Folate Testing

Policy Number: AHS – G2154 – Folate Testing	Prior Policy Name and Number, as applicable:
Effective Date: 06/01/2022	

I. Policy Description

Folate, or vitamin B9, is a generic term for a water-soluble vitamin obtained from the diet that is involved in the transfer of methyl groups (i.e. single carbon-containing groups) in multiple biochemical metabolic pathways, including nucleic acid biosynthesis and methionine/homocysteine metabolism. Folate metabolism is closely linked to vitamin B12, cobalamin. Folate deficiency can be implicated in many disease states and processes; however, it is usually easily remedied with either a change in diet or a dietary supplement of the synthetic form, folic acid (Means Jr & Fairfield, 2020; NIH, 2018).

II. Related Policies

Policy Number	Policy Title
	Not applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quicksearch.aspx?from2=search1.asp& or the manual website.

1. Measurement of serum folate concentration **MEETS COVERAGE CRITERIA** for evaluation of patients when all of the following criteria are met:
   a. patient has been diagnosed with megaloblastic or macrocytic anemia; AND
   b. megaloblastic anemia and/or macrocytosis does not resolve after folic acid treatment
2. Measurement of serum folate concentration **DOES NOT MEET COVERAGE CRITERIA** for any other indications not described above

3. Measurement of RBC folate **DOES NOT MEET COVERAGE CRITERIA** for any indications

IV. Scientific Background

Folate, or vitamin B9, naturally occurs as polyglutamated compounds (pteroylpolyglutamates) in many plant and animal products. The synthetic form is a monoglutamate-containing compound called folic acid. Folic acid is more chemically stable for commercial production and storage, but it is less bioavailable than the naturally occurring folate (Means Jr & Fairfield, 2020). Biochemically, folate is a coenzyme in single-carbon transfers *in vivo* and is directly linked to the cobalamin (vitamin B12) cycle, methionine metabolism, and nucleic acid biosynthesis. Dietary folates are hydrolyzed via γ-glutamylhydrolase (or folate conjugase) prior to absorption in the intestinal mucosa (IOM, 1998). Both folate and vitamin B12 are required for formation of 5,10-methylene tetrahydrofolate, which is the cofactor involved in purine synthesis. Methylenetetrahydrofolate reductase (MTHFR) is the enzyme responsible in converting 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, which is required for methionine synthase, the enzyme that converts homocysteine to methionine. The interlinked one-carbon cycle is depicted in the figure below with the metabolites assayed in clinical laboratories in bold (Finer, Saravanan, Hitman, & Yajnik, 2013).

