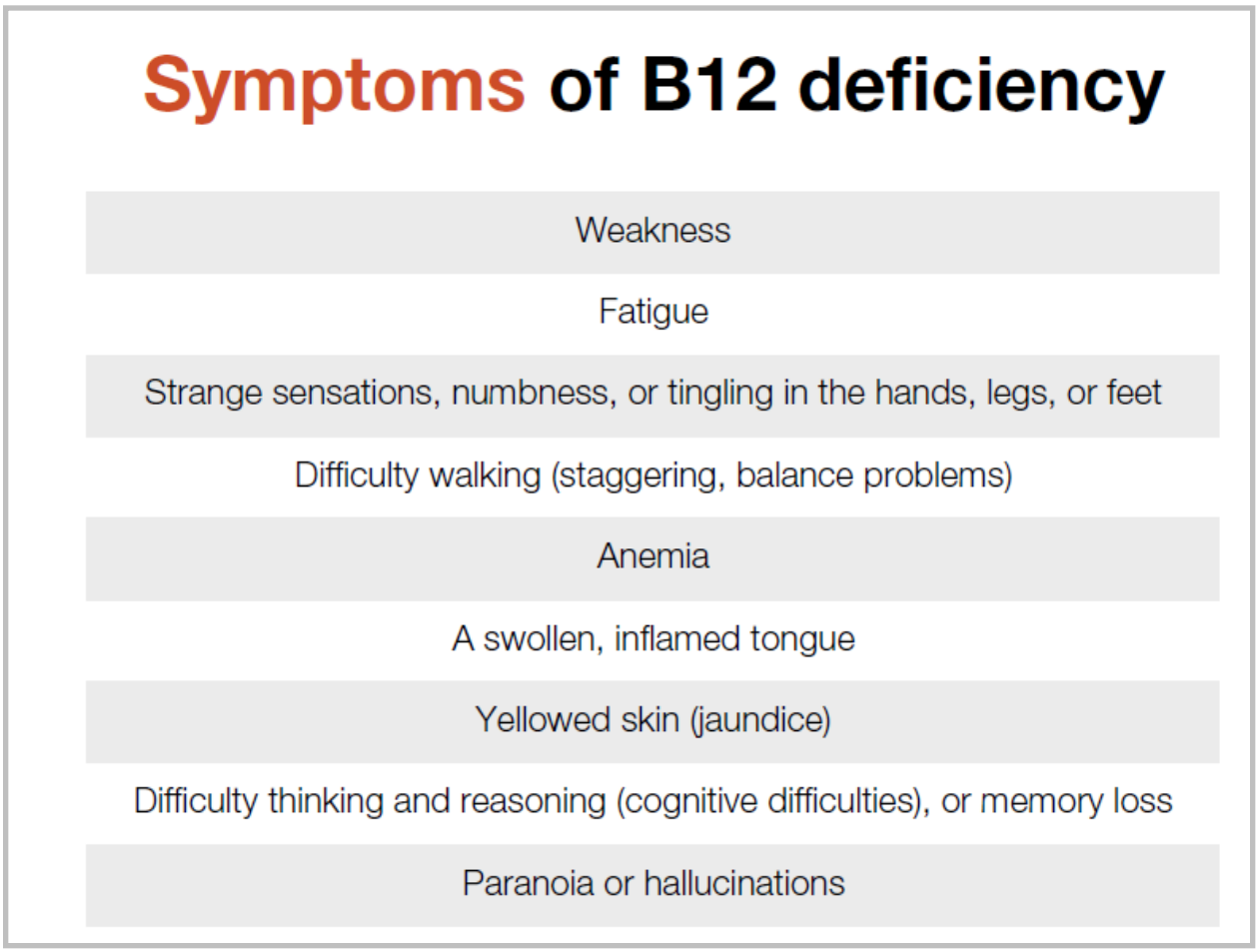
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

