National Institute for Health and Care Excellence

Final

Vitamin B12 deficiency in over 16s: diagnosis and management

[D] Evidence review for tests for identifying cause

NICE guideline NG239

Evidence reviews underpinning recommendations 1.4.1 to 1.4.6 and recommendations for research in the NICE guideline

March 2024

Final

Developed by NICE

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ISBN: 978-1-4731-5732-3

Contents

1.1 Review question

What is the diagnostic accuracy of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy), alone or in combination, for identifying the cause of vitamin B12 deficiency?

1.1.1 Introduction

Vitamin B12 deficiency has a variety of causes, and these causes can also co-exist. Causes include those related to malabsorption (such as autoimmune gastritis or gastric surgery), diet, and recreational use of nitrous oxide with air (gas and air).

It is important to identify the cause of vitamin B12 deficiency because different causes of deficiency are managed in different ways. The consequences of not identifying malabsorption conditions in people with B12 deficiency can be severe, including irreversible neurological damage and pernicious anaemia.

Different tests have varying degrees of sensitivity and specificity for identifying the cause of vitamin B12 deficiency. It is not known which tests lead to the best outcomes for patients. This review seeks to determine the best way of identifying the cause of vitamin B12 deficiency.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Young people and adults with diagnosed vitamin B12 deficiency
Target condition	Vitamin B12 deficiency
Index tests	The following as stand-alone tests, in combination or as staged tests: • Serum intrinsic factor antibody (PA) • Gastric parietal cell antibody (PA) • Gastroscopy with biopsy (PA) • Colonoscopy (terminal ileal disease) • Blood tests for coeliac disease • Pepsinogen (PA) • Gastrin (PA) • Faecal elastase (chronic pancreatitis) • Cobasorb (PA)
Reference standard	Clinical diagnosis (based on combination of tests and clinical judgement)
Statistical measures	• Sensitivity (50%) • Specificity (70%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives). • Predictive values • Likelihood ratios
Study design	• Cross-sectional studies • Diagnostic accuracy observational cohort studies • Systematic reviews of the above

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

Four prospective diagnostic accuracy cohort studies were included in the review.[1-3, 5] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3. The assessment of the evidence quality was conducted with emphasis on test specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as 50% sensitivity and 70% specificity, above which a test would be recommended and 20% sensitivity and 40% specificity below which a test is deemed to be of no clinical use.

Evidence was available from single studies for endoscopic evaluation, intrinsic factor antibody and from two studies for serum gastrin. All but one study applied these tests to diagnose pernicious anaemia in people with vitamin B12 deficiency, with the endoscopic evaluation used to determine the presence of coeliac disease.

No relevant diagnostic test accuracy studies of gastric parietal cell antibody, colonoscopy, blood tests for coeliac disease, pepsinogen, faecal elastase or Cobasorb in people under investigation for cause of vitamin B12 deficiency were identified. Additionally, no studies used a combination of tests as the index test.

See also the study selection flow chart in Appendix C and study evidence tables in Appendix D.

Due to the difficulty in diagnosing the cause of vitamin B12 deficiency, the reference standard for this review was clinical diagnosis based on combination of tests and clinical judgement. As a result, there were several different tests applied as reference standards in the included studies. The Schilling Test was used as a reference standard in two studies, with endoscopic biopsy and parietal cell antibodies acting as the reference standard in a single study each.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the diagnostic evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Akay 2020 [1]	Patients (n=50) with B12 and iron deficiency anaemia referred for upper gastrointestinal endoscopy	Coeliac disease	Endoscopic evaluation (white light endoscopy and magnified	Clinical diagnosis confirmed by biopsy	Country: Turkey

Study	Population	Target condition	Index test	Reference standard	Comments
	Age, mean (SD): 41±11 (20-67) years Gender (male to female ratio): 10:40 Ethnicity: Not reported		flexible spectral imaging colour enhancement (FICE) imaging (reported as two separate index test)		
Ingram 1998 [2]	Patients (n=77) presenting with megaloblastic anaemia No demographic information reported	Pernicious anaemia	Intrinsic factor antibody	Schilling test	Country: South Africa
Miller 1989 [3]	Patients (n=71) who had low B12 determined at the request of a ward or outpatient physician Age: median 62 (20-92) years Gender: >90% were male Ethnicity: not reported	Pernicious anaemia	Serum gastrin (cut-off: 200 pg/mL)	Schilling test	Country: USA
Ness-Abram of 2006 [5]	Patients (n=23) being treated in an outpatient endocrine clinic Age, mean (SD): 47±15 (14-78) years Gender (male to female ratio): 7:108	Pernicious anaemia	Parietal cell antibodies	Gastroscopy	Country: Israel

See Appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on test specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as 50% for sensitivity and 70% for specificity, above which a test would be recommended and 20% sensitivity and 40% specificity below which a test is of no clinical use. These thresholds are lower than those set for tests for diagnosing deficiency because the committee were aware that the sensitivity and specificity of the available tests for cause is generally low. The committee were concerned that setting

higher thresholds for defining a positive outcome would prevent them from recommending any of the tests, which may still have clinical use despite having low accuracy.

Table 3: Clinical evidence summary: diagnostic test accuracy for tests to determine the cause of vitamin B12 deficiency

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Endoscopic evaluation (FICE imaging) for diagnosis of coeliac disease in patients with vitamin B12 deficiency							
1 prospective cohort study	50	Very serious[1]	Not serious	Serious[2]	Serious[3]	Sensitivity= 60% (95%CI 26-88)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Not serious	Specificity= 100% (95%CI 91-100)	VERY LOW
Endoscopic evaluation (white light endoscopy) for diagnosis of coeliac disease in patients with vitamin B12 deficiency							
1 prospective cohort study	50	Very serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 100% (95%CI 69-100)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Not serious	Specificity= 100% (95%CI 91-100)	VERY LOW
Intrinsic factor antibodies for diagnosis of pernicious anaemia in patients with vitamin B12 deficiency							
1 prospective cohort study	77	Serious[1]	Not Serious	Not serious	Not serious	Sensitivity= 90% (95%CI 80-96)	MODERATE
		Serious[1]	Not serious	Not serious	Very serious[4]	Specificity= 56% (95%CI 21-86)	VERY LOW
Serum gastrin (>200 pg/mL) for diagnosis of pernicious anaemia in patients with vitamin B12 deficiency							
1 prospective cohort study	71	Very serious[1]	Not serious	Serious[5]	Not serious	Sensitivity= 90% (95%CI 68-99)	VERY LOW
		Very serious[1]	Not serious	Serious[5]	Serious[6]	Specificity= 82% (95%CI 69-92)	VERY LOW
Parietal cell antibodies for diagnosis of pernicious anaemia in patients with vitamin B12 deficiency							
1 prospective cohort study	7	Very serious[1]	Not serious	Not serious	Serious[3]	Sensitivity= 83% (95%CI 36-100)	VERY LOW
		Very serious[1]	Not serious	Not serious	Very serious[4]	Specificity= 0% (95%CI 0-97)	VERY LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[2] Downgraded by one increment due to indirectness of the index test

[3] Confidence interval cross the decision threshold for 'high sensitivity' (50%)

[4] Confidence interval crossed the decision threshold for both 'low specificity' (40%) and 'high specificity' (70%)

[5] Downgraded by one increment due to indirectness of the reference standard

[6] Confidence interval cross the decision threshold for 'high specificity' (70%)

1.1.7 Economic evidence

There was no economic evidence identified relevant to the review question.

1.2 Review question

What is the clinical and cost effectiveness of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy) for identifying the cause of vitamin B12 deficiency?

1.2.1 Introduction

See section 1.1.1.

1.2.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 4: PICO characteristics of review question

Population	Adults with diagnosed vitamin B12 deficiency.
Interventions	The following as stand-alone tests or in combination: • Serum intrinsic factor antibody (PA) • Gastric parietal cell antibody (PA) • Gastroscopy with biopsy (PA) • Colonoscopy (terminal ileal disease) • Blood tests for coeliac disease • Pepsinogen (PA) • Gastrin (PA) • Faecal elastase (chronic pancreatitis) • Cobasorb (PA) Tests must be followed by appropriate treatment
Comparison	• All tests and combinations of tests compared with each other • No test (treatment only)
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Quality of life (such as EQ5D, SF36) • Patient-reported outcomes (PROM scores including some/all symptoms): - Fatigue - Sleep - Peripheral neuropathy - Cognition - Psychiatric symptoms - Pain • Haematological values • Complications and adverse events (condition related): - Mortality - Self-harm - Nerve damage - Frailty/falls - Severe cognitive effects - Postural hypotension • Complications and adverse events (procedure related): - Bleeding - Perforation - Aspiration • Patient concern around unexpected lab results (health anxiety score)

	• Incorrect/delayed diagnosis • Inappropriate additional tests • Adherence to treatment • Education/work absence Time point: any time point available
Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified

1.2.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.4 Effectiveness evidence

1.2.4.1 Included studies

No relevant clinical studies comparing serum intrinsic factor antibody, gastric parietal cell antibody, gastroscopy with biopsy, colonoscopy, blood tests for coeliac disease, pepsinogen, gastrin, faecal elastase or Cobasorb, with subsequent appropriate treatment, with each other were identified.

See also the study selection flow chart in Appendix C.

1.2.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.2.5 Summary of studies included in the effectiveness evidence

No evidence identified.

1.2.6 Summary of the effectiveness evidence

No evidence identified.

1.2.7 Economic evidence

1.2.7.1 Included studies

No health economic studies were included.

1.2.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.2.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 5: Investigation costs

Resource	Unit costs	Source
Diagnostic Colonoscopy, 19 years and over (FE32Z)	£920	National schedule of NHS costs FY 2020-2021
Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over (FE22Z)	£754	National schedule of NHS costs FY 2020-2021
Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over	£866	National schedule of NHS costs FY 2020-2021
Diagnostic, Upper Gastrointestinal Tract Endoscopic Procedure with Colonoscopy, 19 years and over (FE42Z)	£1,146	National schedule of NHS costs FY 2020-2021
Intrinsic factor antibody test	£16.94	Committee members' (average)
Gastric parietal cell antibody test	£10.21	Committee members' (average)

1.3 The committee's discussion and interpretation of the evidence

1.3.1. The outcomes that matter most

Sensitivity and specificity were identified by the committee as the most important diagnostic accuracy measures during the protocol writing process. When seeking to diagnose the cause of B12 deficiency, specificity was deemed to be more important than sensitivity which was reflected in the decision thresholds of 0.7 and 0.5, respectively. The basis for this decision was that at this point in the pathway, vitamin B12 deficiency has already been diagnosed and the person will be receiving treatment, and it is more important that the cause of the deficiency is correctly identified for patient information as well as long term management decisions.

