ChatGPT

Vitamin B12 Deficiency in Adults: A Comprehensive Review (2010–2025)

Introduction

Vitamin B12 (cobalamin) is an essential water-soluble vitamin required for DNA synthesis, normal red blood cell production (erythropoiesis), and neurological function [1]. In human metabolism, B12 acts as a cofactor for **methionine synthase** (needed to regenerate methionine from homocysteine) and **methylmalonyl-CoA mutase** (needed to convert methylmalonyl-CoA to succinyl-CoA in the Krebs cycle) [2]. Through these roles, B12 is critical for maintaining myelin integrity in the nervous system and for normal hematopoiesis. Deficiency of B12 impairs these pathways, leading to elevated homocysteine and methylmalonic acid (MMA) levels and a spectrum of clinical manifestations affecting the blood, nervous system, and other tissues [3]. On a cellular level, impaired B12-dependent DNA synthesis causes a **nuclear–cytoplasmic maturation asynchrony** in hematopoietic cells: nuclear division lags behind cytoplasmic growth, producing characteristic large **megaloblasts** in the bone marrow [4]. This underlies the megaloblastic anemia seen in B12 (and folate) deficiency. Importantly, vitamin B12 deficiency is typically slowly progressive – owing to substantial body stores – but can eventually lead to irreversible neurologic damage if unrecognized. It remains a significant yet treatable cause of anemia and neurologic dysfunction worldwide.

Absorption, Metabolism, and Storage of B12

Vitamin B12 is obtained primarily from animal-origin foods (meat, fish, dairy, eggs). Its absorption is complex, requiring multiple steps and binding proteins [5]:

- **Gastric phase:** In the stomach, dietary B12 is released from food proteins by pepsin in the presence of gastric acid. The free B12 immediately binds to **R-binder** (also called haptocorrin) secreted in saliva [5]. Gastric parietal cells produce **intrinsic factor (IF)**, but at low pH in the stomach B12 remains attached to R-binder rather than IF.

- **Duodenal phase:** In the duodenum, pancreatic enzymes proteolyze the R-binder, freeing B12. The now-free B12 then binds with intrinsic factor (IF) in the alkaline environment of the small intestine [6]. This B12–IF complex resists digestion and travels onward to the ileum.

- **Ileal uptake:** In the terminal ileum, the B12–IF complex is recognized by the cubam receptor (a complex of **cubilin** and **amnionless** proteins) on enterocytes, allowing receptor-mediated endocytosis [7]. Inside the enterocyte, B12 is released from IF and eventually binds to **transcobalamin II**.

- **Transport and cellular uptake:** B12 bound to transcobalamin II (called **holotranscobalamin**, the "active" fraction) is released into the bloodstream [8]. Holotranscobalamin delivers B12 to tissues by binding transcobalamin receptors on cell membranes. Within cells, B12 is processed in lysosomes

and converted to its two active coenzyme forms: **methylcobalamin** (for cytosolic methionine synthase) and **adenosylcobalamin** (for mitochondrial methylmalonyl-CoA mutase) [9]. Notably, all cobalamin forms in diet or supplements (cyano-, hydroxo-, methyl-, adenosyl-) are converted into these same active forms inside the body [10] – the specific form ingested matters little in terms of ultimate biochemical function.

- **Passive absorption:** In addition to the above **IF-dependent pathway**, a small fraction of B12 can be absorbed by passive diffusion across the gut wall. This accounts for ~1% of an oral dose [11]. While inefficient, it means that very high oral doses of B12 (e.g. 1000–2000 µg) can overcome even a lack of intrinsic factor to some extent, which is the rationale behind oral therapy in pernicious anemia (discussed later).

The human body maintains a substantial reserve of B12. The **liver** is the main storage site, holding about 1–2 mg of B12 – enough for approximately 3–5 years of normal needs if absorption ceased [12]. Vitamin B12 is conserved through **enterohepatic circulation** (B12 is secreted in bile and can be reabsorbed), although a small amount is lost daily in urine and stool (roughly 0.1–0.2% of body stores per day) [13]. Because of these stores and recycling, dietary B12 deficiency usually develops insidiously over several years of inadequate intake. By contrast, **malabsorptive causes** (e.g. pernicious anemia, surgical resection) can lead to deficiency more rapidly (within 1–2 years in severe cases), since absorption is nearly zero even though stores were initially normal. An important exception is exposure to **nitrous oxide**, an anesthetic gas which oxidizes cobalt in B12 and inactivates it; nitrous oxide can precipitate acute neurologic B12 deficiency even in patients with normal B12 stores [14].

Epidemiology

Vitamin B12 deficiency is a common disorder worldwide, especially among older adults. **Global prevalence** estimates for frank B12 deficiency in the general adult population (~20–60 years) are on the order of 3–6%, increasing to around 15–20% in those over age 60 [15]. If one includes "subclinical" deficiency (borderline levels or metabolite evidence of insufficiency), even larger proportions are affected – up to 20% of younger adults and 40% of the elderly may have marginal B12 status in some studies [16]. Prevalence varies by region and population. For example, a UK survey found ~6% prevalence of B12 deficiency in adults <60, rising to ~20% in those >60 [17]. Continental European studies report roughly 2–10% prevalence, depending on the country and B12 cutoff used [18]. In the United States, national data from NHANES indicate at least ~3% of young adults (20–39) are B12-deficient, with higher rates in older groups [18].

Prevalence is generally higher in low- and middle-income countries, likely due to nutritional deficits and gastrointestinal infections. For instance, studies in parts of India report very high rates – in some urban populations, 30–40% or more are B12-deficient, reflecting low intake of animal foods [19]. Similarly, vegetarian or vegan populations are at elevated risk: B12 deficiency can affect a large fraction (estimates of 25–80%) of strict vegetarians/vegans who do not use supplements or fortified foods [20]. Among breastfed infants of B12-deficient mothers, deficiency signs can appear within months after birth if no intervention. Risk also increases with age not only due to diet changes but because malabsorptive conditions (atrophic gastritis, etc.) become more common in the elderly [21]. Certain ethnic and socio-demographic groups with specific dietary patterns or higher Helicobacter pylori prevalence may also have higher rates of B12 deficiency [22].

Etiologies of Vitamin B12 Deficiency

Vitamin B12 deficiency has a multifactorial etiology, spanning **nutritional**, **malabsorptive**, **autoimmune**, and **iatrogenic** causes. The relative frequencies of these causes vary by population. In general, malabsorptive causes (food-bound B12 malabsorption and pernicious anemia) account for the majority of cases in adults [23] [24], while pure dietary deficiency is less common except in certain high-risk groups.

1. Food-Cobalamin Malabsorption (FCM): This broad category refers to any condition in which B12 cannot be normally released from food or is hindered from binding intrinsic factor in the stomach. FCM is now recognized as perhaps the single most common cause of adult B12 deficiency, estimated to account for roughly *50–70%* of cases [25]. It includes: - **Chronic atrophic gastritis:** Gastric mucosal atrophy (whether age-related or H. pylori–related) leads to hypochlorhydria (low acid) and reduced pepsin, impairing the release of B12 from food proteins [26]. Without gastric acid, dietary B12 remains bound to food and cannot attach to IF. Atrophic gastritis is very common in older adults (prevalence ~10–20% or more over age 60) and is a major driver of B12 malabsorption. - **Helicobacter pylori infection:** H. *pylori*-associated gastritis can cause sufficient inflammation and gland loss to reduce intrinsic factor output and acid production, contributing to B12 malabsorption [27]. H. *pylori* is also implicated in some “false-positive” pernicious anemia tests – chronic infection can induce parietal cell antibody production via molecular mimicry with gastric antigens [27]. In regions with high H. *pylori* prevalence, a substantial fraction of B12 deficiency cases may be infection-related rather than strictly autoimmune. - **Prolonged use of acid-suppressing medications: Proton pump inhibitors (PPIs)** and H₂-blockers, by raising gastric pH, can lead to food-cobalamin malabsorption. B12 absorption from food depends on acid; thus long-term PPI therapy (≥12 months) has been associated with B12 deficiency in about 5–15% of users, with risk increasing after 2 or more years (odds ratio ~1.5–2.0 compared to non-users) [28] [29]. Given the widespread use of PPIs in the elderly, this iatrogenic effect is notable. H₂-blockers have a similar though slightly less pronounced effect [29]. Many guidelines recommend monitoring B12 status in patients on long-term acid suppression. - **Pancreatic insufficiency:** Lack of pancreatic proteases (as in chronic pancreatitis or exocrine pancreatic insufficiency) can interfere with B12 absorption. Pancreatic enzymes are needed to degrade R-binder in the duodenum; without them, B12 may not fully transfer to IF. Thus, severe pancreatic insufficiency is a contributing cause of B12 malabsorption [30]. - **Intestinal bacterial overgrowth:** In conditions like blind loop syndrome or stasis, excessive bacteria in the upper small intestine compete for B12. These bacteria can uptake significant amounts of B12, making it unavailable for absorption [31]. This cause is relatively uncommon but can be seen in patients with surgical diverticula, strictures, or severe motility disorders.

Overall, *food-bound B12 malabsorption* (due to any of the above factors) is extremely common in the elderly, explaining why many cases of B12 deficiency in older adults are not classic pernicious anemia but rather secondary to these acquired causes [32] [33].

