

CADTH Health Technology Review

Folate Testing in People With Suspected Folate Deficiency

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Key Messages

- No relevant literature was identified regarding the diagnostic test accuracy, clinical utility, and cost-effectiveness of serum folate testing in people with suspected folate deficiency.
- Additionally, no evidence-based guidelines were identified regarding the use of serum folate testing in people with suspected folate deficiency.

Context and Policy Issues

Folate, also called vitamin B9, is a water-soluble vitamin and 1 of the essential vitamins required for synthesizing nucleic acids and methionine.¹ It is present in foods as folate and in supplements as folic acid.¹ The term *folate* encompasses different active forms of the vitamin.² Circulating folate in the serum is mainly 5-methyltetrahydrofolate (82% to 93%).² Other forms of folate exist, depending on dietary supplementation and food fortification, such as pteroylglutamic acid, 5-formyltetrahydrofolate, tetrahydrofolate, and unmetabolized folic acid.^{3,4}

Folate deficiency due to low intake or poor absorption is associated with neural tube birth defects during pregnancy and macrocytic anemia.¹ Folate deficiency has also been implicated in the development of various conditions, including cognitive impairment and dementia, cardiovascular disease, and colon cancer.¹ The 1998 mandatory folic acid fortification of flour and grain products in Canada and the US at a rate of 150 mcg folic acid/100 g has significantly reduced the prevalence of folate deficiency in the general population from as high as 38% to less than 1% and has been linked to a more than 50% reduction in neural tube defects in newborns.^{5,6} A recent cross-sectional study⁷ that examined the association between macrocytosis and folate deficiency in a population of 46,827 individuals in Calgary, Alberta, found that only 0.2% of individuals were considered folate-deficient (cut off value of < 6 nmol/L), and macrocytosis was not a useful marker for folate deficiency.

Despite the low prevalence of folate deficiency in Canada and the US, serum folate tests continue to be routinely ordered in the assessment of macrocytic anemia or cognitive abnormalities.^{8,9} However, evidence has shown that serum folate tests in both outpatient and inpatient populations provide low yield in detecting folate deficiency and are associated with significantly high cost and charges per deficient result.⁸⁻¹⁰ This has led to the suggestion that serum folate tests should not be routinely ordered, even in patients with macrocytic anemia.¹¹ A previous CADTH report¹² found no evidence for the diagnostic accuracy of folate testing, no literature regarding the cost-effectiveness of folate testing, and insufficient evidence to support the clinical utility of folate testing in patients at risk of folate deficiency. Also in that report, evidence-based guidelines were identified that recommend folate status be tested in specific clinical populations with clear associations with folate deficiency.¹²

The objective of this report is to summarize the evidence regarding the diagnostic test accuracy, clinical utility, and cost-effectiveness of serum folate testing in people with suspected folate deficiency. This report also aims to summarize the recommendations from evidence-based guidelines regarding the use of serum folate testing in people with suspected folate deficiency.

Research Questions

1. What is the diagnostic accuracy of serum folate testing for the diagnosis of folate deficiency in people with suspected folate deficiency?
2. What is the clinical utility of serum folate testing in people with suspected folate deficiency?
3. What is the cost-effectiveness of serum folate testing in people with suspected folate deficiency?
4. What are the evidence-based guidelines regarding the use of serum folate testing in people with suspected folate deficiency?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were folate deficiency AND testing. No filters were applied to limit the retrieval by study type. If possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2012, and February 15, 2022.

Selection Criteria and Methods

One reviewer screened citations and selected studies. Titles and abstracts were reviewed in the first screening level, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	People of all ages with suspected folate deficiency (e.g., presence of unexplained anemia or macrocytosis, or due to variables such as age, diet, family and medical history, or lifestyle)
Intervention	Serum folate testing
Comparator	Q1: No comparator Q2 and Q3: No testing for folate deficiency Q4: Not applicable

Criteria	Description
Outcomes	<p>Q1: Diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value)</p> <p>Q2: Clinical utility (e.g., time to treatment, the severity of symptoms [e.g., fatigue, headaches, heart palpitations], quality of life, neurodevelopmental abnormalities, fetal and neonatal health, adverse events)</p> <p>Q3: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained)</p> <p>Q4: Recommendations regarding best practices (e.g., appropriate patient populations, recommended testing strategies)</p>
Study designs	HTAs, SRs, RCTs, non-randomized studies, economic evaluations, and guidelines

HTA = health technology assessment; Q = question; RCT = randomized controlled trial; SR = systematic review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2012. Studies included in the previous 2015 CADTH report¹² were excluded. Guidelines with unclear methodology were also excluded.

Summary of Evidence

Quantity of Research Available

A total of 683 citations were identified in the literature search. Following the screening of titles and abstracts, 664 citations were excluded, and 19 potentially relevant reports from the electronic search were retrieved for full-text review. Twelve potentially relevant publications were retrieved from the grey literature search for full-text review. None of these 31 potentially relevant articles met the inclusion criteria and were excluded from this report for various reasons. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹³ flow chart of the study selection. Additional references of potential interest are provided in Appendix 2.