1.3.2 The quality of the evidence

The committee acknowledged the limited quality and number of studies included for all index tests included in the protocol. Evidence for all outcomes, except for one, were rated as very low quality. All four of the studies included in the evidence review were at serious or very serious risk of bias. In most cases, this was due to a lack of clarity as to how the participants were selected for the study and a lack of information on whether the index test and reference standards were interpreted in a blinded manner. Where very serious risk of bias was suspected, this was due to bias arising from the flow of participants through the study, with not all participants receiving the same reference standard, or not all participants being included in the final analysis.

No meta-analysis was possible as individual studies per index test were identified. Evidence was available for endoscopy, anti-intrinsic factor antibodies, gastrin, and parietal cell antibodies. The committee noted that the evidence for endoscopy was indirect due to being used to diagnose coeliac disease, rather than autoimmune gastritis (also known as pernicious anaemia), and therefore was of limited use.

No evidence was identified where colonoscopy, blood tests, pepsinogen, faecal elastase or CobaSorb, or combinations of tests, were used as the index test.

1.3.3 Benefits and harms

The committee considered the evidence identified whilst acknowledging the severe limitations in the quality and quantity of data.

Anti-intrinsic factor antibody was viewed as a useful and worthwhile test by the committee. From clinician experience, this test is among the most useful in diagnosing autoimmune gastritis (also known as pernicious anaemia), which was reflected in the clinical evidence with a sensitivity of 90% (95%CI: 80-96%, moderate quality). The specificity of 56% (95%CI: 21-86%), but this was very low quality evidence, and the committee consensus was that a positive anti-intrinsic factor antibody is strongly suggestive of autoimmune gastritis. The committee noted that the evidence for the anti-intrinsic factor antibody test was based on one study in which the prevalence of autoimmune gastritis was high, suggesting that the study population were people strongly suspected of having autoimmune gastritis.

The committee considered that most people with a confirmed deficiency would receive either oral or intramuscular vitamin B12 replacement. If their symptoms did not improve on oral treatment, then the committee recommend considering switching to intramuscular treatment. Therefore, testing for anti-intrinsic factor antibody may not alter the person's treatment. The committee also considered that using the test for everyone would be costly. For these reasons, the committee recommended that anti-intrinsic factor antibody should be considered when autoimmune gastritis is suspected, unless the person has already had a positive test or has had a total gastrectomy or complete terminal ileal resection. They noted that the test would not be useful when someone has already had a positive result as the results would not be different. Where the person has had an a total gastrectomy or complete terminal ileal resection, these procedures will prevent the body from absorbing B12 and will need vitamin B12 replacement. The committee agreed that it was important to test for autoimmune gastritis in pregnancy or during breastfeeding to ensure the health of the person and their baby. For this reason, they also agreed that intramuscular treatment should be started without waiting for test results.

The committee also agreed that a negative result does not necessarily rule out autoimmune gastritis. The lay members felt that a negative intrinsic factor antibody result often led to dismissal of autoimmune gastritis as a possible diagnosis. This interpretation can have severe consequences whereby people are moved onto oral treatment, or treatment is stopped altogether despite the presence of undiagnosed autoimmune gastritis. Therefore, the committee considered that further testing may be required when anti-intrinsic factor antibody is negative and autoimmune gastritis is still suspected. The committee considered the relative advantages and disadvantages of each test.

Gastric parietal cell antibody was considered as a potentially worthwhile test for the diagnosis of autoimmune gastritis. The clinical evidence identified for this test was especially limited, with a single study containing seven participants providing little information of use to the committee. The committee considered that gastric parietal cell antibodies can be determined using the original sample, similarly to intrinsic factor antibody, potentially making it a more practical test as opposed to gastrin. The committee also noted that the anti-gastric parietal cell antibody test was the cheapest of the tests. Despite lacking clinical evidence, the committee felt that this could be a useful second line test in the presence of negative intrinsic factor antibody where autoimmune gastritis is still suspected.

Gastrin was also viewed as a worthwhile test for the diagnosis of autoimmune gastritis. This was supported by the clinical evidence identified with a cut-off of >200 pg/mL resulting in a sensitivity of 90% (95%CI: 68-99%, very low quality) and a specificity of 82% (95%CI: 69-92%, very low quality). Whilst the diagnostic test accuracy data was supportive of gastrin's utility in diagnosing autoimmune gastritis, with both sensitivity and specificity exceeding the clinical decision thresholds, the committee did not feel it was justifiable as an alternative to anti-intrinsic factor antibody as a primary test. This was due to the added difficulty of conducting serum gastrin testing, which requires a separate sample and for the individual to withhold certain medicines, such as protein pump inhibitors, for up to two weeks prior to testing. Intrinsic factor antibody and gastric parietal cell antibodies can be determined using the original sample, making them more convenient for the individual and the clinician alike. The committee did not completely disregard gastrin however, stating that it is still a useful alternative secondary test following a negative intrinsic factor antibody result where autoimmune gastritis is still suspected. An important factor in favour of gastrin is that it is a non-invasive test when compared to procedures such as endoscopy, and biopsy which are often used to diagnose autoimmune gastritis. It is highly likely that individuals would prefer to receive gastrin testing as opposed to more invasive procedures.

The committee discussed the potential value of the CobaSorb test, for which no evidence was identified. This is a relatively new test, which has shown promise in diagnosing autoimmune gastritis, however it is not widely available. It assesses the body's ability to absorb vitamin B12. The committee agreed that, depending on availability, it would be another alternative test for use in the presence of negative anti-intrinsic factor antibody where autoimmune gastritis is still suspected. The committee were also aware that vitamin B12 replacement may need to be stopped before for 3 months before the test can be done. Therefore this may only be advisable in a selected population.

The evidence identified for gastroscopy came from a study aiming to test the diagnostic accuracy of endoscopic evaluation for identifying coeliac disease. The committee agreed that, in isolation, coeliac disease is not a cause of vitamin B12 deficiency. Where coeliac disease is present, multiple deficiencies will be detected and not limited to vitamin B12 alone. Therefore, the committee disregarded this evidence. For guidance relating to coeliac disease, people should refer to the NICE guidance for coeliac disease, which contains information on vitamin B12. Gastroscopy was considered by the committee, from their experience, to be the most definitive test for autoimmune gastritis, but also the most expensive and invasive. The committee considered that gastroscopy is a valid option, but that patient preference would be to avoid invasive investigations where there are non-invasive alternatives available.

There was insufficient evidence to recommend one test over another for the purpose of further testing following a negative anti-intrinsic factor antibody test where autoimmune gastritis is still suspected. Therefore, the committee made a recommendation to consider further investigations, which could include anti-gastric parietal antibody, gastrin, CobaSorb and gastroscopy. Choice of test could be based on availability, patient preference, cost, or other factors. The committee also made a research recommendation to determine the most clinically and cost-effective test in people with anti-intrinsic factor antibody negative test results, to inform future guideline updates.

No evidence was identified for colonoscopy (for terminal ileal disease), faecal elastase (for chronic pancreatitis) or pepsinogen (for autoimmune gastritis). Therefore, the committee decided not to make any recommendations for these tests.

1.3.4 Cost effectiveness and resource use

Published cost effectiveness evidence

No economic evaluations were identified for this review.

Resource use

Indicative costs of antibody tests have been shared by a committee member. Despite the lack of published costs of antibody and serum tests, it is clear they are less costly than gastroscopy or colonoscopy.

The selection of tests depends on local pathways. Most primary care clinicians will only be able to request tests such as the intrinsic factor antibody test and gastric parietal cell antibody. For other investigations such as endoscopy and colonoscopy, a referral will need to be made to secondary care who will then be responsible for requesting appropriate tests. Therefore, the blood tests are likely to give results more quickly. In addition, blood tests are generally preferred by patients as they are better tolerated.

Reflex tests of 'intrinsic factor antibody' tests with the first line B12 tests (active or total B12) may be convenient and reduce repeat phlebotomy appointments however, this change in practice would have a considerable resource impact.

Any recommendation to increase or routinely offer secondary care tests would result in substantial resource impact.

Consideration of cost effectiveness

Identifying the cause will provide utility to patients and potentially influence the length of treatment offered as, in some cases, lifelong treatment may be needed for example, for people with autoimmune gastritis. There may be a possibility that treatment can be stopped if not needed lifelong for example, if people are diagnosed with reversible causes of B12 deficiency such as diet related deficiency. For all types of B12 deficiency there are only limited treatment options which are parenteral and oral B12 replacement treatment. By identifying the cause there may not be any significant change in treatment management, therefore the value of identifying the cause may be limited. However, in the absence of a confirmed aetiology, some people might have treatment incorrectly stopped which might lead to increased costs in the longer term, such as primary care appointments and investigation costs.

The cost effectiveness of each test will depend upon its cost, accuracy and the prevalence of the underlying condition, autoimmune gastritis. The sensitivity of the intrinsic factor test was good. In the clinical study the specificity was low (56%), but the committee consensus was that was that a positive intrinsic factor antibody is strongly suggestive of autoimmune gastritis. This would suggest that intrinsic factor antibody testing could be cost-effective.

As noted in the previous section, the clinical evidence for gastroscopy was very limited. It was considered insufficient to develop a cost-effectiveness analysis. Therefore, the cost effectiveness of gastroscopy to identify the cause of vitamin B12 deficiency is considered uncertain.

Recommendations

The committee considered that in practice, if a clinician strongly suspected autoimmune gastritis, they would usually undertake the intrinsic antibody test as a first line investigation and then consider other investigations. In the absence of economic evidence and good quality clinical evidence on sensitivity and specificity of individual investigations, there was not enough evidence to support a change in practice.

