Pernicious Anemia

Recognizing and Preventing Irreversible Neurological Damage

A PHYSICIAN REFERENCE GUIDE

This guide is intended for physicians and other clinicians evaluating and managing patients with pernicious anemia and related vitamin B12 absorption disorders. It covers diagnostic pitfalls, treatment protocols, and monitoring guidance drawn from current clinical literature and professional society guidelines, with full citations throughout.

A condensed Quick Reference section opens the guide, followed by a full clinical discussion. Both sections cite the same 39-source reference list at the end of the document.

Prepared: July 26, 2026
Source and current version: dittany.com/pa-physician-guide/
This document is a static snapshot; the web version may be updated.

Table of Contents

PHYSICIAN REFERENCE: Recognizing and Preventing Irreversible Neurological Damage

Quick Reference for Physicians — Full Clinical Guide follows

Quick Reference for Physicians

Understanding the Severity of Pernicious Anemia

Pernicious anemia causes vitamin B12 deficiency that results in neurological damage. In approximately 30% of cases, it occurs without anemia or macrocytosis. Neuropsychiatric symptoms frequently represent the initial manifestation and may include depression, anxiety, paresthesia, gait disturbances, and cognitive impairment. Despite its name suggesting anemia as the primary feature, neurological complications often precede and may occur independently of hematological abnormalities.

Without adequate treatment, patients will develop:

- Permanent spinal cord damage (subacute combined degeneration)
- Irreversible peripheral neuropathy
- Permanent cognitive impairment and dementia
- Psychiatric symptoms often misdiagnosed as primary mental illness
- Progressive disability and loss of independence

Clinical significance:

Neurological damage represents the primary pathological consequence of B12 deficiency and occurs before hematological changes. Early intervention prevents irreversible complications, while delayed treatment results in permanent neurological deficits.

Critical Diagnostic Error

Laboratory Values Do Not Reliably Reflect Tissue B12 Status

No blood test can reliably determine whether nervous system tissue has adequate B12, particularly in malabsorption disorders such as pernicious anemia. Normal or elevated laboratory values do not exclude functional B12 deficiency.

Understanding B12 Testing: What Each Test Actually Measures

Serum B12 (Total B12)

- Measures all B12 circulating in blood, including inactive forms
- Poor sensitivity and specificity for detecting deficiency
- Falsely normal in liver disease, kidney disease, and malignancies
- Falsely elevated after recent supplementation while functional deficiency persists
- In untreated pernicious anemia, high-titer intrinsic factor antibodies can interfere directly with the assay, producing spuriously normal or elevated readings even in severe, confirmed deficiency [1]
- Can appear normal or high while the patient remains deficient at the cellular level
- Normal serum B12 documented in patients with severe neurological symptoms

Holotranscobalamin (Active B12)

- Measures B12 bound to transcobalamin, the fraction delivered to cells
- More sensitive than total serum B12 for early deficiency
- Still reflects blood transport rather than intracellular function
- In malabsorption states, transport may appear adequate while cellular utilization fails, especially in nervous tissue
- Normal holotranscobalamin does not rule out neurological B12 deficiency

Methylmalonic Acid (MMA)

- Rises when B12-dependent intracellular enzymes are impaired
- Best available laboratory marker of functional B12 deficiency
- Can be normal despite cellular deficiency
- More than half of individuals with low holotranscobalamin have normal MMA
- Patients with normal MMA, homocysteine, and serum B12 have responded clinically to B12 treatment

Patients who fail to respond to adequate dosing may have a resistance mechanism rather than — or in addition to — pernicious anemia. See *B12 Beyond the Basics* for evaluation and treatment of cellular and autoimmune B12 resistance.

Homocysteine

- Elevated in B12 deficiency (less specific than MMA)

- Can be normal despite functional B12 deficiency
- Also elevated in folate deficiency, kidney disease, and hypothyroidism

The Hierarchy of B12 Assessment

Laboratory markers (in order of reliability):

- Methylmalonic acid (best laboratory marker, but may still miss cellular deficiency)
- Holotranscobalamin (better than serum B12, limited in malabsorption)
- Serum B12 (crude and often misleading)
- Homocysteine (least specific)

Clinical assessment remains central:

- Symptoms are often more reliable than laboratory values for diagnosis and monitoring
- Normal laboratory values do not rule out clinically significant B12 deficiency
- This limitation is well documented in clinical literature and professional guidance

Proper Diagnostic Approach

Primary Diagnostic Tests

Intrinsic Factor Antibodies

Anti–intrinsic factor antibodies are 40–60% sensitive for pernicious anemia, with positivity increasing as disease progresses. Specificity approaches 100%.

