

# Active-B12 (Holotranscobalamin)

## Utility and Routine Use



## Active-B12 assays

### Abbott AxSYM

Launched 2006

### Abbott ARCHITECT

Launched October 2011 (USA December 2011)

### Axis-Shield ELISA

Launched May 2012 (USA in progress)

#### User Countries:

USA	Switzerland	Korea
UK	Germany	Finland
Sweden	Australia	
Netherlands	Turkey	
Czech Republic	Canada	

Validation in Hungary, Slovakia, Poland, Italy, New Zealand, Ukraine



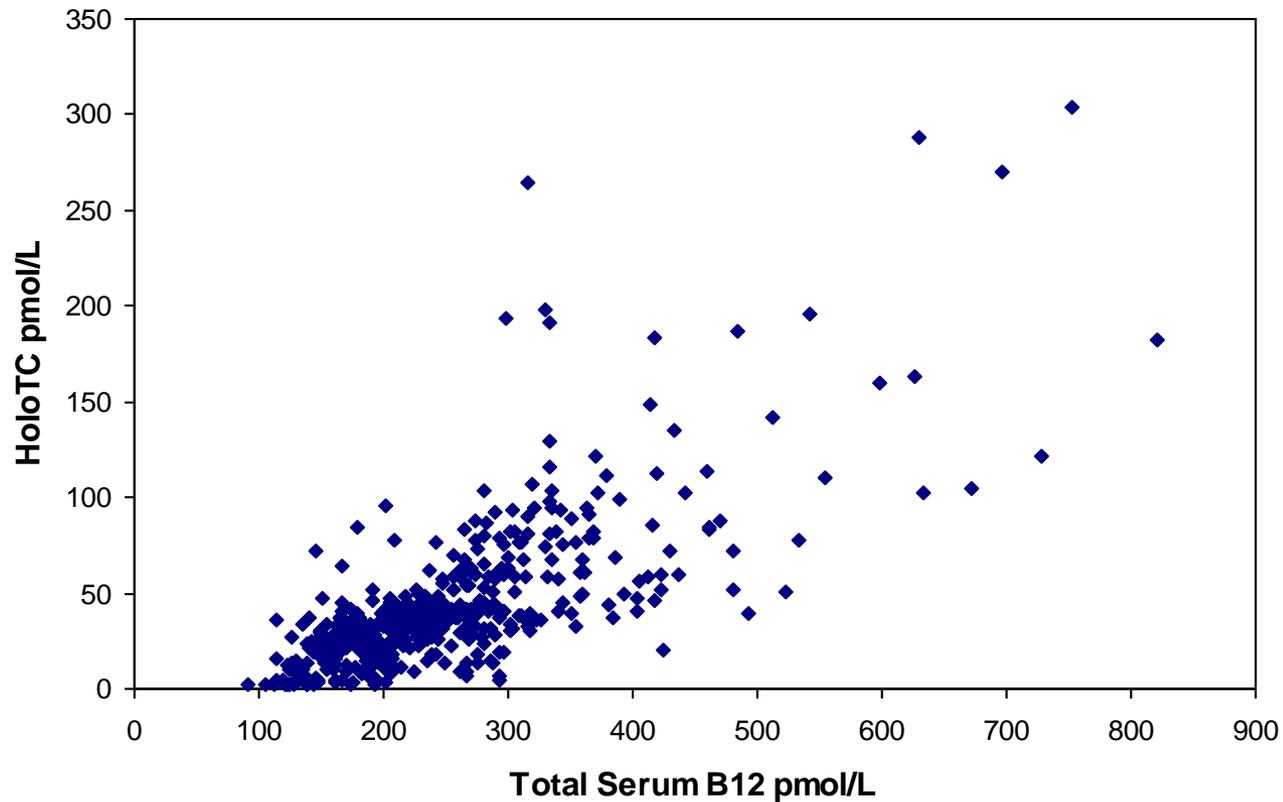
## How is Active-B12 used?

