# Vitamin D Screening and Testing

Health Technology Assessment Program

## Key Questions Public Comment

May 29, 2012

Health Technology Assessment Program

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# Vitamin D Screening and Testing

## *Response to Public Comments on Key Questions*

## May 29, 2012

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**Response to Public Comments, Key Questions**
**Vitamin D Testing and Monitoring**

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document.

Draft key questions for each WA HTA report are posted online in order to gather public input and any additional evidence to be considered in the evidence review. Since key questions guide the evidence report, WA HTA seeks input on whether the questions are appropriate to address its mandate to gather evidence on safety, efficacy, and cost-effectiveness relevant to coverage determinations. Input about the following is especially helpful:

- Are appropriate populations or indications identified?
- Are appropriate comparators identified?
- Are appropriate patient-oriented outcome measures included?
- Are there special policy or clinical considerations that could affect the review?

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cited evidence, the vendor was encouraged to consider inclusion of this evidence in the report.

This document responds to comments from the **Northwest Alliance of MS Centers**. Table 1 provides a summary of comments with responses. No other parties submitted comments.

**Table 1. Public Comments on Key Questions for Vitamin D Testing**

| Comment and Source | Response |
|---|---|
| **November 8, 2011 Comments on Topic (letter from MS Alliance submitted by Eugene May, MD)** | |
| Patients with MS are at increased risk of osteoporosis because of steroid use, immobility, and possibly activated TH17 cells. | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| Compared with individuals with normal vitamin D levels, individuals with lower levels of vitamin D have a significantly higher risk of developing MS. | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| Vitamin D supplementation in patients with MS has been shown to reduce relapse rates. | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| **May 14, 2012 Comments on Key Questions (letter from MS Alliance, submitted by Eugene May, MD)** | |
| **KQ #1.** Longitudinal studies have demonstrated an inverse association between serum vitamin D levels and MS relapses and MRI activity. | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| **KQ #1.** "Regarding cutoff points for testing, one study provided evidence that serum levels of 25(OH)D around 100 can lead to a greater than 80% reduction in the hazard of relapse. In one study of vitamin D supplementation where 25(OH)D levels rose only to a mean of 70 there was no significant change in immunologic markers or activity, although there was a suggestion of a decrease in one immunologic marker of MS immune activity. Other studies have results in supplementation of patients to average levels of 150, 386, and 413, with evidence of efficacy, and no significant toxicity. Most MS neurologists therefore aim for 25(OH)D levels of at least 100." | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| **KQ #2.** "No randomized, controlled, double-blind clinical trials have been performed to evaluate whether manipulation of vitamin D levels has an impact on the course of MS. However, a number of studies have been | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |

| | |
|---|---|
| performed, of various sizes and quality, investigating the effect of vitamin D supplementation in individuals with multiple sclerosis." | |
| **KQ #3.** "There are no harms associated with Vitamin D testing." | Thank you for your comment.<br>The cited references will be considered for inclusion.<br>No change to Key Questions. |
| **KQ #4.** "No data available in the MS population." | Thank you for your comment.<br>This observation will be a useful check on the literature search findings.<br>No change to Key Questions. |
| **KQ #5.** Testing for serum 25(OHD) in a clinical laboratory in King County costs $250. The commenter described usual practice regarding testing in MS patients and potential cost savings. | Thank you for your comment.<br>This is useful information that will be taken into account.<br>No change to Key Questions. |

**Northwest Alliance of MS Centers**
**MSAlliance@live.com**

November 8, 2011

Denise Santoyo
Washington State Health Care Authority
Health Technology Assessment
Program Coordinator

**Jim Bowen, MD**
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**Gary Stobbe, MD**
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**Annette Wundes, MD**
*University of Washington*

Dear Ms. Santoyo

The MS Alliance is a collaboration of all of the MS Centers in the Puget Sound area with members including neurologists, physiatrists and nurse practitioners with expertise in the area of care of multiple sclerosis (MS). Our patients number more than 7,000. Our members have volunteer responsibilities with local and national advisory boards of the National MS Society, the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation. We understand that the Washington State Health Care Authority is considering evaluating the testing of 25(OH) Vitamin D levels. We respectfully submit the following as evidence that vitamin D testing is medically necessary for patients with multiple sclerosis.