2. Autoimmune Pernicious Anemia (PA): Pernicious anemia is defined by autoimmune gastritis that destroys gastric parietal cells and leads to intrinsic factor deficiency. It is the classic cause of severe cobalamin malabsorption. PA accounts for an estimated *15–20% (up to 30%)* of adult B12 deficiency cases in various series [24] [34]. In PA, autoreactive T-cells attack the gastric fundus, and patients often have circulating antibodies to parietal cells (APCA) and intrinsic factor (AIFA). The result is chronic atrophic gastritis of the stomach corpus, with loss of acid and IF production [35]. **Anti-intrinsic factor antibodies** are present in about 50% of cases and can directly bind and neutralize IF [36]. **Anti-parietal cell antibodies** are even more common (~90% of PA patients), but they are less specific (they may appear in other autoimmune

diseases or older age) [36]. The net effect is absence of intrinsic factor, so dietary B12 cannot be absorbed in the ileum.

PA typically has a peak onset in late middle age (ages 60 and above are common). It is more frequent in individuals of Northern European ancestry and in those with other autoimmune conditions. The prevalence of PA is about ~0.1% in the general population, rising to ~1.5–2% in those over age 60 [37]. Historically, pernicious anemia was the most common cause of serious B12 deficiency (hence "pernicious," as it was fatal before B12 treatment was discovered). In many developed countries today, its relative contribution has decreased due to the high prevalence of milder food-related malabsorption and widespread B12 supplementation in fortified foods [38]. Nevertheless, PA remains a significant cause of B12 deficiency, especially for the most **profound** deficiencies (<100 pg/mL) and in certain ethnic groups. It is also the prototypical cause for **life-long B12 dependence**, since the loss of intrinsic factor is usually irreversible.

3. Dietary Deficiency: Insufficient dietary intake of B12 alone (with an otherwise normal GI tract) is an uncommon cause in omnivores, given the abundant B12 in animal foods and the body's long stores. However, strict **vegans** and some **vegetarians** who consume no animal products (and do not take supplemental B12) are at high risk over time [39]. It can take 3-5 years or more of a B12-deficient diet to exhaust body stores, but many vegans eventually develop deficiency unless they supplement. Certain populations with chronically poor diet or malnutrition (e.g. older adults with tea-and-toast diets, chronic alcoholics, or people in areas of famine) may also develop dietary B12 deficiency. Additionally, exclusively breastfed infants of B12-deficient mothers (for example, vegan mothers with unrecognized deficiency) can present with severe deficiency within months, as they have very limited stores and rely entirely on milk B12 [40] [41]. Overall, pure dietary B12 deficiency is most prevalent in developing regions (where animal protein intake is low) and in subgroups with restricted diets. Even in wealthier countries, subclinical low B12 is not uncommon in vegetarians – one study noted that many lifelong vegetarians have B12 levels 30–40% lower than omnivores, and ~11% of vegetarians may be deficient if not supplementing [42].

4. Gastrointestinal Surgical and Disease-Related Causes: Any surgical or pathological removal of B12 absorption sites can cause deficiency: - **Gastrectomy:** Partial or total gastrectomy removes the source of intrinsic factor (and acid). B12 malabsorption often begins a few years after surgery, once hepatic stores are used up [43]. Virtually all patients with total gastrectomy will require B12 supplementation for life. - **Bariatric surgery:** Procedures like **Roux-en-Y gastric bypass** exclude the stomach and proximal duodenum, leading to IF deficiency and less contact of food with IF receptors. Without supplementation, up to 30–40% of gastric bypass patients develop B12 deficiency post-operatively [44]. Guidelines universally recommend B12 supplementation after such surgeries. - **Ileal resection or disease:** The terminal ileum is the sole site of IF-B12 uptake. Surgical resection (e.g. for Crohn's disease) or diseases like Crohn's affecting the ileum can eliminate this absorption site, causing B12 deficiency unless parenteral B12 is provided [45]. Individuals with extensive ileal involvement ($\geq$60 cm) almost always need life-long B12 injections. - **Malabsorptive disorders: Celiac disease**, tropical sprue, or other generalized malabsorption can contribute to B12 deficiency (though folate deficiency is even more common in these). **Inflammatory bowel disease** (Crohn's) as mentioned can cause B12 issues if the ileum is affected. Even **chronic HIV enteropathy** can reduce B12 absorption in some cases. These conditions often cause multi-nutrient malabsorption including B12. - **Diphyllobothrium latum infection:** This **fish tapeworm** (acquired from raw freshwater fish) competes for B12 in the gut and can cause profound B12 deficiency in infected individuals. It was historically noted in Northern Europe (where raw pickled fish was consumed) and still occurs in parts of Asia and in immigrants [46]. While rare, it is a classic cause to consider in the differential, especially if megaloblastic anemia occurs in someone with dietary risk (e.g. raw fish consumption).

5. Medications and Toxin-Induced Deficiency: Several medications can contribute to B12 deficiency: - **Metformin:** The commonly used biguanide for type 2 diabetes can interfere with B12 absorption, possibly by affecting calcium-dependent IF-B12 uptake in the ileum or altering gut motility and microbiota [47]. Approximately 10–30% of chronic metformin users develop low serum B12 levels [48]. A large meta-analysis found B12 deficiency (by lab criteria) in ~23% of metformin-treated patients versus ~17% of non-diabetic controls (OR ~3 for deficiency) [49]. Risk increases with longer duration (≥4–5 years) and higher doses of metformin [50]. Because of this, many guidelines recommend periodic B12 monitoring in patients on long-term metformin therapy [51]. - **Proton Pump Inhibitors and H₂-blockers:** (Discussed above under malabsorption) – long-term use can precipitate or exacerbate B12 deficiency [28]. - **Nitrous oxide:** Chronic nitrous oxide exposure (recreational "laughing gas" abuse or repeated anesthesia) inactivates B12 by oxidizing its cobalt atom, acutely blocking B12-dependent enzymes [52]. It can cause **functional B12 deficiency** even if B12 levels are normal. Patients with subclinical B12 deficiency who are exposed to nitrous (e.g. during surgery) can develop sudden neurologic deterioration. This is a well-documented hazard – for instance, young people abusing nitrous oxide may present with severe myeloneuropathy. Nitrous oxide neuropathy is treated with high-dose B12 and can be irreversible if not caught early [53]. - **Other drugs:** Certain anticonvulsants (e.g. phenobarbital, phenytoin) and **long-term antibiotic use** can alter gut flora or metabolism and have been reported to lower B12 levels modestly [54]. **Chloramphenicol** can interfere with B12 in the marrow (rarely causing a refractory response to therapy). **Colchicine** and **cholestyramine** in high doses can impair B12 absorption as well. **Neomycin** (an antibiotic) and **biguanides** (like metformin) have been specifically cited in older literature for causing malabsorption. High-dose **vitamin C** supplements taken with meals might degrade B12, though clinical significance is doubtful. In practice, aside from metformin and PPIs, most drug effects on B12 are relatively uncommon causes of severe deficiency.

6. Congenital and Inherited Causes: These are very rare in adults (usually presenting in infancy or childhood), but include: - **Imerslund-Gräsbeck syndrome:** A rare autosomal recessive disorder of cubam receptor (cubilin or amnionless mutations) causing B12 malabsorption in childhood. Presents with megaloblastic anemia in early life. - **Intrinsic factor mutations:** Extremely rare cases of congenital intrinsic factor absence or dysfunction (congenital pernicious anemia) present in early childhood with severe deficiency. - **Transcobalamin II deficiency:** An AR disorder where B12 cannot be transported in blood due to TCII defect. Causes failure to thrive and pancytopenia in infants; requires early B12 injections. - **Inherited errors of B12 metabolism:** e.g. *cblC* defect (in cobalamin C metabolism) causing combined methylmalonic acidemia and homocystinuria, which can present in later infancy with neurologic impairment. These conditions are beyond the scope of this review but important in pediatric neurology/hematology.

In summary, the most common causes of B12 deficiency in adults are pernicious anemia and food-related malabsorption (atrophic gastritis, H. pylori, medications), with dietary deficiency playing a role primarily in vegans or the malnourished. Many patients, especially older ones, have multiple contributing factors (e.g. an elderly vegetarian on a PPI with H. pylori – all adding up). A thorough evaluation of B12 deficiency should consider these various potential etiologies.

Clinical Manifestations

Vitamin B12 deficiency can produce a wide array of clinical manifestations, reflecting its impact on hematopoietic, neurologic, and other bodily systems. Classically, it causes a **megaloblastic, macrocytic anemia** along with characteristic neurological syndromes. However, presentations range from asymptomatic lab abnormalities to severe, multisystem disease. Notably, symptoms may develop

insidiously and can be subtle or atypical, especially in older patients. Below we detail the major clinical manifestations by system.

Hematologic Manifestations

Anemia: B12 deficiency commonly causes a **macrocytic anemia**. Red blood cells (RBCs) are enlarged (mean corpuscular volume often 100–130 fL) and may be reduced in number. Patients often experience typical anemia symptoms: fatigue, weakness, dyspnea on exertion, lightheadedness, and pallor. In severe cases, the anemia can be profound (hemoglobin in the 4–8 g/dL range), potentially causing symptoms of heart failure or angina. The anemia is usually **normochromic** (normal MCHC) and **macrocytic**; however, mild B12 deficiency may not elevate MCV much, and if iron deficiency or thalassemia coexists, the MCV can even be normal. Because of ineffective erythropoiesis, the reticulocyte count is *inappropriately low* for the degree of anemia (reflecting the fact that marrow precursors are dying before reaching maturation) [55].