B12 Deficiency - Part Two

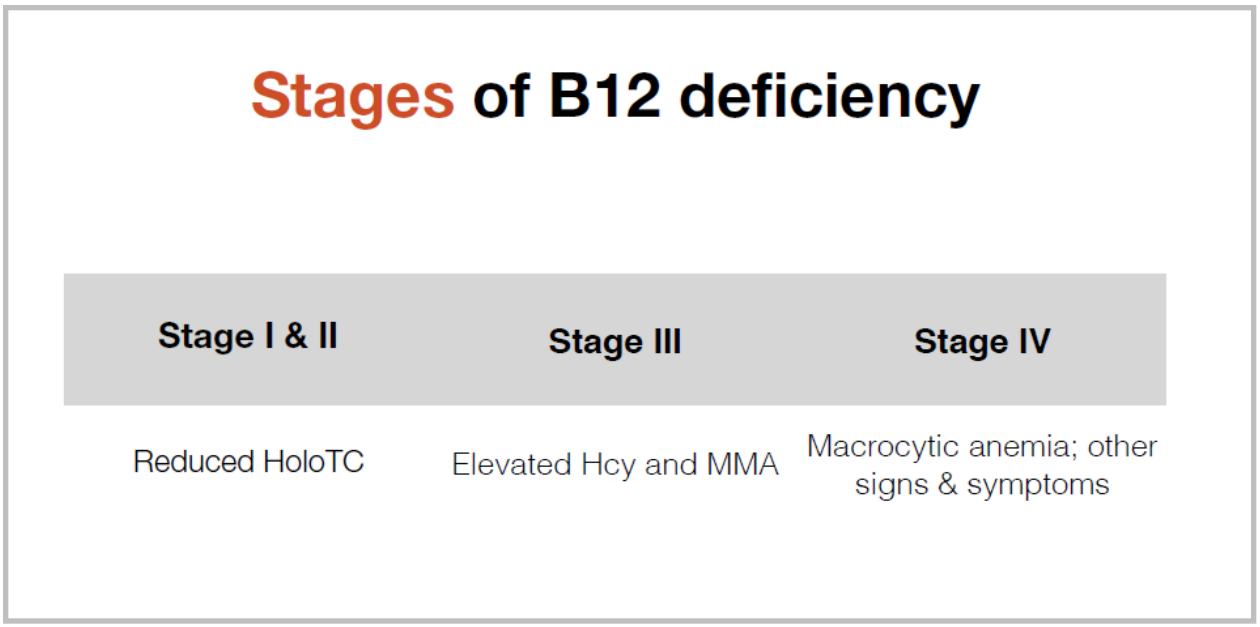


Symptoms of B12 deficiency range from nonexistent when it's mild to severe and irreversible, and they include weakness; fatigue; strange sensations, numbness, or tingling in hands, legs, or feet; difficulty walking such as staggering or balance problems; anemia; a swollen, inflamed tongue; yellow skin; jaundice; difficulty thinking and reasoning; memory loss; and paranoia or hallucinations.

Tick the boxes that correspond to your symptoms.	√	Points
Strange Tiredness		5
The Fogs - Lack of clarity/difficulty in concentrating		5
Breathlessness - 'The Sighs' or 'The Gulps'		5
Brittle Nails		5
Brittle Nails **with ridges**		Extra 5
Pins and needles - usually in your hands and feet		5
Swollen and/ or sore Tongue		5
Sudden unaccountable bouts of diarrhoea		5
Balance Problems		5
General Unsteadiness		5
Vertigo		5
Burning legs or feet		5
Tinnitus		2
Irritability/Anger/Lacking Patience		2
Family History or B12 Deficiency/ Pernicious Anaemia		2
Hair Loss		1
Dry Skin (including scalp)		1
Lack of concentration		1
Memory Loss		1
Insomnia		1
Premature Greying of Hair		1
Psoriasis/Eczema/Acne		1
Rosacea		1
Arrhythmia		1
Vitiligo		1
Anaemia		1
Infertility		1
Dizziness		1
Bleeding Gums/Mouth Ulcers		1
Loss of Appetite/Weight Loss		1
Neuropathic Pain		1
Numbness		1
Depression/Anxiety		1
Confusion		1
Blurred Vision		1