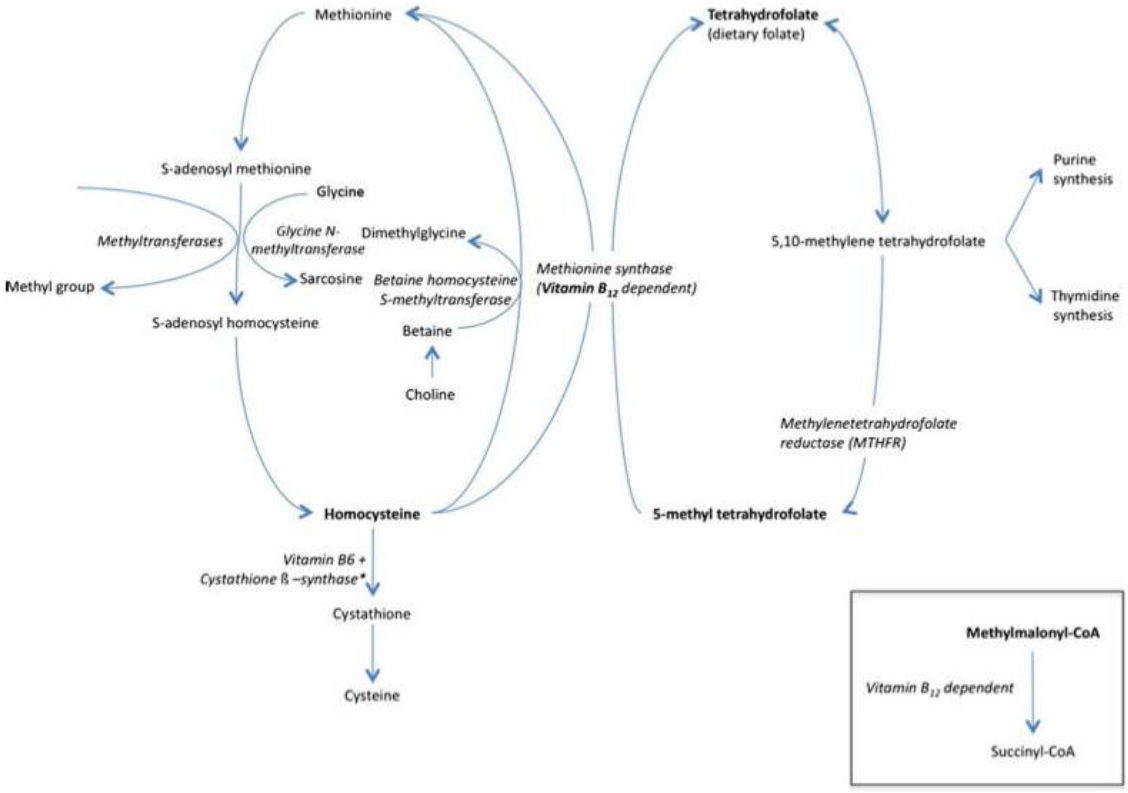

FIGURE 1 The one-carbon cycle. Metabolites readily assayed in clinical laboratories are highlighted in bold.

Role of Folate in Anemia

Anemia occurs when the body lacks healthy red blood cells (RBCs), leading to an insufficient amount of oxygen delivered to tissues. Typical symptoms of anemia include fatigue, weakness, pale skin and lightheadedness.

Macrocytic anemia refers to anemias that have high mean corpuscular volume with large RBCs. Mean corpuscular volume, or mean cell volume, can be defined as the average volume of RBCs in an individual. Megaloblastic anemia is a specific macrocytic anemia due to nucleic acid metabolic defects that result in "nuclear-cytoplasmic dyssynchrony, reduced number of cell divisions in the bone marrow, and nuclear abnormalities in both myeloid and erythroid precursors" caused by folate and/or vitamin B12 deficiency (Means Jr & Fairfield, 2021). These abnormal RBCs are the principle clinical manifestations of folate deficiency and symptoms "include weakness, fatigue, difficulty concentrating, irritability, headache, heart palpitations, and shortness of breath" (NIH, 2018).

Folate and Neural Tube Defects (NTDs)

Neural tube defects (NTDs) develop early in pregnancy and are malformations of the brain and/or spine that include spina bifida and anencephaly. Folate deficiency is directly linked to NTDs. The role of folate in NTD development is not well-characterized. The role of folate in either the methylation cycle or nucleic acid synthesis has been suggested to play a part in NTD development during embryogenesis, and some studies have indicated that it is the bioavailability of specific folates in women that can increase the likelihood of NTDs (Imbard, Benoist, & Blom, 2013; Rothenberg et al., 2004). Women typically do not obtain enough folate from diet alone, so women of childbearing age are recommended to take a synthetic folic acid supplement to decrease the likelihood of NTDs in offspring (Bibbins-Domingo et al., 2017). To decrease the occurrence of NTDs and folate deficiency, the United States and Canada mandated folic acid supplementation to cereal grains in 1998, and as of March 2018 "87 countries have legislation to mandate fortification of at least one industrially milled cereal grain" (FFI, 2018). A review by Imbard et al. (2013) of 17 different studies on the impact of folic acid fortification of NTD rates show that 16 show a decrease in the rate of NTDs. Only a study of the rate of NTDs in California showed no decline since fortification. The reduction of the United States overall was 26-30% since folic acid fortification (Imbard et al., 2013).

