North of Tyne, Gateshead and North Cumbria Area Prescribing Committee

Vitamin B12 management guideline

Approved: January 2020 Amended: March 2022
Review: January 2023

Scope of guidance

Vitamin B12 deficiency is a common finding that can affect people of any age, but its prevalence increases among older people. It is reported to affect around 5% of people aged 65 to 74, and 10% of people aged over 75.[1] However, most of these people have no attributable symptoms and do not have either macrocytosis or anaemia. The routine use of long-term intramuscular hydroxycobalamin replacement in this setting has led to a high burden of treatment for patients and primary care. This guideline aims to support clinicians in the interpretation of the results of B12 testing and management of patients with abnormal results.

Clinical features

The presenting features of B12 deficiency are anaemia, typically macrocytic (e.g. fatigue, lethargy, and dyspnoea) or neurological symptoms (e.g. paraesthesia, numbness, cognitive changes or visual disturbance (yellow-blue blindness)).

Paraesthesia, typically 'pins and needles' of hands and/or feet, are reported by 70% of people with neurological symptoms.[2] The commonest findings on examination are loss of vibration and joint position sense. Other findings on examination may include pallor, lemon tinge to the skin, glossitis and oral ulceration. Neuropsychiatric features are reported to include irritability, depression, psychosis and dementia.

Causes

Vitamin B12 is mainly absorbed in terminal ileum, and this process is aided by intrinsic factor (IF) produced by gastric parietal cells. However, an additional 1% of dietary cobalamin is believed to be absorbed along the length of the gastrointestinal tract independent to IF. The human body stores 2-4mg of B12 (mainly in the liver), which is enough to last for 2-4 years if intake ceases.

Causes of B12 deficiency are gastric atrophy (due to ageing, chronic H. pylori infection or autoimmune-mediated), bowel resection surgery (e.g. bariatric), Crohn's disease, malabsorption (e.g. pancreatic insufficiency or bacterial overgrowth), H. pylori, drugs effecting absorption (e.g. metformin, H2-receptor antagonists and proton pump inhibitors) and a strict vegan diet without appropriate supplementation. Pregnancy and oestrogen supplementation may cause reductions in plasma haptocorrin B12 leading to reductions in measured B12 levels without true deficiency.

Pernicious anaemia

Pernicious anaemia (PA) is the term for autoimmune-mediated gastric atrophy with destruction of the gastric parietal cells that produce intrinsic factor. It is more likely to occur in people with other autoimmune disorders (e.g. type 1 diabetes, thyroid disease, Addison's disease, vitiligo or hypoparathyroidism). It is reported to have a peak age of onset around 60 years and a prevalence around 1/1000 in the UK.[3,4] PA is the cause of only a small proportion B12 deficiency.

Identification of B12 deficiency

Serum vitamin B12 levels can be measures to test for B12 deficiency. Testing for folate deficiency is done concurrently as the biochemical pathways and many features of deficiency are closely interlinked. Interpretation of vitamin B12 levels is complicated by the frequency of asymptomatic low levels of uncertain significance and by the fact that patients with strong clinical features of B12 deficiency who respond to replacement therapy may have vitamin B12 levels within the reference range.

Elevated levels of methylmalonic acid (MMA) and total plasma homocysteine (tHcy) are alternative biomarkers of B12 deficiency. However, both can also be elevated in older age and in the presence of renal impairment.[7] Intrinsic factor antibodies (IFAB) and gastric parietal cell antibodies (GPCAB) have been found in the serum of some people with PA but it is unknown if they have any pathogenic role. IFAB have a high specificity (98 to 99%) but a low sensitivity (around 50%) for the detection of PA. False positive IFAB are associated with other autoimmune diseases and older age.[5,6]

Routine use of these tests in unselected patients is not recommended but may be useful in specific situations. IFAb should be measured where there is a strong clinical suspicion of B12 deficiency despite a B12 level within the normal range or in situations such as pregnancy where the normal range is uncertain. MMA and tHcy testing cannot be sent from primary care and if it is felt that they are required testing should be discussed with haematology. Please note that IFAb testing, MMA and tHcy all need to be tested before B12 replacement is commenced.

Pregnancy and oestrogen containing contraceptives

Falls in serum vitamin B12 levels are a normal part of pregnancy and thought to be physiological. In the absence of symptoms of deficiency low levels are uninterpretable. If symptomatic check IFAb as these may be useful in establishing the aetiology in this group. If IFAbs are positive treat as pernicious anaemia. If IFAb are negative but there is a strong clinical suspicion of B12 deficiency then give 3 doses of IM hydroxycobalamin to cover pregnancy and reassess 2 months post-partum. For non-specific asymptomatic low B12 levels repeating B12 testing 2-3 months post-partum is adequate.