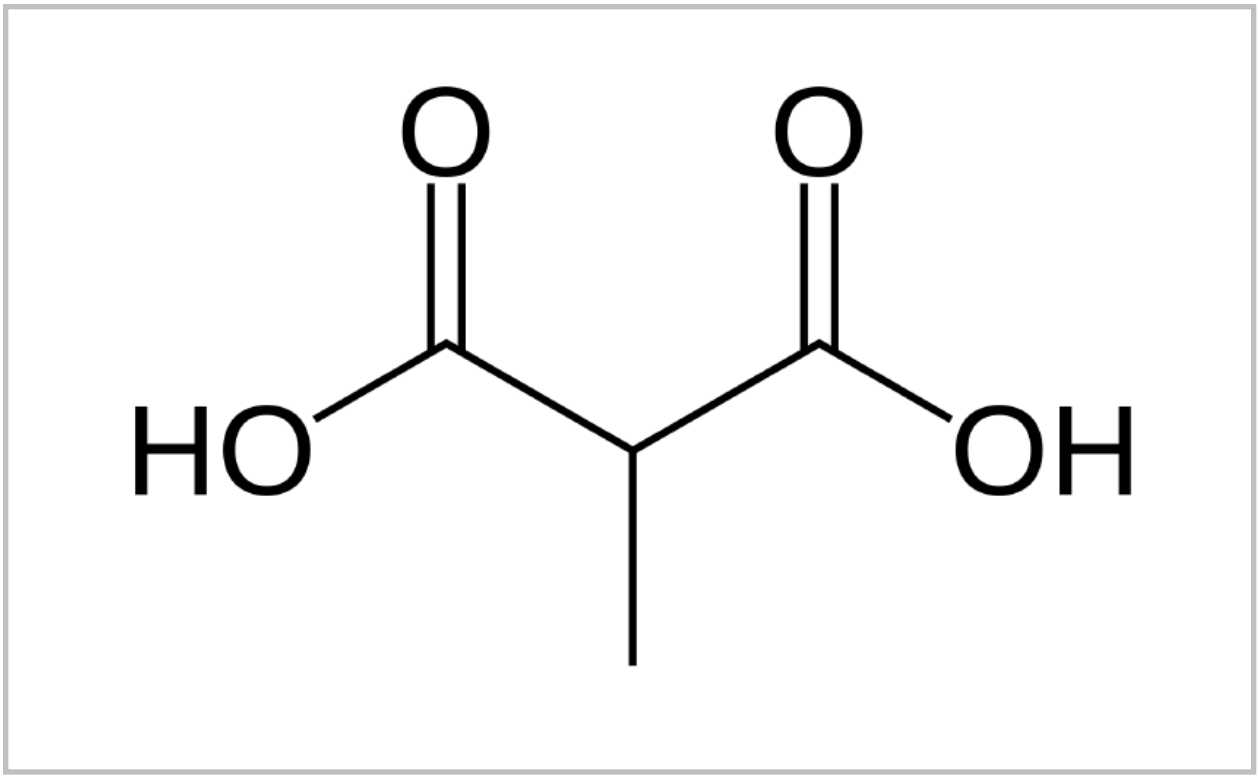
Adopted from: www.pernicious-anemia-society.org

The Pernicious Anemia Society has put together a questionnaire that may be helpful for identifying people with B12 deficiency based on symptoms. However, remember that the early stages of B12 deficiency are often asymptomatic, so you can't rely on questionnaires like this. If a patient does score 66 or higher on this questionnaire, B12 deficiency is very likely. If he scores one through 65, B12 deficiency is somewhat likely, increasing with a higher score.