1.3.5 Other factors the committee took into account

Throughout the discussion of the clinical evidence, the practicality of conducting each test was considered. As previously mentioned, anti-intrinsic factor and gastric parietal cell antibodies can be determined using the same blood sample as B12 and methylmalonic acid

(MMA), which are proposed as the tests to diagnose vitamin B12 deficiency. The use of the same sample for all tests (B12, MMA, anti-intrinsic factor, and gastric parietal cell antibodies) is more practical for both the individual – only needing to provide a single sample – and the clinician, who can request additional testing on the sample that is already at the laboratory. With this practicality in consideration, it was suggested that reflex testing, where intrinsic factor antibody determination is carried out, could be done when a low B12 concentration is detected in a sample. This would reduce the waiting time for the clinician to receive the test result, potentially allowing a diagnosis of autoimmune gastritis and treatment initiated.

One issue identified with this approach is that the original sample is stable for 48 hours, after which the sample must be frozen, or a fresh sample collected. It has been recommended that people with borderline B12 values, deemed as between 180-350 ng/L, should have MMA testing to confirm B12 deficiency. This testing would exceed the 48-hour period in which a sample remains stable. Therefore, the sample would require freezing whilst waiting for MMA to be determined, and then defrosting before intrinsic factor antibody could be determined. This process would delay the reporting of the results to the clinician, extending the time to diagnosis and potentially delaying initiation of treatment. What was unclear to the committee was if the reflex testing or clinician requested testing approach is the most clinically and cost-effective in practice. Therefore, the committee decided to make a research recommendation.

1.3.6 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.6 and the research recommendations on what is the clinical and cost effectiveness of reflex anti-intrinsic factor antibody testing versus clinician-requested anti-intrinsic factor antibody testing; and what is the clinical and cost effectiveness of pepsinogen, gastrin, parietal cell antibodies and CobaSorb in identifying the cause of vitamin B12 deficiency in people with negative anti-intrinsic factor antibody test results.

1.4 References

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Appendices

Appendix A – Review protocols

A.1 Accuracy of tests

Review protocol for diagnostic accuracy of tests for determining the cause of vitamin B12 deficiency

Field	Content
PROSPERO registration number	CRD42022345225
Review title	What is the diagnostic accuracy of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy), alone or in combination, for identifying the cause of vitamin B12 deficiency?
Review question	What is the diagnostic accuracy of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy), alone or in combination, for identifying the cause of vitamin B12 deficiency?
Objective	To determine the accuracy of tests for identifying the cause of vitamin B12 deficiency.
Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE

	English language studies Human studies Other searches: Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Vitamin B12 deficiency
Population	Inclusion: Adults with diagnosed vitamin B12 deficiency
Test	The following as stand-alone tests, in combination or as staged tests: Serum intrinsic factor antibody (PA) Gastric parietal cell antibody (PA) Gastroscopy with biopsy (PA) Colonoscopy (terminal ileal disease) Blood tests for coeliac disease Pepsinogen (PA) Gastrin (PA)

	Faecal elastase (chronic pancreatitis) Cobasorb (PA)
Reference standard	Clinical diagnosis (based on combination of tests and clinical judgement)
Types of study to be included	Inclusion: Cross-sectional studies Diagnostic accuracy observational cohort studies Systematic reviews of the above Exclusion: Case-control studies
Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values Non-English language studies. Conference abstracts.
Context	NA
Primary outcomes (critical outcomes)	Sensitivity (50%) Specificity (70%) Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives). Predictive values Likelihood ratios
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

	A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.	
Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2. Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary.	
Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.	
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Age (older adults over 65 years vs. younger adults) for intrinsic factor antibody only	
Type and method of review		Intervention

		Diagnostic		
		Prognostic		
		Qualitative		
		Epidemiologic		
		Service Delivery		
		Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	27/07/2022			
Anticipated completion date	01/11/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches			
	Piloting of the study selection process			
	Formal screening of search results against eligibility criteria			
	Data extraction			
	Risk of bias (quality) assessment			
	Data analysis			
Named contact	5a. Named contact National Guideline Centre			

	5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer] Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in

	line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE	
Other registration details		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345225	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords		
Details of existing review of same topic by same authors		
Current review status		Ongoing
		Completed but not published
		Completed and published
		Completed, published and being updated
		Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

A.2 Test and treat

Review protocol for clinical effectiveness of tests for identifying cause of B12 deficiency

Field	Content
PROSPERO registration number	CRD42022350627
Review title	What is the clinical and cost effectiveness of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy) for identifying the cause of vitamin B12 deficiency?
Review question	What is the clinical and cost effectiveness of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy) for identifying the cause of vitamin B12 deficiency?
Objective	To evaluate the most clinically and cost-effective way to identify the cause of vitamin B12 deficiency.
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches:

	• Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Vitamin B12 deficiency
Population	Inclusion: Adults with diagnosed vitamin B12 deficiency.
Intervention	The following as stand-alone tests or in combination: • Serum intrinsic factor antibody (PA) • Gastric parietal cell antibody (PA) • Gastroscopy with biopsy (PA) • Colonoscopy (terminal ileal disease) • Blood tests for coeliac disease • Pepsinogen (PA) • Gastrin (PA) • Faecal elastase (chronic pancreatitis) • Cobasorb (PA) Tests must be followed by appropriate treatment.
Comparator	• All tests and combinations of tests compared with each other • No test (treatment only)

Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified
Other exclusion criteria	Non-English language studies Conference abstracts
Context	NA

Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• quality of life (such as EQ5D, SF36)
	• patient-reported outcomes (PROM scores including some/all symptoms):
	  ○ fatigue
	  ○ sleep
	  ○ peripheral neuropathy
	  ○ cognition
	  ○ psychiatric symptoms
	  ○ pain
	• haematological values
	• complications and adverse events (condition related):
	  ○ mortality
	  ○ self-harm
	  ○ nerve damage
	  ○ frailty/falls
	  ○ severe cognitive effects
	  ○ postural hypotension
	• complications and adverse events (procedure related):
	  ○ bleeding

	○ perforation ○ aspiration • patient concern around unexpected lab results (health anxiety score) • incorrect/delayed diagnosis • inappropriate additional tests • adherence to treatment • education/work absence Time point: any time point available
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.

Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)
Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:

	• Age (older adults >65 years and younger adults <65 years) for intrinsic factor antibody test only			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	27/07/2022			
Anticipated completion date	01/11/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☐
	Piloting of the study selection process		☐	☐
	Formal screening of search results against eligibility criteria		☐	☐
	Data extraction		☐	☐
	Risk of bias (quality) assessment		☐	☐

	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer] Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or		

	part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE	
Other registration details	NA	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022350627	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords		
Details of existing review of same topic by same authors	NA	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	NA	

Details of final publication	www.nice.org.uk

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[4] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

These literature search strategies were used for the following reviews:

- What is the diagnostic accuracy of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy), alone or in combination, for identifying the cause of vitamin B12 deficiency?
- What is the clinical and cost effectiveness of tests and investigations (including tests for serum intrinsic factor antibody and gastric parietal cell antibody, and gastroscopy and colonoscopy) for identifying the cause of vitamin B12 deficiency?

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[4]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. No search filters were applied.

Table 6: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 15 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 15 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, 15 December 2022 Cochrane Central Register of Controlled Trials to Issue 12 of 12, 15 December 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 15 December 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/

2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Antibodies/ or Autoantibodies/ or Antibodies, Blocking/ or Immunoassay/
29.	((autoantibod* or antibod* or anti bod*) adj4 (serum or test* or assay* or immunoassay* or immunochromatograph* or assay*or level* or concentration*)).ti,ab,kf.
30.	Intrinsic Factor/
31.	((intrinsic or antiintrinsic or anti IF) adj4 (autoantibod* or antibod* or anti bod*)).ti,ab,kf.
32.	(IF Ab or IFAB or IFBA).ti,ab,kf.
33.	Parietal Cells, Gastric/
34.	((gastric or antigastric or parietal or antiparietal or anti PC or oxyntic) adj4 (autoantibod* or antibod* or anti bod*)).ti,ab,kf.
35.	(PC Ab or GPCA or APCA).ti,ab,kf.
36.	Endoscopy, Gastrointestinal/ or Endoscopes, Gastrointestinal/
37.	((upper or gastrointestinal or gastro intestinal or GI) adj2 (endoscop* or exam*)).ti,ab,kf.
38.	Endoscopy, Digestive System/
39.	esophagogastroduodenoscop*.ti,ab,kf.
40.	Gastroscopy/ or Gastroscopes/
41.	gastroscop*.ti,ab,kf.
42.	Colonoscopy/ or Colonoscopes/
43.	(colonoscop* or coloscop*).ti,ab,kf.

44.	exp Pepsinogens/
45.	pepsinogen*.ti,ab,kf.
46.	exp Gastrins/
47.	gastrin*.ti,ab,kf.
48.	Pancreatic Elastase/
49.	elastase.ti,ab,kf.
50.	(cobasorb or coba-sorb).ti,ab,kf.
51.	Celiac Disease/
52.	(coeliac* or celiac*).ti,ab,kf.
53.	exp Immunoglobulin A/
54.	(immunoglobulin A or IgA).ti,ab,kf.
55.	Transglutaminases/
56.	(transglutaminase* or tTGA or tTG).ti,ab,kf.
57.	exp Glutens/
58.	(gluten* or glutenin* or gliadin*).ti,ab,kf.
59.	or/28-58
60.	27 and 59