The interpretation of B12 results in women taking oestrogen containing HRT or oral contraception is difficult and ideally levels should only be checked when there is clinical suspicion of B12 deficiency. Asymptomatic mild reductions in B12 levels are difficult to interpret and can usually be managed with dietary advice of supplementation.

Neuropsychiatric changes

Correction of low B12 levels in the absence of macrocytic anaemia or peripheral neuropathy had no effect compared to placebo on psychiatric state or well-being in people over age 65.[8] No correlation has been detected between low B12 levels and cognitive decline in longitudinal studies.[9] Nor have intervention studies demonstrated a clear benefit for cognition with B12 supplementation with borderline deficiency (typically in the range 136 to 200ng/L).[10-14] There is also only limited correlation between low B12 levels (136-203 ng/L) in older people with regards to either the development of macrocytosis or anaemia.[15] In addition, no strong association has been found between borderline B12 levels and peripheral nerve function.[16]

References

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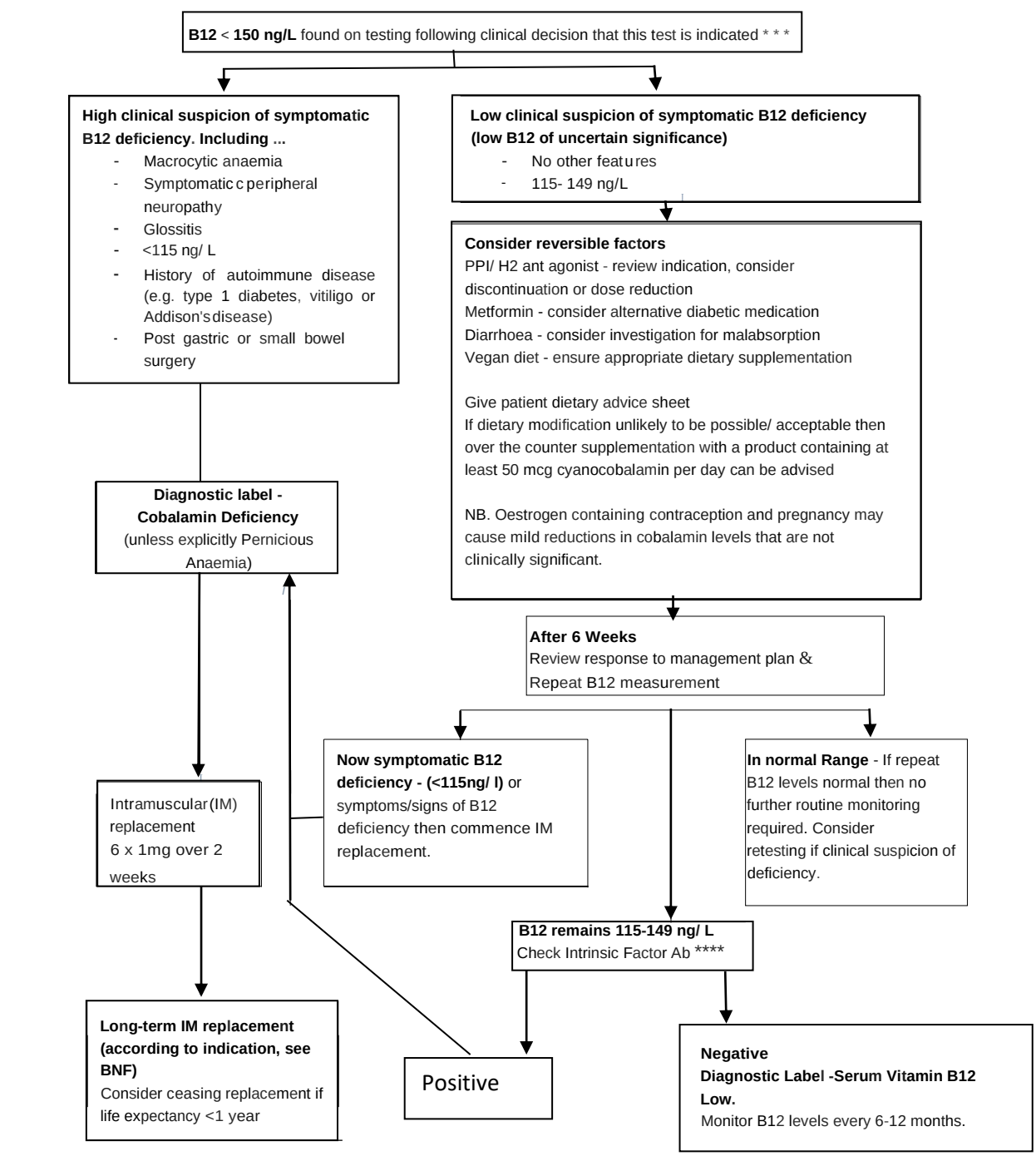
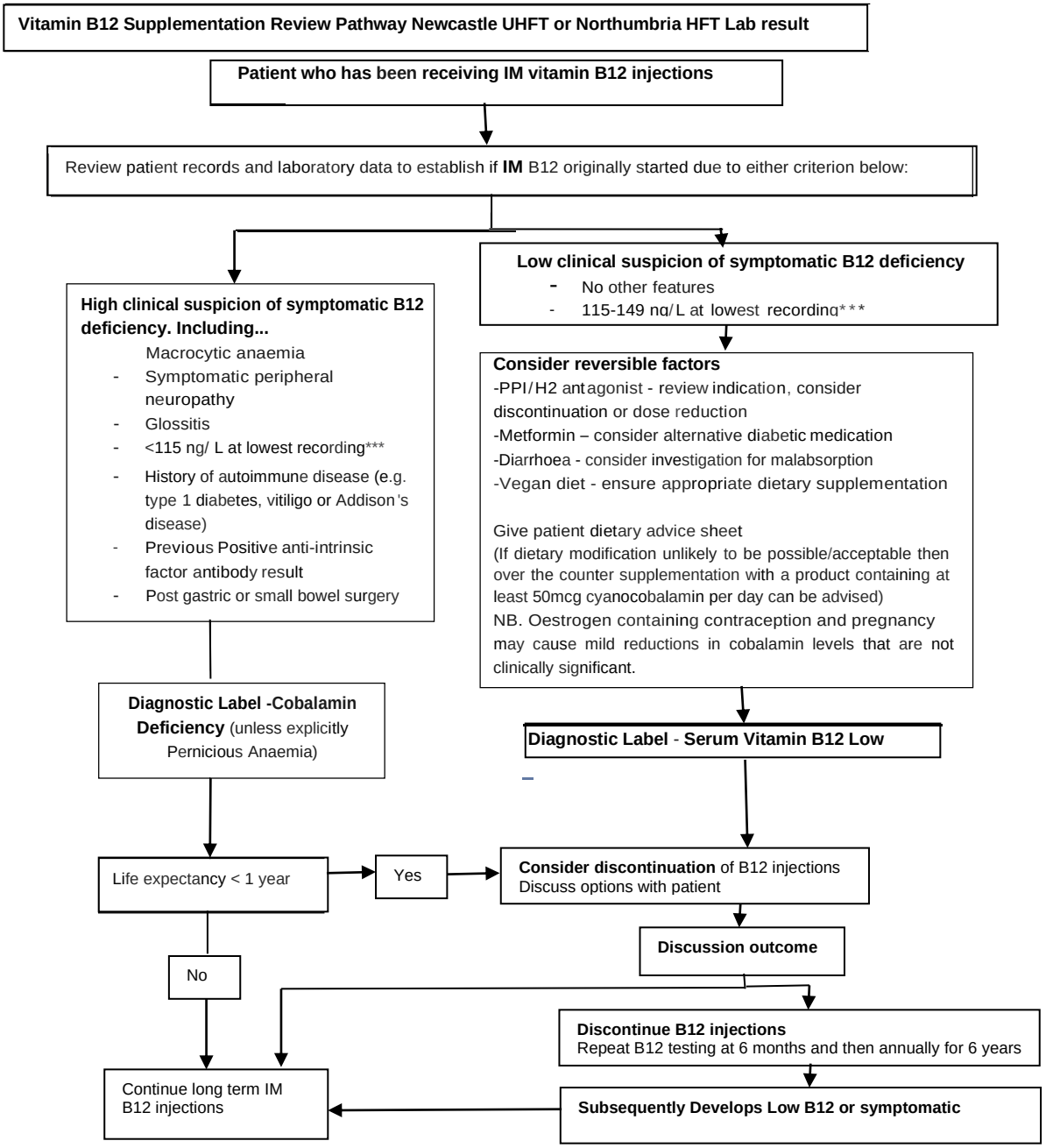
Low Vitamin B12 Management Pathway Newcastle or Northumbria Lab result