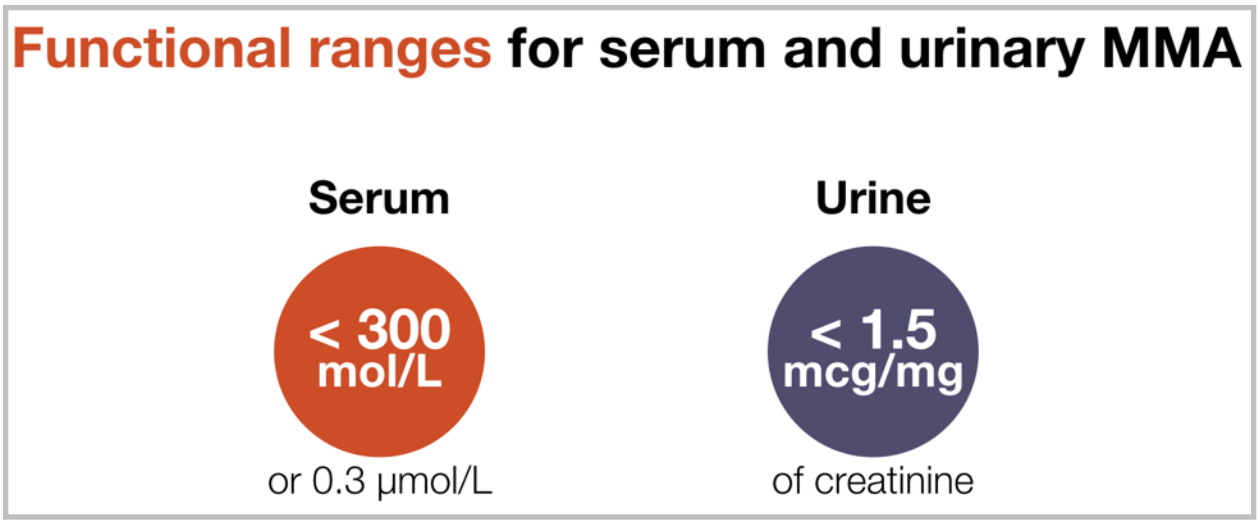


It's really important to realize that there are four stages of B12 deficiency. During stages one and two, plasma and cell stores of B12 become depleted, and the concentration of holotranscobalamin-2, or holoTC, is reduced. That's the only clinical marker that will be observable in stages one and two. During stage three, functional B12 imbalance is characterized by elevated homocysteine and urinary or serum MMA concentrations, methylmalonic acid, in the blood. In stage four, the clinical signs and symptoms of B12 deficiency become evident. These are signs such as macrocytic anemia and symptoms such as peripheral neuropathy or brain fog, and they do not appear until the final stage of B12 deficiency, and that's really important to understand. By then, in the case of some of the neurological symptoms, it may be too late to reverse them. This is what makes early diagnosis so crucial, and it's why I include B12, homocysteine, and urinary and serum MMA as part of my Case Review workup, and it's why I cannot understand why these markers are not part of an initial workup in the primary care setting.

Now, let's talk a bit about markers for B12 deficiency. HoloTC is composed of vitamin B12 attached to transcobalamin, and it represents the biologically active part of B12 that can be delivered to the cells and perform all of the functions of B12. Of all of the biomarkers for B12 deficiency, holoTC is considered the most sensitive. It is the only marker that can detect B12 deficiency in stages one and two, whereas urinary methylmalonic acid and homocysteine typically don't become elevated until stage three. HoloTC is available, though not widely, in the U.K., Europe, Australia, and some other countries, but for some reason, it's very hard to find in the U.S. Quest and other labs listed it on their websites at one point back in 2013, but it's not there any more, and it's only available, as far as I know, from corresponding with Axis Shield, the company that makes the test, at nine hospitals or medical centers in the U.S., including the Mayo Clinic at the time of this recording, so I have not been able to find a way of incorporating it into my regular blood work yet, although I'd very much like to do so.



