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Vitamin B₁₂ and folate tests: the ongoing need to determine appropriate use and public funding.

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Introduction

Criteria have been developed for assessing the safety, effectiveness and cost-effectiveness of *new* and *emerging* health interventions. Additional challenges exist in identifying opportunities for reducing the use of *existing* health technologies or procedures that are potentially overused, (cost-) ineffective or unsafe.(1) Criteria have been proposed to ‘flag’ technologies that might warrant further investigation under quality improvement programs.(1) These criteria are: new evidence, geographic variations in use; provider variations in care; technology development; temporal variations in volume; public interest or controversy; consultation; assess new intervention and displace old; leakage; legacy items; use not in accordance with clinical guidelines; or nomination from clinical groups. Following such a nomination by members of the clinical laboratory community regarding B₁₂ and folate tests, we sought to determine if these tests met other criteria. This article intends to encourage debate and discussion around the appropriate use of these tests.

Diagnosing vitamin B₁₂ and/or folate deficiencies is difficult. There are diverse symptoms (such as malaise, fatigue, and neurological symptoms) and signs (including megaloblastic anaemia and cognitive impairments). Defining target ‘conditions’ is therefore difficult. Tests include full blood count and blood film examination, serum B₁₂, serum folate, and red cell folate (RCF) assays, as well as examination of metabolic markers such as methylmalonic acid (MMA) and homocysteine (Hcy). Untreated B₁₂ deficiencies may cause serious health problems, including permanent

neurological damage (which may occur with low serum B₁₂ without haematological changes). Maternal folate deficiencies have been associated with neural tube defects in infants. Potential B₁₂ or folate deficiencies therefore need to be appropriately investigated and managed.

The utility of a diagnostic test is influenced in part by its precision (the ability of a test to faithfully reproduce its own result) and its diagnostic accuracy (ability to discriminate between a target condition and health). Evidence (as outlined below) suggests serum B₁₂ tests have poor discriminative ability in many situations, while the most useful folate investigation remains debated.

The only systematic review and meta-analysis of the diagnostic accuracy of serum B₁₂ tests (conducted by members of our group) suggests these tests often misclassify individuals as either B₁₂ deficient or B₁₂ replete.⁽²⁾ These findings are consistent with other reports in the literature, such as noted by Stabler who state “...false negative and false positive values are common (occurring in up to 50% of tests) with the use of the laboratory reported lower limit of the normal range as a cutoff point for deficiency”.⁽³⁾ Stabler also comments that there ‘...is often poor agreement when samples are assayed by different laboratories or with the use of different methods’.⁽³⁾ Carmel notes “widespread CBLA [competitive-binding luminescence assay] malfunction”, with assay failure rates of 22% to 35% (interference due to intrinsic factor antibodies may explain some of this variation).⁽⁴⁾ While Carmel suggests that “falsely normal cobalamin concentrations are infrequent in patients with clinically expressed deficiency”, he notes challenges in diagnosing ‘subclinical deficiency’ (mild metabolic abnormalities without clinical signs or symptoms).⁽⁵⁾ Assessing this

evidence base is complicated by a lack of a universally accepted gold standard, difficult to define target conditions and variable clinical presentations, and variable cut-off values used to define deficiency.

For investigating folate status, RCF assays are thought to be less susceptible to short term dietary intake than are assays for serum folate. However according to Galloway and Rushworth the RCF assay “is more complex to perform than the serum folate assay and requires more steps in sample handling before analysis, and this may be one of the reasons why the precision of the [RCF] assay is less than that of the serum folate assay”.(6)

As discussion continues over which folate test is preferable, new evidence relating to the prevalence of folate deficiencies in countries with mandatory food fortification has shifted the focus toward the need to perform any folate investigations in these jurisdictions. In Australia, prevalence estimates from a sample of inpatients and outpatients suggest folate deficiency now stands at 0.5%, an 85% reduction in absolute numbers from April 2009.(7) While there is currently no evidence to suggest that the prevalence of folate deficient megaloblastic anaemia has been reduced, the low frequency of low serum RCF test results in folate fortified countries supports the perspective that there is “no longer any justification in ordering folate assays to evaluate the folate status of patients”.(8)