Embase (Ovid) search terms

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language

27.	antibody/ or autoantibody/ or blocking antibody/ or antibody blood level/ or immunoassay/
28.	((autoantibod* or antibod* or anti bod*) adj4 (serum or test* or assay* or immunoassay* or immunochromatograph* or level* or concentration*)).ti,ab,kf.
29.	intrinsic factor/
30.	((intrinsic or antiintrinsic or anti IF) adj4 (autoantibod* or antibod* or anti bod*)).ti,ab,kf.
31.	(IF Ab or IFAB or IFBA).ti,ab,kf.
32.	stomach parietal cell/
33.	parietal cell antibody/
34.	((gastric or antigastric or parietal or antiparietal or anti PC or oxyntic) adj4 (autoantibod* or antibod* or anti bod*)).ti,ab,kf.
35.	(PC Ab or GPCA or APCA).ti,ab,kf.
36.	gastrointestinal endoscopy/ or digestive endoscope/
37.	((upper or gastrointestinal or gastro intestinal or GI) adj2 (endoscop* or exam*)).ti,ab,kf.
38.	digestive tract endoscopy/ or esophagogastroduodenoscopy/
39.	esophagogastroduodenoscop*.ti,ab,kf.
40.	gastroscopy/ or gastroscope/
41.	gastroscop*.ti,ab,kf.
42.	colonoscopy/ or colonoscope/
43.	(colonoscop* or coloscop*).ti,ab,kf.
44.	pepsinogen/ or pepsinogen i/ or pepsinogen ii/
45.	pepsinogen*.ti,ab,kf.
46.	gastrin/ or gastrin blood level/
47.	gastrin*.ti,ab,kf.
48.	elastase/
49.	elastase.ti,ab,kf.
50.	(cobasorb or coba-sorb).ti,ab,kf.
51.	celiac disease/
52.	(coeliac* or celiac*).ti,ab,kf.
53.	immunoglobulin A/
54.	(immunoglobulin A or IgA).ti,ab,kf.
55.	protein glutamine gamma glutamyltransferase/
56.	(transglutaminase* or tTGA or tTG).ti,ab,kf.
57.	gluten/ or gliadin/ or gliadin antibody/
58.	(gluten* or glutenin* or gliadin*).ti,ab,kf.
59.	or/27-58
60.	26 and 59

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Vitamin B 12 Deficiency] explode all trees
#2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) near/4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)):ti,ab
#3.	MeSH descriptor: [Anemia, Macrocytic] explode all trees
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) near/3 (anemia* or anaemia*)):ti,ab
#5.	MeSH descriptor: [Intrinsic Factor] this term only
#6.	intrinsic factor:ti,ab

#7.	(or #1-#6)
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 not #8
#10.	MeSH descriptor: [Antibodies] this term only
#11.	MeSH descriptor: [Autoantibodies] this term only
#12.	MeSH descriptor: [Antibodies, Blocking] this term only
#13.	MeSH descriptor: [Immunoassay] this term only
#14.	((autoantibod* or antibod* or anti bod*) near/4 (serum or test* or assay* or immunoassay* or immunochromatograph* or assay*or level* or concentration*)):ti,ab,kw
#15.	MeSH descriptor: [Intrinsic Factor] this term only
#16.	((intrinsic or antiintrinsic or anti IF) near/4 (autoantibod* or antibod* or anti bod*)):ti,ab,kw
#17.	(IF Ab or IFAB or IFBA):ti,ab,kw
#18.	MeSH descriptor: [Parietal Cells, Gastric] this term only
#19.	((gastric or antigastric or parietal or antiparietal or anti PC or oxyntic) near/4 (autoantibod* or antibod* or anti bod*)):ti,ab,kw
#20.	(PC Ab or GPCA or APCA):ti,ab,kw
#21.	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only
#22.	MeSH descriptor: [Endoscopes, Gastrointestinal] this term only
#23.	((upper or gastrointestinal or gastro intestinal or GI) near/2 (endoscop* or exam*)):ti,ab,kw
#24.	MeSH descriptor: [Endoscopy, Digestive System] this term only
#25.	esophagogastroduodenoscop*:ti,ab,kw
#26.	MeSH descriptor: [Gastroscopy] this term only
#27.	MeSH descriptor: [Gastroscopes] this term only
#28.	gastroscop*:ti,ab,kw
#29.	MeSH descriptor: [Colonoscopy] this term only
#30.	MeSH descriptor: [Colonoscopes] this term only
#31.	(colonoscop* or coloscop*):ti,ab,kw
#32.	MeSH descriptor: [Pepsinogens] explode all trees
#33.	pepsinogen*:ti,ab,kw
#34.	MeSH descriptor: [Gastrins] explode all trees
#35.	gastrin*:ti,ab,kw
#36.	MeSH descriptor: [Pancreatic Elastase] this term only
#37.	elastase:ti,ab,kw
#38.	(cobasorb or coba-sorb):ti,ab,kw
#39.	MeSH descriptor: [Celiac Disease] this term only
#40.	(coeliac* or celiac*):ti,ab,kw
#41.	MeSH descriptor: [Immunoglobulin A] explode all trees
#42.	(immunoglobulin A or IgA):ti,ab,kw
#43.	MeSH descriptor: [Transglutaminases] this term only
#44.	(transglutaminase* or tTGA or tTG):ti,ab,kw
#45.	MeSH descriptor: [Glutens] explode all trees
#46.	(gluten* or glutenin* or gliadin*):ti,ab,kw
#47.	(or #10-#46)
#48.	#9 and #47

Epistemonikos search terms

1.	(title:("b12 deficien*" OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:("b12 deficien*" OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:("intrinsic factor autoantibod*" OR "intrinsic factor antibod*" OR "intrinsic factor anti bod*" OR "antiintrinsic factor autoantibod*" OR "antiintrinsic factor antibod*" OR "antiintrinsic factor anti bod*" OR "anti IF autoantibod*" OR "anti IF antibod*" OR "anti IF anti bod*" OR "IF Ab" OR IFAB OR IFBA OR "parietal cell autoantibod*" OR "parietal cell antibod*" OR "parietal cell anti bod*" OR "antiparietal cell autoantibod*" OR "antiparietal cell antibod*" OR "antiparietal cell anti bod*" OR "anti PC autoantibod*" OR "anti PC antibod*" OR "anti PC anti bod*" OR "PC Ab" OR GPCA OR APCA OR "gastrointestinal endoscop*" OR "gastro intestinal endoscop*" OR "upper GI endoscop*" OR esophagogastroduodenoscop* OR gastroscop* OR colonoscop* OR coloscop* OR pepsinogen* OR gastrin* OR elastase OR cobasorb OR "coba-sorb" OR coeliac* OR celiac* OR "immunoglobulin A" OR IgA OR transglutaminase* OR tTGA OR tTG OR gluten* OR glutenin* OR gliadin*) OR abstract:("intrinsic factor autoantibod*" OR "intrinsic factor antibod*" OR "intrinsic factor anti bod*" OR "antiintrinsic factor autoantibod*" OR "antiintrinsic factor antibod*" OR "antiintrinsic factor anti bod*" OR "anti IF autoantibod*" OR "anti IF antibod*" OR "anti IF anti bod*" OR "IF Ab" OR IFAB OR IFBA OR "parietal cell autoantibod*" OR "parietal cell antibod*" OR "parietal cell anti bod*" OR "antiparietal cell autoantibod*" OR "antiparietal cell antibod*" OR "antiparietal cell anti bod*" OR "anti PC autoantibod*" OR "anti PC antibod*" OR "anti PC anti bod*" OR "PC Ab" OR GPCA OR APCA OR "gastrointestinal endoscop*" OR "gastro intestinal endoscop*" OR "upper GI endoscop*" OR esophagogastroduodenoscop* OR gastroscop* OR colonoscop* OR coloscop* OR pepsinogen* OR gastrin* OR elastase OR cobasorb OR "coba-sorb" OR coeliac* OR celiac* OR "immunoglobulin A" OR IgA OR transglutaminase* OR tTGA OR tTG OR gluten* OR glutenin* OR gliadin*)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Vitamin B12 deficient population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 7: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies

Database	Dates searched	Search filters and limits applied
	Quality of Life 1946 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies
	Quality of Life 1974 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31 March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31 March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2022	English language

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.

16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	quality-adjusted life years/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	Economics/
49.	Value of life/
50.	exp "Costs and Cost Analysis"/
51.	exp Economics, Hospital/
52.	exp Economics, Medical/
53.	Economics, Nursing/
54.	Economics, Pharmaceutical/
55.	exp "Fees and Charges"/
56.	exp Budgets/
57.	budget*.ti,ab.

58.	cost*.ti.
59.	(economic* or pharmaco?economic*).ti.
60.	(price* or pricing*).ti,ab.
61.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
62.	(financ* or fee or fees).ti,ab.
63.	(value adj2 (money or monetary)).ti,ab.
64.	or/48-63
65.	27 and 47
66.	27 and 64
67.	limit 66 to yr="2014 -Current"
68.	65 or 67

Embase (Ovid) search terms

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	quality adjusted life year/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/

31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/27-47
49.	health economics/
50.	exp economic evaluation/
51.	exp health care cost/
52.	exp fee/
53.	budget/
54.	funding/
55.	budget*.ti,ab.
56.	cost*.ti.
57.	(economic* or pharmaco?economic*).ti.
58.	(price* or pricing*).ti,ab.
59.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
60.	(financ* or fee or fees).ti,ab.
61.	(value adj2 (money or monetary)).ti,ab.
62.	or/49-61
63.	26 and 48
64.	26 and 62
65.	limit 64 to yr="2014 -Current"
66.	63 or 65

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Vitamin B 12 Deficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Anemia, Macrocytic EXPLODE ALL TREES
#3.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis))
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*))
#5.	(intrinsic factor)
#6.	#1 OR #2 OR #3 OR #4 OR #5