- Reflex test following indeterminate Total B12 result
- Direct replacement for Total B12

### Clinical conditions

- Investigation of suspected pernicious anaemia alongside GPC Ab and IF Ab
- Gastroenterology patients
- Pregnancy

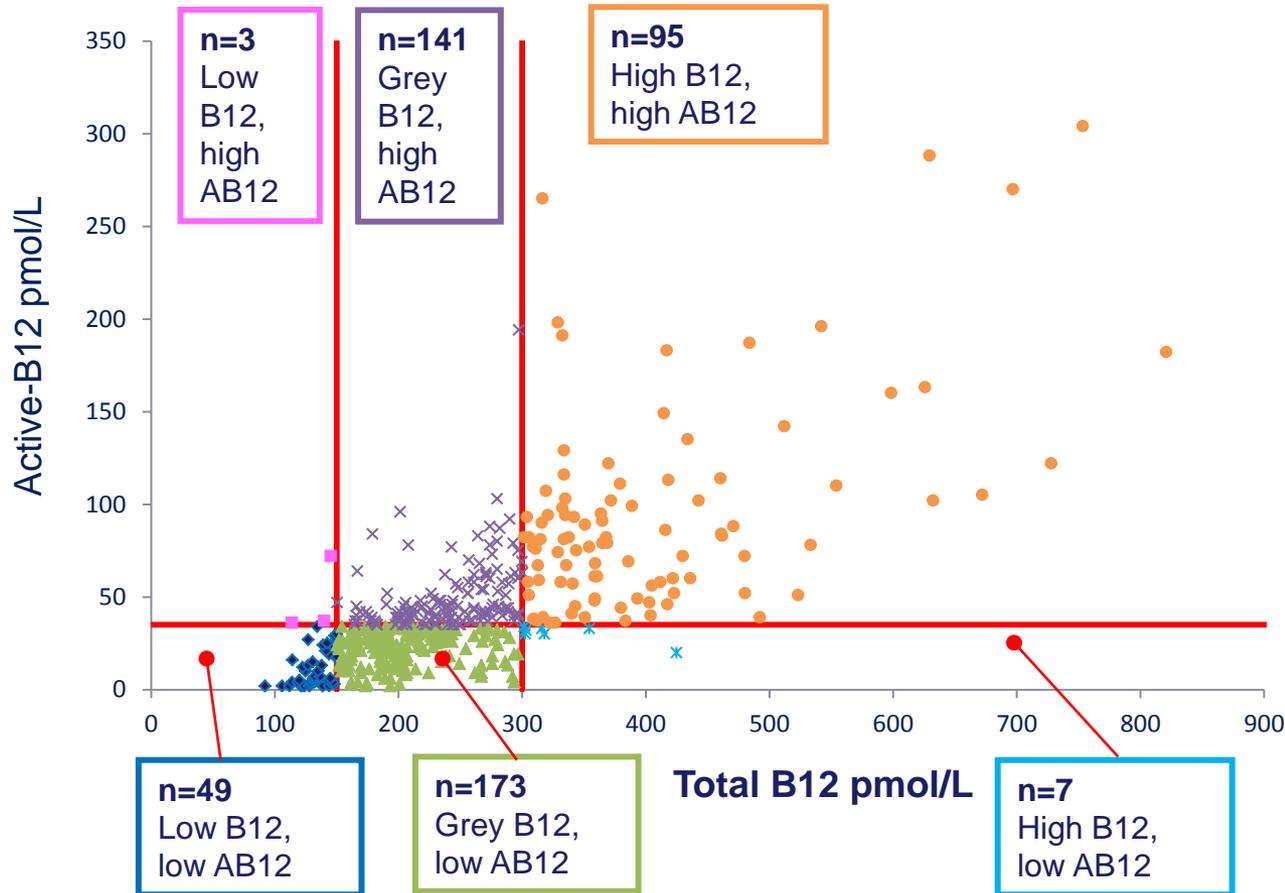
## Correlation of Total B12 with Active-B12



n = 468

Spearman correlation  $r = 0.74$

## Correlation of Total B12 with Active-B12



n=468 patients

314 results (67%) are immediately indeterminate by Total B12.