Pancytopenia: In more advanced deficiency, other blood cell lines are affected. Leukopenia (especially neutropenia) and thrombocytopenia can occur, so that some patients have **pancytopenia** mimicking bone marrow failure [56]. B12 and folate deficiencies are classic reversible causes of pancytopenia [57]. Typically, B12 deficiency will cause anemia first, with neutropenia and thrombocytopenia in more severe or prolonged cases [58]; isolated thrombocytopenia is less common (usually if platelets are low, anemia and neutropenia are also present) [59].

Macro-ovalocytes and Hypersegmented Neutrophils: The peripheral blood smear provides important clues. The RBCs are often **macro-ovalocytes** – large, oval-shaped red cells [60]. There is typically **anisopoikilocytosis** (variation in size and shape of RBCs) [61]. Neutrophils characteristically show **hypersegmentation** of their nuclei: neutrophils with $\geq$5 lobes are seen (with some neutrophils having 6–7 lobes) [62]. Finding even a few hypersegmented neutrophils can be an early indicator of megaloblastic anemia, sometimes before anemia is significant. One definition is that >5% of neutrophils have $\geq$5 lobes or any have 6 lobes. Hypersegmented neutrophils are not seen in simple iron deficiency or thalassemia, making this finding fairly specific to megaloblastic processes (B12/folate deficiency) [63].

Ineffective erythropoiesis and hemolysis: Because of impaired DNA synthesis, many developing erythroid cells die in the bone marrow (intramedullary apoptosis). This **ineffective erythropoiesis** leads to a release of cell breakdown products – notably **lactate dehydrogenase (LDH)** and **indirect bilirubin** – so these are often elevated in serum [64]. Patients can develop mild **jaundice** (oftentimes a lemon-yellow tint of the skin) from the elevated bilirubin, combined with pallor from anemia. Despite this hemolysis, the reticulocyte count remains low because production is just as impaired as destruction. Haptoglobin may be normal or mildly low. The combination of macrocytic anemia, low reticulocytes, high LDH, and high bilirubin is very suggestive of megaloblastic anemia due to B12 or folate deficiency.

Bone marrow findings: Although a bone marrow biopsy is usually not needed to diagnose B12 deficiency, if performed it shows a **hypercellular** marrow with a marked **megaloblastic maturation** of erythroid precursors [65]. Erythroblasts are unusually large and have immature-appearing nuclei with open chromatin (reflecting the DNA synthesis delay), while their cytoplasm is more mature (due to unaffected RNA/protein synthesis). This is the classic nuclear-cytoplasmic asynchrony. Granulocyte precursors are also abnormal, with giant metamyelocytes and hypersegmented forms. Megakaryocytes may be abnormally large. These marrow changes can help distinguish megaloblastic anemia from other causes of macrocytosis if there is diagnostic uncertainty.

Pseudo-thrombotic microangiopathy (Pseudo-TTP): A rare but dramatic hematologic presentation of severe B12 deficiency is **microangiopathic hemolytic anemia with thrombocytopenia**, which can mimic thrombotic thrombocytopenic purpura (TTP) [66]. Patients present with hemolysis (schistocytes on smear, high LDH, low haptoglobin), thrombocytopenia, and even neurologic symptoms, raising concern for TTP. However, in B12 deficiency there is usually macrocytosis and neutrophil hypersegmentation, and **reticulocyte count is low** (whereas in TTP the marrow responds with high retics) [66]. Critically, **ADAMTS13 enzyme activity is normal** in B12 deficiency (unlike the severe reduction typical in TTP) [66]. This condition has been called **"pseudo-TMA"** or **"pseudo-TTP"**. By some estimates, up to ~2.5–5% of severe megaloblastic anemia cases can exhibit microangiopathic features [67]. Unfamiliarity with this can lead to misdiagnosis: one review noted ~40% of reported cases were initially mistaken for TTP [68]. Fortunately, recognizing B12 deficiency as the cause spares the patient from unnecessary plasma exchange. All patients with unexplained hemolytic anemia and schistocytes should have B12 levels checked to rule this out [69]. Treatment with B12 leads to rapid resolution of the hemolysis and thrombocytopenia in true pseudo-TTP.

Neurologic Manifestations

Vitamin B12 is crucial for neurologic function, and deficiency can lead to demyelination in both the **peripheral and central nervous system**. The classic neurological syndrome is **subacute combined degeneration (SCD) of the spinal cord**, involving demyelination of the dorsal (posterior) columns and lateral corticospinal tracts. However, B12 deficiency can also cause peripheral nerve damage, cognitive and psychiatric changes, and other neurological issues. Neurologic features may occur **with or without anemia**, and in about 20–30% of cases, significant neurologic symptoms occur in the absence of any hematologic abnormalities [70].

Subacute Combined Degeneration (Posterolateral Cord Syndrome): This refers to demyelination of the **dorsal columns** (causing loss of position/vibration sense) and the **lateral corticospinal tracts** (causing weakness and spasticity) in the spinal cord. Patients typically develop **paresthesias** (tingling, "pins-and-needles" sensations) in the feet and hands, **gait instability** (ataxia from loss of proprioception in the legs), and distal **weakness** that can progress proximally. On examination, there may be reduced vibration and joint-position sense in the feet, a positive Romberg sign (swaying with eyes closed, due to sensory ataxia), and signs of corticospinal tract involvement such as **spasticity**, **hyperreflexia**, and **Babinski upgoing toes** if the lateral columns are significantly affected. Patients might describe difficulty walking in the dark (when visual compensation for loss of proprioception is removed). If untreated, SCD can progress to severe weakness and paraplegia. B12 deficiency should be high on the differential for any unexplained myelopathy, especially if there are accompanying hematologic or systemic clues. Notably, **nitrous oxide exposure** can precipitate an acute SCD even in individuals with only marginal B12 levels [71]. SCD is potentially reversible if treated early, but long-standing damage (many months or more) may be permanent.

Peripheral Neuropathy: B12 deficiency can cause a **peripheral polyneuropathy** that may be independent of or in addition to SCD. This is often a sensorimotor axonal neuropathy, typically with a stocking-glove distribution of numbness, tingling, and burning sensations in the feet and hands. Loss of reflexes and mild distal weakness can occur (from peripheral nerve involvement, distinguished from the spastic weakness of spinal cord involvement). Sometimes neuropathy is the predominant feature, and it can be misdiagnosed as diabetic neuropathy or chronic inflammatory neuropathy. B12 should be checked in any idiopathic peripheral neuropathy because it is a treatable cause.

Cognitive and Psychiatric Changes: Vitamin B12 is important for cerebral functioning, and deficiency can lead to **neuropsychiatric manifestations**. Patients may experience **memory loss**, **forgetfulness**, and mild **cognitive impairment**. In more advanced cases, **dementia** can occur, sometimes even resembling Alzheimer-type dementia in older patients. Mood changes such as **depression**, **irritability**, and its flip side, **apathy**, are described. Rarely, B12 deficiency can cause **psychosis** or **hallucinations** – an extreme presentation historically termed *"megaloblastic madness."* These neuropsychiatric effects can occur even without anemia or macrocytosis, which is why B12 deficiency is sometimes screened for in patients with cognitive decline or psychiatric symptoms. Many of these changes are reversible with B12 therapy if recognized in time.

Autonomic and Other Neurologic Features: Severe B12 deficiency can involve autonomic nerves, leading to **impotence** in men or **orthostatic hypotension** (lightheadedness on standing due to blood pressure drop). **Vision changes** can occur due to **optic neuropathy** (gradual bilateral central vision loss from optic nerve demyelination). B12 deficiency has also been associated with **restless legs syndrome** and **loss of taste or smell** in some cases.

Neurologic manifestations can be the *sole* presenting features of B12 deficiency, which makes diagnosis challenging. About a quarter of patients with neurologic B12 deficiency have no anemia [70]. In such cases, a high index of suspicion is required. Clues may be subtle (macrocytosis without anemia, or a history of risk factors). If B12 is borderline, checking methylmalonic acid can help confirm tissue B12 deficiency in patients with neurologic signs [72]. Prompt treatment is critical, as neurological damage can become permanent after 6–12 months of onset. Even with treatment, recovery of neurologic function is variable – peripheral nerves may regenerate over months, but spinal cord damage may only partially improve.

Other Systemic Manifestations

Gastrointestinal: B12 deficiency often affects rapidly-dividing epithelial cells like those in the GI tract. A classic finding is **atrophic glossitis** – the tongue becomes smooth, shiny, and beefy-red, with loss of papillae (sometimes called "Hunter's glossitis"). Patients may complain of tongue pain or burning and taste changes. Glossitis is relatively specific for B12 deficiency (also seen in folate or iron deficiency) and often coexists with angular cheilitis (fissures at the corners of the mouth). Anorexia (loss of appetite) and weight loss are common, partly from the illness and possibly due to glossitis affecting eating. Some patients have mild **epigastric discomfort** or **diarrhea**, due to mucosal changes in the gut. B12 deficiency is also associated with **helicobacter pylori** gastritis and achlorhydria in pernicious anemia, which can cause dyspepsia symptoms.

Skin and Mucocutaneous: *Hyperpigmentation* of the skin is an occasionally reported manifestation. Patients (especially with darker complexions) may develop a diffuse hyperpigmentation or patchy darkening on the hands, feet, and even mucosa [73] [74]. Classically, the knuckles and distal extremities show a bluish-black hyperpigmentation in some cases. This reverses with B12 treatment over weeks. The mechanism is not well understood. Additionally, **vitiligo** (autoimmune depigmentation) is more common in pernicious anemia due to the autoimmune milieu. **Hair** changes (brittle or thinning hair) and **nail** changes (brownish nail discoloration or longitudinal melanonychia) have been described in B12 deficiency and usually normalize after treatment [74]. Recurrent mouth ulcers can also occur. Overall, skin and hair manifestations are less frequent but can be clues in context.

