



Red Blood Cell Folate Testing for Clinicians

SYNOPSIS AND RELEVANCE

Testing of serum folate levels is the preferred method for detecting nutritional folate deficiency. Adherence to using serum folate levels for this purpose can:

1. Ensure that serum folate testing is a first line test for detecting folate deficiency.
2. Reduce the utilization of less useful markers of folate deficiency like the red blood cell (RBC) folate test.
3. Impact patient care by ensuring that the most clinically useful tests are used to diagnose folate deficiency.

INSIGHTS

1. Folate deficiency is relatively rare in the United States because of widespread supplementation of foods with folate.
2. Serum folate levels are preferred over RBC folate for assessing the folate status of patients.

BACKGROUND

Folate levels are frequently performed on patients with suspected nutritional deficiency or anemia, in particular, macrocytic anemias. Concerns over the relationships between folate deficiency and neural tube defects led to a Food and Drug Administration (FDA) mandate to fortify foods with folic acid in the 1990s. Folate deficiency is suspected in patients with reduced hemoglobin and hematocrit who have an elevated mean cell volume (MCV). Folate levels can be measured in serum and in erythrocytes (RBC folate). Approximately 95% of folate is located within erythrocytes, so historically, RBC folate has been thought to better assess longer-term folate storage, whereas serum folate levels may reflect more recent dietary folate intake. While RBC folate levels may better estimate longer-term storage levels, RBC levels generally add no diagnostic value to a serum folate level in detecting folate deficiency. Vitamin B12 levels should also be tested in patients with a megaloblastic anemia because folic acid supplements may correct the hematologic changes in B12 deficiency but do not halt the progression of neurologic disease.

Folate levels are typically measured by a sensitive competitive binding protein assay, however, folate results can vary between laboratories depending on the test system and methodology used. One reason serum folate levels are preferred is that RBC folate levels demonstrate higher analytical variation than serum folate levels because of the additional pre-treatment steps (ie, red cell lysis to release folate) needed to perform the RBC folate test. Many laboratories send out RBC folate tests because of these technical issues. MTHFR mutations may also alter the distribution of folate in red cells and may cause further analytic variability using the RBC technique. RBC folate levels may also be affected by RBC oxygen saturation and hemoglobin content.

Furthermore, a number of studies have demonstrated that RBC and serum folate testing provide equivalent data and that RBC folate testing is not necessary. Thus, routine testing of both serum and RBC folate is discouraged. Serum folate levels are much more widely performed by laboratories of all sizes, whereas RBC folate testing is referred to outside laboratories in most cases. Widespread folic acid supplementation has dramatically reduced the incidence of folate deficiency in the United States, further calling into question the utility of folate testing in general. For patients who are supplemented with folate, serum levels may better reflect responses to folate therapy. Other than rare, unusual circumstances, such as suspicion of a hereditary folate-related enzyme or transport protein deficiency, there are no additional indications for RBC folate testing outside of those for serum folate testing.

The routine use of serum folate levels to detect nutritional folate deficiency may increase the value of this testing for providers and patients by:

- Establishing an accurate and timely diagnosis of patients with nutritional folate deficiencies.
- Improving the performance of the diagnostic strategy used at your institution to detect folate deficiency.
- Facilitating the evaluation of patients with folate deficiency for your health care professionals in a collaborative manner.
- Enhancing the training and education of providers who routinely test patients for folate vitamin deficiencies.

- Ensuring that your health information technology services support the decision making of health care providers who utilize nutritional folate testing by optimizing the electronic test ordering and laboratory test resulting systems.
- Impacting the volume of patients being evaluated correctly for folate deficiencies.

REFERENCES

1. Baron JM, Dighe AS. The role of informatics and decision support in utilization management. *Clinica Chimica Acta*. 2014;427:196-201. doi:10.1016/j.cca.2013.09.027
2. De Bruyn E, Gulbis B, Cotton F. Serum and red blood cell folate testing for folate deficiency: new features? *Eur J Haematol*. 2013; 92:354-359. doi:10.1111/ejh.12237
3. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol*. 2014;166(4):496-513.
4. 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. doi:10.1515/cclm-2012-0639
5. 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. doi:10.1136/jcp.56.12.924
6. Gudgeon P, Cavalcanti R. Folate testing in hospital inpatients. *Am J Med*. 2015; 128:56-59.
7. Ismail O, Chin-Yee I, Gob A, et al. Reducing red blood cell folate testing: a case study in utilisation management. *BMJ Open Quality*. 2019;8:e000531. doi:10.1136/bmjopen-2018-000531
8. Jaffe JP, Schilling RF. Erythrocyte folate levels: a clinical study. *Am J Hematol*. 1991; 36(2):116-121. doi: 10.1002/ajh.2830360210
9. Joelson DW, Fiebig EW, Wu AHB. Diminished need for folate measurements among indigent populations in the post folic acid supplementation era. *Arch Pathol Lab Med*. 2007;131(3):477-480. doi:10.1043/1543-2165(2007)131[477:DNFFMA]2.0.CO;2
10. MacMillan TE, Gudgeon P, Yip PM, Cavalcanti RB. Reduction in unnecessary red blood cell folate testing by restricting computerized physician order entry in the electronic health record. *Am J Med*. 2018; 131:939-944. doi: 10.1016/j.amjmed.2018.03.044
11. McDowell MA, Lacher DA, Pfeiffer CM, et al. Blood folate levels: the latest HANES results. NCHS data brief number 6, May 2008. Center for Disease Control. Page reviewed November 26, 2015. Accessed May 2, 2023. <https://www.cdc.gov/nchs/products/databriefs/db06.htm>
12. Owen WE, Roberts WL. Comparison of five automated serum and whole blood folate assays. *Am J Clin Pathol*. 2003; 120(1):121-126. doi:10.1309/L2U6-HH5K-AYG4-8L40
13. Pillay TS, Oosthuizen NM. Why are we still measuring red cell folate instead of just serum folate? *J Clin Pathol*. 2014; 67(4):289. doi:10.1136/jclinpath-2013-202086
14. Robinson AR, Mladenovic J. Lack of clinical utility of folate levels in the evaluation of macrocytosis or anemia. *Am J Med*. 2001; 110(2):88-90. doi:10.1016/s0002-9343(00)00670-7
15. 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. doi:10.1001/jamainternmed.2014.3593