Critical limitation: 40–60% of pernicious anemia patients will have negative intrinsic factor antibody tests.

An important clinical note: intrinsic factor antibody testing is a qualitative test. Any detectable level of antibody is a positive result. Some laboratories now report results on a numerical scale with an institutional "normal range," which has led some clinicians to interpret low positive values as negative or inconclusive. This is incorrect. The test has very low sensitivity — 40–60% of PA patients will test negative — but specificity approaches 100%. A detectable antibody at any level is diagnostically significant and should not be dismissed on the basis of a quantitative threshold.

Two antibody types exist:

- Type 1 (blocking antibodies) prevent B12 binding to intrinsic factor
- Type 2 (binding antibodies) prevent the B12–IF complex from attaching to intestinal receptors

Parietal Cell Antibodies

Present in approximately 90% of pernicious anemia patients but less specific and found in ~10% of the general population.

Methylmalonic Acid (MMA)

Useful to confirm deficiency in low-normal B12 states, but normal MMA does not exclude deficiency.

Homocysteine

May be elevated in B12 deficiency but is less specific than MMA.

Clinical Assessment

- Complete blood count with peripheral smear (macrocytosis, hypersegmented neutrophils) [2]
- Comprehensive symptom assessment (neurological, psychiatric, gastrointestinal) [3]
- Family history of autoimmune disease [4]
- Personal history of autoimmune disorders [5]

Diagnostic Principles

- Clinical symptoms should guide diagnosis rather than isolated laboratory values
- Normal serum B12, holotranscobalamin, MMA, or homocysteine do not exclude deficiency — nor does an elevated serum B12, since high-titer intrinsic factor antibodies can interfere directly with the assay and produce spuriously elevated readings in severe, untreated disease [1]
- A significant proportion of patients have negative antibody tests
- Negative antibody serology reflects only the autoimmune pathway and does not exclude deficiency arising from a different point of failure in the absorption cascade
- When clinical suspicion is high, empirical treatment should not be delayed
- Clinical response to B12 therapy can confirm diagnosis when laboratory testing is inconclusive

Treatment Essentials

Evidence-Based Protocol

- **Neurological involvement:** 1000 mcg IM or SC on alternate days until no further improvement, then as required to maintain improvement [6, 7, 8]

- **No neurological involvement:** 1000 mcg IM or SC three times weekly for 2 weeks, then every 2–3 months [6, 7, 8]
- Lifelong treatment required
- Many patients require more frequent dosing than standard protocols [9, 10, 7]

Common Treatment Errors

- Using serum B12 or other laboratory values to guide treatment frequency
- Inadequate initial loading doses
- Premature reduction of injection frequency
- Dismissing symptom recurrence between injections
- Supplementing folic acid without documented folate deficiency

---

This completes the Quick Reference for Physicians. A comprehensive clinical guide follows.

Pernicious Anemia Diagnosis and Management — Clinical Guide

Understanding the Severity of Pernicious Anemia

Pernicious anemia is a progressive neurological condition. Vitamin B12 deficiency can be responsible for neurological damage, which can occur in the absence of any anemia or macrocytosis (approximately 25–30% of PA cases). Neuropsychiatric symptoms are often the first manifestation. Even though the name *pernicious anemia* suggests anemia is always present, this is often not the case.

Without adequate treatment, patients will develop:

- Permanent spinal cord damage (subacute combined degeneration) [11, 10]
- Irreversible peripheral neuropathy [12]
- Permanent cognitive impairment and dementia [11]
- Psychiatric symptoms that are often misdiagnosed as primary mental illness [13]
- Progressive disability and loss of independence [14]

Early intervention is essential. Neuropsychiatric symptoms can precede hematological signs and are often the presenting manifestation of B12 deficiency [11]. Typically, neurological symptom improvement is slower than hematological improvement, and the degree of neurological recovery is inversely proportional to the severity and duration of symptoms before treatment [10]. Delayed or inadequate treatment guarantees permanent neurological damage [12].

Critical Point: Neurological signs often generate a clinical picture of combined sclerosis of the spinal cord [6]. Neurological manifestations may only partially regress despite prolonged and high-dose vitamin B12 therapy, leading to irreversible sequelae [13].