Cardiovascular: B12 deficiency causes elevated homocysteine, which is a risk factor for arterial and venous thrombosis. High homocysteine can promote endothelial dysfunction and hypercoagulability [75]. Some studies have linked elevated homocysteine to increased risk of atherosclerosis, stroke, and venous clots. However, trials of homocysteine-lowering (with B12, folate, B6) have not clearly shown cardiovascular benefit [76], so this remains a point of debate. It is plausible that severe homocysteine elevations (as in combined B12/folate deficiency) contribute to thrombosis. B12 deficiency rarely can present as **venous thromboembolism** (unprovoked clots), and in those cases checking homocysteine is informative. Treating B12 will normalize homocysteine and may reduce this risk factor. From an anemia standpoint, severe anemia can cause high-output cardiac failure or exacerbate angina, which improves with anemia correction.

Bone and Osteoporosis: Chronic B12 deficiency has been linked to reduced bone mineral density and an increased risk of **osteoporosis** and fractures [77]. Epidemiologic studies show that adults with low B12 levels tend to have lower BMD and higher fracture rates than those with normal B12 [78]. Several mechanisms have been proposed: - **Hyperhomocysteinemia:** Elevated homocysteine (due to B12 and folate deficiency) may impair collagen cross-linking in bone matrix, leading to weaker bone structure. High homocysteine is recognized as a risk factor for osteoporotic fractures, and lowering homocysteine (with B vitamins) has been hypothesized to improve bone quality. - **Impaired osteoblast function:** B12 is thought to play a role in osteoblast maturation, possibly via S-adenosylmethionine (SAM)–dependent DNA methylation reactions. B12 deficiency may blunt osteoblast activity – animal models have shown reduced bone formation in B12-deficient states [79]. One study found that B12-deficient mice had growth retardation and osteoporosis due to an inability of osteoblasts to mature (which could be rescued by growth hormone via IGF-1 stimulation) [80]. - **Increased osteoclastogenesis:** Some research suggests low B12 (and the resulting high MMA/homocysteine) might stimulate osteoclast formation, tipping the balance toward bone resorption [81]. - **Common risk factors:** Older patients with B12 deficiency (e.g. pernicious anemia) often have other risk factors for osteoporosis (age, dietary issues), so part of the association is epidemiologic.

Given these links, it is recommended to ensure adequate B12 levels in patients at risk for osteoporosis. B12 supplementation in deficient individuals may improve bone turnover markers [82], though it's unclear if it significantly improves BMD unless there is frank deficiency. In practice, patients with pernicious anemia or chronic B12 deficiency should be counseled on bone health (calcium/vitamin D, DEXA screening as appropriate).

Reproductive: Vitamin B12 plays a role in fertility and fetal development. Severe B12 deficiency in women can cause **infertility** or recurrent miscarriages, which often resolve upon treatment. Men with B12 deficiency can have low sperm counts and abnormal sperm morphology/motility (and rarely impotence), which may improve with B12 therapy. During pregnancy, B12 needs are increased; B12 deficiency in pregnancy (especially if coupled with folate deficiency) can contribute to **neural tube defects** in the fetus and developmental delays in infants. Therefore, it's important to identify and treat B12 deficiency in pregnant patients (particularly vegetarians) and to ensure breastfed infants of vegan mothers receive B12 supplementation. Some guidelines recommend all pregnant vegetarians take B12 supplements.

Immunologic: There is some evidence that B12 deficiency can lead to immune system disturbances. Neutropenia from B12 deficiency may impair the ability to fight infections. Some studies have noted reduced NK cell activity in B12-deficient patients and improvement after B12 therapy. These effects are not fully characterized, but they underscore the systemic impact of B12. Additionally, because pernicious anemia is autoimmune, patients often have other autoimmune processes as discussed below.

In summary, B12 deficiency should be thought of as a multisystem disorder. Classically, it involves the **triad** of anemia, gastrointestinal disturbance (glossitis), and neurologic issues, but not all need be present. For example, a patient may present with neuropathy and hyperpigmentation but no anemia, or with anemia and cognitive changes but no glossitis. The potential irreversibility of the neurologic damage makes early recognition vital.

Diagnosis

Diagnosing vitamin B12 deficiency involves demonstrating low B12 status and identifying the cause, while differentiating it from other causes of macrocytosis or neurologic disease. Key points in diagnosis include laboratory tests for B12 levels and related markers, blood smear examination, and tests for pernicious anemia.

Complete Blood Count (CBC) and Blood Smear: The CBC typically shows a **macrocytic anemia** (high MCV) with low reticulocytes. Hemoglobin can range from mildly low to very low depending on severity. If the MCV is >110 fL and especially if there is accompanying neutropenia or thrombocytopenia, a megaloblastic process is likely. The **peripheral smear** is invaluable: finding macro-ovalocytes and hypersegmented neutrophils strongly suggests B12 or folate deficiency [83]. Other findings like anisocytosis and occasional Howell-Jolly bodies (nuclear DNA remnants in RBCs) may be seen due to ineffective erythropoiesis [60]. If target cells or stomatocytes are present, or if macrocytosis is mild, consider liver disease or alcohol effect. If macrocytosis is absent (MCV normal) but B12 deficiency is strongly suspected (e.g. neurological signs), remember that coexisting microcytic anemia or recent bleeding could mask macrocytosis.

Vitamin B12 Level: Serum B12 (cobalamin) level is the primary diagnostic test. Levels <~200 pg/mL (<148 pmol/L) are usually considered **deficient**, especially if symptomatic. Levels between ~200–300 pg/mL are often deemed **borderline/indeterminate**. However, the exact cutoffs can vary by lab and some use slightly higher cutoffs (e.g. <250 pg/mL as low). In Japan and some parts of Europe, the lower limit of normal B12 is set much higher (around 500–550 pg/mL) [41], based on observations that neurologic symptoms can occur at "low-normal" levels by US standards. In practice, if a patient has neurologic or hematologic signs and a B12 level in the low-normal range, further investigation is warranted (with metabolites or treatment trial). **False-normal B12 levels** can occur in certain contexts: for example, liver disease or myeloproliferative disorders can raise B12 (due to increased binding proteins), masking a tissue deficiency. Also, the B12 assay might detect biologically inactive B12 analogues in some cases (or patient antibodies can interfere). Thus, B12 level must be interpreted in context. If clinical suspicion is strong but B12 is “normal,” check metabolites or specialized tests.

Methylmalonic Acid (MMA) and Homocysteine: These are metabolic intermediates that accumulate when B12 (or folate) is insufficient: - **MMA:** Elevated MMA is a specific marker of B12 deficiency. B12 is required for conversion of methylmalonyl-CoA to succinyl-CoA; without B12, MMA levels rise in blood and urine. An **elevated MMA** (typically >0.4 µmol/L) strongly suggests B12 deficiency if renal function is normal. MMA is more sensitive than serum B12, often rising before B12 is frankly low. It’s especially useful in those with borderline B12 levels: if MMA is high, it indicates true tissue B12 deficiency. **Important:** Renal impairment can cause MMA to rise (reduced clearance), so mild elevations must be interpreted with caution in older patients or those with CKD. But a normal MMA effectively *rules out* clinically significant B12 deficiency [84] (in the absence of renal failure). - **Homocysteine:** B12 (and folate and B6) are required for homocysteine metabolism, so homocysteine levels rise in both B12 and folate deficiencies. **Elevated homocysteine** is a sensitive but nonspecific marker – it could indicate B12 or folate deficiency (or B6), or other conditions. If

homocysteine is normal and MMA is normal, it is very unlikely that a significant B12 or folate deficiency is present [84]. The combination of **normal homocysteine + normal MMA** essentially rules out B12 deficiency in almost all cases [84]. On the other hand, **elevated homocysteine with normal MMA** points more toward folate deficiency. **Both MMA and homocysteine elevated** suggests B12 deficiency (possibly combined with folate def). These tests are often done together when the B12 level is borderline. In practice, many clinicians skip straight to treatment if B12 is borderline and there are suggestive signs, rather than obtaining these markers, due to cost or time.

Holotranscobalamin (Active B12): This newer test measures the fraction of B12 bound to transcobalamin II (which is delivered to cells). It may become low earlier in B12 deficiency (because total B12 can be maintained by inert B12 on haptocorrin). A low holotranscobalamin (<35 pmol/L) indicates deficiency even if total B12 is normal. Active B12 assays are not yet standard everywhere but are used in some settings to improve early detection.

Folate levels: Since folate deficiency can produce nearly identical blood findings (macrocytic anemia), it is routine to check **serum folate** (or RBC folate) alongside B12. Folate (vitamin B9) deficiency is usually due to diet or malabsorption and can coexist with B12 deficiency. A low folate with normal B12 points to folate deficiency as the cause of megaloblastosis; however, **concurrent deficiencies** exist in some cases (e.g. malnutrition or malabsorption can cause both). Folate deficiency does *not* cause the neurologic syndrome seen in B12 deficiency. It's crucial to identify which, or both, vitamins are deficient, because treating folate deficiency alone will correct the anemia but **can worsen the neurologic problems of B12 deficiency** (by allowing more DNA synthesis without fixing the myelin issues). Therefore, if there is any doubt, clinicians often supplement both vitamins.

