Vitamin D Screening and Testing

Scheduled Presentations

<table>
<thead>
<tr>
<th>Name / Representing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Eugenie F. May, MD / NW Alliance of Multiple Sclerosis Centers</td>
</tr>
<tr>
<td>1 Nesanet Mitku, MD / NW Alliance of Multiple Sclerosis Centers</td>
</tr>
</tbody>
</table>
Disclosure

Any unmarked topic will be considered a “Yes”

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Research funding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

______________________________________________________________________________

______________________________________________________________________________

______________________________________________________________________________

If yes to #7, provide name and funding Sources:

______________________________________________________________________________

______________________________________________________________________________

______________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

[X] Signature  22.04.12  Eugene F. May

Date  Print Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
## Disclosure

Any unmarked topic will be considered a "Yes"

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<tbody>
<tr>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).</td>
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[Signature] 10/18/12  [Printed Name]  [Printed Name]

For questions contact: Christine Maetens
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

Conflict of Interest Form  Page 2 of 2
## Disclosure

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X __________________________  10/29/2012 Susan Ott

Signature                                    Date                                    First Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
CURRICULUM VITAE  1/5/2012

Susan Marie Ott

1. Personal Data: Place of birth: United States

2. Education:
   1966-1970   B.A. (Biology) Stanford University, Stanford, CA
   1970-1974   M.D., University of Washington, Seattle, WA

3. Postgraduate training:
   1974-1978   Residency, Family Practice and Internal Medicine
                University of California at Davis, Sacramento, CA
   1979-80     Staff Physician, Group Health Cooperative, Seattle, WA
   1980-82     Fellow in nephrology, University of Washington, Seattle, WA

4. Faculty positions:
   7/78-12/78   Clinical Instructor, Division of Emergency Medicine, Department of
                Medicine, University of California at Davis, Sacramento, CA
   7/82        Acting Instructor, Department of Medicine, University of Washington
   11/83       Assistant Professor, Department of Medicine
   4/87        Adjunct Assistant Professor, Radiology
   8/88        Adjunct Assistant Professor, Pathology
   7/89        Associate Professor, Department of Medicine; Adjunct
                Radiology, Pathology, and Orthopaedics
   7/10        Professor, Department of Medicine; Adjunct
                Radiology, Pathology, and Orthopaedics

5. Hospital positions:  Medical staff of University of Washington Medical Center.

6. Honors:
   1982        Younger Scientist Award to attend Fifth Workshop on Vitamin D
   1984        Clinical Investigator Award (N.I.H.)
   1990        Young Investigator Award, International Symposium on Osteoporosis
   2003        MERLOT Classics Award for Health Sciences online learning resource

7. Board Certification:
   1977-83     American Board of Family Practice
   1978        American Board of Internal Medicine
   1982        American Board of Internal Medicine, Nephrology


9. Professional Organizations:
   1984        International Society of Nephrology
   1984        King County Medical Association
   1999        International Society for Bone and Mineral Research
10. Teaching responsibilities:
   Attending for medical students, internal medicine residents and endocrinology fellows who rotate through metabolic bone clinic
   Lectures and conferences to housestaff and medical students
   Lectures for CME courses (local and international)

                    Journal of Clinical Endocrinology and Metabolism (1994-9)
                    Journal of Clinical Densitometry

12. National Responsibilities:
    Data Safety and Monitoring Committee for NIH clinical nutrition/bone trials

13. Local Responsibilities:
    Member of Faculty Senate, 2003-5.
    Scientific Advisory Committee, General Clinical Research Center (2008 – present)

14. Research Funding
    R01 AG030086-01A2 (Scholes) 2008-2013
    NIH/NIA
    Oral Contraceptives Use and Fractures around the Menopausal Transition
    Major Goals: To investigate the effects of patterns of oral contraceptive use on fracture risk during later reproductive and early postmenopausal years.
    Role: Co-Investigator

Bibliography:

a) Research articles in peer reviewed journals


guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral

70. Beasley JM, Ichikawa LE, Ange BA, Spangler L, LaCroix AZ, Ott SM, Scholes D. Is protein intake

71. Spangler L, Ott SM, Scholes D. Utility of automated data in identifying femoral shaft and

72. Scholes D, Hubbard RA, Ichikawa LE, et al. Oral contraceptive use and bone density change in
adolescent and young adult women: a prospective study of age, hormone dose, and discontinuation. J

a(2) **Reviews or editorials in peer review journals**

73. Ott SM. Should women get screening bone mass measurements? (editorial) Ann Intern Med


81. Ott SM. Does estrogen play a role in renal osteodystrophy? Seminars in Dialysis 1995;8:4-11.


83. Ott SM. Editorial: Calcimimetics - New drugs with the potential to control hyperparathyroidism. J Clin
Endocrinol Metab 1998; 83; 1-3.