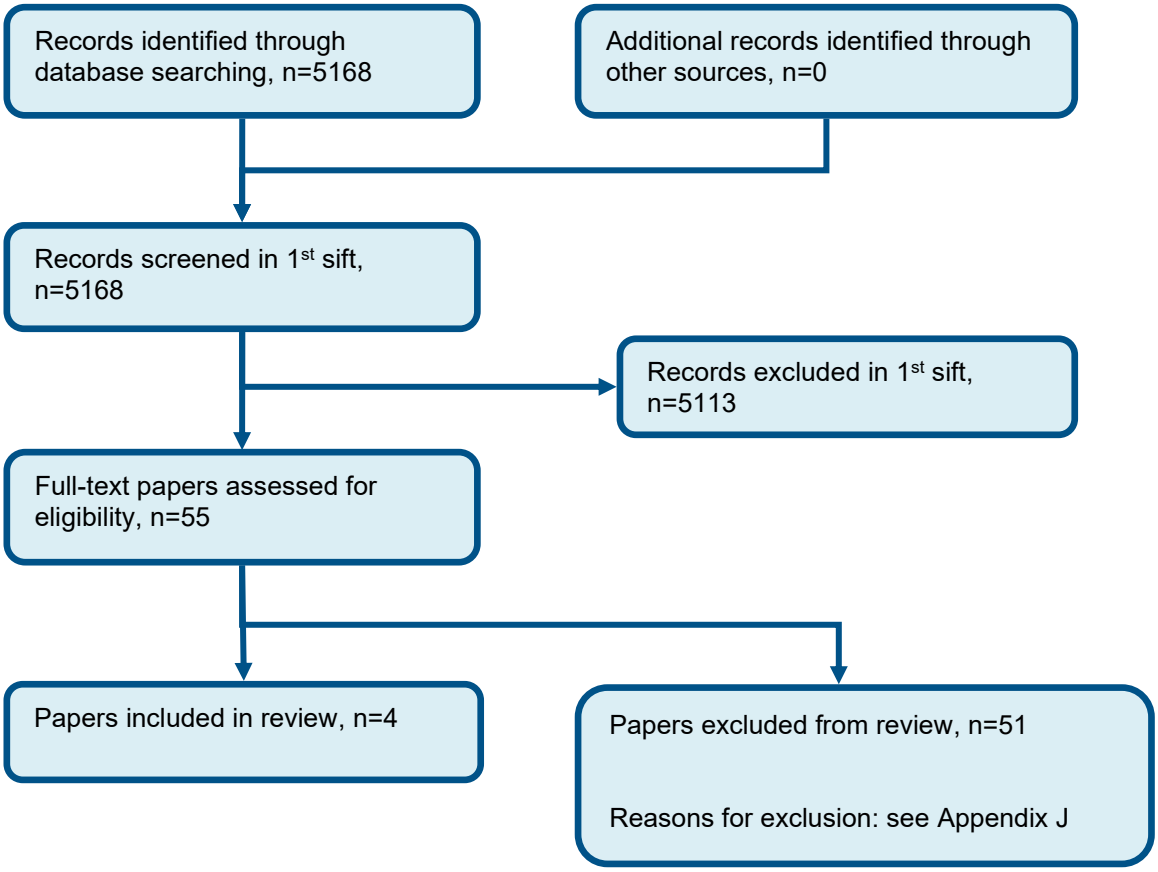
INAHTA search terms

1.	(Anemia, Pernicious)[mh] OR (Vitamin B 12 Deficiency)[mh] OR (pernicious anemia) OR (pernicious anemia) OR (B12) OR (B 12)

Appendix C - Effectiveness evidence study selection

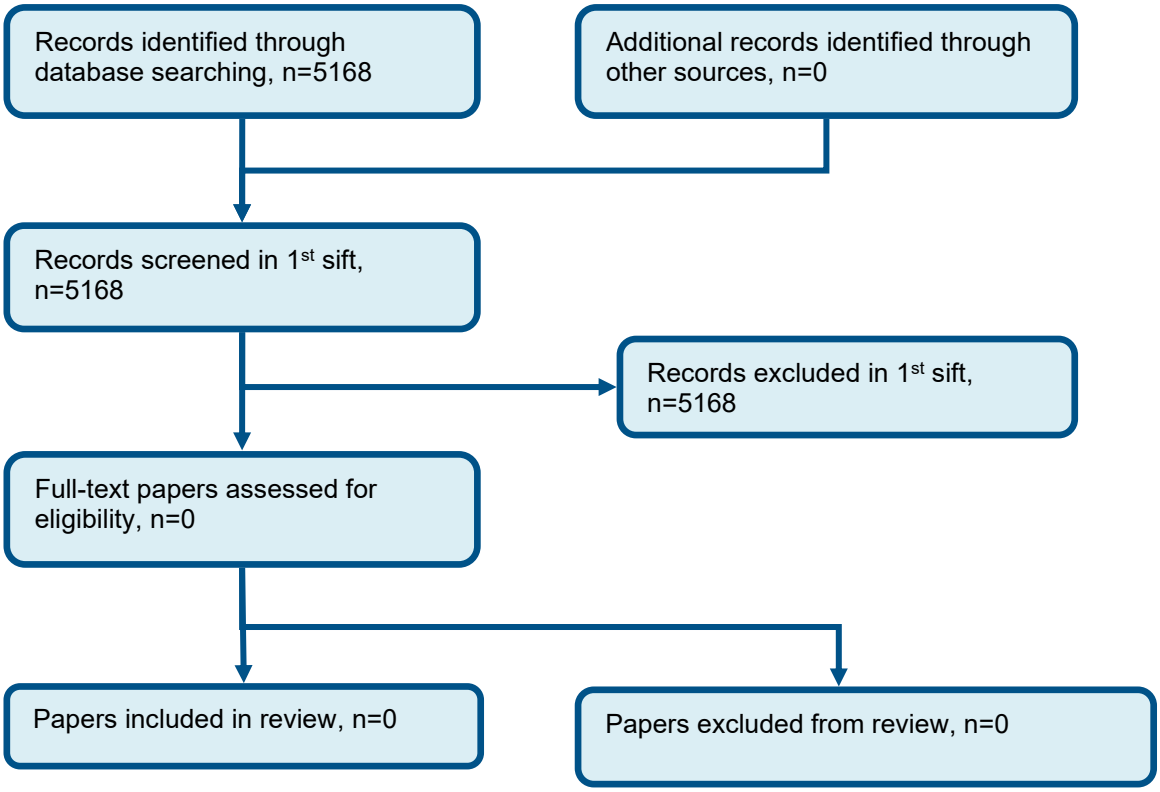
C.1 Accuracy of tests

Figure 1: Flow chart of clinical study selection for the review of diagnostic accuracy of tests for determining the cause of vitamin B12 deficiency



C.2 Test and treat

Figure 2: Flow chart of clinical study selection for the review of effectiveness of tests for identifying cause of B12 deficiency



Appendix D – Effectiveness evidence

D.1 Accuracy of tests

Reference	**Akay 2020[1]**
Study type	Diagnostic accuracy observational cohort study
Study methodology	Data source: Patients with B12 and iron deficiency anaemia who were referred to the Gastroenterology Clinic of a Turkish hospital for upper gastrointestinal endoscopy.
Number of patients	n = 50
Patient characteristics	Age, mean (SD): mixed; 41±11 (20-67) years Gender (male to female ratio): 10:40 Ethnicity: Not reported Setting: Gastroenterology clinic of a Turkish hospital Country: Turkey Inclusion criteria: None reported Exclusion criteria: None reported
Target condition(s)	Coeliac disease
Index test(s) and reference standard	Index test **Endoscopic evaluation** Patients underwent upper gastrointestinal endoscopy after at least 8 hours of fasting and were evaluated with Fujinon EG-490ZW5 high resolution magnified endoscope (Fuji Photo Optical Co., Ltd., Saitama, Japan). A transparent hood was placed on the endoscope tip to ensure good image quality during the procedure and to prevent gastric or duodenal content migration to the area under investigation. After standard videoendoscopic examination by the same endoscopist, standard endoscopic images, magnified and magnified/FICE images of the duodenum were recorded (at least 3 images). Magnification was done by 40-80 times enhancement. Isolated areas in the bulbs and second part of the duodenum were magnified and evaluated, and two biopsies (not four quadrants) were taken for

<table>
<tr><td>Reference</td><td colspan="5">Akay 2020[1]</td></tr>
<tr><td></td><td colspan="5">pathological evaluation after imaging.
Evaluation by white light, high resolution, magnified endoscope, and FICE images
Endoscopic images were first blindly evaluated under standard white light endoscopy (WLE) and were recorded as with or without any celiac-compatible imaging findings (decrease in the number of circular folds, mosaic/nodular velvety appearance, scalloped duodenal folds, grooves, fissurations, etc.). Subsequently, magnified endoscopy and magnified/FICE images were evaluated, and the findings were divided into three groups, i.e., normal, partial villous atrophy, and total atrophy, and recorded.

<u>Reference standard</u>
Tissue transglutaminase IgA anti-body
Biopsy specimens were placed in a 10% formol solution and delivered to the pathology department. After macroscopic sampling and standardized close system tissue follow-up, the specimens were embedded into paraffin then sliced into 4–5-micron sections by a semi-automated system. These slices were evaluated by the same pathologist using hematoxylin & eosin staining. For duodenal biopsies in which intraepithelial lymphocytes were increased, immunohistochemically CD3 antibodies were also applied.

Time between measurement of index test and reference standard: Immediate</td></tr>
<tr><td>2×2 table
Flexible spectral imaging colour enhancement (FICE)/endoscopic image</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td></td></tr>
<tr><td></td><td>Index test +</td><td>10</td><td>0</td><td>10</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>40</td><td>40</td><td></td></tr>
<tr><td></td><td>Total</td><td>10</td><td>40</td><td>50</td><td></td></tr>
<tr><td>2x2 table
White light endoscopy</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td></td></tr>
<tr><td></td><td>Index test +</td><td>6</td><td>0</td><td>6</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>4</td><td>40</td><td>44</td><td></td></tr>
<tr><td></td><td>Total</td><td>10</td><td>40</td><td>50</td><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Flexible spectral imaging colour enhancement (FICE)/endoscopic image</u>
Sensitivity: 60% (95%CI 26-88)
Specificity: 100% (95%CI 91-100)

<u>White light endoscopy</u>
Sensitivity: 100% (95%CI 69-100)
Specificity: 100% (95%CI 91-100)</td></tr>
<tr><td>Source of funding</td><td colspan="5">None reported</td></tr>
</table>

Reference	**Akay 2020[1]**
Limitations	Risk of bias: Very serious due to unclear patient selection (no information provided), unclear application of the index test (unclear if blinded) and unclear application of the reference standard (unclear if blinded and unclear what the reference standard was), lack of clarity if index test and reference standard were interpreted without knowledge of each other and Indirectness: Serious due to index test being used for a different diagnosis to that specified in the review protocol (used for coeliac disease, protocol specified pernicious anaemia)
Comments	Sensitivity and specificity data calculated from 2x2 data reported in study