* If causing neurological deficit then replacement is recommended to continue until symptomatic improvement ends.
*** Note depends upon Lab reference range. 150ng/L is the NHFT labs lower limit of normal and 115-149 ng/l is between 75-99% of the lower limit of normal. NUHFT use normal range of 145-596pMol/L and 111-145pMol/L as the lower limit of normal.
**** IFAb have a low sensitivity and negative predictive value, but a high specificity for pernicious anaemia and testing at this point in the pathway may help clarify the need for IM replacement



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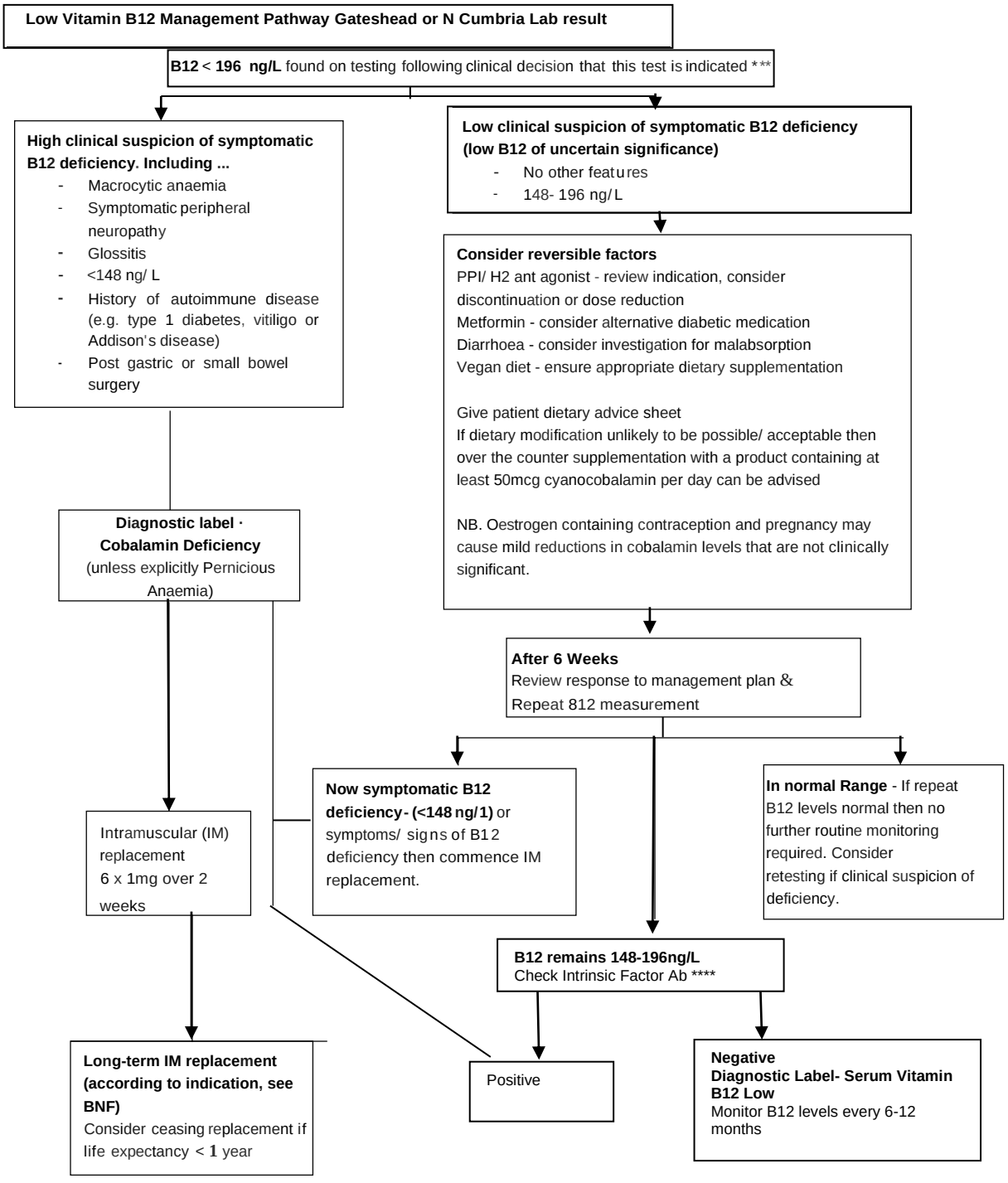
•• **Fully replete body B12 stores may last up to 6 years. If there is no evidence of deficiency redeveloping after this time, then long-term monitoring is not required.