B12 absorption depends on a sequential biological cascade with multiple distinct failure points — from gastric acid production and intrinsic factor secretion through pancreatic enzyme activity, ileal receptor function, and intracellular transport. Autoimmune destruction of parietal cells is one pathway through that cascade. Chronic *H. pylori* infection, pancreatic insufficiency, ileal disease, surgical resection, congenital defects, and other mechanisms can produce identical neurological outcomes through different points of failure. Standard antibody testing interrogates only the autoimmune pathway. A patient whose absorption has failed at any other point will test negative and may go untreated while neurological damage progresses. [15, 16, 17]

Early symptoms are often mild and easily dismissed or normalized by patients themselves, which delays diagnosis independent of any testing limitations. Treatment halts progression and produces improvement in most patients with subacute combined degeneration, but complete resolution occurs only in a minority. The degree of recovery is inversely proportional to the severity and duration of untreated deficiency.

Treatment Protocol Errors to Avoid

Common Mistakes

1. Using laboratory values to guide treatment frequency

Serum B12 concentrations rise with treatment regardless of whether the dosing interval is adequate, so they provide no information about treatment effectiveness. Use clinical symptoms to determine injection frequency [10].

Serum B12, holotranscobalamin, MMA, and homocysteine can all normalize before tissue repair occurs. In pernicious anemia and other malabsorption states, blood transport markers do not reliably reflect nervous system B12 status.

2. Inadequate loading doses

Standard "monthly B12 shots" are insufficient for initial treatment [9]. Guidelines from the British Society for Haematology recommend injections three times per week for two weeks in patients without neurologic deficits. If neurologic deficits are present, injections should be given every other day for up to three weeks or until no further improvement is noted [6].

3. Premature reduction of treatment frequency

Major Error: Reducing injection frequency as soon as the patient feels better or laboratory values normalize [10].

Many patients require more frequent dosing than standard protocols suggest [10, 7]. Once a diagnosis of B12 deficiency due to poor absorption has been made, therapy should be maintained lifelong.

4. Dismissing symptom recurrence between injections

This is one of the most common and consequential errors in pernicious anemia management. When patients report symptoms returning before their next scheduled injection, this represents clinical evidence of inadequate dosing frequency.

See the section on symptom recurrence between injections below for detailed guidance.

5. Inappropriate folic acid supplementation

Folate levels should be determined to exclude macrocytic anemia secondary to folate deficiency and because treating B12-deficient patients with folate alone may worsen associated neurologic damage. Only supplement folic acid if folate deficiency is documented [18].

Evidence-Based Treatment Protocol

Initial Phase

- Treatment of pernicious anemia and other macrocytic anemias **with neurological involvement**: 1000 mcg on alternate days until no further improvement, then frequency adjusted to maintain improvement [6, 7, 8]
- Treatment of pernicious anemia and other macrocytic anemias **without neurological involvement**: 1000 mcg three times per week for 2 weeks, then frequency adjusted to maintain symptom control [6, 7, 8]

Maintenance Phase

Standard maintenance protocols suggest B12 every 1–3 months, but this represents a starting point, not a fixed endpoint. Clinical reality shows significant individual variation:

- Many patients require more frequent dosing than standard protocols [10, 7]
- Frequency must be individualized based on symptom control, not laboratory values [10]
- No maximum injection frequency exists — some patients require daily, weekly, or twice-weekly injections
- Symptom recurrence before the next scheduled injection indicates inadequate dosing frequency
- Adjustment should be based on clinical response over 6–12 months

The lack of clinical improvement after 4–8 weeks for anemia and after 6–12 months for neurological signs could suggest that symptoms are not due to B12 deficiency or that dose or route requires adjustment.

Route of Administration

Intramuscular or subcutaneous B12 is the standard route for pernicious anemia treatment, particularly when neurological symptoms are present.

Some studies report that very high-dose oral B12 (1000–2000 mcg daily) can normalize serum B12 and metabolic markers through passive diffusion [19]. However, these studies have significant limitations:

- Small sample sizes and short follow-up periods
- Outcomes measured were blood markers, not intracellular or neurological outcomes
- No long-term neurological outcome data
- Blood markers can normalize while cellular deficiency persists

Clinical Decision Making

Given that:

- Neurological damage can become irreversible
- Laboratory markers do not reliably reflect tissue B12 status
- Treatment response must be individualized
- The consequences of under-treatment are permanent

Intramuscular/subcutaneous administration remains the recommended route, particularly for:

- Patients with neurological involvement
- Initial treatment and loading phases
- Patients with inadequate symptom response

Treatment frequency should be guided by clinical response, not laboratory values.