Vitamin D deficiency is an important modifiable risk factor for osteoporosis. Patients with multiple sclerosis (MS) are at significantly increased risk of osteoporosis and osteopenia.[1,2,3,4] Recent research has demonstrated that low bone density occurs in early MS[5] and calls for a proactive preventative approach. Over time, patients with MS are at high risk of osteoporosis due to steroid use, immobility and perhaps even activated TH17 cells.[6,7,8,9]

Evidence from large prospective epidemiologic studies suggests that compared with individuals with normal vitamin D levels, individuals with lower levels of vitamin D have a significantly higher risk of developing MS.[12,13] In patients with multiple sclerosis, large numbers are deficient in vitamin D, as measured by 25(OH) vitamin D.[14] A randomized controlled study conducted over 52 weeks in Canada included 49 MS patients (45 with relapsing remitting and 4 secondary progressive MS) of which 25 patients received escalating doses of vitamin D (up to 40,000 iu/day)for 28 weeks followed 10,000iu/day along with calcium supplementation for 12 weeks. In the group treated with escalating doses of vitamin D compared to control there was a reduction in annualized relapse rate as well as a higher proportion of relapse free patients at the end of the study period. There was no evidence of renal calcification, disturbances of cardiac rhythm or any other adverse events.[15] Immune cells have vitamin D3 receptors, and data from both the experimental autoimmune encephalomyelitis mouse model and human studies have shown that vitamin D affects the immune system by a number of mechanisms suppression of the proinflammatory cytokines IFNγ and TNFα and induction of the regulatory cytokine TGFβ.[14,15]

On the basis of this and other clinical and epidemiological studies, assessment of vitamin D level and treatment of vitamin D deficiency is now an accepted practice at MS Centers in the USA. This testing is particularly important in the Northwest where vitamin D deficiency is quite common owing to reduced sunlight.

Vitamin D deficiency is a treatable condition that may have an adverse effect on MS and the MS patients in Washington are particularly susceptible to osteoporosis. On behalf of health practitioners involved in MS care and with our patients' best interests in mind, we request that 25 (OH) vitamin D testing for patients with multiple sclerosis be considered medical necessary.

Sincerely,

Members of the MS Alliance

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**Northwest Alliance of MS Centers**
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14 May 2012

TO: Washington Health Technology Assessment Program
RE: Vitamin D Screening and Testing

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To Whom It May Concern,

The Northwest Alliance of MS Centers is a collaboration of the Multiple Sclerosis Centers in the Puget Sound area with members including neurologists and physiatrists with expertise in the area of care of multiple sclerosis (MS). Our patients number more than 7,000. Our members have responsibilities with local and national advisory boards of the National MS Society, the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation.

Vitamin D deficiency is a treatable condition. Research is increasingly showing that Vitamin D deficiency may have an adverse effect on MS. In addition, MS patients are susceptible to osteoporosis because of immobility, and falling because of unsteadiness, all leading to increased risk of fractures. As a result, bone health and Vitamin D homeostasis is critically important in this population of vulnerable individuals.

To date, most of the research regarding the relationship between Vitamin D and MS has been uncontrolled and has involved relatively small numbers of patients. There are a number of studies ongoing and planned that should better define over the next decade the dosage form, dosing, target levels, and pathophysiology of Vitamin D in MS. However, in the mean time, the preponderance of the evidence suggests that individuals with MS benefit from replenishment of Vitamin D levels.

Vitamin D testing is fairly inexpensive and safe. The frequency of Vitamin D deficiency is high in the Northwest and people with MS are an especially vulnerable population for this condition. Thus, the test has a high-yield in MS. Therefore, we believe that serum 25-hydroxy Vitamin D testing presents worthy cost savings for individuals with MS and for the healthcare system, as a whole.