The next marker is methylmalonic acid, or MMA. MMA is converted into succinic acid via an active B12-dependent enzyme, so if MMA levels are high, it suggests that active B12 is lacking. Remember from the stages of B12 deficiency that MMA won't increase until stage three, but as of now, it's one of the better clinical markers that we have because holoTC isn't yet widely available, in the U.S. at least. There are two ways to measure MMA: in the serum and in the urine. Each has advantages and disadvantages. I like to run both tests, and I've found urine MMA to be a more sensitive marker than serum MMA, but how you interpret these tests obviously depends on the patient's health status. If there is any question of impaired kidney function, serum MMA would probably be more accurate, and if the patient has SIBO or gut dysbiosis, urine MMA would be more accurate.



As I mentioned, I run both as part of the Case Review blood panel. The Organix Comprehensive profile from Genova has urine MMA, and serum MMA is available through LabCorp, Quest, and other conventional labs. I currently don't have a functional range for serum MMA. I use the provided lab range, though if it's high-normal, remember it's an inverse marker, in the presence of other B12 deficiency markers, I would definitely pay attention to that.

On the Organix test, when it's marked high, that's actually high-normal or functionally high. Genova Diagnostics' lab lists a normal reference range for urinary MMA of less than 2.3 mcg/mL of creatinine, with a suggested optimal range below 1.7, yet a study with elderly subjects suggests that a value of 1.5 may be a better threshold for detecting clinical B12 deficiencies.

Serum homocysteine levels at different stages of B12 deficiency

	Stage I & II B12 deficiency	Stage III B12 deficiency
Homocysteine (µmol/L)	**8.5** (5.9–54.0)	**13.1** (7.2–47.4)

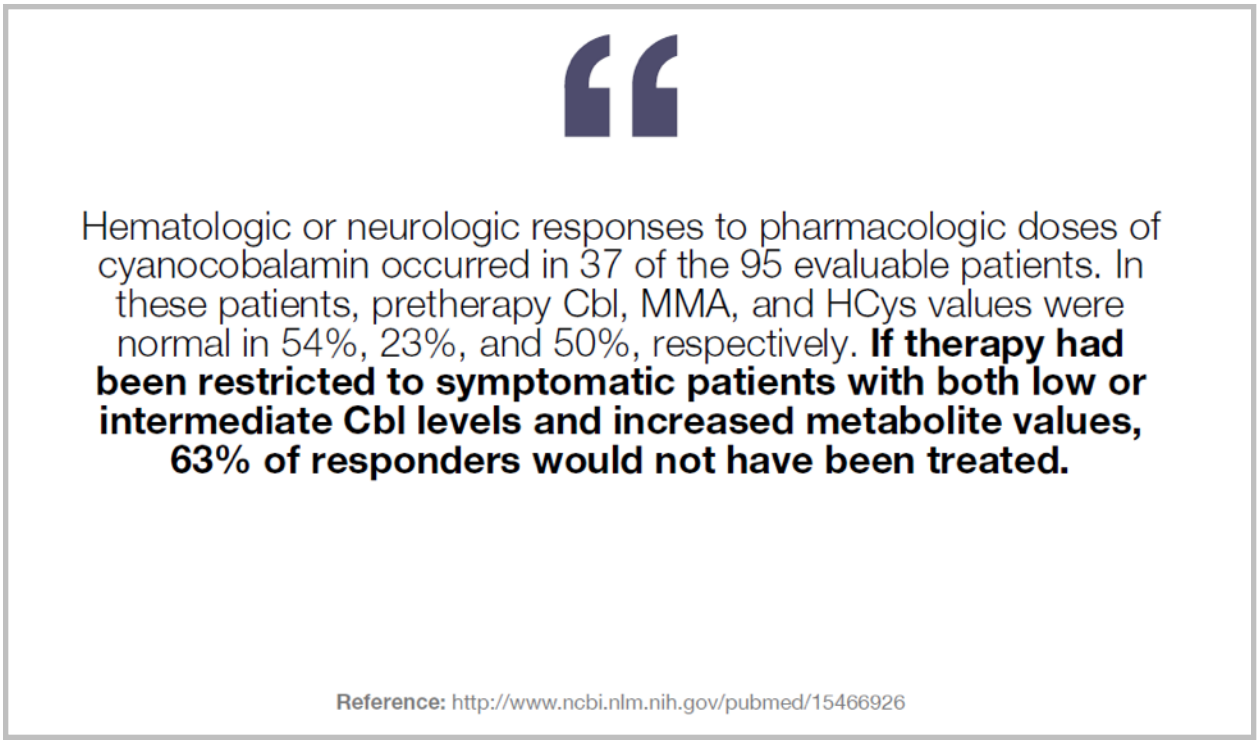
Reference: http://ajcn.nutrition.org/content/78/1/131/T2.expansion.html

