JAMA Clinical Guidelines Synopsis

# Gastrointestinal Evaluation of Iron Deficiency Anemia

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**GUIDELINE TITLE** 2020 AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia

**DEVELOPER** American Gastroenterological Association (AGA)

**RELEASE DATE** September 1, 2020 (the guideline will be updated every 3 years; next update is due in 2023)

**FUNDING SOURCE** AGA Institute

**TARGET POPULATION** Adults with iron deficiency anemia (IDA), excluding those with refractory IDA

**MAJOR RECOMMENDATIONS**

- Diagnosis: Increase the ferritin cutoff from less than 15 ng/mL to less than 45 ng/mL to diagnose IDA (strong recommendation; high-quality evidence).
- Evaluation: (1) In asymptomatic postmenopausal women and men, the AGA recommends bidirectional endoscopy over no endoscopy (strong recommendation; moderate-quality evidence). (2) In asymptomatic premenopausal women, the AGA suggests bidirectional endoscopy over iron replacement therapy only (conditional recommendation; moderate-quality evidence).

## Summary of the Clinical Problem

Anemia of any cause is present in approximately 6% of the US population and increases with age, more so in people in racial minority populations. For example, according to National Health and Nutrition Examination Survey data, from 2003 to 2012 the prevalence of anemia in Black men increased from 5.1% to 11.8% and in Black women from 17.5% to 25.0%.[1] Iron deficiency anemia is an important specific cause of anemia with an estimated prevalence of approximately 3% in the adult population. Iron deficiency anemia is twice as prevalent among Black women and Hispanic women compared with White women[2] and can be caused by either decreased iron availability or increased iron requirements after blood loss from the gastrointestinal (GI) or genitourinary tract.[3] The AGA guideline notes significant practice variation in the definition and diagnostic evaluation of IDA and presents an evidence-based approach to this condition.[4]

Multimedia

## Characteristics of the Guideline Source

The members of the guideline panel were selected by the AGA. The members had no relevant conflicts of interest, although most were gastroenterologists, a composition that could possibly be associated with procedural overuse related to specialty bias.[5] The panel used GRADE methodology and the accompanying technical review[6] included both randomized clinical trials and nonrandomized comparative studies. The guideline underwent independent peer review and public comment (**Table**).

## Evidence Base

Recommendations with the highest level of evidence included a higher ferritin cutoff for the diagnosis of IDA and a recommendation for bidirectional endoscopy in asymptomatic postmenopausal women and men with IDA. To evaluate an appropriate ferritin level for the diagnosis of IDA, the panel evaluated studies that correlated ferritin levels with low bone marrow iron stores. The defined threshold for IDA based on ferritin level was less than 13 g/dL in men and less than 12 g/dL in women. The panel sought to balance the sensitivity and specificity for the ferritin cutoff, evaluating more than 220 systematic reviews and meta-analyses. The panel concluded that ferritin had a high sensitivity and specificity compared with mean cell volume, transferrin saturation, protoporphyrin, and red blood cell distribution width.[6]

Increasing the ferritin threshold to values below 45 ng/mL improved the sensitivity of marrow-confirmed diagnosis of IDA from 0.59 (95% CI, 0.55-0.62) to 0.85 (95% CI, 0.82-0.87) and decreased the specificity from 0.99 (95% CI, 0.89-0.99) to 0.92 (95% CI, 0.91-0.94).[6] This shift increased the number of patients recommended for further evaluation, potentially leading to fewer missed diagnoses. Based on population cohort study prevalence rates of iron deficiency and GI tract malignancy, the panel estimated that the number of missed colon cancers would decrease from 128 to 47 per 1 million premenopausal women and from 298 to 109 per 1 million men and postmenopausal women. The estimated number of missed gastroesophageal cancers decreased as well, from 32 to 12 per 1 million premenopausal women and from 66 to 24 per 1 million men and postmenopausal women.[6]

The panel also evaluated the evidence for performing bidirectional endoscopy (ie, both esophagogastroduodenoscopy and colonoscopy) in evaluation of patients with IDA. Due to a lack of studies in any patient population that compared bidirectional endoscopy with clinical observation or empirical oral iron therapy alone, the panel used indirect evidence from systematic reviews of colonoscopy, observational cohort studies, and cross-sectional studies regarding the frequency of GI lesions and malignancies in patients with IDA. Combining 16 studies with bidirectional endoscopy in men and postmenopausal women with IDA suggested an overall lower GI tract malignancy rate of 8.9% (95 CI, 8.3%-9.5%) and upper GI tract malignancy rate of 2% (95% CI, 1.7%-2.3%).[6] Because some studies

**Table. Guideline Rating**

| Standard | Rating |
|---|---|
| Establishing transparency | Good |
| Management of conflict of interest in the guideline development group | Good |
| Guideline development group composition | Fair |
| Clinical practice guideline–systematic review intersection | Good |
| Establishing evidence foundations and rating strength for each of the guideline recommendations | Good |
| Articulation of recommendations | Good |
| External review | Fair |
| Updating | Good |
| Implementation issues | Fair |

included symptomatic patients, this number is likely an overestimate of the actual yield in these 2 cohorts.

In additional to evaluating endoscopy in men and postmenopausal women, the guidelines assessed bidirectional endoscopy among premenopausal women. Premenopausal women are more likely to have IDA, typically attributed to menorrhagia. The panel used indirect evidence from 9 screening trials to estimate a lower GI tract malignancy rate of 0.9% (95% CI, 0.3%-1.9%) and upper GI tract malignancy rate of 0.2% (95% CI, 0.0%-0.9%).[6] This approach assumed history taking to identify another obvious source of chronic blood loss and consideration of GI tract symptoms during evaluation. Because dual bleeding sources are rare, the panel suggested that identification of an obvious abnormality consistent with the symptoms and bleeding (such as a mass lesion or large ulceration) may make further evaluation unnecessary in premenopausal women. The guideline also discussed the importance of considering celiac disease, even in asymptomatic patients, and made a conditional recommendation for noninvasive testing for *Helicobacter pylori* in patients with unrevealing bidirectional endoscopy. The guideline conditionally recommended against use of routine endoscopic biopsies for diagnosis of autoimmune atrophic gastritis due to a paucity of literature support.

## Benefits and Harms

The principal benefit of lowering the threshold for endoscopic evaluation is enhanced detection of cancer, although other GI tract lesions such as ulcers and inflammatory bowel disease may also be found. Harms associated with evaluation of IDA include patient time, discomfort, missed work, and uncommon adverse events from endoscopic procedures, such as perforation; higher health care utilization; and cost. By also screening individuals with ferritin levels in the 15- to 45-ng/mL range followed by bidirectional endoscopy, the number of false-positive results will increase from an estimated 82 to 655 per 1 million men and postmenopausal women and from an estimated 329 to 2632 per 1 million premenopausal women receiving these procedures.[6] Perforations would be expected to increase as well, from an estimated 0.08 to 0.62 per 1 million men and postmenopausal women and from an estimated 0.31 to 2.48 per 1 million premenopausal women. Thus, benefits of the expanded ferritin range for investigation are balanced against these harms, with less of an advantage in premenopausal women.

## Discussion

In men and postmenopausal women with IDA, a strong recommendation was made for bidirectional endoscopy, noting that the underlying risk of malignancy is several-fold higher in IDA than in an asymptomatic colorectal screening cohort, and recent trends of increasing colorectal cancer incidence among individuals younger than 50 years. While the World Health Organization continues to recommend a ferritin level cutoff of 15 ng/mL for diagnosing IDA, setting a higher ferritin threshold will also help identify patients with IDA in whom inflammation due to rheumatologic disease, chronic infections, or malignancy has increased ferritin above 15 ng/mL. A recent Cochrane review suggested an intermediate ferritin threshold of 30 ng/mL for diagnosis of IDA.[7]

In premenopausal women, the guideline recommendation is only conditional, driven by reduced specificity for cancer when menstrual blood loss is a competing cause of IDA and by a lower rate of GI tract cancer detection in premenopausal women, compared with the rates found in men and postmenopausal women with IDA. The guideline makes the assumption that the rate of cancer in premenopausal women is that of an average 50-year-old woman (0.6 per 1000) and notes that "patients who place a high value on avoiding the small risk of endoscopy, particularly those who are young and might have other plausible reasons for IDA, and a low value on the very small risk of missing a gastrointestinal malignancy would reasonably select an initial course of iron replacement therapy and no initial bidirectional endoscopy."

## Areas in Need of Future Study or Ongoing Research

Although this guideline provides useful interim guidance, further studies are needed to evaluate the yield of IDA evaluation at higher ferritin levels and to delineate the relative contributions of upper and lower GI tract endoscopy to actionable diagnoses. Designing adequately powered randomized trials will be challenging, especially with growing use of immunochemical tests for colon cancer diagnosis in general and in more diverse populations.[8] Racial and socioeconomic disparities in colorectal cancer mortality are well described, underscoring the need for approaches to IDA diagnosis and evaluation that are widely affordable and that also use a health equity lens.[9] Large primary care databases exploring IDA recognition and outcomes in various populations may provide additional insights.[10]


### ARTICLE INFORMATION

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**Conflict of Interest Disclosures:** None reported.


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