Intrinsic Factor Antibody and Parietal Cell Antibody: These tests help confirm **pernicious anemia** as the cause of B12 deficiency: - **Anti-Intrinsic Factor Antibodies (AIFA):** A positive intrinsic factor blocking antibody test is highly specific for pernicious anemia (specificity ~100% when positive). It's present in about 50%–60% of patients with PA [36]. AIFA is the diagnostic hallmark of pernicious anemia. However, because of modest sensitivity, a negative test does not exclude PA. - **Anti-Parietal Cell Antibodies (APCA):** Parietal cell antibodies are present in ~85–90% of pernicious anemia patients [36] but they are non-specific – about 10% of healthy elderly and patients with other autoimmune diseases also have APCA. APCA is useful as a supportive clue (especially if extremely high titer), but by itself it is not conclusive. Notably, chronic H. pylori infection can induce APCA as well [85]. A positive APCA with a negative AIFA might still indicate PA if clinical context fits, but one must interpret carefully. Many clinicians will diagnose PA if B12 is low, APCA is positive (in a patient with, say, thyroid disease), and no other cause is evident – even if AIFA is negative (since AIFA can be transiently negative or in low titer in some PA cases).

Gastric Biopsy and Serum Gastrin/Pepsinogen: In cases of suspected pernicious anemia or to assess gastric mucosal status, an upper GI endoscopy with biopsies can be done. Histology can confirm **autoimmune metaplastic atrophic gastritis** (AMAG) with corpus/fundus atrophy and intestinal metaplasia. The presence of **ECL-cell hyperplasia** or carcinoid tumors in the stomach also supports longstanding PA. Non-invasively, **fasting serum gastrin** is often markedly elevated in PA (due to achlorhydria removing feedback inhibition on G-cells), while **pepsinogen I** is low (due to loss of chief cells). A **pepsinogen I : II ratio** <3 is a marker of gastric corpus atrophy [86]. These tests are not routine but can be supportive; for example, high gastrin and low pepsinogen I strongly suggest pernicious anemia if B12 is low.

Bone Marrow Examination: Rarely performed solely for B12 diagnosis, but if a bone marrow biopsy is done for unexplained cytopenias, the finding of megaloblastic maturation can point toward B12 or folate deficiency as the cause. Marrow exam may be needed if multiple diagnoses are possible (e.g., to distinguish MDS from B12 deficiency) – though usually checking B12/folate and response to therapy suffices.

Differential Diagnosis: - **Folate deficiency:** as mentioned, causes an identical megaloblastic anemia (macrocytic, hypersegmented neutrophils, low retic). Key differences: folate def usually from diet or alcohol, develops faster (months), and does not cause the neurologic symptoms seen in B12 deficiency. Serum folate levels (low) and MMA (normal in folate def) help distinguish. Often both deficiencies coexist, so both vitamins may need replacement. - **Alcoholism and liver disease:** These can cause macrocytosis (MCV 100–110) but *without* megaloblastic changes. Target cells and spur cells may be present in liver disease. Liver disease can also elevate B12 levels (due to release from damaged liver or increased binding proteins), so a high-normal B12 doesn't exclude deficiency in an alcoholic patient – rely on metabolites or clinical picture. - **Hypothyroidism:** Severe hypothyroidism can cause macrocytic anemia (mechanism not fully clear, possibly reduced RBC production). TSH testing will identify this. Treating hypothyroidism corrects the macrocytosis. - **Myelodysplastic Syndromes (MDS):** MDS can cause macrocytosis and cytopenias, and sometimes has hypercellular marrow with dysplastic cells, which can mimic megaloblastic anemia. However, B12/folate levels will be normal or high in MDS. MDS generally occurs in older patients and can have other features (e.g. pelgeroid neutrophils, abnormal platelets). If B12 and folate are normal and there is unexplained macrocytic anemia, a bone marrow biopsy may be done to evaluate for MDS. - **Medication effects:** Certain drugs cause macrocytosis without megaloblastic anemia, such as hydroxyurea (seen in patients with polycythemia or SCD), zidovudine (AZT) for HIV, and chemotherapy agents. These usually are known from history. Antifolate drugs (methotrexate, trimethoprim) cause a functional folate deficiency and thus a megaloblastic picture – checking red cell folate can confirm and leucovorin (folinic acid) can treat it. - **Copper deficiency:** Deficiency of copper can cause anemia, neutropenia, and even myeloneuropathy similar to B12 deficiency [87]. This is an often overlooked cause of macrocytosis/pancytopenia and neurologic symptoms. It can occur in patients with malabsorption (e.g. after gastric bypass or with high zinc intake which blocks copper absorption). Copper deficiency can cause a vacuolar myelopathy resembling SCD of B12. Serum copper and ceruloplasmin levels should be checked if clinical suspicion (especially if B12 is normal). Replacement of copper reverses the hematologic manifestations, though neurologic recovery may be slow [87]. - **Combined deficiencies:** Mixed nutritional deficiencies (e.g. B12 + iron or B12 + folate) can yield misleading results. For instance, concomitant iron deficiency might counteract the macrocytosis of B12 deficiency, leading to a near-normal MCV. Always assess iron studies, folate, and B12 all together in a macrocytic anemia, especially in older or malnourished patients, to ensure all deficiencies are detected.

In practice, once macrocytic anemia is found, labs for B12, folate, TSH (for hypothyroid), and perhaps homocysteine/MMA are the next step. If B12 comes back low, one can proceed with treatment and etiologic workup for the cause (PA vs others). If B12 is borderline, MMA can help confirm. And if everything is normal but macrocytosis persists, consider bone marrow biopsy for MDS or other occult causes.

Management

The management of B12 deficiency involves two main goals: (1) **Repletion of vitamin B12** to reverse the deficiency and treat symptoms, and (2) **Addressing the underlying cause** (if possible) to prevent recurrence. B12 repletion can be achieved via intramuscular injections or high-dose oral supplementation, and in either case the outcomes are generally excellent if started before permanent damage occurs.

Vitamin B12 Replacement Therapy

Parenteral (Intramuscular) B12 Therapy: Traditional therapy for B12 deficiency, particularly when due to malabsorption, has been intramuscular (IM) injection of vitamin B12. Parenteral B12 bypasses the GI tract entirely and is effective regardless of the cause of deficiency. - The typical regimen for **cyanocobalamin (IM):** 1000 µg (1 mg) injections. A common schedule is **daily or every-other-day 1 mg IM for 1–2 weeks** (to refill body stores), then weekly 1 mg IM for about a month, then monthly 1 mg IM as maintenance [88]. Variations exist; some clinicians give daily for 5 days, then weekly x4, etc. The key is a loading phase followed by ongoing maintenance for those with irreversible causes. In severe anemia, transfusion is rarely needed (the marrow typically recovers quickly with B12). - **Hydroxocobalamin** IM (1 mg) is another injectable form, often used in Europe/UK. It has a longer half-life in the body. In the UK, for example, maintenance for pernicious anemia is hydroxocobalamin 1 mg IM every 3 months after an initial loading phase [89]. - IM therapy reliably reverses hematologic abnormalities and can improve neurologic symptoms, especially if started early. IM B12 is considered first-line when there are serious neurologic symptoms or if compliance with orals is doubtful [90] [91]. It produces a very rapid rise in B12 levels. - **Subcutaneous** injections can also be used (the B12 is usually given deep subcutaneously or intramuscularly; both routes have similar efficacy). - Side effects of B12 injections are minimal (the injections can cause some local pain, and rarely allergic reactions). Because B12 is water-soluble, there is no risk of overdose; any excess is excreted.

High-Dose Oral B12 Therapy: In the past two decades, evidence has shown that oral replacement of B12 in high doses can be as effective as parenteral therapy for many patients [92]. Even in pernicious anemia (no intrinsic factor), roughly 1% of a large oral dose can be absorbed by passive diffusion. Key points: - Effective oral therapy requires a **high dose**, typically 1000–2000 µg (1–2 mg) of B12 daily [92]. This ensures enough passive absorption to meet needs. Lower doses (e.g. 50–100 µg) in a standard multivitamin are not sufficient to treat deficiency. - Studies and consensus guidelines have found oral B12 (1–2 mg daily) to produce equivalent outcomes to IM injections in mild-to-moderate deficiency, even when malabsorption is present [93]. For example, a meta-analysis and a 2024 Delphi consensus agreed that 1000–2000 µg/day orally can be used **even in pernicious anemia or other malabsorptive states**, with good outcomes [93] [92]. Thus, oral B12 is a legitimate alternative to injections for many patients. - Oral therapy is especially attractive for patients who prefer to avoid injections, and in healthcare systems where frequent clinic visits are a barrier. Patients need to be reliable with daily pill intake for it to work. - Typically, oral B12 is given daily for life if used as sole therapy. Some protocols still start with a brief IM loading to rapidly refill stores and then switch to oral for maintenance, but this may not be strictly necessary in all cases [94] [91]. - Some countries use **sublingual** B12 (which is essentially oral, just dissolved under the tongue) at similar doses. There is no clear evidence that sublingual is superior to swallowed oral tablets; the efficacy is comparable because absorption ultimately is via the GI tract after swallowing saliva. - **Efficacy:** Oral B12 at 1–2 mg/day raises B12 levels and corrects hematologic indices in the vast majority of patients. Follow-up levels can be checked to ensure response. If a patient fails to respond to oral therapy (persistent anemia or neurologic issues), one should question compliance or consider switching to IM. - Guidelines vary: Canada and some European countries endorse oral B12 as first-line for many patients (except those with severe neuro symptoms) [95]. The UK (NICE) historically has favored IM for all pernicious anemia, though even there patient preferences are being considered more. The 2024 UK NICE guideline allows that oral cyanocobalamin can be considered in some non-PA cases or maintenance.