Using common 150pmol/L Total B12 cut-off, 180 patients (38%) would be considered deficient by Active-B12.



## Introduction of Active-B12 as reflex

### Total B12 test

<150pmol/L

150 – 300 pmol/L

>300pmol/L

Likely deficient

Resolve with Active-B12

Unlikely deficient\*

\* Due to false positives and false negatives, all total B12 results could be confirmed with Active-B12

## Introduction of Active-B12 as front-line test

### Subjects at risk of B12 deficiency

Active-B12 <35pmol/L

Active-B12 ≥35pmol/L

Likely deficient

Unlikely deficient\*

\* Renal patients should be further investigated

## Advantages over Total B12

- Fewer grey-zone results – less additional testing
- No IF Ab interference – significant failing in all Total B12 assays
- Cost savings – less Ab testing or MMA testing when used in algorithms
- Lab throughput – faster than Total B12



## Interference from IF Ab in Total B12 assays

**SIEMENS**

### Urgent Field Safety Notice

12-17

May 2012

Dimension Vista® System

Recall of ALL lots (list on page 3)

B12 Flex® Reagent Cartridge (K6442) – Elevated Results due to Intrinsic Factor Blocking Antibody Interference

“Siemens Healthcare Diagnostics has confirmed that the presence of Intrinsic Factor Blocking Antibody (IFBA) in some patients can result in a false and significant elevation in the reported concentration of vitamin B12 on the Dimension Vista® System. Siemens’ data indicate that the elevation is highly variable, and in some cases, values below the cutoff for B12 deficiency (i.e. 254 pg/mL) were reported as greater than 2000 pg/mL.

All vitamin B12 results obtained from the Dimension Vista® System are impacted by this issue, starting in **January 2008**”

*Failures of Cobalamin assays in Pernicious Anemia* Carmel and Agrawal, NEJM 2012 367;4  
*Spurious Elevations of Vitamin B12 with Pernicious Anemia* Yang and Cook, NEJM 2012 366;18



## Highly complex denaturation step

Total B12 assay	Active-B12 assay
<p>Typically 2-3 reagents for multiple pre-treatment steps:</p> <p><u>High pH</u> Denatures TC and HC to release B12 for capture</p> <p><u>Reductant</u> Denature anti-IF autoantibodies</p> <p><u>Cobinamide</u> Blocking agent to prevent B12 re-binding to TC/HC that renatures</p> <p><u>KCN</u> rIF capture has different affinities for different forms of B12, KCN converts all B12 to single form.</p>	<p>No pre-treatment:</p> <p>Specific monoclonal binds HoloTC – no cross-reactivity for ApoTC or HoloHC.</p>
Detect B12 bound to rIF	Detect bound HoloTC



## Throughput improvement

- Denaturation can be up to 15 minutes on some platforms
- No pre-analytical denaturation for Active-B12 – specific monoclonal for Holotranscobalamin.
- Subsequent impact on instrument throughput:
  - Abbott Architect Total B12 – 100 tests per hour
  - Abbott Architect Active-B12 – 200 tests per hour



## Active-B12 in PA investigation – laboratory cost savings

- Lab algorithm reflexed all Total B12 results below 190pmol/L (258pg/mL) to GPC Ab and IF Ab tests
- New algorithm reflexes all Total B12 results below 190pmol/L (258pg/mL) to Active-B12
- Active-B12 results >35pmol/L are deemed non-deficient
- Results <35pmol/L are sent for Ab tests
- 50% reduction in samples sent for expensive Ab tests



# Published evaluations – Netherlands

Published online on 2 February 2012 Ann Clin Biochem, doi: 10.1258/acb.2011.011039

## Original Article

### Screening for metabolic vitamin B<sub>12</sub> deficiency by holotranscobalamin in patients suspected of vitamin B<sub>12</sub> deficiency: a multicentre study

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#### Abstract

**Background:** Vitamin B<sub>12</sub> deficiency occurs frequently, especially among the elderly. However, screening for vitamin B<sub>12</sub> deficiency is hampered by poor sensitivity of the existing total vitamin B<sub>12</sub> assay. Methylmalonic acid (MMA) is considered as the most representative indicator of metabolic vitamin B<sub>12</sub> deficiency and is used as such in this study. The aim of this study was to validate the clinical usefulness of holotranscobalamin (holoTC) as an initial screening assay for metabolic vitamin B<sub>12</sub> deficiency in a mixed patient population.

