Biomarkers	Total B12	HoloTC	MMA
How useful is it for assessing exposure (intake)?	+ Overall good sensitivity. Poor specificity. Predictive value improved when combined with HoloTC or MMA. Not appreciably influenced by recent intake. Sensitivity and specificity are confounded by pregnancy, liver disease, high white cell count, renal disease.	++ Good sensitivity and specificity. Predictive value improved when combined with vitamin B12. Measures functional component of serum vitamin B12. Reflects recently absorbed vitamin B12 and falls sooner in negative balance. May be used as a surrogate for vitamin B12 absorption.	++ Very good sensitivity. Moderately good specificity confounded by renal impairment, bacterial overgrowth. Reverts to normal within 7-10d of vitamin B12 repletion.
How useful is it for assessing status (short-, long-term)?	+ Better for assessing long-term rather than short-term status. Concentrations decrease relatively late in depletion.	++ Good for short-term status and appears to remain useful for long-term status as well.	++ Good for both short-term and long-term status.
How useful is it for assessing function?	+ Generally not useful except in extreme or well-established deficiency/depletion.	+ Reliable to assess function in that it generally reflects and is congruent with MMA. Also useful as a surrogate of vitamin B12 absorption function. May correlate with cognitive function and brain volume.	+++ Directly reflects biochemical vitamin B12 adequacy and status and is therefore a functional marker except when confounders are present.
Determinants or confounders (e.g. age, sex, pregnancy, lactation, infection, polymorphisms)?	Age (particularly in elderly), pregnancy and lactation, drugs, polymorphisms (haptocorrin, HC). Renal disease. Liver disease. High white blood cell count.	Age? Pregnancy and lactation? Polymorphism (TC 776C>T) Renal disease.	Age. Pregnancy. Renal disease. Bacterial overgrowth.
Accepted cut-offs indicating deficient/normal/excess states?	Subclinical deficiency: <300pg/ml(<220pmol/L) Deficiency: <200pg/ml (<148pmol/L)	<35pmol/L (subclinical and clinical) Cutoffs vary in different reports (e.g. <22 pmol/L)	>260nmol/L deficient (subclinical and clinical)
Other relevant issues: modifiers of validity (e.g. infection)	Assay standardisation Sample processing and storage	Assay standardisation Sample processing and storage	Assay standardisation Sample processing and storage
Population vs individual?	Both	Both	Both
Applicable in resource-constrained situations (e.g technical, sample storage, cost)?	Limited. Microbiological assay offers accurate results at low cost but requires manual handling and has limited throughput.	Very limited. Only one method in widespread use; requires ELISA capability or automated instrumentation.	Very limited. Expensive. Requires special instrumentation (LC-MS or GC-MS)
Multiple biomarkers needed?	Yes. Sensitivity and specificity (predictive value) improved in conjunction with HoloTC or MMA.	No. But predictive value improved with vitamin B12 or MMA.	No. But improves the predictive value of vitamin B12 or HoloTC when used in conjunction.
Other (clinical) information needed?	Yes. Haematological findings. Neurological findings. Dietary intake. Presence of renal impairment.	Yes. Haematological findings. Neurological findings. Dietary intake. Presence of renal impairment.	Yes. Presence of renal impairment. Evidence of bacterial overgrowth.

+, useful; ++, very useful; +++, extremely useful.

Adapted from R.Green *Indicators for assessing folate and vitamin B12 status and for monitoring the efficacy of intervention strategies*
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