Reference	**Ingram 1998[2]**
Study type	Diagnostic accuracy observational cohort study
Study methodology	Data source: patients presenting with megaloblastic anaemia at the Chris Hani Baragwanath Hospital
Number of patients	n = 77
Patient characteristics	Age, mean (SD): Not reported Gender (male to female ratio): Not reported Ethnicity: Not reported Setting: Chris Hani Baragwanath Hospital Country: South Africa Inclusion criteria: None reported Exclusion criteria: Pregnant or lactating patients
Target condition(s)	Pernicious anaemia
Index test(s) and reference standard	Index test Intrinsic factor antibody results were reported as positive or negative, determined using the IFbAb phase Solid kit. Reference standard The Schilling test was based on the Dicopac isotope test for B12 malabsorption. Part 1) Patients were given a capsule containing 0.25µg labelled (^{58}CO) cyanocobalamin. An unlabelled cyanocobalamin injection of 1000µg was then given intramuscularly over the following two hours. Urine was then collected over the next 24 hours. A sample of the urine was then analysed for ^{58}CO content by means of a gamma counter and compared to standard solutions provided with the kit. Part 2) The test was repeated as above except that the ^{58}CO capsule was replaced by a capsule containing both labelled cyanocobalamin (^{57}CO) and intrinsic factor. A positive Schilliing test was interpreted as

Reference	**Ingram 1998[2]**
	a Schilling Part 1 <7% and a Schilling Part 2 >7% or more ^{57}CO vitamin B12 excreted in Part 2 than in Part 1 (^{58}CO vitamin B12). Ratios of ^{57}CO (Part 2) / ^{58}CO (Part 1) of percentage isotope were also calculated – a ratio of >1.3 is deemed as diagnostic of pernicious anaemia and a ration of >1.2 indicates some lack of intrinsic factor. Time between measurement of index test and reference standard: Not reported
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	61	4	65
Index test −	7	5	12
Total	68	9	77

Statistical measures	Index text Sensitivity: 90% (95%CI 80-96) Specificity: 56% (95%CI 21-86)
Source of funding	Financial support from the Medical Research Council, National Cancer Association and South African Institute for Medical Research
Limitations	Risk of bias: Serious due to unclear patient selection (no information provided) and unclear application of the reference standard (unclear if blinded) Indirectness: Not serious
Comments	Sensitivity and specificity data calculated from 2x2 data reported in study

Reference	**Miller 1989[3]**
Study type	Diagnostic accuracy prospective cohort study
Study methodology	Data source: patients who had low serum B12 determined as requested by a ward or outpatient physician at one major and four regional hospitals
Number of patients	n = 71
Patient characteristics	Age, median (range): mixed, 62 (20-92) years Gender (male to female ratio): Not reported, >90% were male Ethnicity: Not reported

Reference	**Miller 1989[3]**
	Setting: Hospital Country: USA Inclusion criteria: None reported Exclusion criteria: None reported
Target condition(s)	Pernicious anaemia
Index test(s) and reference standard	Index test Fasting serum gastrin levels were determined by a commercial radioimmunoassay kit (normal range 0-200 pg/mL). Positivity was determined as >200 pg/mL Reference standard The absorption of a capsule of 0.64 pg of vitamin B12 radiolabelled with 0.52 pCi of ^{57}CO was measured by body counting using a fixed gamma camera. A repeat (stage 2) study using 60 mg of intrinsic factor was done in patients showing decreased B12 absorption. In some patients with high or normal serum gastrins, the absorption of a 0.64 pg ^{57}CO B12 capsule admixed with 25 g of desiccated egg yolk was measured prior to that of the unbound vitamin. Twenty-five grams of egg yolk contained 1.30 pg of B12. Time between measurement of index test and reference standard: Not reported
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	18	9	27
Index test −	2	42	44
Total	20	51	71

Statistical measures	Index text Sensitivity: 90% (95%CI 68-99) Specificity: 82% (95%CI 69-92)
Source of funding	None reported
Limitations	Risk of bias: Very serious due to unclear patient selection (no information provided), unclear application of the reference standard (unclear if blinded) and high risk of bias arising from patient flow (not all patients received the same reference standard) Indirectness: Serious due to lack of clarity of final diagnosis with reference standard
Comments	Sensitivity and specificity data calculated from 2x2 data reported in study

Reference	**Ness-Abramof 2006[5]**
Study type	Diagnostic accuracy prospective cohort study
Study methodology	Data source: chart review of patients treated in a hospital-affiliated outpatient endocrine clinic
Number of patients	n = 23 (subset of 115 patients that had low B12 (<133 pmol/L) and had both serum gastrin and parietal cell antibodies measured. Other patients had autoimmune thyroid disease but normal B12 levels)
Patient characteristics (based on whole population)	Age, mean (SD): mixed, 47±15 (14-78) years Gender (male to female ratio): 7:108 Ethnicity: Not reported Setting: Hospital Country: Israel Inclusion criteria: Patients diagnosed with autoimmune thyroid disease Exclusion criteria: Patients who were strict vegetarians, had previous gastrointestinal surgery, had a history of malabsorption or were taking gastric acid suppressive medications
Target condition(s)	Pernicious anaemia
Index test(s) and reference standard	Index test In all patients, lab tests were done to determine thyroid stimulating hormone, free T4, B12 and thyroid antibodies. Patients with positive thyroid antibodies were included in the study. If B12 was below 133 pmol/L, fasting serum gastrin and parietal cell antibodies (PCA) were measured. PCA was the index test used in this study. PCA was determined by indirect immunofluorescence with mouse gastric mucosa as substrate. A titre higher than 1:20 was deemed as positive. Reference standard Gastroscopy Time between measurement of index test and reference standard: Not reported

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	5	1	6
Index test −	1	0	1
Total	6	1	7

Reference	**Ness-Abramof 2006[5]**
Statistical measures	Index text Sensitivity: 83% (95%CI 36-100) Specificity: 0% (95%CI 0-97)
Source of funding	None reported
Limitations	Risk of bias: Very serious due to unclear patient selection (no information provided), unclear application of the index test, unclear application of the reference standard (unclear if blinded) and high risk of bias arising from the patient flow (9 of 32 patients didn't receive the index test or reference standard) Indirectness: Serious due to concerns the reference standard differs from that in the review protocol
Comments	Sensitivity and specificity data calculated from 2x2 data reported in study

D.2 Test and treat

No evidence identified.

Appendix E – Forest plots

E.1 Accuracy of tests

Figure 3: Endoscopic evaluation (FICE) vs clinical diagnosis confirmed by biopsy for diagnosis of coeliac disease

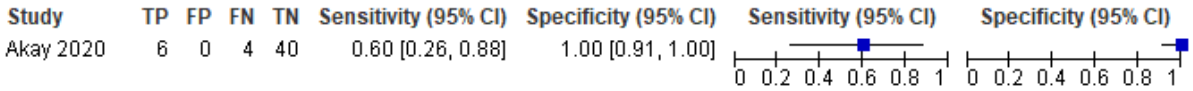


Figure 4: Endoscopic evaluation (WLE) vs clinical diagnosis confirmed by biopsy for diagnosis of coeliac disease

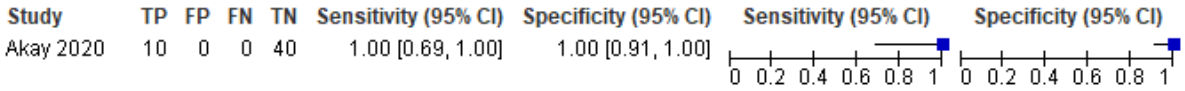


Figure 5: Intrinsic factor antibody vs Schilling test for diagnosis of pernicious anaemia

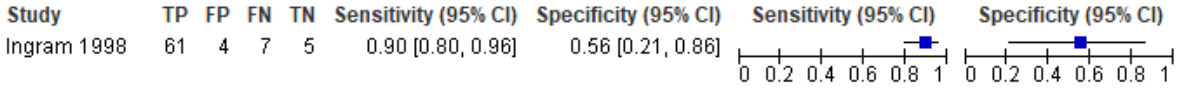


Figure 6: Serum gastrin (cut-off 200 pg/mL) vs Schilling test for diagnosis of pernicious anaemia

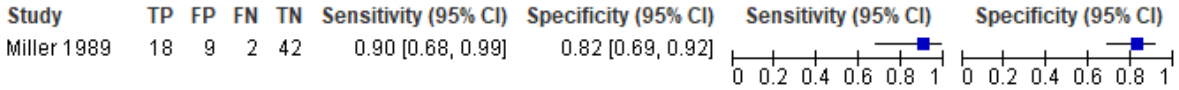
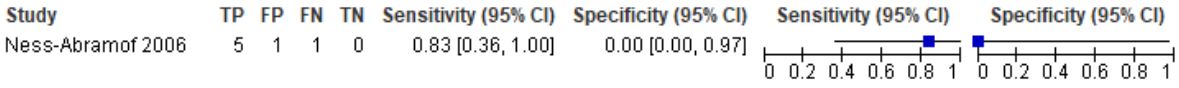


Figure 7: Parietal cell antibodies vs gastroscopy for diagnosis of pernicious anaemia



E.2 Test and treat

No evidence identified.