Causes of Folate Deficiency

Folate deficiency can be caused by dietary intake. Nutritional deficits may occur due to diet, alcoholism, depression, and even overcooked foods. Many malabsorptive disorders, such as celiac disease and ulcerative colitis, can also result in a decrease in folate uptake. Further, bariatric procedures may result in decreased absorption, and drugs, including methotrexate and trimethoprim that inhibit dihydrofolate reductase (DHFR), can also cause a folate deficiency. It is also important to note that an increased need of folate for DNA synthesis during pregnancy and lactation, chronic hemolytic anemias, exfoliative skin diseases, and hemodialysis cause folic acid deficiency (Means Jr & Fairfield, 2021).

Methodology of Folate Testing

Folate concentrations have been measured from serum, erythrocytes (RBC), and urine. Serum folate levels may not "differentiate between what may be a transitory reduction in folate intake or chronic folate deficiency accompanied by depleted folate stores and functional changes" (IOM, 1998). RBCs have a lifespan of approximately 120 days, and folate is only taken in during initial erythropoiesis (red blood cell production); consequently, RBC folate concentrations are less likely to be affected by transitory dietary fluctuations. However, Wu, Chanarin, Slavin, and Levi (1975) show that both RBC folate and serum folate levels correlate to hepatocyte folate levels (IOM, 1998; Wu et al., 1975). Galloway and Rushworth (2003) released a study in conjunction with the National Pathology Alliance review in the United Kingdom comparing data of laboratories of the National Health Service that routinely use serum folate testing only, RBC folate testing only, or both serum and RBC folate testing

together. The researchers conclude that there is no need to use both tests to determine folate concentration as an initial screen. "The serum folate assay provided equivalent information to the measurement of red cell folate and evidence from the literatures [sic] suggest that the serum folate assay should be the method of choice" (Galloway & Rushworth, 2003).

Clinical Utility and Validity

A study by Shojania and von Kuster (2010) investigated the use of serum folate testing (SF) and RBC folate testing (RF) in cases of anemia in a country that has mandated folic acid supplementation in grain products. By examining the data for folate testing in anemia at two different teaching hospitals in Canada, they report that in one hospital in 2001 "11 out of 2154 (0.5%) SF were low (<7.0 nmol/L) and 4 out of 560 (0.7%) RF were low (<417 nmol/L). In no subject with low SF or RF could the anemia be attributed to folate deficiency." For the other hospital, the data from 1999-2001 shows that "19 out of 991 (1.9%) had low RF (<225 nmol/L) but in only 2 patients (0.2%) the low RF was in folate deficiency anemia range" (Shojania & von Kuster, 2010). The authors conclude that neither serum folate testing nor RBC folate testing is justified in cases of anemia for folic acid fortified countries due to such low incidence rates of folate deficiency anemia.

Another study by Joelson, Fiebig, and Wu (2007) examined the records of three different hospitals in the U.S. that service a high number of indigent patients. The researchers reported the data from three non-consecutive years (1997, 2000, and 2004) to examine the impact of folate fortification in food products. Using the RBC folate levels only with a RBC folate cutoff value of 160 ng/mL (363.6 nmol/L), "the combined incidence of folate deficiency decreased from 4.8% in 1997 to 0.6% in 2004…Even when the folate concentration was found to be low, the majority of these subjects did not have macrocytosis." This study included a total of 4134 RBC folate tests performed over the course of three years. It is of interest to note that the number of tests performed increased from 813 in 1997 to 1759 in 2004. The authors do note of a potential limitation of the study since the data of the patients cannot be separated into specific groups (pregnant women, alcoholics, socioeconomic classes, and so on). The authors conclude "that folate deficiency has become a rare event in the United States, and the utility of routine folate measurements for patients with anemia and/or increased mean corpuscular volume are difficult to justify" (Joelson et al., 2007).