• If causing neurological deficit then replacement is recommended to continue until symptomatic improvement ends.
• • • Note depends upon Lab reference range. 197ng/ L is the N Cumbria UHFT labs lower limit of normal and 148-196 ng/l is between 75-99% of the lower limit of normal. South Tyneside Labs including Gateshead FT use 191ng/L as the lower limit of normal, for clarity this guide uses the higher value.
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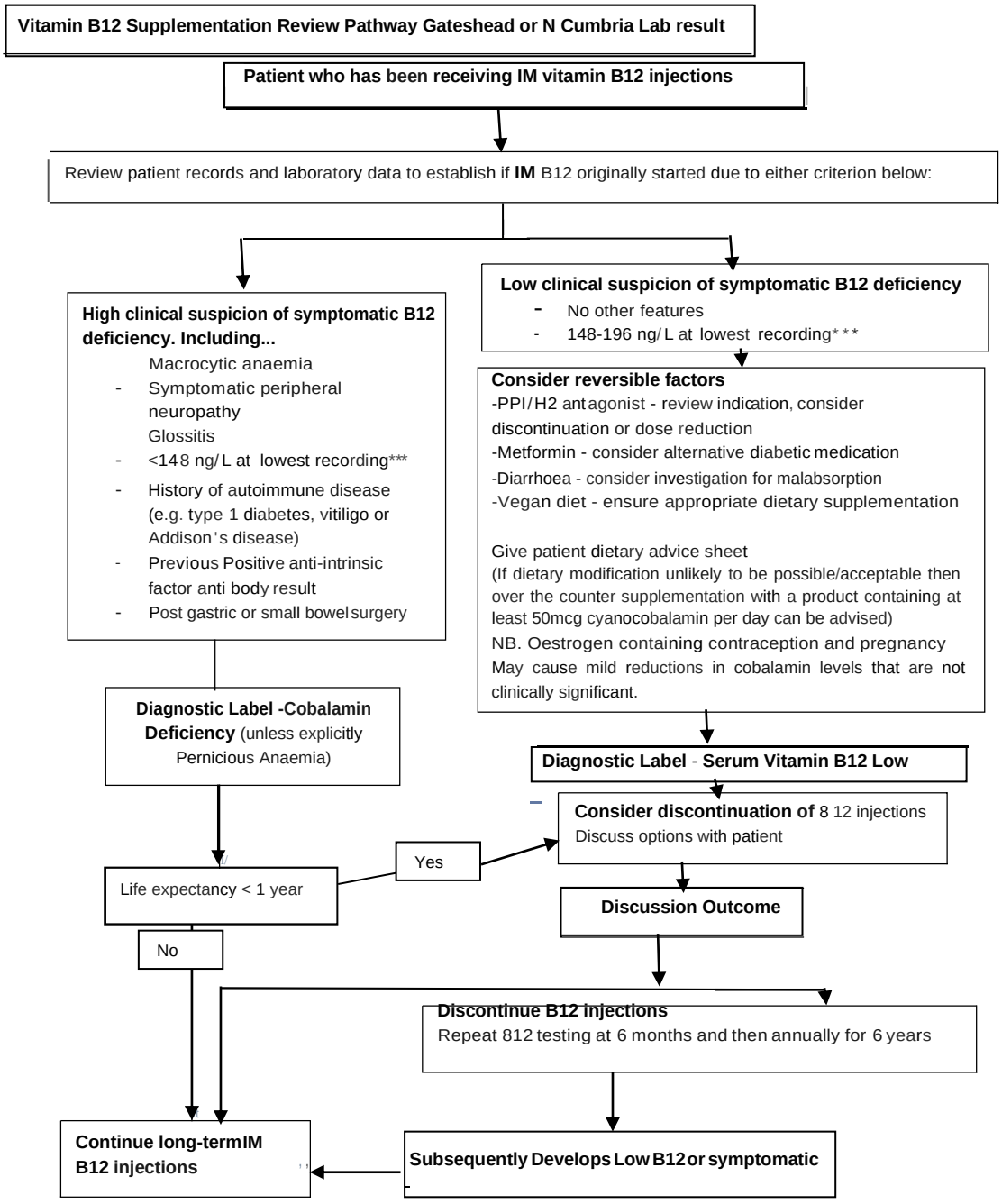

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