**Methods:** Three hundred and sixty blood samples were collected by five Dutch hospitals. Vitamin B<sub>12</sub> and holoTC in serum were measured (AxSYM, Abbott). MMA in serum was measured by tandem mass spectrometry (LC-MS/MS).

**Results:** Receiver operating curve (ROC) analysis demonstrated a greater area under the curve (AUC) for holoTC than for vitamin B<sub>12</sub> in detecting vitamin B<sub>12</sub> deficiency characterized by three predefined cut-off levels of MMA. A cut-off value of 32 pmol/L of holoTC resulted in the highest sensitivity (83%) with acceptable specificity (60%) in detecting MMA concentrations above 0.45 μmol/L. The combination of vitamin B<sub>12</sub> and holoTC did not improve diagnostic accuracy at this cut-off level.

**Conclusions:** HoloTC has a better diagnostic accuracy than vitamin B<sub>12</sub> and can replace the existing vitamin B<sub>12</sub> assay as a primary screening test in patients suspected of vitamin B<sub>12</sub> deficiency. Critical evaluation of cut-off values of holoTC indicated that a cut-off value of 32 pmol/L can be considered in screening for metabolic vitamin B<sub>12</sub> deficiency (defined by MMA > 0.45 μmol/L) in a mixed patient population.

Ann Clin Biochem 2012; 1–6. DOI: 10.1258/acb.2011.011039

#### Introduction

Vitamin B<sub>12</sub> deficiency occurs frequently in the elderly and can be caused by several factors like impaired absorption or inadequate dietary intake.<sup>1</sup> Humans cannot synthesize vitamin B<sub>12</sub> (i.e. cobalamin) and therefore it has to be obtained through the diet. Vitamin B<sub>12</sub> deficiency is commonly asymptomatic in the early stages, but can later on be associated with macrocytic anaemia and typical neurological symptoms, either alone or in combination.<sup>2,3</sup> These symptoms are, however, far from specific and are variable in their presence and severity. Establishing vitamin B<sub>12</sub> deficiency on objective grounds is therefore challenging. In

most studies, the measurement of the metabolic consequence of vitamin B<sub>12</sub> deficiency, an increase in methylmalonic acid (MMA), has been applied.<sup>4–7</sup> A shortage of vitamin B<sub>12</sub> leads to insufficient activity of the enzyme methylmalonyl-CoA mutase, and hence to accumulation of its substrate MMA.

MMA is considered as the gold standard in the diagnosis of metabolic vitamin B<sub>12</sub> deficiency.<sup>8</sup> However, MMA can only be measured by complex, specialized methods which are relatively expensive. Vitamin B<sub>12</sub> measurement in serum is frequently used as a first-line assay in screening for vitamin B<sub>12</sub> deficiency. Diagnostic accuracy of this assay is hampered

Annals of Clinical Biochemistry 2012; 1–6

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n=360 samples collected across 5 hospitals

MMA cutoff μM	AUC Total B12	AUC HoloTC
>0.32	0.63	0.70
>0.45	0.70	0.78
>0.77	0.73	0.92

*“HoloTC has a better diagnostic accuracy than vitamin B12 and can replace the existing vitamin B12 assay as a primary screening test in patients suspected of vitamin B12 deficiency”*