Homocysteine is another marker that can be useful, but as with MMA, it won't go out of range until stage three of B12 deficiency. Recall from the second slide that methylcobalamin, the active form of B12, is a cofactor for methionine synthase. This is required for the synthesis of the amino acid methionine from homocysteine in the methylation cycle. If homocysteine is high, it suggests that methylcobalamin levels may be low. However, folate is also required for the conversion of homocysteine back into methionine, so high homocysteine levels are not specific to B12 deficiency. They may indicate deficiency of folate, B12, or both. Note that although the lab range for homocysteine goes up to 16, in one study it ranged from 7.2 to 47.4 in people with stage three B12 deficiency, with an average level of 13.1. Another study found that a homocysteine level of below 7.5 correlates with the lowest level of chromosomal damage in lymphocytes and an optimal level of DNA repair. So I have set the upper end of the homocysteine functional range at 7 to be conservative.

Lower end of B12 functional range: 450 pg/mL

Serum B12 is the most commonly used marker for assessing B12 status. It measures B12 bound to two circulating proteins. Only one carries B12 for uptake. It's widely recognized to be unreliable for detecting mild-to-marginal B12 deficiency. Studies have shown that people with serum B12 levels between 211 and 350, which is at the low end of the normal range, experienced the effects of B12 deficiency. Other studies have shown that serum B12 levels above 406 correlate with the lowest levels of chromosomal damage found in lymphocytes and probably other cells. I've set the lower end of the functional range for B12 at 450 to provide a wider margin of safety, especially because we're using other markers in the Case Review panel such as homocysteine and MMA. If I wasn't using those other markers, I would probably set the serum B12 lower limit even higher at maybe 500 or 550, as they do in Japan, to catch more people who may be dealing with B12 deficiency.

Be aware that a high serum B12 does not necessarily rule out functional or active B12 deficiency. In fact, some clinicians view high serum B12 in the absence of any supplementation as a sign of impaired B12 metabolism and possibly low active B12 levels, and I have seen this several times in my practice.



It's really important to be aware that evaluating patients' B12 status using only MMA, homocysteine, and serum B12 may still miss cases of B12 deficiency. One study assessed the B12 status of patients in critical care and found the following: hematologic or neurologic responses to pharmacologic doses of cyanocobalamin incurred in 37 of the 95 evaluable patients. In these patients, pretherapy cobalamin, MMA, and homocysteine values were normal in 54 percent, 23 percent, and 50 percent, respectively. If therapy had been restricted to symptomatic patients with

both low or intermediate cobalamin levels and increased metabolite values, 63 percent of responders would not have been treated.

This finding also highlights how important it is not to rely on a single method of diagnosis. Given that the holoTC test is not yet widely available in the U.S., and B12 supplements are nontoxic even at very high doses, the risk of not treating is much higher than the risk of treating unnecessarily, and we'll talk about this later when we discuss treatment.

Once B12 deficiency gets to the final stage, it can cause megaloblastic or macrocytic anemia. At that point, you'll see other markers of B12 deficiency in the comprehensive blood chemistry or CBC, such as low red blood cell count, low hemoglobin, low hematocrit, and elevated MCV, MCHC, MCH, and RDW, and we'll cover these in more detail in the macrocytic anemia unit.