Nasal and Other Routes: A nasal B12 gel or spray (typically 500 µg in one nostril weekly) is available and can maintain B12 levels after initial IM correction. This is mostly used for maintenance in mild cases or

convenience (e.g. **cyanocobalamin nasal spray** weekly for patients in remission). Its efficacy is similar to oral high-dose for maintenance, but it's more expensive. Sublingual lozenges (500–2000 µg) are also used by some patients and are essentially equivalent to oral. There is ongoing research into B12-loaded nanopatches or other novel delivery, but currently, IM and oral remain the mainstays.

Duration of therapy: This depends on the cause: - If the cause is irreversible (pernicious anemia, surgical absence of absorption sites), **lifelong therapy** is required. Typically IM injections monthly for life or daily oral for life. - If the cause is dietary and can be corrected (e.g. a vegan who will start eating B12 or taking supplements), then therapy can be given until stores are replete and diet is improved – for example, treat for 1–2 years and then reassess dietary intake. In practice, many will still recommend ongoing low-dose oral supplementation thereafter to ensure levels remain good. - If the cause is temporary (e.g. B12 deficiency from a resectable Diphyllobothrium latum infection or short-term malabsorption), treat for a period (months to a year) and confirm resolution of the issue, then monitor. But true temporary causes are few. - Notably, **pernicious anemia requires indefinite treatment** – historically an untreated PA was fatal within a few years, whereas treated patients now have normal lifespans but must continuously receive B12.

Monitoring response: An important part of management is to ensure the patient is responding to therapy: - **Reticulocyte count** should rise within 3–5 days of starting B12 injections, often peaking around day 7–10. This is a sign of bone marrow regeneration (termed the "reticulocyte rush"). The patient may feel a bit better as this happens, though high-output cardiac symptoms can transiently occur as the marrow uses energy to produce cells. - **Hemoglobin** will start increasing after about 1–2 weeks and typically normalizes by 1–2 months of therapy. The MCV will gradually come down to normal. By ~8 weeks, blood counts should be completely corrected. Persistence of anemia beyond 2 months should prompt re-evaluation for other causes or non-adherence. - **Neurologic symptoms:** These improve more variably. Some patients note improvement in neuropathy or gait within days to weeks; others take 3–6 months for maximal recovery. If symptoms were present for a long time (say >1 year), full recovery is less likely. However, continued slight improvement can occur up to 12 months. If there is no improvement in neurologic signs after a couple of months, one should recheck B12 levels (ensure they've risen) and consider alternative or additional diagnoses. - **Biochemical markers:** MMA and homocysteine levels should normalize after B12 repletion. If they remain high despite normal B12 level, it suggests ongoing functional deficiency or another issue (like renal failure affecting MMA or a concomitant folate deficiency affecting homocysteine). - **Follow-up B12 level:** Some clinicians re-measure B12 a few months after starting therapy (especially if on oral) to ensure it's in a robust range (>300–400 pg/mL). This can confirm adequate absorption in oral therapy cases. On injections, levels often rise very high (thousands) which is fine. - Once stable, B12 levels can be checked yearly or as needed (many patients on lifelong therapy don't need frequent levels if it's clear they're getting adequate replacement).

Addressing Ongoing Neurologic Issues: If after adequate B12 treatment the patient's neurological symptoms do not improve, one should investigate other causes. The 2024 Delphi consensus, for example, emphasized re-evaluating if neurologic symptoms persist – perhaps the B12 dose wasn't sufficient or another neuropathy is present [96] [97]. In some cases, physicians may switch a patient from oral to IM if neurologic recovery is suboptimal, on the theory that higher serum levels might aid nerve healing (though evidence is limited) [97]. Physical therapy and neurorehabilitation can be helpful for patients with gait impairment or neuropathy during recovery.

Treating the Underlying Cause

In tandem with replacing B12, it's critical to manage the cause of deficiency and any associated conditions:

- **Pernicious anemia (Autoimmune Gastritis):** Since intrinsic factor can't be restored, these patients will be on lifelong B12 therapy. It's important to **monitor for gastric cancer/carcinoids** (see Special Considerations below). Also, PA patients often have **iron deficiency** (from associated achlorhydria causing poor iron absorption) – check iron studies and supplement if needed. Screen for other autoimmune diseases (thyroid, etc.) as appropriate. Family members might benefit from periodic B12 checks as PA can cluster in families. Patients should be informed that they have a lifelong condition requiring continuous B12, and that if they stop treatment, symptoms will recur in a couple of years.
- **Dietary deficiency:** Ensure the patient adopts a B12-rich diet or continues on oral supplementation long-term. For vegans, this means routinely taking a B12 supplement or B12-fortified foods (nutritional yeast, fortified cereals, plant milks, etc.). It should be stressed that diet alone (without animal products or fortified sources) is insufficient. Follow-up levels can ensure adequacy. Pregnant or lactating women on vegan diets need particular attention to B12 intake to protect the baby.
- **Helicobacter pylori infection:** If diagnosed (via biopsy or breath/stool test), it should be treated with appropriate antibiotic therapy. Eradicating H. pylori may improve B12 absorption and can at least remove one factor contributing to deficiency. (B12 therapy still needed to correct current deficiency.)
- **Medication-induced:** If possible, reduce or discontinue the offending drug. For example, if a patient on long-term metformin develops B12 deficiency, one might attempt to reduce the dose or ensure they are on B12 supplementation. Many diabetics on metformin are simply given oral B12 supplements empirically after a few years. If a PPI is not absolutely indicated, it could be deprescribed or switched to a less potent H2 blocker, etc. Of course, many patients will need to remain on these medications; in those cases, continuing B12 supplementation is the answer.
- **Malabsorptive conditions:** For celiac disease, treat with a gluten-free diet which may allow better absorption (though B12 supplementation should be continued until levels normalize). For bacterial overgrowth, antibiotics (rifaximin or others) can clear the overgrowth and improve B12 levels, though often still need supplements in interim. In Crohn's disease, manage the active disease (immunosuppressants, etc.) but recognize if the ileum is significantly affected, B12 injections are likely needed indefinitely.
- **Surgeries:** For gastric bypass or significant ileal resection, anticipate B12 deficiency – such patients should be placed on prophylactic B12 (typically IM monthly or high-dose oral) immediately post-op and continued for life [98]. This prevents deficiency from developing. Many bariatric surgery programs include routine B12 injections or sublingual B12 as part of their protocol.
- **Concurrent deficiencies:** Often patients benefit from a general nutritional replenishment. Folate, iron, and other vitamins should be checked and replaced if needed, to optimize hematologic response. If folate is low or borderline, it's common to give folic acid in addition to B12 (provided B12 is given first to avoid precipitating neuro issues).

Supportive Care and Symptomatic Treatment

- If anemia is severe (Hb <6–7 and symptomatic), blood transfusions can be considered carefully. However, once B12 therapy is started, the marrow will often respond briskly, so transfusion is usually avoidable unless there is cardiac ischemia or hemodynamic instability.

- Physical therapy and assistive devices for neuropathy (e.g., canes, walkers) may be needed early on. Occupational therapy can help those with coordination or cognitive difficulties.
- Painful paresthesias might be managed with neuropathic pain agents (e.g. gabapentin) while awaiting B12 response.
- Dietary consultation can be helpful for vegetarians or malnourished patients to ensure proper ongoing B12 intake.
- In cases of severe neuropsychiatric manifestations (e.g. confusion or psychosis), hospital admission and safety measures may be warranted during initial treatment, as improvement may take days to weeks.
- No specific antidote beyond B12 exists; folate should *not* be given alone in B12 deficiency because it can worsen neurologic progression. If folate is also low, both should be repleted.

Monitoring and Follow-Up

Once deficiency is treated and the patient is stable: - **Regular follow-up:** Ensure compliance with therapy (especially for oral B12). For injections, often a primary care schedule is set up (e.g. visit every 1–3 months for injection). - **Lab monitoring:** Check CBC and B12 perhaps 1–2 months after therapy initiation, then every 6–12 months. In pernicious anemia, some clinicians eventually just monitor clinically if the patient reliably gets injections, since relapses are unlikely on treatment. - **Metabolic markers:** not needed routinely if patient is doing well, but MMA and homocysteine could be rechecked in unusual cases (like if neurologic symptoms persist to ensure they normalized, indicating adequacy of dosing). - **Associated conditions:** Monitor for **gastric cancer** in PA (see below), screen/treat **thyroid disease** if autoimmune, etc. - **Education:** Patients should be educated on the nature of their condition. Those on lifelong therapy should know the importance of not discontinuing it. They should also inform future providers of their diagnosis (to avoid misinterpretation of high B12 levels from injections, etc.). MedicAlert bracelets are optional but some PA patients carry them to indicate they need B12.