Urinary folate levels do not reflect either the stored folate concentrations or the fluctuations in folate concentration due to transitory dietary changes. Only about 1-2% of the folate excreted in the urine is unmetabolized and "excretion continued in the face of advanced folate depletion" (IOM, 1998). One study of ten postmenopausal women on a low folate diet measured folate turnover using urinary testing of folate and folate metabolites. "Folate intake did not significantly influence ApABG (*para*-acetamidobenzoylglutamate) or pABG (*para*-aminobenzoylglutamate) excretion." ApABG and pABG along with pterins are the major folate catabolites. The authors conclude that "the rate of folate catabolite excretion is related mainly to masses of slow-turnover folate pools governed by long-term folate intake" (Gregory, Swendseid, & Jacob, 2000).

Epstein-Peterson et al. (2020) collected and analyzed all folate tests performed in 2017 at an academic cancer center. In total, 937 patients were tested 1065 times; approximately 7% of tests indicated a folate deficiency, and folate deficiency was significantly associated with a higher risk of death (P=0.01) (Epstein-Peterson et al., 2020).

V. Guidelines and Recommendations

Centers for Disease Control and Prevention (CDC) (CDC, 1991, 1992, 2018)

The "CDC urges all women of reproductive age to take 400 micrograms (mcg) of folic acid each day, in addition to consuming food with folate from a varied diet, to help prevent some major birth defects of the baby's brain (anencephaly) and spine (spina bifida)" (CDC, 2018). This recommendation includes all women of reproductive age planning to become pregnant or not, as about half of U.S. pregnancies are unplanned.

Morbidity and Mortality Weekly Report (MMWR)

Both in 1991 and 1992, the CDC addressed the need for women to consume folic acid daily. In the first recommendation, the CDC recommended that women who had already had at least one pregnancy with a neural tube defect (NTD) to consume 4 mg of folic acid per day. "Women should take the supplement from at least 4 weeks before conception through the first 3 months of pregnancy." This recommendation required a physician's supervision and "were not intended for 1) women who have never given birth to an infant or had a fetus with a neural tube defect, 2) relatives of women who have had an infant or fetus with a neural tube defect, 3) women who themselves have spina bifida, or 4) women who take the anticonvulsant valproic acid—a known cause of spina bifida (CDC, 1991)."

In 1992, the CDC modified the recommendation to include all women of childbearing age to consume folate since the addition of folate would potentially decrease the number of NTDs by 50%. "All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin [B12] deficiency, care should be taken to keep total folate consumption at less than 1 mg per day, except under the supervision of a physician. Women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice (CDC, 1992)." Neither recommendation from the CDC included a requirement for either serum folate or red blood cell folate concentration.

Institute of Medicine (IOM) (IOM, 1998)

The Institute of Medicine released their detailed report titled "Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline" in 1998. This report does not outline any recommendation concerning determining the concentration of either serum folate or red blood cell folate concentrations; however, the table below outlines their recommendations concerning the upper limits (UL) of daily intake of folate for various groups (taken from (IOM, 1998)):

ULs for Infants	
0–12 months	Not possible to establish for supplemental folate
ULs for Children	
1–3 years	300 µg/day of folate from fortified foods or supplements
4–8 years	400 µg/day of folate from fortified foods or supplements
9–13 years	600 µg/day of folate from fortified foods or supplements
14–18 years	800 µg/day of folate from fortified foods or supplements
ULs for Pregnancy	
14–18 years	800 µg/day of folate from fortified foods or supplements
19 years and older	1,000 µg/day of folate from fortified foods or supplements
ULs for Lactation	
14–18 years	800 µg/day of folate from fortified foods or supplements
19 years and older	1,000 µg/day of folate from fortified foods or supplements

The IOM does specifically state that "individuals who are at risk of vitamin B_{12} deficiency …may be at increased risk of the precipitation of neurological disorders if they consume excess folate." Vitamin B_{12} deficiency can be due to dietary deficiencies (such as a complete vegan diet), pernicious anemia, gastrectomy, atrophic gastritis, bacterial infection, pancreatic insufficiency, and terminal ileal disease or resection (IOM, 1998).