Heil et al Ann Clin Biochem 2012:1-6



## Published evaluations – Korea

Korean J Lab Med 2010;30:185-9  
DOI: 10.3343/kjlm.2010.30.2.185

■ Brief Communication ■ Diagnostic Immunology ■

### Relationship between the Levels of Holotranscobalamin and Vitamin B12

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To date, the determination of serum vitamin B12 levels has been the most common laboratory test for the assessment of vitamin B12 status; however, the diagnostic accuracy of this test is low. To obtain a more sensitive marker, a new test to measure holotranscobalamin (holoTC) levels has been introduced. In this study, we assessed 45 patients for whom a vitamin B12 test had been requested and 139 anemic patients. We investigated the associations between the levels of homocysteine (Hcy) and those of holoTC, serum vitamin B12, and folate and assessed the diagnostic value of holoTC levels as a marker for vitamin B12 deficiency. We also determined the precision of the AxSYM holoTC assay by calculating the coefficient of variance (CV). The within-run and between-run precision values were excellent, as all CV values were less than 3.5%. The holoTC levels were low (<35 pmol/L) in 7 samples, and 6 of these samples had normal total serum vitamin B12 levels. In 2 of these samples, high Hcy levels (>12 μmol/L) indicated vitamin B12 deficiency. Thus, the holoTC levels were more sensitive than the serum vitamin B12 levels for indicating vitamin B12 status. If the serum vitamin B12 level is 151-300 pmol/L, the levels of holoTC alone or in combination with serum vitamin B12 levels are likely to be more useful markers than serum vitamin B12 levels alone. (Korean J Lab Med 2010;30:185-9)

**Key Words:** Holotranscobalamin, Vitamin B12 deficiency, Vitamin B12, Homocysteine

Vitamin B12 is essential for cellular metabolism, particularly DNA synthesis and regulation. Vitamin B12 deficiency may cause severe and irreversible damage, and early detection of vitamin B12 deficiency is important. While vitamin B12 status is currently determined by performing blood tests to assess serum vitamin B12 levels, the diagnostic accuracy of these tests is low [1, 2].

To obtain a more sensitive marker of vitamin B12 status, a new test involving measurement of the levels of holotranscobalamin (holoTC)—transcobalamin—vitamin B12

complex—has been introduced [3-7]. HoloTC promotes global cellular uptake of cobalamin by specific receptors; therefore, it may be more sensitive than serum vitamin B12 levels in indicating vitamin B12 status [8]. We investigated the association between the levels of holoTC and serum vitamin B12, determined the diagnostic value of holoTC levels in populations susceptible to vitamin B12 deficiency, and performed a precision test for the AxSYM holoTC assay.

We included 45 samples from patients for whom a serum vitamin B12 test had been requested because of conditions such as dementia with Alzheimer's disease, Parkinson's disease, cancer, including adenocarcinoma of the stomach, unstable angina, and infarction. We also included 139 samples from patients with normocytic or macrocytic anemia who were admitted to Dong-A University Hospital between August 2007 and March 2008. The 5 patients with adenocarcinoma of the stomach had undergone total or subtotal

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185

n=184 patients:  
n=45 where B12 requested (Alzheimers,  
stomach cancer, Parkinsons)  
n=139 normocytic or macrocytic anaemia

*“On the basis of these results, we concluded that the holo-TC levels may be more suitable than serum vitamin B12 levels to obtain information about vitamin B12 status. If the serum vitamin B12 level is between approximately 151-300 pmol/L, holoTC alone or in combination with the serum vitamin B12 is likely to be more useful than serum vitamin B12 levels alone to indicate vitamin B12 status”*

# Published evaluations – Italy

Clin Chem Lab Med 2010;48(2):249-253 © 2010 by Walter de Gruyter • Berlin • New York, DOI 10.1515/CCLM.2010.032

## Determination of serum holotranscobalamin concentrations with the AxSYM active B<sub>12</sub> assay: cut-off point evaluation in the clinical laboratory

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### Abstract

**Background:** A reliable early marker is required for diagnosis of cobalamin deficiency. We calculated an appropriate holotranscobalamin (HoloTC) cut-off point for identifying cobalamin deficiency using an immunoenzymatic assay.