Summary of Findings

No relevant literature or evidence-based guidelines were identified regarding the diagnostic test accuracy, clinical utility, cost-effectiveness, or recommendations for serum folate testing in people with suspected folate deficiency; therefore, no summary can be provided.

Limitations

No potential limitations were identified as the literature search was extended up to 10 years.

Conclusions and Implications for Decision- or Policy-Making

Conclusions could not be drawn regarding the clinical effectiveness, cost-effectiveness, and recommendations for serum folate testing in people with suspected folate deficiency because no relevant literature was identified to answer the research questions.

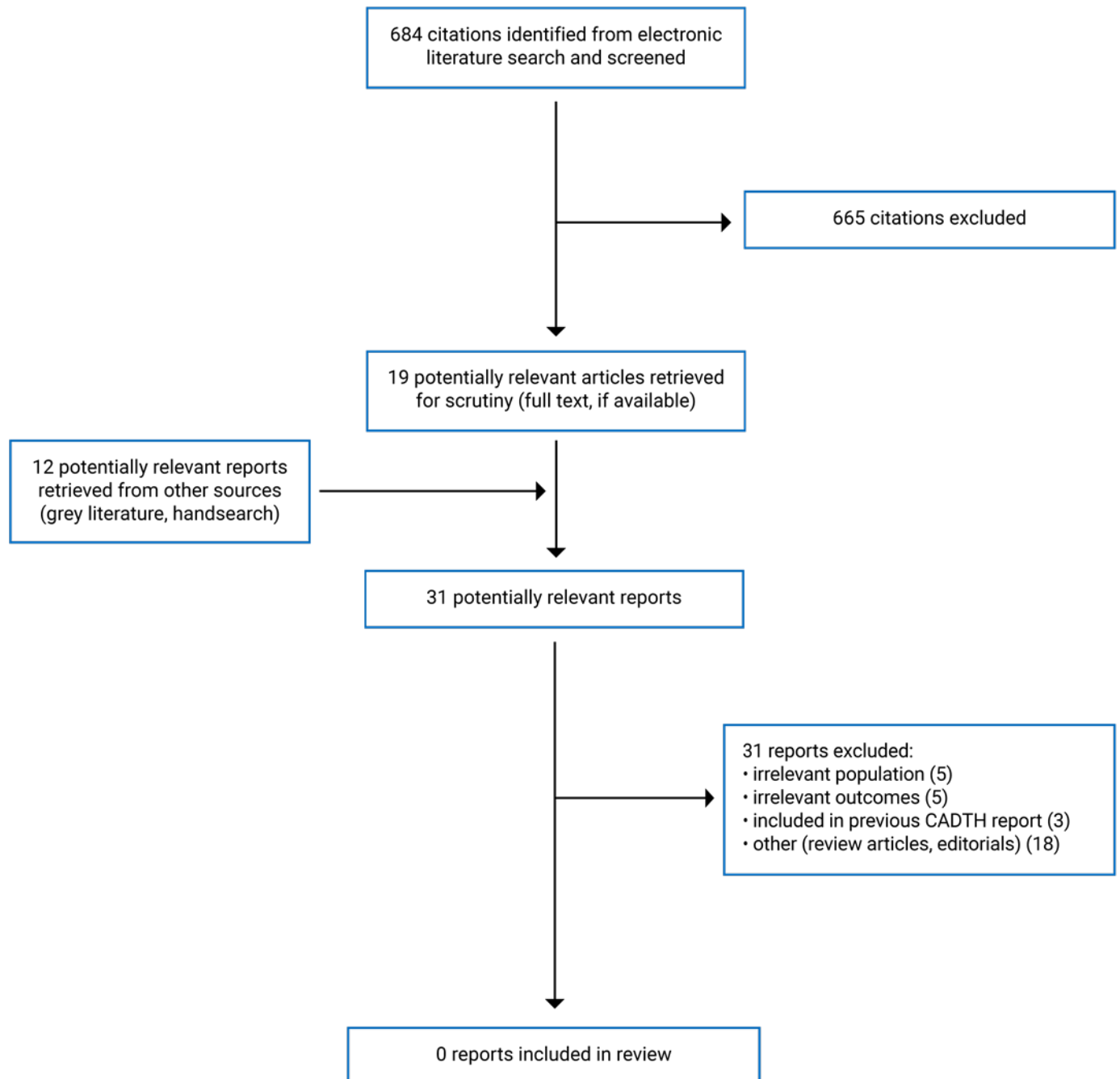
Research examining the clinical utility and cost-effectiveness of serum folate testing in people with suspected folate deficiency is needed to investigate whether the test remains effective in the era of folic acid fortification diet. The absence of this evidence precludes the creation of new guidelines for folate testing to provide high-value patient care.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: References of Potential Interest

Previous CADTH Reports

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