American Society for Clinical Pathology (ASCP)/Choosing Wisely (ASCP, 2017)

The ASCP published a recommendation in 2017 in Choosing Wisely, an American Board of Internal Medicine (ABIM) initiative, where they clearly state the following: "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." They indicate that the drastic decrease in folic deficiency in both the U.S. and Canada after mandated folic acid supplementation in foods no longer requires for either serum folate or red blood cell folate concentrations be tested. "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" (ASCP, 2017).

The Doctors of BC (formerly the British Columbia Medical Association) (BCMA, 2012)

The Guidelines & Protocols Advisory Committee of the British Columbia Medical Association in conjunction with the Province of British Columbia released their guidelines concerning folate and folate deficiency. They state that "serum folate and red blood cell (RBC) folate tests are no longer being offered (except at Vancouver General Hospital and St. Paul's hospital under limited indications and require approval from the respective Medical Biochemist on call)" because of the drastic decrease in folate deficiency in the province. "In two outpatient laboratories in British Columbia, 99.8% and 99.1% of folate tests were normal in 2010…If folate deficiency is suspected, it is reasonable to give oral folic acid (0.4-1 mg/day) without doing laboratory investigation for deficiency at least until the hemoglobin and mean corpuscular volume normalizes (or longer if the underlying cause cannot be eliminated) (BCMA, 2012)."

National Pathology Alliance (of the United Kingdom) (Galloway & Rushworth, 2003)

The National Pathology Alliance of the United Kingdom in 2003 published in the *Journal of Clinical Pathology* their recommendation "that serum folate measurements provide equivalent information to red cell folate measurements."

American Association of Clinical Endocrinologists (AACE)/The American College of Endocrinology (ACE), The Obesity Society (TOS), American Society for Metabolic and Bariatric Surgery (ASMBS), Obesity Medicine Association (OMA), and American Society of Anesthesiologists (ASA) (Gonzalez-Campoy et al., 2013; Handelsman et al., 2015; Jellinger et al., 2017; Mechanick et al., 2019)

In 2013, the AACE, ACE, and TOS issued joint guidelines regarding healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults (Gonzalez-Campoy et al., 2013). Based on the data from the National Health and Nutrition Examination Survey (NHANES), they state "that patients with vitamin B_{12} deficiency had higher folate levels, were more likely to be anemic, and had more cognitive impairment that those with normal serum folate levels" [evidence level (EL) 2]. They evaluate the evidence concerning the link between folate and cardiovascular disease as EL4 and the link between NTDs and folate as EL1. With respect to pregnancy nutritional needs, they "should be assessed prior to conception to improve pregnancy outcome…All women of childbearing age should consume at least 400 µg dietary equivalents of folate per day" [EL4] and that during pregnancy the daily amount should be increased to 600 µg [EL3].

The AACE and ACE in 2015 released their *Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan* (Handelsman et al., 2015). Concerning patients with diabetic nephropathy, the suggest that they "undergo annual or more frequent assessment of electrolytes". For those with anemia, iron, transferrin saturation (TSAT), ferritin, vitamin B_{12}, and folate levels "should be further investigated" [EL4].

In 2017, the AACE and ACE released their guidelines for management of dyslipidemia and prevention of cardiovascular disease (Jellinger et al., 2017). Since bile acid sequestrant treatments such as cholestyramine can cause folate depletion in children, they recommend that children on such treatments supplement their diet with a multivitamin. They also note that folate, B6, and B12 supplementation can help mediate hyperhomocysteinemia, but that the supplements do not reduce risk of atherosclerotic cardiovascular disease.

In 2019, the AACE, ACE, and TOS issued joint guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient (Mechanick et al., 2019) . Here, as part of a pre-operative bariatric surgery checklist that has a "Grade A" recommendation, they include "nutrient screening with iron studies, B_{12} and folic acid (RBC folate, homocysteine, methylmalonic acid optional) …consider more extensive testing in patients undergoing malabsorptive procedures based on symptoms and risks." With regards to patients who become pregnant after having a bariatric procedure, they recommend (with Grade D) having laboratory screenings done each trimester for folate deficiency along with iron, calcium, B_{12}, and fat-soluble vitamins. With a Grade C, they state that "nutritional anemias resulting from malabsorptive bariatric surgical procedures might also involve deficiencies in vitamin B12, folate, protein, copper, selenium, and zin and should be evaluated when routine screening for iron deficiency anemia is negative."