Symptom Recurrence Between Injections

This presentation is common in inadequately treated pernicious anemia and is frequently discounted when clinicians rely on laboratory values instead of clinical assessment.

Inadequate Treatment Indicators

Patients may report:

- Improvement after injection followed by gradual symptom return
- Shortening symptom-free intervals
- Counting days until the next injection
- Functional decline before scheduled dosing

Common symptoms include:

- Fatigue
- Cognitive impairment
- Mood changes
- Neurological symptoms (tingling, numbness, balance problems)
- Sleep disturbance

This pattern indicates:

- Inadequate dosing interval
- Repeated cycles of partial deficiency
- Risk of progressive neurological damage

In pernicious anemia, the goal is not laboratory normalization. The goal is prevention of neurological damage and maintenance of function. If symptoms recur despite "normal" labs, treatment is inadequate.

Red Flags for Pernicious Anemia

Neurological Symptoms (Primary Treatment Indicator)

- Peripheral neuropathy (tingling, numbness, burning in hands or feet) [21]
- Subacute combined degeneration of the spinal cord [20]
- Balance problems, unsteady gait, falls [22]
- Cognitive impairment, memory problems, dementia-like symptoms [23]
- Psychiatric symptoms: depression, anxiety, mood swings, psychosis [24]
- Fatigue unresponsive to rest [25]

Critical Understanding:

Severe neurologic impairment, usually subacute combined system degeneration, occurs in cobalamin deficiency. However, vitamin B12 deficiency may also present as peripheral neuropathy, psychosis, depression, or leukoencephalopathy.

Monitoring Treatment

- Clinical symptoms should receive the highest priority

- Routine serum B12 monitoring has no diagnostic value for patients on regular parenteral B12: levels rise with treatment regardless of dosing adequacy and cannot indicate whether the interval is sufficient [10]
- MMA and homocysteine retain some value that serum B12 lacks: persistent elevation despite adequate dosing can flag a non-responder needing further workup, rather than simply confirming the original diagnosis [26]
- Renal impairment confounds MMA and multiple non-B12 conditions confound homocysteine, so neither replaces clinical judgment
- Adjust treatment frequency based on symptom control
- Increase frequency if symptoms recur between injections

Differential Diagnosis

Primary Mimics

- **Myelodysplastic syndrome (MDS):** Can mimic PA hematologically; check B12/folate before bone marrow biopsy [27]
- **Acute leukemia:** Pancytopenia with abnormal blood cells
- **Folate deficiency:** Identical megaloblastic anemia; requires concurrent testing
- **Iron deficiency anemia:** Can coexist with PA (up to 50%) and mask macrocytosis [28]

Ferritin is frequently omitted from iron panels or excluded by reference ranges too wide for functional deficiency. Ferritin is an acute phase reactant and can read normal or high in the presence of concurrent autoimmune or inflammatory activity, masking true iron deficiency. Transferrin saturation is a more reliable indicator of iron status in this population. Serum iron alone is not useful — it fluctuates throughout the day and reflects recent intake rather than iron stores [28].

Other Absorption Failure Pathways

Some autoimmune processes disrupt absorption without producing detectable intrinsic factor antibodies, and advanced parietal cell destruction can leave too few cells remaining to sustain an antibody response, so a negative result is compatible with long-standing, severe disease.

- Dietary deficiency (vegans, strict vegetarians)
- Malabsorption syndromes (Crohn's disease, celiac disease, bacterial overgrowth)
- Surgical causes (gastrectomy, gastric bypass, ileal resection)
- Medication-induced (PPIs, metformin, H2 blockers)

- Parasitic infection (*Diphyllobothrium latum*)

Long-Term Monitoring and Surveillance

Gastric Cancer Surveillance [29]

Pernicious anemia patients have:

- 2–3× increased risk of gastric adenocarcinoma
- 11× increased risk of gastric carcinoid tumors

European guideline recommendations [30]:

- Initial endoscopy with topographical biopsies
- Surveillance endoscopy every 3–5 years for advanced atrophy
- Shorter intervals for pre-neoplastic lesions

Iron Deficiency Monitoring [28]

- Up to 50% develop concurrent iron deficiency
- Annual iron panel (ferritin, iron, TIBC)
- Achlorhydria impairs dietary iron absorption