**Methods:** Determination of the cut-off threshold and correlation between HoloTC and the other diagnostic parameters routinely used for vitamin B<sub>12</sub> deficiency [total vitamin B<sub>12</sub> (tB<sub>12</sub>), folate, homocysteine] were measured in 250 routine blood specimens from 107 men (mean age 59.0 ± 18.8 years) and 143 women (mean age 54.2 ± 23.1 years). The inclusion criterion was serum tB<sub>12</sub> concentration <221 pmol/L.

**Results:** Analytical performance results agreed with those reported by others. A weak correlation (R = 0.42) was found between HoloTC and tB<sub>12</sub>. A 40 pmol/L cut-off threshold was chosen for HoloTC and the associated sensitivity and

specificity was 0.86 and 0.66, respectively. Out of 250 tested samples, 126 showed tB<sub>12</sub> concentrations 139–221 pmol/L (gray zone, GZ) and 124 had tB<sub>12</sub> concentrations <139 pmol/L (low, L). Values less than the cut-off for HoloTC were present in 68.2% and 37.9% of cases in the GZ and L group, respectively (p < 0.01), and in 53.2% of subjects.

**Conclusions:** Our results confirmed the analytical reliability of the AxSYM HoloTC assay. The method is adequate for routine use and a cut-off threshold of 40 pmol/L is appropriate for assessing cobalamin deficiency in populations with reduced tB<sub>12</sub> values.

Clin Chem Lab Med 2010;48:249–53.

**Keywords:** analytical performance; holotranscobalamin; immunoenzymatic assay; vitamin B<sub>12</sub>.

### Introduction

Vitamin B<sub>12</sub> or cobalamin, a micronutrient supplied by meat and dairy products, is essential for mammalian intracellular metabolism, particularly metabolism of one-carbon groups and cell proliferation and differentiation (1, 2).

Low nutritional intake or impaired intestinal absorption of vitamin B<sub>12</sub> may lead to a negative balance and eventually to functional deficiency when tissue storages are depleted.

Cobalamin deficiency has clinical consequences such as megaloblastic anemia in severely deficient individuals, and a variety of progressive neurological diseases that occur in the absence of hematological complications, and hypochromocytopenia, associated with several pathological conditions including cardiovascular diseases, birth defects, neuropsychiatric disorders and dementia (3–5).

Determination of vitamin B<sub>12</sub> concentrations is useful in the prevention, diagnosis and/or prognosis of a variety of disorders directly or indirectly associated with defects in the metabolic pathways of this vitamin. However, serum total vitamin B<sub>12</sub> (tB<sub>12</sub>) concentrations are a dubious marker of actual functional B<sub>12</sub> status because in some cases it correlates poorly with hematologic indices (6). Cobalamin deficiency develops insidiously over the years, caused either by an autoimmune disease, such as pernicious anemia, or due to nutritional deficiency. Therefore, early and reliable diagnosis of vitamin B<sub>12</sub> deficiency is essential because of the latent nature of this disorder and the possible risk of irreversible neurological damage (7) which may be prevented by vitamin supplementation.

n=250 where Total B12 <221pmol/L

		Total B12	
		<140	≥140
HoloTC	<40	79	54
	≥40	84	84

*“In conclusion, determination of HoloTC concentrations may be used as a complementary diagnostic strategy to avoid the development of pathological conditions (macrocytic anaemia or neurological disease) before symptoms emerge, and should also be used for large scale screening of subjects at latent risk of cobalamin deficiency”*

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## HoloTC in practice – Melbourne Pathology, Australia

### Protocol offers the test to every patient with Total B12 <200pmol/L

“...From our experience reviewing these cases, Active B12 has advantage over total B12 in assessing B12 status of an individual. Active B12 was helpful in excluding B12 deficiency falsely ‘identified’ by low total B12 such as in pregnancy. It is also helpful in confirming true B12 deficiency missed by a normal total B12 in patients such as those with iron deficiency and hypothyroidism.”

“Active B12 has fulfilled our expectation in being a robust assay that improves the assessment of vitamin B12 status. It provides reassurance to us that we have contributed to improved patient care. The routine availability of this assay differentiates our laboratory as a progressive provider of quality pathology.”