National Institute for Health and Care Excellence (NICE) [(NICE, 2015) reaffirmed 2019]

The National Institute for Health and Care Excellence (NICE) of the Department of Health in the United Kingdom published their extensive guidelines concerning bladder cancer on February 25, 2015. Within the section concerning the follow-up treatment for muscle-invasive bladder cancer, they recommend a protocol after radical cystectomy that includes "monitoring for metabolic acidosis and B12 and folate deficiency at least annually."

American Academy of Family Physicians (AAFP) (Kaferle & Strzoda, 2009)

The AAFP released the recommendations concerning macrocytosis and macrocytic anemia in 2009. Of note, they state that "serum folate levels are not useful because they fluctuate rapidly with dietary intake and are not cost effective. RBC folate levels more accurately correlate with folate stores and should be performed if folate deficiency is suspected." They give the following key recommendation (with evidence rating of "C" or "consensus, disease-oriented evidence, usual practice, expert opinion, or case series") to "obtain red blood cell folate level if other etiologies are not found (serum folate levels may be misleading)." In the evaluation of macrocytic anemia, they included a flowchart outlining the order of steps and tests to be taken, including when the RBC folate level should be checked. For a patient exhibiting a mean corpuscular volume 100 fL and an abnormal peripheral smear showing megaloblastic features and a reticulocyte count under 2%, they should have their RBC folate level measured only if the vitamin B_{12} level is >400 pg. The flowchart is included below (Kaferle & Strzoda, 2009).