Another proposed ‘flag’ for quality improvement occurs when older technologies become superseded by more effective methods.(1) For example, over time multiple technologies for analysing vitamin B₁₂ status have become available, including assays

for measuring holotranscobalamin (HoloTC- bioavailable B₁₂), as well as metabolic markers such as MMA and Hcy. However, like all tests, these are imperfect: HoloTC is expensive, not routinely available, itself reliant on poorly defined serum B₁₂ reference ranges, and yet to be confirmed as a superior test than the serum B₁₂ assay. Hcy measurement is subject to artefactual increases due to collection practices, and variable reference ranges. The availability of MMA tests is restricted to some clinical and research laboratories. As a result, the optimal procedure for measuring B₁₂ is unclear. As previously noted, while a number of approaches exist for assessing folate status (including RCF and serum assays), there is currently no consensus on the most appropriate laboratory investigation process.

Australian Medicare utilisation data demonstrate substantial growth in the use of item number 66602, which relates to the combined use of serum B₁₂ and folate tests. Between financial years 2000/2001 to 2010/2011, use increased from 1,082 services per 100,000 population to 7,243 services per 100,000 population (21.78% average annual growth rate).(9) Over the same period, spending on pathology services overall grew at an average annual rate of 6.3%.

Geographic variation is also present, with reimbursement for item 66602 ranging from 2,329 per 100,000 population (Northern Territory) to 8,561 per 100,000 population (New South Wales).(9) While some of this variation may be due to demographic differences and traditionally under-serviced populations (e.g. Indigenous Australians), the substantial differences in temporal and geographic use serves to raise more questions about appropriate use of these tests, and whether or not under or over use is present.

Available guidelines related to the use of vitamin B₁₂ and folate tests also vary widely in their recommendations. While some recommend B₁₂ and folate tests as screening tools in commonly encountered illnesses such as dementia, others suggest restricting testing to patients who have already undergone pre-test investigations (such as full blood examinations; however we note that neurological damage may occur in patients with low serum B₁₂ levels and without haematological changes).(10, 11) Guidelines may differ on key recommendations, such as the preferred first line investigation for establishing folate status, while others question the utility of folate investigations at all in folate fortified jurisdictions.(12-14)

With wide variability in guideline recommendations, and with few appearing to consider the diagnostic accuracy of B₁₂ or folate tests, determining the extent to which services have ‘leaked’ beyond their clinical indications is difficult; however an example of possible leakage is available. Bayram et al. note that use of serum B₁₂ tests in patients presenting with weakness and tiredness is not supported by any available guidelines.(15) Despite this, a large study of general practitioners indicates that from 2002-2008, their use of serum B₁₂ tests in patients presenting with weakness and tiredness increased by 105%.(15)

Discussion

Tests for investigating the status of vitamin B₁₂ and folate levels have become widely used in clinical practice. Yet existing evidence suggests that the diagnostic accuracy of serum B₁₂ tests is difficult to determine and may be highly variable. While other tests are available for investigating B₁₂ and/or folate deficiency (such as HoloTC, MMA and Hcy), the diagnostic accuracy of these tests is also contested. Challenges

in examining the diagnostic accuracy of serum B₁₂ tests include highly variable clinical presentations, lack of a gold standard and inconsistent cut-off values used to define deficiency. While the most useful test for investigating folate status remains debated (serum or RCF), mandatory folate fortification in Australia may question the ongoing use of these tests at all.

Temporal variation in use and geographic differences in how these tests are employed are both evident in Australian data. Moreover, available clinical guidelines are highly inconsistent in their recommendations. Collectively, the issues of test accuracy, wide variability in test use, and inconsistent guideline recommendations suggest that the use of vitamin B₁₂ and folate tests is an area with much scope for quality improvement.

To improve the use of these tests, further assessment is needed that examines the complexity associated with clinical decision making, and the various factors influencing why doctors request these tests. The decision to request an investigation such as a B₁₂ or folate test may be driven by a range of factors, including ease of use, cost, absence of significant patient risk, the perceived need to respond to patient requests, lack of appreciation of the diagnostic accuracy of the tests, or ready availability of results.⁽¹⁶⁾ Understanding how these factors influence the use of B₁₂ and folate tests may be best acquired through direct consultation with key stakeholder groups such as general practitioners, pathologists, specialists and consumers, and is a critical step in advancing the assessment of these tests.

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