MELBOURNE  
PATHOLOGY

*“We take it personally”*



## HoloTC in practice – Erasmus Medical Centre, Netherlands

### **HoloTC is offered routinely with a cut-off of 32pmol/L**

**“Active-B12 appears to be a better predictor of disturbed B12-dependent metabolism than Total B12.”**

**“Accepting MMA  $>0.45\mu\text{mol/L}$  as a reference standard for Vitamin B12 deficiency the Active-B12 assay demonstrates a better sensitivity and specificity in detecting Vitamin B12 deficiency than the Total B12 assay in a mixed collection of diagnostic samples.”**

**“For the detection of B12-deficiency Active-B12 can replace Total B12 as a first-line diagnostic aid; no reason for combination with Total B12.”**

**Erasmus MC**  
University Medical Center Rotterdam



## HoloTC in practice – GSTS Pathology, UK

**“Primary interest is the development and application of novel markers of vitamins to improve patient care.”**

**“The majority (up to 80%) of serum vitamin B12 is not bio-available. Current assays measure total vitamin B12 which leads to a grey area where deficient patients can be missed - there is a poor correlation between circulatory total B12 and B12 status at the tissue level. Conversely patients can inappropriately be classified to a deficient state with the inconvenience and expense of long term supplementation regimes.”**

**“The Nutristasis Unit will be providing this new nutritional marker from September and GSTS will be the first to offer it outside of research environment in the UK.”**



## HoloTC in practice – The Doctor's Laboratory, UK

“Conventional tests for Vitamin B12 measure total serum Vitamin B12, not metabolically active B12. It is better understood now that total B12 levels are not as clearly correlated with clinical symptoms as they might be. Clinically significant vitamin B12 deficiency can occur, and B12 status misclassified, even with Total Vitamin B12 levels apparently within normal range. Measuring **Active B12** is diagnostically more accurate for detecting B12 deficiency that requires therapy”

“It is fair to say that **Active B12** and Total B12 do show good agreement at the extremes (ie “very deficient” or “not at all deficient”) but there is a large grey zone of indeterminate range between normal and abnormal which is likely to be misclassified if total serum B12 alone is relied upon. It is therefore expected that by testing with **Active B12**, findings will be less in number, but more clinically relevant.

All Vitamin B12s will be replaced by **Active B12** whether requested as a single test, or requested with red cell or serum folate”



THE DOCTORS  
LABORATORY



## Further information

HOMOCYSTEINE AXIS-SHIELD HEPARIN

### ACTIVE-B12 EIA

the next level of B12 testing

- Home
- B12 Deficiency
- Active B-12
- Testing for Active-B12
- Publications and News
- Links
- Meetings and Exhibitions
- Contact Us

"Today, we can conclude that holoTC seems more suitable than total vitamin B-12 for diagnosis of vitamin B-12 deficiency" Prof. Ebba Nexø, American Journal of Clinical Nutrition, 2011

#### Low HoloTC but not Total B12 is associated with risk of dementia

The ACTIVE-B12 (Holotranscobalamin) assay from Axis-Shield is a new and innovative way of assessing Vitamin B12 levels and offers improved accuracy, sensitivity and specificity over the current out-dated front-line tests.

We aim to continue to present new findings into the clinical usefulness of measuring Active-B12 (Holotranscobalamin). We aim to make the test as widely available as possible, in the routine laboratory setting and for research, with the goal of improving the lives of patients suffering from Vitamin B12 deficiency.

Keep checking this site for new research findings in this area that should make the task of diagnosing vitamin B12 deficiency easier for the laboratorian, the doctor and the patient.

#### ACTIVE-B12 TESTING NOW AVAILABLE AT SECOND UK SITE

Private Active-B12 (Holotranscobalamin) testing is now available from The Doctor's Laboratory in the UK. For more information please see the TDL site.

#### ACTIVE-B12 MEETINGS AND EXHIBITIONS

Axis-Shield will be attending international conferences and exhibitions in the UK, India and Germany in 2013. For more details please see the Meetings and Exhibitions pages.

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