Appendix F – GRADE tables

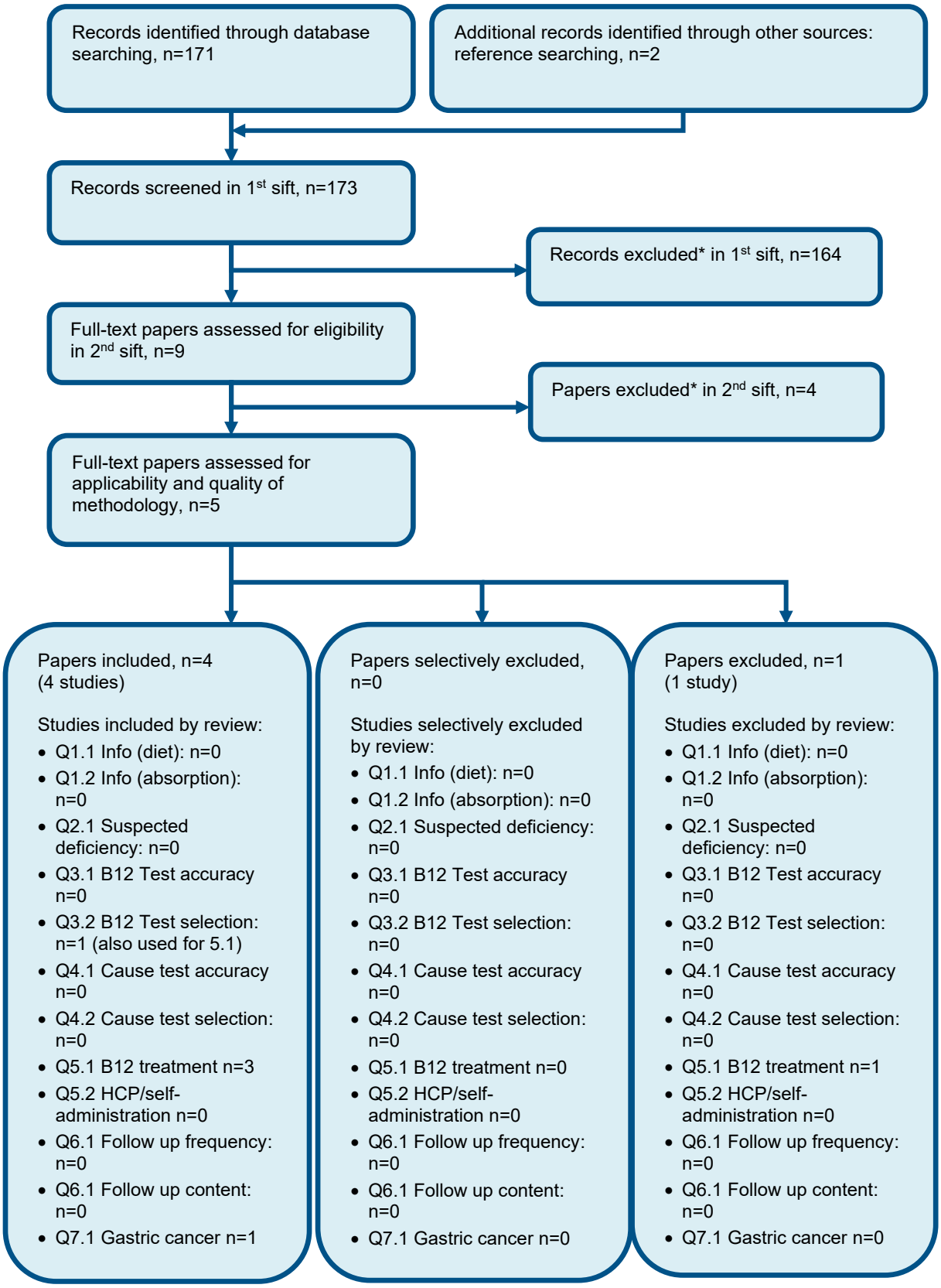
F.1 Accuracy of tests

Not applicable.

F.2 Test and treat

No evidence identified.

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

No relevant studies were identified.

Appendix I – Health economic model

No original economic modelling was undertaken for this review.

Appendix J – Excluded studies

J.1 Clinical studies

J.1.1 Accuracy of tests

Table 8: Studies excluded from the clinical review

Study	Code [Reason]
Abdulmanea, A.A., Alsaeed, A.H., Shaik, A.P. et al. (2014) Pernicious anemia in patients with macrocytic anemia and low serum B12. Pakistan Journal of Medical Sciences 30(6)	- Population not relevant to this review protocol
Aon, Mohamed, Taha, Sherif, Mahfouz, Khaled et al. (2022) Vitamin B12 (Cobalamin) Deficiency in Overt and Subclinical Primary Hypothyroidism. Clinical medicine insights. Endocrinology and diabetes 15: 11795514221086634	- Population not relevant to this review protocol
ARDEMAN, S and CHANARIN, I (1965) ASSAY OF GASTRIC INTRINSIC FACTOR IN THE DIAGNOSIS OF ADDISONIAN PERNICIOUS ANAEMIA. British journal of haematology 11: 305-14	- Population not relevant to this review protocol
Aydin, Y., Tutuncu, Y.A., Ceran, F. et al. (2011) Is helicobacter pylori infection one of the actual causes of vitamin B12 deficiency?. Duzce Medical Journal 13(3): 23-28	- Reference standard not relevant to this review protocol
Belghith, Amel; Mahjoub, Sonia; Ben Romdhane, Neila (2015) Causes of vitamin B12 deficiency. La Tunisie medicale 93(11): 678-82	- Study not reported in English
Bizzaro, Nicola and Antico, Antonio (2014) Diagnosis and classification of pernicious anemia. Autoimmunity reviews 13(45): 565-8	- Review article but not a systematic review

Study	Code [Reason]
Bolann, B J, Solli, J D, Schneede, J et al. (2000) Evaluation of indicators of cobalamin deficiency defined as cobalamin-induced reduction in increased serum methylmalonic acid. Clinical chemistry 46(11): 1744-50	- Study aiming to diagnose a condition not relevant to this review protocol
Borch, K (1986) Epidemiologic, clinicopathologic, and economic aspects of gastroscopic screening of patients with pernicious anemia. Scandinavian journal of gastroenterology 21(1): 21-30	- Study design not relevant to this review protocol
Borch, K and Liedberg, G (1984) Prevalence and incidence of pernicious anemia. An evaluation for gastric screening. Scandinavian journal of gastroenterology 19(2): 154-60	- Study design not relevant to this review protocol
Brandsborg, M, Elsborg, L, Andersen, D et al. (1977) Gastrin concentrations in serum and gastric mucosa in patients with pernicious anaemia. Scandinavian journal of gastroenterology 12(5): 537-41	- Data not reported in an extractable format or a format that can be analysed
Campbell, Alison K, Miller, Joshua W, Green, Ralph et al. (2003) Plasma vitamin B-12 concentrations in an elderly latino population are predicted by serum gastrin concentrations and crystalline vitamin B-12 intake. The Journal of nutrition 133(9): 2770-6	- Study design not relevant to this review protocol
Carmel, R (1992) Reassessment of the relative prevalences of antibodies to gastric parietal cell and to intrinsic factor in patients with pernicious anaemia: influence of patient age and race. Clinical and experimental immunology 89(1): 74-7	- Study design not relevant to this review protocol
Carmel, R (1988) Pepsinogens and other serum markers in pernicious anemia. American journal of clinical pathology 90(4): 442-5	- Population not relevant to this review protocol
Chan, J and Chan, H Y F (2011) Usefulness of thyrogastric immune features as predictors of pernicious anaemia that lacks intrinsic factor antibody. International journal of laboratory hematology 33(4): 400-8	- Index test not relevant to this review protocol
Chanarin, I. (1987) How to diagnose (and not misdiagnose) pernicious anaemia. Blood Reviews 1(4): 280-283	- Study design not relevant to this review protocol

Study	Code [Reason]
Chanarin, I, Malkowska, V, O'Hea, A M et al. (1985) Megaloblastic anaemia in a vegetarian Hindu community. Lancet (London, England) 2(8465): 1168-72	- Study design not relevant to this review protocol
Chang, Julia Yu-Fong, Wang, Yi-Ping, Wu, Yang-Che et al. (2015) Blood profile of oral mucosal disease patients with both vitamin B12 and iron deficiencies. Journal of the Formosan Medical Association = Taiwan yi zhi 114(6): 532-8	- Study design not relevant to this review protocol
Chen, W L, Morishita, R, Eguchi, T et al. (1985) Evaluation of a new assay kit for intrinsic factor blocking antibody (type I) as an aid in the diagnosis of pernicious anemia. Journal of nutritional science and vitaminology 31(5): 491-8	- Study design not relevant to this review protocol
Chiang, Meng-Ling, Jin, Ying-Tai, Chiang, Chun-Pin et al. (2020) Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with vitamin B12 deficiency. Journal of dental sciences 15(1): 34-41	- Data not reported in an extractable format or a format that can be analysed
Couderc, A.-L., Camalet, J., Schneider, S. et al. (2015) Cobalamin deficiency in the elderly: Aetiology and management. A study of 125 patients in a geriatric hospital. Journal of Nutrition, Health and Aging 19(2): 234-239	- Study design not relevant to this review protocol
Dholakia, K-R, Dharmarajan, T-S, Yadav, D et al. (2005) Vitamin B12 deficiency and gastric histopathology in older patients. World journal of gastroenterology 11(45): 7078-83	- Study aiming to diagnose a condition not relevant to this review protocol
Dickey, William (2002) Low serum vitamin B12 is common in coeliac disease and is not due to autoimmune gastritis. European journal of gastroenterology & hepatology 14(4): 425-7	- Population not relevant to this review protocol
Esposito, G., Dottori, L., Pivetta, G. et al. (2022) Pernicious Anemia: The Hematological Presentation of a Multifaceted Disorder Caused by Cobalamin Deficiency. Nutrients 14(8): 1672	- Review article but not a systematic review
Fairbanks, V F, Lennon, V A, Kokmen, E et al. (1983) Tests for pernicious anemia: serum	- Study design not relevant to this review protocol

Study	Code [Reason]
intrinsic factor blocking antibody. Mayo Clinic proceedings 58(3): 203-4	
Fang, S. and Davison, J. (2021) Investigation and management of vitamin b12 deficiency: Experience in a tertiary paediatric centre. Archives of Disease in Childhood 106(suppl1): a95	- Conference abstract
Forshaw, J and Harwood, L (1971) Diagnostic value of the serum folate assay. Journal of clinical pathology 24(3): 244-9	- Index test not relevant to this review protocol
Ghazi, H A (1972) Effect of serum vitamin B 12 binding on intrinsic factor antibody detection in pernicious anaemia. Acta haematologica 47(5): 264-8	- Population not relevant to this review protocol
Harmandar, Ferda A; Dolu, Suleyman; Cekin, Ayhan H (2020) Role of Pernicious Anemia in Patients Admitted to Internal Medicine with Vitamin B12 Deficiency and Oral Replacement Therapy as a Treatment Option. Clinical laboratory 66(3)	- Study design not relevant to this review protocol
Htut, T.W.; Thein, K.Z.; Oo, T.H. (2021) Pernicious anemia: Pathophysiology and diagnostic difficulties. Journal of Evidence-Based Medicine 14(2): 161-169	- Review article but not a systematic review
Hughes, Jing W, Muegge, Brian D, Tobin, Garry S et al. (2017) HIGH-RISK GASTRIC PATHOLOGY AND PREVALENT AUTOIMMUNE DISEASES IN PATIENTS WITH PERNICIOUS ANEMIA. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 23(11): 1297-1303	- Population not relevant to this review protocol
Humbert, P, Lopez de Soria, P, Fernandez-Banares, F et al. (1994) Magnesium hydrogen breath test using end expiratory sampling to assess achlorhydria in pernicious anaemia patients. Gut 35(9): 1205-8	- Population not relevant to this review protocol
IRVINE, W J, DAVIES, S H, HAYNES, R C et al. (1965) SECRETION OF INTRINSIC FACTOR IN RESPONSE TO HISTAMINE AND TO GASTRIN IN THE DIAGNOSIS OF ADDISONIAN PERNICIOUS ANEMIA. Lancet (London, England) 2(7409): 397-401	- Population not relevant to this review protocol

Study	Code [Reason]
Junca, J, Flores, A, Granada, M L et al. (2000) The relationship between idiopathic thrombocytopenic purpura and pernicious anaemia. British journal of haematology 111(2): 513-6	- Population not relevant to this review protocol
Khan, S, Del-Duca, C, Fenton, E et al. (2009) Limited value of testing for intrinsic factor antibodies with negative gastric parietal cell antibodies in pernicious anaemia. Journal of clinical pathology 62(5): 439-41	- Reference standard not relevant to this review protocol
Lahner, E. and Annibale, B. (2009) Pernicious anemia: New insights from a gastroenterological point of view. World Journal of Gastroenterology 15(41): 5121-5128	- Review article but not a systematic review
Lahner, Edith, Norman, Gary L, Severi, Carola et al. (2009) Reassessment of intrinsic factor and parietal cell autoantibodies in atrophic gastritis with respect to cobalamin deficiency. The American journal of gastroenterology 104(8): 2071-9	- Population not relevant to this review protocol
Martin-Alcolea, Mariam, Rodriguez-Hernandez, Ines, Aldea, Marta et al. (2017) Chronic proton pump inhibition therapy in the diagnostic accuracy of serum pepsinogen I and gastrin concentrations to identify pernicious anaemia. Clinical biochemistry 50(9): 481-484	- Population not relevant to this review protocol
Miller, A, Furlong, D, Burrows, B A et al. (1992) Bound vitamin B12 absorption in patients with low serum B12 levels. American journal of hematology 40(3): 163-6	- Study design not relevant to this review protocol
Nimo, R E and Carmel, R (1987) Increased sensitivity of detection of the blocking (type I) anti-intrinsic factor antibody. American journal of clinical pathology 88(6): 729-33	- Population not relevant to this review protocol
Oo, Thein Hlaing (2019) Diagnostic difficulties in pernicious anemia. Discovery medicine 28(155): 247-253	- Review article but not a systematic review
Pruthi, R.K. and Tefferi, A. (1994) Pernicious anemia revisited. Mayo Clinic Proceedings 69(2): 144-150	- Review article but not a systematic review

Study	Code [Reason]
Salinas, Maria, Flores, Emilio, Lopez-Garrigos, Maite et al. (2020) High frequency of anti-parietal cell antibody (APCA) and intrinsic factor blocking antibody (IFBA) in individuals with severe vitamin B12 deficiency - an observational study in primary care patients. Clinical chemistry and laboratory medicine 58(3): 424-429	- Study design not relevant to this review protocol
Schneede, J. and Ueland, P.M. (2005) Novel and established markers of cobalamin deficiency: Complementary or exclusive diagnostic strategies. Seminars in Vascular Medicine 5(2): 140-155	- Review article but not a systematic review
Sobczynska-Malefora, Agata, Delvin, Edgard, McCaddon, Andrew et al. (2021) Vitamin B12 status in health and disease: a critical review. Diagnosis of deficiency and insufficiency - clinical and laboratory pitfalls. Critical reviews in clinical laboratory sciences 58(6): 399-429	- Review article but not a systematic review
Song, Ik-Chan, Lee, Hyo Jin, Kim, Han-Jo et al. (2013) A multicenter retrospective analysis of the clinical features of pernicious anemia in a Korean population. Journal of Korean medical science 28(2): 200-4	- Population not relevant to this review protocol
Sukumar, N. and Saravanan, P. (2019) Investigating vitamin B12 deficiency. BMJ (Online) 365: l1865	- Study design not relevant to this review protocol
Tozzoli, Renato, Kodermaz, Graziano, Perosa, Anna Rosa et al. (2010) Autoantibodies to parietal cells as predictors of atrophic body gastritis: a five-year prospective study in patients with autoimmune thyroid diseases. Autoimmunity reviews 10(2): 80-3	- Population not relevant to this review protocol
Tun, Aung Myint, Thein, Kyaw Zin, Myint, Zin War et al. (2017) Pernicious Anemia: Fundamental and Practical Aspects in Diagnosis. Cardiovascular & hematological agents in medicinal chemistry 15(1): 17-22	- Review article but not a systematic review
Varis, K, Samloff, I M, Ihamaki, T et al. (1979) An appraisal of tests for severe atrophic gastritis in relatives of patients with pernicious anemia. Digestive diseases and sciences 24(3): 187-91	- Population not relevant to this review protocol
Wentworth, B.J. and Copland, A.P. (2018) Revisiting vitamin B12 deficiency: A clinician's	- Review article but not a systematic review

Study	Code [Reason]
guide for the 21st century. Practical Gastroenterology 42(12)	
Wu, Yang-Che, Wu, Yu-Hsueh, Chang, Julia Yu-Fong et al. (2020) Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in atrophic glossitis patients with vitamin B12 deficiency. Journal of the Formosan Medical Association = Taiwan yi zhi 119(3): 720-727	- Study design not relevant to this review protocol

J.1.2 Health Economic studies

None.

J.2 Test and treat

J.2.1 Studies excluded from the clinical review

No records screened as full texts.

J.2.2 Health Economic studies

None.

Appendix K – Research recommendations – full details

K.1 Research recommendation

What is the clinical and cost-effectiveness of reflex anti-intrinsic factor antibody testing versus clinician requested anti-intrinsic factor antibody testing?

K.1.1 Why this is important

Anti-intrinsic factor antibodies can be determined using the same blood sample as taken for B12 and methylmalonic acid (MMA) testing. Therefore, reflex testing, automatically carrying out an anti-intrinsic factor antibody test on all samples in which low vitamin B12 concentration is detected, is an option. This would have practical advantages such as only requiring the individual to provide one sample, reducing the waiting time for the test result, as well as potentially allowing a faster diagnosis of autoimmune gastritis and initiation of appropriate treatment. However, people with borderline B12 values, should have MMA testing to confirm B12 deficiency, which would exceed the 48-hour period in which a sample remains stable. The sample would require freezing whilst waiting for MMA to be determined, then defrosting before intrinsic factor antibody could be determined, delaying the test results, extending the time to diagnosis and potentially delaying initiation of treatment. Research is therefore required to determine whether the reflex testing or clinician requested testing approach is most clinically and cost-effective in practice.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	By comparing outcomes of people undergoing reflex testing for anti-intrinsic factor antibodies with clinician requested testing, the most clinically effective approach for diagnosing autoimmune gastritis in people with low B12 can be established.
Relevance to NICE guidance	The research would inform future guideline updates.
Relevance to the NHS	The outcome would affect the type of testing approach being offered by the NHS to people with vitamin B12 deficiency to identify autoimmune gastritis.
National priorities	Not applicable
Current evidence base	No randomised or non-randomised studies reporting outcomes of serum intrinsic factor antibody testing were identified.
Equality considerations	None known

K.1.3 Modified PICO table

Population	People with diagnosed vitamin B12 deficiency.
Intervention	Reflex testing for anti-intrinsic factor antibodies on low B12 concentration.
Comparator	Clinician requested testing for anti-intrinsic factor antibodies on low B12 concentration.
Outcome	• Quality of life (such as EQ5D, SF36) • Patient-reported outcomes (PROM scores including some/all symptoms): ○ fatigue

	○ sleep ○ peripheral neuropathy ○ cognition ○ psychiatric symptoms ○ pain • Haematological values • Complications and adverse events (condition related): ○ mortality ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • Complications and adverse events (procedure related) • Patient concern around unexpected lab results (health anxiety score) • Incorrect/delayed diagnosis • Inappropriate additional tests • Adherence to treatment • School/education/work absence
Study design	Randomised controlled trial
Timeframe	Short term and long term
Additional information	None

K.2 Research recommendation

What is the clinical and cost-effectiveness of pepsinogen, gastrin, parietal cell antibodies and CobaSorb in identifying the cause of vitamin B12 deficiency in people with negative anti-intrinsic factor antibody test results?

K.2.1 Why this is important

A positive anti-intrinsic antibody test result is strongly suggestive of autoimmune gastritis; however, a negative result is not as reliable for ruling out the presence of autoimmune gastritis. Therefore, further investigations are often needed if autoimmune gastritis is still suspected. There is insufficient evidence to recommend any test over another, therefore further research is needed to determine the most effective test in people with negative anti-intrinsic factor antibody test results.

K.2.2 Rationale for research recommendation

Importance to ‘patients’ or the population	Some people with negative anti-intrinsic factor antibody test results have autoimmune gastritis but require different tests for diagnosis. By comparing different testing strategies, the strategy leading to the best outcomes can be established.
Relevance to NICE guidance	The research would inform future guideline updates.

Relevance to the NHS	The outcome would affect the type of testing offered by the NHS to people with vitamin B12 deficiency and negative anti-intrinsic factor antibody test results, to identify autoimmune gastritis.
National priorities	Not applicable
Current evidence base	There is very limited evidence for the diagnostic accuracy of gastrin and parietal cell antibody tests and no evidence for the diagnostic accuracy of pepsinogen or Cobasorb tests. There is no data on the clinical and cost effectiveness of any of these tests.
Equality considerations	None known

K.2.3 Modified PICO table

Population	People with diagnosed vitamin B12 deficiency and negative anti-intrinsic factor antibody test results.
Intervention	• Pepsinogen • Gastrin • Parietal cell antibodies • Cobasorb
Comparator	All tests compared with each other (including combinations and sequences of tests)
Outcome	• Quality of life (such as EQ5D, SF36) • Patient-reported outcomes (PROM scores including some/all symptoms): ○ fatigue ○ sleep ○ peripheral neuropathy ○ cognition ○ psychiatric symptoms ○ pain • Haematological values • Complications and adverse events (condition related): ○ mortality ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • Complications and adverse events (procedure related) • Patient concern around unexpected lab results (health anxiety score) • Incorrect/delayed diagnosis • Inappropriate additional tests • Adherence to treatment • School/education/work absence
Study design	Randomised controlled trial

Timeframe	Short term and long term
Additional information	None