On behalf of health practitioners involved in MS care and with our patients' best interests in mind, we have chosen to respond to your Key Questions, and respectfully request that Vitamin D testing for patients with MS be considered medical necessary.

**KQ1: Has a relationship between serum vitamin D and health outcomes been demonstrated and have clinically valid cutoff points for serum vitamin D measurement been defined *(clinical validity)* with multiple sclerosis?**

Several longitudinal studies have demonstrated inverse correlations between serum vitamin D levels and the rate of MS relapses and MRI activity.[1,2,3] It has been demonstrated that every 10 mmol increase in serum 25(OH)D levels in an MS population was associated with a 9% reduction in risk of relapse.[3]

Regarding cutoff points for testing, one study provided evidence that serum levels of 25(OH)D around 100 can lead to a greater than 80% reduction in the hazard of relapse.[3] In one study of vitamin D supplementation where 25(OH)D levels rose only to a mean of 70, there was no significant change in immunologic markers or activity, although there was a suggestion of a decrease in one immunologic marker of MS immune activity.[4] Other studies have resulted in supplementation of patients to average levels of 150,[5] 386,[6] and 413,[7] with evidence of efficacy, and no significant toxicity. Most MS neurologists therefore aim for 25(OH)D levels of at least 100.

**KQ2: Is there evidence that testing for serum vitamin D levels improves health outcomes *(clinical utility)* in patients who already have multiple sclerosis?**

No randomized, controlled, double-blind clinical trials have been performed to evaluate whether manipulation of vitamin D levels has an impact on the course of MS. However, a number of studies have been performed, of various sizes and quality, investigating the effect of vitamin D supplementation in individuals with multiple sclerosis.[4,5,6,7,8,9,10] The preponderance of the evidence suggests a reduction of relapse rates and reduction in serum markers of immune activity associated with replacement that results in higher serum levels of vitamin D.

**KQ3: Are there harms associated with Vitamin D testing or with subsequent supplementation?**

There are no harms associated with Vitamin D testing.

In the studies of Vitamin D supplementation in multiple sclerosis, the only significant complication reported was hypercalcemia.[9] In that study, calcitriol was used as a supplement and the individuals with clinically significant toxicity were felt to be noncompliant with their diets. Safety and tolerability studies in the MS population [6,7,10] have since used doses of cholecalciferol as high as 40,000 IU per day for six weeks and 20,000 per day for 12 weeks, with some increased urinary calium:creatinine ratios,[7] but with no clinically significant adverse events reported.

**KQ4: What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in:**

**a. Healthy populations?**

**b. Populations who already have chronic disease, according to factors such as:**

**Patient characteristics**

**i. Age or life stage**

**ii. Race or ethnicity**

**iii. Geographic location**

**iv. Nutritional status, diet, or personal use of calcium/vitamin D supplements**

**v. Lifestyle factors such as smoking**

**vi. Obesity**

**vii. Baseline serum vitamin D level**

**viii. Baseline risk of the health outcome of interest**

**Testing parameters**
**i. Assay used**
**ii. Frequency of monitoring**
**iii. Time of year**

No data available in the MS population

**KQ5: What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?**

The cost of vitamin D testing varies from laboratory to laboratory and depending on the vitamin D test that was ordered. The most accepted Vitamin D test for reliability and clinical relevance is serum 25-hydroxy Vitamin D, measured in ng/ml. This test costs about $250 when performed at a clinical laboratory in King County and is the only Vitamin D test that is regularly performed. In the setting of MS care, patients may undergo Vitamin D testing at the time of diagnosis and repeat testing depending on clinician practices and initial results. Abnormal low or high values may require repeat testing in 2-6 months after adjustments in dietary intake or vitamin D supplementation. Based on clinical trends, we may assume that the average person with MS will undergo Vitamin D testing once per year at an unadjusted cost of $250.

Potential cost savings from treatment of Vitamin D deficiency include risk reduction for osteoporosis and related morbidities[11] and the potential therapeutic effects on the disease course of multiple sclerosis, as noted above.

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