these studies for evaluating iron deficiency:

- Certain abnormal blood count values (i.e., decreased Mean Corpuscular Volume (MCV), decreased hemoglobin/hematocrit when the MCV is low or normal, or increased Red cell Distribution Width (RDW) and low or normal MCV)
- Abnormal appetite (pica)
- Acute or chronic gastrointestinal blood loss
- Hematuria
- Menorrhagia
- Malabsorption
- Status post-gastrectomy
- Status post-gastrojejunostomy
- Malnutrition
- Preoperative autologous blood collection(s)
- Malignant, chronic inflammatory and infectious conditions associated with anemia which may present in a similar manner to iron deficiency anemia
- Following a significant surgical procedure where blood loss had occurred and had not been repaired with adequate iron replacement.

The following presentations are examples that may support the use of these studies for evaluating iron overload:

- Chronic Hepatitis
- Diabetes
- Hyperpigmentation of skin
- Arthropathy
- Cirrhosis
- Hypogonadism
- Hypopituitarism
- Impaired porphyrin metabolism
- Heart failure
- Multiple transfusions
- Sideroblastic anemia
- Thalassemia major
- Cardiomyopathy, cardiac dysrhythmias and conduction disturbances

**POLICY**

BeaconLBS recommends that for the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

**Table 1. HCPCS Codes (Alphanumeric, CPT® AMA)**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>82728</td>
<td>Ferritin</td>
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<tr>
<td>83540</td>
<td>Iron</td>
</tr>
<tr>
<td>83550</td>
<td>Iron Binding capacity</td>
</tr>
<tr>
<td>84466</td>
<td>Transferrin</td>
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</table>

**ICD-10 Diagnosis Codes (Proven)**

CMP-007 Serum Iron
ICD10_v2.3

**Limitations**

1. Iron studies should be used to diagnose and manage iron deficiency or iron overload states. These tests are not to be used solely to assess acute phase reactants where disease management will be unchanged. For example, infections and malignancies are associated with elevations in acute phase reactants such as ferritin, and decreases in serum iron concentration, but iron studies would only be medically necessary if results of iron studies might alter the management of the primary diagnosis or might warrant direct treatment of an iron disorder or condition.

2. If a normal serum ferritin level is documented, repeat testing would not ordinarily be medically necessary unless there is a change in the patient’s condition, and ferritin assessment is needed for the ongoing management of the patient. For example, a patient presents with new onset insulin-dependent diabetes mellitus and has a serum ferritin level performed for the suspicion of hemochromatosis. If the ferritin level is normal, the repeat ferritin for diabetes mellitus would not be medically necessary.
3. When an End Stage Renal Disease (ESRD) patient is tested for ferritin, testing more frequently than every three months requires documentation of medical necessity (e.g., other than chronic renal failure or renal failure, unspecified).

4. It is ordinarily not necessary to measure both transferrin and TIBC at the same time because TIBC is an indirect measure of transferrin. When transferrin is ordered as part of the nutritional assessment for evaluating malnutrition, it is not necessary to order other iron studies unless iron deficiency or iron overload is suspected as well.

5. It is not ordinarily necessary to measure either iron/TIBC (or transferrin) and ferritin in initial patient testing. If clinically indicated after evaluation of the initial iron studies, it may be appropriate to perform additional iron studies either on the initial specimen or on a subsequently obtained specimen. After a diagnosis of iron deficiency or iron overload is established, either iron/TIBC (or transferrin) or ferritin may be medically necessary for monitoring, but not both.

6. It would not ordinarily be considered medically necessary to do a ferritin as a preoperative test except in the presence of anemia or recent autologous blood collections prior to the surgery.
REFERENCES


## POLICY HISTORY/REVISION HISTORY

<table>
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<th>Date</th>
<th>Action/Description</th>
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<tr>
<td>12/07/2017</td>
<td>Annual Policy Review Completed - Updated ICD10 codes as per CMS recommendations.</td>
</tr>
<tr>
<td>01/21/2018</td>
<td>Updated ICD10 codes as per CMS recommendations.</td>
</tr>
<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>12/03/2015</td>
<td>Annual Policy Review Completed – changes made: Added ICD10 code for anemia: E61.1</td>
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<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ ICD10 PDF files.</td>
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