Special Considerations and Preventive Aspects

Pernicious Anemia and Gastric Cancer Surveillance

Patients with pernicious anemia (autoimmune metaplastic atrophic gastritis) have an increased risk of gastric neoplasia. Chronic atrophic gastritis leads to intestinal metaplasia and dysplasia over time: - **Gastric Carcinoma:** The risk of gastric adenocarcinoma (particularly intestinal type, non-cardia) is roughly 2-3 times higher in PA patients than in the general population [99]. One large study found an odds ratio ~2.18 for gastric cancer in PA [99]. The risk is thought to be due to long-standing mucosal atrophy and pernicious gastritis rather than B12 per se. - **Carcinoid Tumors:** PA is also associated with gastric carcinoid tumors (type I gastric NETs) arising from ECL-cell hyperplasia due to achlorhydria (hypergastrinemia). The OR for carcinoid in PA is even higher (since nearly all type I carcinoids occur in this setting).

Surveillance guidelines: There is some debate on how to manage this risk: - Many experts recommend at least a **one-time endoscopic evaluation** upon diagnosis of pernicious anemia, especially if the patient is middle-aged or older [100]. The British Society of Gastroenterology, for example, suggests considering a baseline endoscopy with biopsies in individuals $\geq$50 years old with newly diagnosed pernicious anemia [100]. The endoscopy can document the extent of atrophy/metaplasia (which can be staged by OLGA/OLGIM systems) and check for any neoplastic lesions at the outset. - For **ongoing surveillance**, practices vary. Some suggest that if baseline biopsies show advanced atrophy or intestinal metaplasia (OLGA stage III or

IV), periodic endoscopies (every 3 years or so) are warranted [101]. Patients with pernicious anemia who have OLGA stage III/IV gastritis fall into a high-risk category for gastric cancer (similar to other causes of extensive gastric atrophy) [102]. One cost analysis suggested focusing surveillance on PA patients with OLGA 3–4 could yield a reasonable number-needed-to-scope of ~5 to detect one neoplasia [103]. - If initial endoscopy is normal and shows only mild changes (stage I–II), some gastroenterologists forego regular surveillance and just advise patients to report any new GI symptoms promptly. Others might do a repeat scope in 5–10 years. - In practice, many PA patients are under the care of both hematology and gastroenterology. It's important their B12 is treated (which we do) and that their **gastric issues** are not forgotten once anemia resolves. At minimum, patients should be counseled on reporting refractory GI symptoms like new abdominal pain or melena.

Additionally, pernicious anemia patients often have other gastric pathology: - They frequently have benign **gastric polyps** (fundic gland polyps) due to the long-term achlorhydria and hypergastrinemia. - Testing for **H. pylori** is still relevant. Some PA patients also have H. pylori infection contributing to atrophy; eradicating H. pylori might theoretically reduce cancer risk (though PA's atrophy is primarily autoimmune).

Bottom line: Treating the B12 corrects the anemia but does not remove the cancer risk from the gastric mucosa. So these patients should remain vigilant. Many centers will perform periodic endoscopy (every 3–5 years) on confirmed PA patients, especially if they had any dysplasia or extensive metaplasia on initial biopsy.

Autoimmune Disease Associations

Pernicious anemia is an autoimmune disease, and it commonly coexists with other autoimmune disorders. This reflects a general predisposition to autoimmunity. - The strongest association is with **autoimmune thyroid disease**. Patients with PA have a high prevalence of Hashimoto's thyroiditis and, to a lesser extent, Graves' disease. Conversely, patients with autoimmune thyroiditis have increased prevalence of B12 deficiency. Studies have found, for example, ~20% of patients with Hashimoto's have circulating parietal cell antibodies [104], and some develop PA. Approximately 10% of PA patients have autoimmune thyroid disease clinically. It is reasonable to check TSH in a patient with newly diagnosed PA, and periodically thereafter, since hypothyroidism might develop. - **Type 1 Diabetes (T1DM):** There is a known association between PA and T1DM (both involve organ-specific autoimmunity). About 5% of type 1 diabetics have B12 deficiency or PA [105], and screening for B12 levels in longstanding T1DM is sometimes recommended. Conversely, a small percentage of PA patients will have islet cell antibodies or overt T1DM. - **Vitiligo:** Patchy depigmentation of the skin (vitiligo) is more common in PA patients due to autoimmune attack on melanocytes. It's mostly a cosmetic issue but is a clue to underlying autoimmunity if seen with anemia. - **Other autoimmune conditions:** These include **Addison's disease** (adrenal insufficiency), **hypoparathyroidism**, and **Sjogren's syndrome** – all reported at higher frequency in PA patients. **Myasthenia gravis** and **pernicious leucopenia** are rarer associations. **Rheumatoid arthritis** and **systemic lupus** may coexist as well (though not necessarily related to PA). - Some studies have quantified these associations: e.g., one found 21% of Hashimoto's patients had parietal cell antibodies [104], and other research shows a higher incidence of B12 deficiency in those with **autoimmune polyendocrine syndromes** (like Schmidt syndrome). - **Implications:** Clinicians managing PA should consider screening for associated conditions. At least **TSH** (thyroid function) should be checked initially and perhaps every few years. If symptoms suggest (e.g. hyperpigmentation and hypotension might prompt adrenal testing for Addison's, etc.), further targeted tests are done. Likewise, patients with known other autoimmune diseases who develop anemia or neuropathy should have B12 checked, as they might be developing pernicious anemia.

Autoimmune associations also mean that pernicious anemia can cluster in families (not PA per se, but family members may have thyroid disease, diabetes, etc. and possibly B12 issues).

Special Populations: Pregnancy and Older Adults

Pregnancy: Pregnant individuals have increased requirements for B12 (due to increased maternal blood volume and fetal needs). While folate deficiency is a more widely recognized cause of neural tube defects, B12 deficiency is also implicated in adverse pregnancy outcomes like *neural tube defects, intrauterine growth restriction, preeclampsia, and miscarriage*. Vegans or women with pernicious anemia need careful monitoring in pregnancy. It's recommended that women planning pregnancy ensure adequate B12 status. Prenatal vitamins often contain some B12 (though usually only ~2–12 µg), which is enough for women with normal absorption but not if the mother has pernicious anemia – those patients should stay on their regular B12 injections through pregnancy (B12 shots are safe in pregnancy). Newborn infants rely on maternal B12; undiagnosed maternal deficiency can lead to infant developmental delays, hypotonia, and megaloblastic anemia in the first year of life. Thus, obstetricians will sometimes check B12 levels in women who are at risk (vegetarian, prior malabsorptive surgery, etc.). Treating a B12-deficient pregnant woman is crucial for both mother and baby: improvement in energy and neurologic function in the mother, and prevention of neurologic damage in the fetus. No fetal harm from B12 therapy has been noted; indeed, it's essential.

Older Adults: The prevalence of B12 deficiency increases with age. Many older adults have atrophic gastritis or are on medications (metformin, PPIs) that predispose to low B12. Additionally, B12 deficiency in the elderly may manifest primarily as cognitive decline or gait disorder, which can be mistaken for "normal aging" or dementia. There is ongoing debate about whether routine screening for B12 deficiency in asymptomatic elderly is cost-effective. Some guidelines do recommend periodic B12 testing in patients over 60–65, especially if they have any anemia or neurological symptoms (even mild). The threshold for treating borderline B12 in an older person might be lower, given the potential cognitive benefits. Notably, some neurologists believe that certain cases of dementia or neuropathy in the elderly attributed to "age" may actually be due to years of subclinical B12 deficiency. Japanese practice, for instance, defines B12 deficiency at <500 pg/mL partly to catch these cases, and it's hypothesized this could relate to lower rates of cognitive decline in some studies [106]. In any event, treating B12 deficiency in an older patient can significantly improve quality of life – many will notice better energy, cognition, and mobility once repleted. Also, older patients may have difficulty with injections (due to frailty or poor access to clinics), so oral therapy is a convenient option if no severe neuro impairment. An important practical point: even mild B12 deficiency in the elderly can contribute to falls (via neuropathy or postural hypotension), so correction is part of fall prevention in those identified.

Another consideration: **homocysteine and cognition** – high homocysteine (from low B12/folate) has been associated with cognitive decline. Some trials of B-vitamin supplementation in cognitively impaired elderly showed slowing of brain atrophy in those with high homocysteine. While not conclusively proven to prevent dementia, ensuring adequate B12 (and folate) is a low-risk intervention that may help some individuals with memory issues.