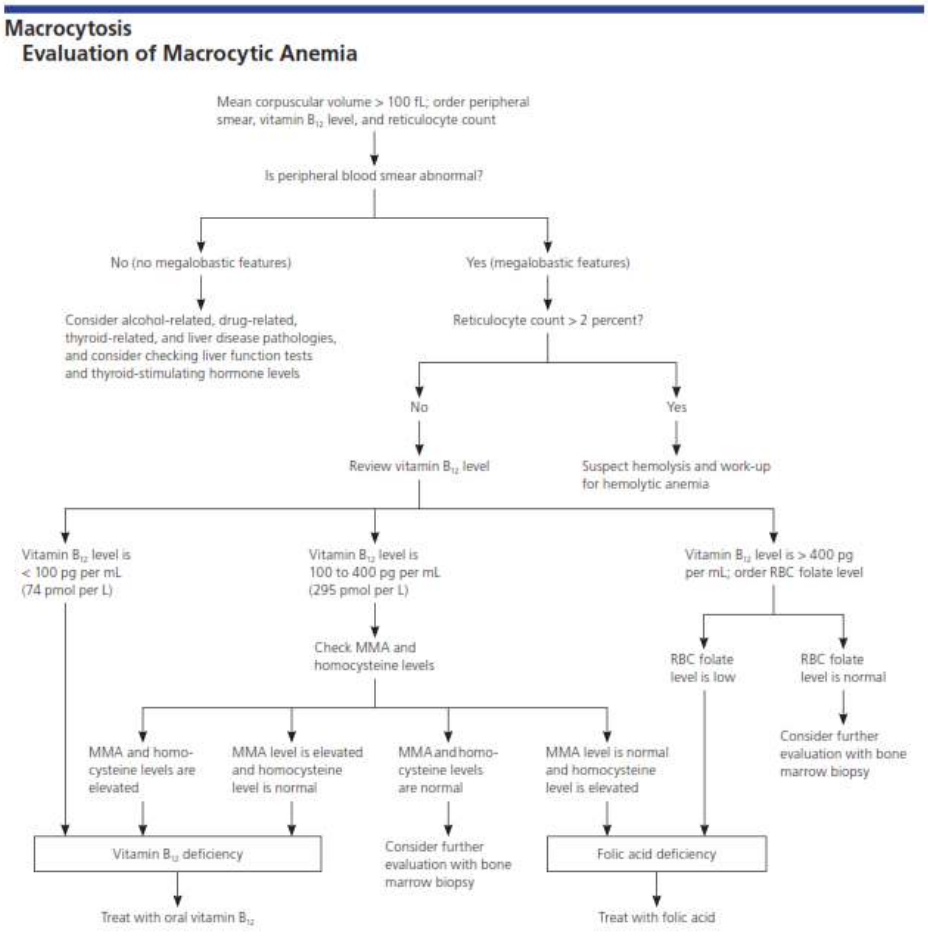

Figure 3. Algorithm for the evaluation of macrocytic anemia. (RBC = red blood cell; MMA = methylmalonic acid.)

American Academy of Neurology (AAN) (AAN, 2009; Knopman et al., 2001)

In 2001, the AAN updated their practice parameters for the diagnosis of dementia. Within the section concerning the comorbidities that should be screened in an initial assessment for dementia, they recommend folate testing along with complete blood count, serum electrolytes, B_{12}, blood urea nitrogen/creatinine, syphilis serology, thyroid function, and glucose. They did note that as of that time

"no studies were identified that evaluated these recommendations" since the last practice parameters released in 1994.

In 2009, the AAN published guidelines regarding the management and care of women with epilepsy (WWE) during pregnancy. These guidelines state that "Folic acid supplementation is generally recommended to reduce the risk of MCMs [major congenital malformations] during pregnancy, and although the data are insufficient to show that it is effective in WWE, there is no evidence of harm and no reason to suspect that it would not be effective in this group. Therefore, all women of childbearing potential, with or without epilepsy, should be encouraged to take at least 0.4 mg of folic acid daily prior to conception and during pregnancy. There was insufficient published information to address the dosing of folic acid (AAN, 2009)."

Kidney Disease Improving Global Outcomes (KDIGO) (McMurray et al., 2012)

KDIGO released their updated *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease* in 2012. They gave a "not graded" recommendation for "in patients with CKD [chronic kidney disease] and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia:

- Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferring saturation (TSAT)
- Serum vitamin B_{12} and folate levels"

They also state that "RBC folate levels can be measured when serum folate levels are equivocal or when there is concern that recent dietary intake may obscure underlying folate deficiency using serum levels alone."

Australian National Blood Authority (NBA, 2012)

The Australian National Blood Authority of the National Health and Medical Research Council of Australia released their *Patient Blood Management Guidelines: Module 2 Perioperative*, an extensive set of guidelines concerning the perioperative patient. They include a preoperative hemoglobin assessment that requires the preoperative tests for full blood count, iron studies (including ferritin), CRP, and renal function. If the patient is anemic and has a ferritin level > 100 mcg/L, then, they state to "check B12/folate levels and reticulocyte count" for possible anemia due to a chronic disease or inflammation. As a footnote, they include "check B12/folate if macrocytic or if there are risk factors for deficiency (e.g. decreased intake or absorption), or if anaemia is unexplained."

American Society for Parenteral and Enteral Nutrition (ASPEN) & Society of Critical Care Medicine (SSCM) (Choban, Dickerson, Malone, Worthington, & Compher, 2013; Mehta et al., 2017; NGC, 2013, 2016)

In 2013, ASPEN and SSCM issued joint clinical guidelines concerning the nutrition support of hospitalized obese adults. With a "Recommendation: Weak" status, they recommended "in acutely ill hospitalized patients with history of these procedures [sleeve gastrectomy, gastric bypass, or biliopancreatic diversion ± duodenal switch], evaluation for evidence of depletion of iron, copper, zinc, selenium, thiamine, folate, and vitamins B_{12} and D is suggested as well as repletion of deficiency states" (Choban et al., 2013).