Associated Autoimmune Conditions [31]

Screen for:

- Thyroid disease (≈40%) — TSH, anti-TPO
- Type 1 diabetes (≈10%) — glucose, HbA1c
- Addison's disease — cortisol if indicated
- Vitiligo, myasthenia gravis — clinical exam

Treatment Response Monitoring

Hematologic Response

- Reticulocytosis within 5–7 days
- Hemoglobin ↑ ~1 g/dL per week
- Full recovery in 6–8 weeks

Neurologic Response

- Slower than hematologic response
- Maximal recovery may take 6–12 months or longer
- Recovery inversely related to delay and severity
- Monitor function, not labs

Special Populations

- **Pregnancy:** B12 deficiency can cause reversible infertility, and pregnancy increases B12 requirements; untreated deficiency is associated with neural tube defects [32, 33]
- **Pediatric:** juvenile pernicious anemia is a rare autosomal recessive condition presenting between 4 and 28 months, often with proteinuria, and requires lifelong treatment [34]
- **Elderly:** prevalence is higher after age 60, presentation is often atypical, and polypharmacy complicates diagnosis [35]

Key Takeaways for Clinical Practice

- Neurological damage precedes or occurs without anemia [7]
- No blood test reliably reflects nervous system B12 status [6]
- Clinical symptoms guide treatment frequency [7]
- Normal labs do not exclude deficiency
- Lifelong treatment is required [36]
- Many patients need more frequent injections [7]
- Symptom recurrence indicates inadequate dosing
- Early treatment prevents irreversible damage [37]
- Negative antibody tests do not rule out PA [6]
- Empirical treatment is appropriate when suspicion is high
- Risks of undertreatment exceed overtreatment [38]

When standard treatment fails and lab values remain unremarkable despite persistent neurological symptoms, consider cellular resistance mechanisms. See *B12 Beyond the Basics: Pernicious Anemia, Cellular Resistance, and Functional Deficiencies* for diagnostic and treatment guidance on B12 resistance, including the anti-CD320 autoimmune mechanism identified in a 2024 study in *Science Translational Medicine* [39].

For Professional Use Only

References

1. Yang DT, Cook RJ. Spurious elevations of vitamin B12 with pernicious anemia. N Engl J Med. 2012;366(18):1742–1743. https://pubmed.ncbi.nlm.nih.gov/22551146/
2. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 2006;4(3):236–241.
3. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003;67(5):979–986. https://pubmed.ncbi.nlm.nih.gov/12643357/
4. Shipton MJ, Thachil J. Vitamin B12 deficiency — a 21st century perspective. Clin Med (Lond). 2015;15(2):145–150. https://pubmed.ncbi.nlm.nih.gov/25824066/
5. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. N Engl J Med. 1997;337(20):1441–1448. https://pubmed.ncbi.nlm.nih.gov/9358143/
6. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496–513. https://pubmed.ncbi.nlm.nih.gov/24942828/
7. Pernicious Anaemia Society. Clinical guidelines and resources. 2024. https://pernicious-anaemia-society.org/
8. BC Guidelines. Cobalamin (Vitamin B12) and folate deficiency — diagnosis and management. Government of British Columbia; 2023. https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12
9. Healton EB, Savage DG, Brust JC, Garrett TJ, Lindenbaum J. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore). 1991;70(4):229–245. https://pubmed.ncbi.nlm.nih.gov/1648656/

10. Obeid R, Andrès E, Češka R, et al. Diagnosis, treatment and long-term management of vitamin B12 deficiency in adults: a Delphi expert consensus. J Clin Med. 2024;13(8):2176. https://pubmed.ncbi.nlm.nih.gov/38673453/
11. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. Am Fam Physician. 2017;96(6):384–389. https://pubmed.ncbi.nlm.nih.gov/28925645/
12. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603–2611. https://pubmed.ncbi.nlm.nih.gov/28360040/
13. Andres E, Serraj K. Optimal management of pernicious anemia. J Blood Med. 2012;3:97–103. https://pubmed.ncbi.nlm.nih.gov/23028239/
14. Seage CH, Bennett A, Ward N, et al. A systematic review of symptoms of pernicious anemia. Food Nutr Bull. 2024;45(1_suppl):S34–S39. https://pubmed.ncbi.nlm.nih.gov/38987871/
15. Patient-reported characteristics study. medRxiv. 2024. https://www.medrxiv.org/content/10.1101/2024.08.30.24312837 (preprint, not peer-reviewed)
16. Medscape. Megaloblastic anemia overview. https://emedicine.medscape.com/article/204066-overview
17. StatPearls. Pernicious anemia. https://www.ncbi.nlm.nih.gov/books/NBK540989
18. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5(11):949–960. https://pubmed.ncbi.nlm.nih.gov/17052662/
19. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005;(3):CD004655. https://pubmed.ncbi.nlm.nih.gov/16034940/
20. Hemmer B, Glocker FX, Schumacher M, et al. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. J Neurol Neurosurg Psychiatry. 1998;65(6):822–827. https://pubmed.ncbi.nlm.nih.gov/9854956/
21. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988;318(26):1720–1728. https://pubmed.ncbi.nlm.nih.gov/3374544/
22. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, van der Klauw MM. The many faces of cobalamin (vitamin B12) deficiency. Mayo Clin Proc Innov Qual Outcomes. 2019;3(2):200–214. https://pubmed.ncbi.nlm.nih.gov/31193945/
23. Goebels N, Soyka M. Dementia associated with vitamin B12 deficiency. J Neuropsychiatry Clin Neurosci. 2000;12(3):389–394. https://pubmed.ncbi.nlm.nih.gov/10956574/
24. Hutto BR. Folate and cobalamin in psychiatric illness. Compr Psychiatry. 1997;38(6):305–314. https://pubmed.ncbi.nlm.nih.gov/9406735/

25. Andres E, Vogel T, Federici L, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ. 2004;171(3):251–259. https://pubmed.ncbi.nlm.nih.gov/15289425/
26. Pernicious Anaemia Society. Methylmalonic acid and homocysteine. https://pernicious-anaemia-society.org/articles/methylmalonic-acid-and-homocysteine/
27. Randhawa J, Ondrejka SL, Setrakian S, Taylor H. What should I know before ordering a bone marrow aspiration/biopsy in patients with vitamin B12 deficiency? BMJ Case Rep. 2013;2013:bcr2013010200.
28. Rogez J, Urbanski G, Vinatier E, et al. Iron deficiency in pernicious anemia. Eur J Intern Med. 2024.
29. Murphy G, Dawsey SM, Engels EA, et al. Cancer Risk After Pernicious Anemia in the US Elderly Population. Clin Gastroenterol Hepatol. 2015;13(13):2282–2289.
30. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51(4):365–388. https://pubmed.ncbi.nlm.nih.gov/30841008/
31. Betterle C, et al. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327–364. https://pubmed.ncbi.nlm.nih.gov/12050123/
32. Molloy AM, Kirke PN, Brody LC, Scott JM, Mills JL. Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development. Food Nutr Bull. 2008;29(2 Suppl):S101–S111. https://pubmed.ncbi.nlm.nih.gov/18709885/
33. Nie L, Liu X, Li X, et al. Beyond folate: the emerging role of maternal vitamin B12 in neural tube development. Nutrients. 2025;17(12):2040. https://pubmed.ncbi.nlm.nih.gov/40573151/
34. Grasbeck R. Imerslund-Gräsbeck syndrome (selective vitamin B12 malabsorption with proteinuria). Orphanet J Rare Dis. 2006;1:17. https://pmc.ncbi.nlm.nih.gov/articles/PMC1513194/
35. Andres E, Federici L, Serraj K, Kaltenbach G. Update of nutrient-deficiency anemia in elderly patients. Eur J Intern Med. 2008;19(7):488–493. https://pubmed.ncbi.nlm.nih.gov/19013375/
36. National Institute for Health and Care Excellence. Vitamin B12 deficiency in over 16s: diagnosis and management. NICE Guideline NG239. March 2024. https://www.nice.org.uk/guidance/ng239

37. Solomon LR. Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment. Blood Rev. 2007;21(3):113–130. https://pubmed.ncbi.nlm.nih.gov/16814909/
38. Green R, Allen LH, Bjørke-Monsen AL, et al. Vitamin B12 deficiency. Nat Rev Dis Primers. 2017;3:17040. https://pubmed.ncbi.nlm.nih.gov/28660890/
39. Pluvinage JV, Ngo T, Fouassier C, et al. Transcobalamin receptor antibodies in autoimmune vitamin B12 central deficiency. Sci Transl Med. 2024;16(753):eadl3758. https://doi.org/10.1126/scitranslmed.adl3758

For Professional Use Only