Global Guidelines and Regional Differences

There is no single worldwide standard for B12 deficiency management; however, most approaches share core principles. Some differences include: - **Diagnostic thresholds:** As noted, countries like Japan (and some in Europe) use higher lower-normal cutoffs for B12 (around 500 pg/mL) [41], aiming to catch

deficiency early, especially neurologic cases. In the US and UK, labs often use ~200 pg/mL as the lower limit, which some experts feel is too low. This means a patient considered “normal” in the US at 250 pg/mL might be treated as deficient in Japan. Many experts advocate for a middle ground (~300–350 pg/mL) as a more practical cutoff for investigation or treatment, especially if symptoms are present [107]. - **Treatment routes:** Historically, the UK, parts of Europe, and many developing countries favored **injectable B12** for confirmed deficiency (particularly pernicious anemia). The UK’s NHS, for example, provides hydroxocobalamin IM as the standard therapy every 3 months for maintenance. In contrast, Canada and some European guidelines endorse **high-dose oral B12** as equally acceptable first-line therapy for patients without severe neurological involvement [95]. The US has no unified guideline, but practice is mixed – many clinicians still start with injections, but patient preference and cost are increasingly leading to oral usage. - **Guideline availability:** Some regions (e.g. Latin America) have less formal national guidelines for B12, so practitioners follow global best practices or internal medicine textbook recommendations. For instance, an analysis found that Brazil has *no unified national guideline* for B12 deficiency; as a result, management in Brazil generally aligns with the international consensus (diagnose by low B12 ± MMA, treat with injections or high-dose oral, etc.) [108]. Similarly, many Asian countries without specific guidelines simply adhere to practices from literature (with possibly more reliance on injections due to cultural norms or availability). - **Prophylaxis:** Some countries consider adding B12 fortification to foods (like folic acid in flour). The US and Canada have folate-fortified grains but not B12; however, there are calls to consider B12 fortification for certain staples to help the elderly and vegetarians. No major country has mandated B12 fortification yet, though a few have voluntary enrichment of some products. - **Monitoring and screening:** Guidelines differ on whom to screen. For example, the British NICE 2024 guidance (NG239) suggests checking B12 in people with risk factors (vegans, metformin users, etc.) or anemia, rather than universal screening [109] [110]. Some endocrinology guidelines recommend periodic B12 checks in diabetics on metformin (e.g. every 2–3 years). Japan’s approach of treating low-normal B12 is another example of a more aggressive stance, potentially linking to preventive healthcare and their lower dementia rates, though this is observational [111]. - **Patient preference:** Recent international consensus (like the Delphi in 2024) emphasizes incorporating patient preference into route of B12 administration [112]. This is a shift from older paternalistic approaches of defaulting to injections. So modern management, globally, is trending toward a more individualized plan.

In summary, despite minor regional differences, the foundational treatment (supplying B12 and monitoring response) is consistent worldwide. Textbooks such as *Harrison’s* and *Cecil’s* reinforce that prompt B12 repletion is the priority, and the choice of oral vs IM can be tailored to the patient [93]. In resource-limited settings, oral high-dose B12 offers a cost-effective solution that avoids injections. In settings with reliable healthcare follow-up, either method works, and guidelines are evolving accordingly.

Prevention Strategies

Preventing B12 deficiency involves targeting at-risk groups and addressing modifiable factors: - **Dietary prevention:** People following vegan or strict vegetarian diets should take a regular B12 supplement or consume B12-fortified foods. Nutritional education is key – for example, explaining that seaweed or certain mushrooms touted as B12 sources actually contain analogues that are not bioavailable and can even interfere with B12 absorption [113]. Many vegan advocacy groups and physicians now stress B12 supplementation as non-negotiable for vegans. Similarly, patients with chronic alcoholism or malnutrition should receive multivitamins including B12 to prevent deficiency. - **Medication-related:** For patients starting long-term metformin, some guidelines recommend baseline and periodic B12 level checks, or empiric B12 supplementation after a few years. With long-term PPI use, especially in older patients, clinicians should have a low threshold to supplement B12 or monitor levels. Since these drug effects are

common, some have proposed that any patient on metformin >4 years or a PPI >5 years should be on a B12-containing multivitamin or have B12 checked intermittently [114]. - **Post-surgery:** Bariatric surgery patients typically receive life-long vitamin supplementation (including B12, iron, calcium, vitamin D, folate). Adherence to these regimens is crucial for prevention of deficiencies. Healthcare teams must reinforce the importance of the vitamin regimen in follow-up. Similarly, patients with short bowel syndrome affecting the ileum should be maintained on B12 injections prophylactically. - **General aging population:** Some countries debate fortifying foods commonly consumed by the elderly (e.g. fortified cereals with B12) since absorption of protein-bound B12 declines with age. Many oral B12 supplements are cheap and over-the-counter; encouraging seniors to take a daily multivitamin or B-complex could reduce deficiency prevalence. At the very least, routine senior multivitamins usually provide ~25 µg of B12, which may help offset marginal intakes (though for true pernicious anemia, more is needed). - **Public health recommendations:** Ensuring that prenatal vitamins contain B12 addresses the needs of pregnant women, particularly important in regions where vegetarian diets are prevalent (e.g. in India, where vegetarian mothers have higher risk of B12 deficiency affecting their infants [115]). - **Education:** Educating clinicians to recognize risk factors and subtle presentations is a form of prevention – e.g., checking B12 in an older patient with cognitive changes or an ataxic gait can catch deficiency before irreversible damage. Also, educating patients (especially those with pernicious anemia) about their condition ensures they adhere to maintenance therapy and understand the importance of not stopping treatment.

In a nutshell, B12 deficiency is largely preventable in today's world: animal-derived food is plentiful for those who consume it, and inexpensive supplements exist for those who don't. The main challenges remain awareness and access. As one example, a subset of elderly patients in assisted-living might have poor diets and undiagnosed atrophic gastritis – including a B12 level in annual bloodwork could detect many cases before anemia becomes severe. The balance of cost vs yield is debated, but targeted prevention for high-risk groups is widely accepted.

Conclusion

Vitamin B12 deficiency is an "old" disorder that continues to pose new challenges. It is common, potentially serious, but eminently treatable. The period 2010–2025 has seen advancements in our understanding of B12 absorption, recognition of broader causes (like widespread metformin use contributing to deficiency), and validation of oral therapy as an effective option for many patients. We have also gained clarity on the subtler effects of B12 deficiency – from cardiovascular risks of homocysteine to links with osteoporosis and cognitive decline.

From a clinical perspective, the keys to success are **vigilance** and **comprehensiveness**: Think of B12 deficiency in relevant clinical scenarios (unexplained anemia, neuro symptoms, malabsorption settings, etc.), confirm it with appropriate tests (including metabolites when needed), and treat it completely. Treatment not only means normalizing a lab value, but fully repleting body stores, alleviating symptoms, and managing associated conditions. For example, in pernicious anemia, one must treat the anemia and also follow the patient for gastric cancer risk and other autoimmune diseases. In a diabetic on metformin, one should correct the deficiency and consider prophylaxis to prevent recurrence.

Modern guidelines emphasize an individualized approach – taking into account patient preferences (oral vs injection), co-morbidities, and local resource availability [112]. Fortunately, vitamin B12 therapy is simple and safe, whether given by shot or by pill. Hematologic responses are usually dramatic, and even neurologic

improvements can be remarkable if the deficiency is caught in time. In an era where neurologic diseases like dementia are prevalent, correcting a reversible cause like B12 deficiency is extremely rewarding.

In summary, vitamin B12 deficiency remains a multifaceted condition bridging nutrition, hematology, and neurology. By integrating insights from laboratory science, clinical medicine, and population health (as compiled in internal medicine and hematology texts like Harrison's, Cecil's, Wintrobe's, and Hoffman's), clinicians can effectively diagnose and treat this condition [57] [56]. The result is the prevention of serious complications such as irreversible neuropathy, myelopathy, or misdiagnoses like TTP – truly a triumph of early recognition and intervention in modern medicine. Each treated patient, who regains vitality and neurologic function from something as simple as vitamin replacement, stands as a testament to the importance of "thinking B12" in the appropriate clinical moments.

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1 2 3 5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 43 44 45 47 48 49 50 51 52 53 54 66 68 69 75 76 77 78 79 82 85 88 89 90 91 92 93 94 95 96 97 98 104 108 109 110 112 114 Vitamin B12 Deficiency in Adults_ A Comprehensive Review (2010–2025).pdf
file://file_00000000ead461f598fe28fea77580e5

4 87 Megaloblastic Anemia - StatPearls - NCBI Bookshelf
https://www.ncbi.nlm.nih.gov/books/NBK537254/

19 42 70 86 105 115 Comprehensive Review of Vitamin B12 Deficiency_ St (1).pdf
file://file_00000000bde861f5aabab1a3120efa52

40 41 106 107 111 113 Vitamin B12:Everything You Need to Know about | Clancy Medical Group
https://www.clancymedicalgroup.com/vitamin-b12/

46 56 57 58 59 71 72 MCU 2022 Cecil Essentials of Medicine 10th Edition - PDFCOFFEE.COM
https://pdfcoffee.com/mcu-2022-cecil-essentials-of-medicine-10th-edition-pdf-free.html

55 60 61 62 64 65 83 84 Megaloblastic anemia - Wikipedia
https://en.wikipedia.org/wiki/Megaloblastic_anemia

63 Hypersegmented neutrophil - Wikipedia
https://en.wikipedia.org/wiki/Hypersegmented_neutrophil

67 Current hematological findings in cobalamin deficiency. A study of ...
https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2257.2006.00755.x

73 Hyperpigmentation as a Primary Symptom of Vitamin B12 Deficiency
https://pmc.ncbi.nlm.nih.gov/articles/PMC9551622/

74 Vitamin B12 Deficiency and its Numerous Skin Manifestations
https://www.actasdermo.org/en-vitamin-b12-deficiency-its-numerous-articulo-S1578219015002528

80 B Vitamins, Homocysteine and Bone Health - PMC - PubMed Central
https://pmc.ncbi.nlm.nih.gov/articles/PMC4425139/

81 Vitamin B(12) deficiency stimulates osteoclastogenesis ... - PubMed
https://pubmed.ncbi.nlm.nih.gov/19363664/

99 Pernicious Anemia, Atrophic Gastritis, and the Risk of Cancer
https://www.cghjournal.org/article/S1542-3565(15)00971-4/fulltext

100 British Society of Gastroenterology guidelines on the diagnosis ... - Gut
https://gut.bmj.com/content/68/9/1545

101 102 103 Cost of detecting gastric neoplasia by surveillance endoscopy in ...
https://www.sciencedirect.com/science/article/abs/pii/S1590865816308246