In 2016, ASPEN and SSCM issued their *Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient*. The committee recommended that "evaluation for and treatment of micronutrient deficiencies such as calcium, thiamin, vitamin B12, fat-soluble vitamins (A, D, E, K), and folate, along with the trace minerals iron, selenium, zinc, and copper, should be considered" (NGC, 2016). In 2017, ASPEN and SSCM updated their *Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient*. These guidelines do not mention folate testing (Mehta et al., 2017).

Academy of Nutrition and Dietetics (AND) (Thompson et al., 2017)

The AND released their *Oncology evidence-based nutrition practice guideline* in 2013 and reaffirmed the guideline in a 2017 publication. On the "Assessment of Biochemical Data Medical Tests, and Procedures on Adult Oncology Patients" portion, the committee recommended with "Consensus, Imperative" that "the RDN [Registered Dietitian Nutritionist] should evaluate available data and recommend as indicated: biochemical data, medical tests and procedures of adult oncology patients" and included on their list is "Nutritional anemia profile (hemoglobin, hematocrit, folate, B12, iron)". "Assessment of these factors is needed to effectively determine nutrition diagnoses and plan the nutrition interventions."

European Crohn's and Colitis Organisation (ECCO) (Dignass et al., 2015)

ECCO's guidelines concerning irritable bowel disorders (IBD) included an extensive discussion on causes and treatments of anemia in IBD—both iron deficiency anemia and non-iron deficiency anemia. With an [EL 5], they state that "deficiencies of Vitamin B_{12} and folate should be treated to avoid anaemia. Serum levels of vitamin B_{12} and folic acid should be measured at least annually, or if macrocytosis is present. Patients at risk for vitamin B_{12} or folic acid deficiency [eg small bowel disease or resection] need closer surveillance. The recommended timelines are based on expert opinions and reflect common clinical practice, but do not apply to patients with extensive small bowel resection, extensive ileal Crohn's disease, or ileal-anal pouch."

American College of Gastroenterology (ACG) (Rubio-Tapia, Hill, Kelly, Calderwood, & Murray, 2013) (reaffirmed 2016)

In their guidelines and recommendations concerning the diagnosis and management of celiac disease (CD) in 2013, the ACG recommended the following statement with *Conditional recommendation, low level of evidence*: "People with newly diagnosed CD should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12."

US Preventive Services Task Force (USPSTF) (Bibbins-Domingo et al., 2017)

The USPSTF in 2017 updated their 2009 recommendation regarding folic acid supplementation in women of childbearing age. The USPSTF gives an "A" recommendation "that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid." The USPSTF does not make any statement regarding folate screening for women not of childbearing age.

British Committee for Standards in Haematology (BCSH) (Devalia, Hamilton, & Molloy, 2014; Killick et al., 2016)

In 2014, the BCSH released guidelines on folate deficiencies. They noted that "routine red cell folate testing is not necessary because serum folate alone is sufficient in most cases." However, they also acknowledged that "in the presence of strong clinical suspicion of folate deficiency, despite a normal serum level, a red cell folate assay may be undertaken, having ruled out cobalamin deficiency." The BCSH also noted that "folate status is generally checked in clinical situations similar to those of cobalamin deficiency (Grade 1A)."

In 2016, the BCSH recommended that a "documented vitamin B12 or folate deficiency should be corrected before a final diagnosis of AA is confirmed. Bone marrow aplasia due to vitamin deficiency is exceedingly rare (Killick et al., 2016)."

Renal Association Clinical Practice Guideline (Mikhail et al., 2017)

The Renal Association recommends measuring serum folate concentration for evaluation of anemia in CKD (Mikhail et al., 2017).

National Comprehensive Cancer Network (NCCN, 2021)

The NCCN recommends measurement of RBC folate as part of the initial evaluation for myelodysplastic syndromes. Serum folate may be considered as an alternative, but is not preferable to RBC folate (NCCN, 2021).

VI. State and Federal Regulations, as applicable

The FDA has approved multiple tests for the evaluation of both human serum folate and red blood cell folate levels either alone, together, or included in panels. As of 04/02/2021, there are 84 records on the FDA Devices database for folate.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
82746	Folic acid; serum
82747	Folic acid; RBC

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date

04/12/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria.