Anthem

Clinical UM Guideline

Subject: Red Blood Cell Folic Acid Testing
Guideline #: CG-LAB-15
Status: Reviewed

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Description

This document addresses the use of red blood cell (RBC) folic acid laboratory testing, also known as RBC folate. RBC folic acid measures the level of vitamin B_9, folate. RBC folic acid no longer meets the standard of care in evaluating an individual's folate levels because serum folate is a more accurate and reliable measurement of folate levels.

Clinical Indications

Not Medically Necessary:

RBC folic acid testing is considered **not medically necessary** in all cases.

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 are Not Medically Necessary:

CPT

82747	Folic acid; RBC

ICD-10 Diagnosis

	All diagnoses

Discussion/General Information

Vitamin B_9 exists in several forms, naturally as various forms of folate or in a synthetic form as folic acid. Folate is a water-soluble vitamin found in a variety of foods including green, leafy vegetables, fruits, cereals and grains, nuts, and meats. Deficiencies are linked to neural tube defects in infants and megaloblastic anemia and increased concentrations of homocysteine (Joelson, 2007). Humans are unable to synthesize folate and depend on dietary sources of folate or folic acid. Folate deficiency is very sensitive to dietary intake and responds well to treatment (Aslinia, 2006). Since the United States mandated fortification of processed grains with folic acid in 1998, the rate of folate deficiency has become a "rare event" (Joelson, 2007). The prevalence of very low or deficient serum folate levels, defined as < 3 µg/L (< 7 nM), prior to the fortification program was as high as 18.3% (De Bruyn, 2014). Following mandated fortification, deficit rates fell to 0.056% to 0.2% (Ashraf, 2008; De Bruyn, 2014; Theisen-Toupal, 2014).

In the past, microbiological assays were used to measure folate status in clinical settings. Competitive folate protein binding assays have largely replaced the microbiological assays as they are less expensive and easier to use. However, assays for measuring RBC folate levels have been unreliable and results vary widely based on the test used (Aslinia, 2006; Shane, 2011). The assays to measure folate levels are competitive protein binding assays using a folate binding protein such as *β-lactoglobulin* (Gilfix, 2014). These assays have limitations because various forms of folate bind with the folate binding proteins with varying affinities. This results in lower concentrations being reported compared to results obtained from microbiological assays. The interpretation of these results against the recognized ranges and cutoffs is problematic, as the guidelines addressing folate status adequacy ranges and cutoffs were developed using microbiological assays with *L. casei* (Gilfix, 2014; Shane, 2011). Approximately 95% of folate is located within RBCs. While RBC folate should theoretically be more stable and less susceptible to rapid changes in dietary intake, these assays have large imprecisions that limit their usefulness (Gilfix, 2014). Low RBC folate levels have been documented in several conditions including alcohol use, pregnancy, vitamin B_{12} deficiency and in anticonvulsant medication usage (Aslinia, 2006).

De Bruyn and associates (2014) examined the relationships between serum/RBC folate with other parameters (for example vitamin B_{12} and homocysteine). The authors also examined the use of RBC folate to detect folate deficiency. The overall goal of the study was to determine the most appropriate method to diagnose folate deficiency, determine specific abnormal serum folate concentration levels and whether serum folate is an accurate measure of folate body stores. Retrospective samples for serum folate (n=63,113) and RBC folate (n=18,115) were analyzed as well as serum vitamin B_{12}, homocysteine and RBC values (count, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) when available. There was a positive correlation between serum and RBC folate, showing that the use of both tests is redundant. The authors list the drawbacks of RBC folate testing noting:

> Assays for RBC folate are far from standardized and include manual sample pretreatments, implying possible sources of errors: incomplete hemolysis, suboptimal hydrolysis of folylpolyglutamate, binding of folate to hemoglobin, folate degradation, hemoglobin denaturation or folate trapping in the case of vitamin B12 deficiencies.

Multiple studies have reported that RBC folate levels do not provide any additional relevant information over that provided by serum folate levels (Farrell, 2013; Galloway, 2003; Gilfix, 2014).

Definitions

Red Blood Cell Folic Acid: Laboratory measurement that reflects folate body stores and turnover during the preceding 3-4 months. Low RBC values are a later indication of low or declining folate levels in the body.

Serum Folate: Laboratory measurement that reflects current folate intake/balance. Low serum folate values are an early indication of low or declining folate levels in the body.

References

Peer Reviewed Publications:

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2. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 2006; 4(3):236-241.
3. Breu AC, Theisen-Toupal J, Feldman LS. Serum and red blood cell folate testing on hospitalized patients. J Hosp Med. 2015; 10(11):753-755.
4. De Bruyn E, Gulbis B, Cotton F. Serum and red blood cell folate testing for folate deficiency: new features? Eur J Haematol. 2014; 92(4):354-359.
5. Farrell CJ, Kirsch SH, Herrmann M. Red cell or serum folate: what to do in clinical practice? Clin Chem Lab Med. 2013; 51(3):555-569.
6. Galloway M, Rushworth L. Red cell or serum folate? Results from the National Pathology Alliance benchmarking review. J Clin Pathol. 2003; 56(12):924-926.
7. Gilfix BM. Utility of measuring serum or red blood cell folate in the era of folate fortification of flour. Clin Biochem. 2014; 47(7-8):533-538.
8. Joelson DW, Fiebig EW, Wu AH. Diminished need for folate measurements among indigent populations in the post folic acid supplementation era. Arch Pathol Lab Med. 2007; 131(3):477-480.
9. Shane B. Folate status assessment history: implications for measurement of biomarkers in NHANES. Am J Clin Nutr. 2011; 94(1):337S-342S.
10. Theisen-Toupal J, Horowitz G, Breu A. Low yield of outpatient serum folate testing: eleven years of experience. JAMA Intern Med. 2014; 174(10):1696-1697.
11. Wu AH. Folate testing: time to retire your VCR. JAMA Intern Med. 2014; 174(10):1697-1698.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Folate Testing: A Review of the Diagnostic Accuracy, Clinical Utility, Cost-Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Jul 23. Available at: https://www.ncbi.nlm.nih.gov/books/NBK310976/. Accessed on August 28, 2023.

Websites for Additional Information

1. National Institute of Health (NIH). Office of Dietary Supplements. Folate. Updated November 1, 2022. Available at: https://ods.od.nih.gov/factsheets/Folate-Consumer/. Accessed on August 28, 2023.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Discussion and References section.
Reviewed	11/10/2022	MPTAC review. Updated References section.
Reviewed	11/11/2021	MPTAC review. Updated Discussion and References section.
New	11/05/2020	MPTAC review. Initial document development.
