

## ***Folate Testing***

**Effective:** June 1, 2024

**Next Review:** January 2025

**Last Review:** January 2024

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Folate (vitamin B9) is a water-soluble vitamin that plays an essential role in red blood cell production and other cellular processes. Folate deficiency can cause anemia as well as neural tube defects during fetal development.

### **MEDICAL POLICY CRITERIA**

- I. Serum folate testing may be considered **medically necessary** in patients with a clinically documented underlying disease or condition which is specifically associated with folate deficiency, as listed in Appendix I.
- II. Serum folate testing is considered **not medically necessary** unless there is clinical documentation of an underlying disease or condition specifically associated with folate deficiency, as listed in Appendix I.
- III. Testing for folate in red blood cells is considered **not medically necessary** for all indications.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## LIST OF INFORMATION NEEDED FOR REVIEW

### SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes, including documentation of blood testing and applicable treatment history of underlying disease/condition associated with folate deficiency
- Blood draw date
- Diagnosis

### CROSS REFERENCES

[Vitamin D Testing](#), Laboratory, Policy No. 52

### BACKGROUND

#### FOLATE DEFICIENCY

Folate, also known as vitamin B9, is a water-soluble vitamin that has a variety of physiologic effects, most prominently in red blood cell production, and it plays a crucial role in the synthesis of DNA and RNA and cell division. Folate, along with other B vitamins, is also involved in homocysteine metabolism. Folate deficiencies are known to cause health problems including anemia and neural tube defects. The primary clinical manifestation of folate deficiency is macrocytic anemia, a form of anemia in which red blood cells are abnormally large. In the U.S., folate deficiency has become rare, as bread and other processed grain products have been fortified with folic acid since 1998.<sup>[1, 2]</sup> Folate deficiency is usually the result of inadequate dietary intake or absorption, and often coexists with deficiencies in other nutrients.<sup>[3, 4]</sup>

Folate is found in a variety of food sources, such as fruits, vegetables, nuts, dairy products, grains, and meats (see Table 1). The daily value of folate recommended by the U.S. Food and Drug Administration (FDA) for adults is 400 micrograms (mcg) of dietary folate equivalents (DFE), where 1 mcg DFE equals 1 mcg of food folate, 0.6 mcg of fortified folic acid in food, or 0.5 mcg folic acid supplement taken without food.<sup>[4]</sup>

**Table 1. Folate Content of Common Foods<sup>[4, 5]</sup>**

Food	Micrograms Dietary Folate Equivalent	% of Daily Value
Spinach, boiled, ½ cup	131	33
Breakfast cereals, fortified with 25% of the daily value	100	26
Rice, white, medium grain, cooked, ½ cup	90	22
Asparagus, boiled, 4 spears	89	22
Spaghetti, cooked, enriched, ½ cup	74	19
Broccoli, chopped, frozen, cooked, ½ cup	52	13
Bread, white, 1 slice	50	13

Food	Micrograms Dietary Folate Equivalent	% of Daily Value
Orange, 1 small	29	7
Egg, 1 large hard boiled	22	6

## FOLATE TESTING

When folate deficiency is suspected, initial testing includes a complete blood count (CBC) and peripheral smear. Both folate deficiency and vitamin B12 deficiency can cause a clinically similar macrocytic anemia, so serum testing for these nutrients is generally performed to confirm the diagnosis.<sup>[3]</sup>

In addition to serum testing, folate levels in red blood cells can also be tested. Serum levels fluctuate with dietary intake, while the folate in red blood cells represents the folate that was available when the cell was produced. Because red blood cells have a lifespan of approximately 120 days, this measure is less susceptible to transitory diet changes. However, the added value of this testing is limited.

## EVIDENCE SUMMARY

Research has clearly demonstrated that folate deficiency can cause megaloblastic, macrocytic anemia and, when present during pregnancy, can lead to neural tube defects in a developing embryo. For this reason, folic acid supplementation is generally recommended for individuals who are pregnant or may become pregnant.<sup>[6]</sup>

Because folate is involved in homocysteine metabolism, and homocysteine levels have been associated with a variety of conditions, including cardiovascular disease and dementia, folic acid supplementation has also been proposed to reduce the risk of developing these conditions. However, there is limited data to support supplementation for this purpose. Additionally, low serum folate levels have been linked to other disorders, such as depression, osteoporosis, and cancer, but this evidence is not strong for a causal role.

Folate testing is sometimes performed as part of routine wellness check-ups in asymptomatic patients and in patients who present with a variety of conditions or symptoms not specifically associated with folate deficiency. There is little value to this testing, due to the low incidence of folate deficiency.

## METHODS OF EVIDENCE ASSESSMENT

Validation of the clinical use of any diagnostic test requires the demonstration of three key components:

- Analytic validity, including reproducibility and precision.
- Clinical validity (i.e., sensitivity, specificity, and positive and negative predictive value) which describes the ability of a test to accurately predict clinical outcomes in appropriate populations of patients.
- Clinical utility is a key aspect of evaluating clinical test performance, and it reflects how the results of a study can be used to change management of the patient and whether

these changes in management lead to clinically important improvements in health outcomes.

The focus of the following literature review is on evidence related to the clinical utility of folate testing for indications not listed in Appendix I. In order to establish clinical utility, evidence from randomized controlled trials is required to demonstrate the following:

1. How test results are used to guide treatment decisions that would not otherwise be made in the absence of testing, and
2. Whether those decisions result in improved primary health outcomes associated with the disease or condition being treated.

Numerous RCTs and systematic reviews have evaluated the impact of folate supplementation on a variety of health outcomes,<sup>[7-20]</sup> however, in these studies supplementation was not based on the results of the folate testing. Additionally, most have not reported that folic acid supplementation was associated with a clinically meaningful improvement in health outcomes other than the prevention of neural tube defects<sup>[10, 15]</sup> and reduction of side effects in patients receiving methotrexate for rheumatoid arthritis.<sup>[9, 18]</sup>

The focus of the following evidence summary is on well-designed randomized controlled trials (RCTs) (including large patient groups, and long-term follow-up), and systematic reviews of RCTs evaluating the impact of folate testing on health outcomes.

## **TECHNOLOGY ASSESSMENTS**

The Canadian Agency for Drugs and Technologies in Health (CADTH) published an evidence evaluation for folate testing in 2015.<sup>[21]</sup> The authors identified a single systematic review and two non-randomized studies, as well as nine evidence-based guidelines. The systematic review included two retrospective studies and did not provide evidence of clinical utility for folate testing.<sup>[22]</sup> Similarly, the non-randomized retrospective studies did not report a meaningful change in management or health outcomes as a result of the testing.<sup>[23, 24]</sup> No studies were identified that evaluated the diagnostic accuracy or clinical utility of red blood cell folate testing compared to serum folate testing.

CADTH published an updated review of the evidence for folate testing in 2022 but did not identify any studies that met their inclusion criteria.<sup>[25]</sup>

## **ADDITIONAL STUDIES**

No systematic reviews, RCTs, or controlled trials evaluating folate testing have been published since the technology assessments above. However, observational studies in various settings have concluded that the diagnostic yield of such testing is generally very low in areas that fortify grain products.<sup>[1, 2, 26-31]</sup>

## **PRACTICE GUIDELINE SUMMARY**

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY, THE OBESITY SOCIETY, AMERICAN SOCIETY FOR METABOLIC & BARIATRIC SURGERY, OBESITY MEDICINE ASSOCIATION, AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS**

A 2019 update of joint guideline, Clinical Practice Guidelines for The Perioperative Nutrition,

Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures, included a recommendation for the use of a preprocedural checklist, which included the following item:<sup>[32]</sup>

“Nutrient screening with iron studies, B<sub>12</sub> and folic acid (RBC folate, homocysteine, methylmalonic acid optional), and 25-vitamin D (vitamins A and E optional); consider more extensive testing in patients undergoing malabsorptive procedures based on symptoms and risks.”

An additional recommendation in this guideline states that:

“Patients who become pregnant following bariatric procedure should have nutritional surveillance and laboratory screening for nutrient deficiencies every trimester, including iron, folate, vitamin B<sub>12</sub>, vitamin D, and calcium, and if after a malabsorptive procedure, fat-soluble vitamins, zinc, and copper (Grade D).”

### **AMERICAN COLLEGE OF GASTROENTEROLOGY**

The American College of Gastroenterology Guideline on the Diagnosis and Management of Celiac Disease was updated in 2023, and includes the following in the flowchart on the approach to monitoring celiac disease:<sup>[33]</sup>

“Other tests may include complete blood count, alanine aminotransferase, aspartate aminotransferase, vitamins (A, D, E, B<sub>12</sub>), copper, zinc, folic acid, ferritin, and iron.”

No specific recommendations regarding folate or folic acid testing were listed.

### **AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS**

A 2017 Practice Bulletin from the American College of Obstetricians and Gynecologists (ACOG) included the following Level A (based on good and consistent scientific evidence) recommendations:<sup>[34]</sup>

- All women planning a pregnancy or capable of becoming pregnant should take 400 micrograms of folic acid supplementation daily. Supplementation should begin at least 1 month before pregnancy and continue through the first 12 weeks of pregnancy.
- Women at high risk of NTDs should take 4 mg (4,000 micrograms) of folic acid daily. The daily supplement should be initiated 3 months before pregnancy and continued until 12 weeks of gestational age.

Folate testing was not included in the recommendations.

### **AMERICAN SOCIETY FOR CLINICAL PATHOLOGY/CHOOSING WISELY**

The American Society for Clinical Pathology (ASCP) published the following recommendations as part of the “Choosing Wisely” campaign, which is aimed at reducing overuse and unnecessary medical services:<sup>[35]</sup>

- “Do not order red blood cell folate levels at all.
- In adults, consider folate supplementation instead of serum folate testing in patients with macrocytic anemia.”

The recommendations included this rationale:

“Since 1998, when the United States and Canada mandated that foods with processed grains be fortified with folic acid, there has been a significant decline in the incidence of folate deficiency. For the rare patient suspected of having a folate deficiency, simply treating with folic acid is a more cost-effective approach than blood testing. While red blood cell folate levels have been used in the past as a surrogate for tissue folate levels or a marker for folate status over the lifetime of red blood cells, the result of this testing does not, in general, add to the clinical diagnosis or therapeutic plan.”

## **NATIONAL COMPREHENSIVE CANCER NETWORK**

The National Comprehensive Cancer Network guidelines for myelodysplastic syndromes (v.3.2023) include a recommendation to test red blood cell (RBC) folate levels, stating, “RBC folate and serum folate levels should not be considered equivalent, and RBC folate is preferred. RBC folate levels are more indicative of folate stores, whereas serum folate levels are reflective of recent nutrition.”<sup>[36]</sup>

## **U.S. PREVENTIVE SERVICES TASK FORCE**

The U.S. Preventive Services Task Force (USPSTF) recommends that “all persons planning to or who could become pregnant take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid.”<sup>[6]</sup> No recommendation was made regarding folate testing.

## **WORLD HEALTH ORGANIZATION**

In 2015, the World Health Organization (WHO) published thresholds for determining folate status according to laboratory test type.<sup>[37]</sup> This guideline did not include any recommendations regarding what individuals or populations should be tested for folate deficiency.

## **SUMMARY**

There is research showing that folate plays an essential role in promoting embryonic development and red blood cell formation, however there is considerable uncertainty with respect to the clinical utility of testing, both in healthy, asymptomatic populations and for conditions not directly associated with folate deficiency. Studies have generally reported a lack of evidence demonstrating how folate testing alters treatment decisions or improves health outcomes. While there are guidelines that recommend folic acid supplementation for certain populations, there are no evidence-based clinical practice guidelines that recommend routine folate testing or screening. Therefore, folate testing is considered not medically necessary in the absence of conditions specifically associated folate or other B vitamin deficiency.

There is research showing that red blood cell folate testing does not provide additional value compared with serum testing. The American Society for Clinical Pathology recommends against this testing. Therefore, red blood cell folate testing is considered not medically necessary for all indications.

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## CODES

Codes	Number	Description
CPT	82746	Folic acid; serum
	82747	Folic acid; RBC
HCPCS	None	

Appendix I
Folate deficiency anemia
Megaloblastic anemia
Nutritional anemia
Vitamin B12 deficiency anemia
Transcobalamin II deficiency
Vitamin B deficiency
Dementia
Alzheimer's disease
Myalgic encephalomyelitis/chronic fatigue syndrome
Crohn's disease
Celiac disease
Tropical sprue
Blind loop syndrome
Intestinal malabsorption
Whipple's disease
Bariatric surgery status

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