31.

85. Bachrach LK, Cundy T, Ott SM. Depot medroxyprogesterone acetate in teens: A risk for bone health?


88. Del Puente A, Migliaccio S, Esposito A, Lello S, Ott SM. A reappraisal of therapeutic approaches to


95. Ott SM. What is the optimal duration of bisphosphonate therapy? Cleveland Clinic J of Med 2011;78:619-630.

b) Book chapters


c) Published books, videos, software, etc.


d) Other publications:


23. Ott SM, Woodson GC, Huffer WE. Bone histomorphometric changes in women with postmenopausal osteoporosis treated with etidronate. in proceedings of the Third International Symposium on Osteoporosis, Copenhagen, Denmark. 1990:


32. Ott SM. Alendronate in anorexia nervosa [letter]. J Clin Endocrinol Metab. 2005 Sep;90(9):5508.


Vitamin D Screening & Testing

State Agency Utilization & Outcomes

G. Steven Hammond, Chief Medical Officer
Department of Corrections
November 16, 2012

Background

• In recent years there has been intense interest in the possible role of vitamin D in health and disease
  – A central role for vitamin D in bone metabolism has long been appreciated.
  – Given the ubiquitous distribution of vitamin D receptors throughout the body, there is much interest in possible additional important physiologic roles.
  – Epidemiologic studies showing correlations of serum vitamin D levels or history of dietary vitamin D intake with various states of health and disease has sparked much interest in the potential therapeutic value of manipulating (augmenting) vitamin D levels to achieve health benefits.
However, many questions remain unanswered:

- What are “normal”, “inadequate”, “deficient”, “optimal”, or “excessive” vitamin D levels? (Extremely important question because definitions determine “prevalence” of “vitamin D deficiency”)
  - And how are seasonal variations to be accommodated in such interpretation?
- Aside from settings where benefit is proven (e.g., rickets, osteoporosis, elderly at risk for fall) is there health benefit to taking vitamin D supplements?
- Is there health benefit to screening and/or monitoring of vitamin D levels to guide therapeutic supplementation?

Vitamin D deficiency or inadequacy is known to be central to several disease processes:

- Known cause of rickets and osteomalacia
- A cause of secondary hyperparathyroidism
- A sequela of intestinal malabsorption

Vitamin D supplementation may improve outcomes in osteoporosis and elderly persons at risk for falls
Vitamin D Screening & Testing

AMD Workgroup Perspective

Initial Primary Criteria Ranking
(Prior to review of agency utilization data or evidence report)

- **Safety** = Medium
- **Efficacy** = High
- **Cost** = High

Vitamin D Screening & Testing

**Current State Policy**

**Medicaid** - Covered

**PEB** – Covered
Regence considers vitamin D testing not medically necessary in the absence of clinical documentation of an underlying disease or condition specifically associated with vitamin D deficiency.

**Labor and Industries** - Covered

**Department of Corrections** – Restricted
Requires preauthorization.
Vitamin D Screening & Testing

Medicare Policies

National Coverage Decision - None

CMS Local Coverage Decisions - None

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### Agency Utilization

<table>
<thead>
<tr>
<th>Agency</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>4-Yr Total</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEB: Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>204,804</td>
<td>210,501</td>
<td>213,487</td>
<td>212,596</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% agency pop.)</td>
<td>(6.9%)</td>
<td>(11.8%)</td>
<td>(14.4%)</td>
<td>(13.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount Paid</td>
<td>$794K</td>
<td>$1.4M</td>
<td>$1.5M</td>
<td>$1.0M</td>
<td>$4.8M</td>
<td></td>
</tr>
<tr>
<td>Avg Tests/Patient (95% upper limit/pt)</td>
<td>1.3</td>
<td>2.7</td>
<td>1.3</td>
<td>2.4</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Average Paid/Test</td>
<td>$44</td>
<td>$44</td>
<td>$40</td>
<td>$31</td>
<td>$39</td>
<td>-10.3%</td>
</tr>
</tbody>
</table>

| **Medicaid: Pop.** | 392,808 | 416,871 | 424,230 | 435,187 | | |
| Patients | 6,849 | 14,874 | 21,450 | 21,432 | | |
| (% agency pop.) | (1.7%) | (3.6%) | (5.1%) | (4.9%) | | |
| Amount Paid | $341K | $707K | $975K | $898K | $2.9M | |
| Avg Tests/Patient (95% upper limit/pt) | 1.3 | 2.7 | 1.3 | 2.7 | 1.3 | |
| Average Paid/Test | $38 | $37 | $35 | $32 | $35 | -5.6% |

1 Patients who were treated in multiple years are counted once in the 4-year total. * Adjusted for population growth
Vitamin D Screening & Testing

Agency Utilization

Vitamin D test CPT codes used in analysis:
- 82306 (25-OH Vitamin D)
- 82652 (1, 25-dihydroxy Vitamin D)

CPT 82306 is the predominantly used code.

<table>
<thead>
<tr>
<th>Agency</th>
<th>% Total Tests</th>
<th>% Total Payments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEB</td>
<td>4.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>4.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>L&amp;I</td>
<td>16.9%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

PEB

Vitamin D Testing - Utilization by Age & Gender

<table>
<thead>
<tr>
<th>Age</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>4-Yr Overall(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14,042</td>
<td>24,892</td>
<td>30,794</td>
<td>27,884</td>
<td>62,537</td>
</tr>
<tr>
<td>0-17</td>
<td>277</td>
<td>464</td>
<td>736</td>
<td>735</td>
<td>1,774</td>
</tr>
<tr>
<td>18-34</td>
<td>1,221</td>
<td>2,518</td>
<td>3,148</td>
<td>3,229</td>
<td>7,513</td>
</tr>
<tr>
<td>35-49</td>
<td>3,303</td>
<td>6,421</td>
<td>8,065</td>
<td>7,223</td>
<td>15,946</td>
</tr>
<tr>
<td>50-64</td>
<td>7,854</td>
<td>13,126</td>
<td>15,946</td>
<td>13,636</td>
<td>30,183</td>
</tr>
<tr>
<td>65-79</td>
<td>1,252</td>
<td>2,115</td>
<td>2,626</td>
<td>2,716</td>
<td>6,322</td>
</tr>
<tr>
<td>80+</td>
<td>135</td>
<td>248</td>
<td>273</td>
<td>345</td>
<td>799</td>
</tr>
<tr>
<td>% Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>57%</td>
<td>60%</td>
<td>58%</td>
<td>56%</td>
<td>57%</td>
</tr>
<tr>
<td>18-34</td>
<td>81%</td>
<td>82%</td>
<td>79%</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>35-49</td>
<td>81%</td>
<td>79%</td>
<td>76%</td>
<td>75%</td>
<td>76%</td>
</tr>
<tr>
<td>50-64</td>
<td>79%</td>
<td>76%</td>
<td>72%</td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>65-79</td>
<td>67%</td>
<td>62%</td>
<td>59%</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>80+</td>
<td>70%</td>
<td>63%</td>
<td>64%</td>
<td>64%</td>
<td>65%</td>
</tr>
</tbody>
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\(^1\) Patients who receive tests in multiple years are counted once in the 4-year overall total.
### Medicaid

**Vitamin D Testing - Utilization by Age & Gender**

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<thead>
<tr>
<th>Age</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>4-Yr Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6,849</td>
<td>14,875</td>
<td>21,450</td>
<td>21,432</td>
<td>48,870</td>
</tr>
<tr>
<td>0-17</td>
<td>632</td>
<td>1,385</td>
<td>1,963</td>
<td>2,370</td>
<td>4,995</td>
</tr>
<tr>
<td>18-34</td>
<td>1,106</td>
<td>2,855</td>
<td>4,557</td>
<td>4,344</td>
<td>10,854</td>
</tr>
<tr>
<td>35-49</td>
<td>1,795</td>
<td>3,934</td>
<td>5,711</td>
<td>5,318</td>
<td>12,464</td>
</tr>
<tr>
<td>50-64</td>
<td>2,751</td>
<td>5,791</td>
<td>8,116</td>
<td>7,940</td>
<td>17,209</td>
</tr>
<tr>
<td>65-79</td>
<td>476</td>
<td>752</td>
<td>907</td>
<td>1,161</td>
<td>2,713</td>
</tr>
<tr>
<td>80+</td>
<td>89</td>
<td>158</td>
<td>196</td>
<td>299</td>
<td>635</td>
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</tbody>
</table>

% Female

<table>
<thead>
<tr>
<th>Age</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>4-Yr Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>47%</td>
<td>54%</td>
<td>52%</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>18-34</td>
<td>76%</td>
<td>75%</td>
<td>74%</td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td>35-49</td>
<td>76%</td>
<td>73%</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>50-64</td>
<td>77%</td>
<td>71%</td>
<td>70%</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td>65-79</td>
<td>78%</td>
<td>74%</td>
<td>70%</td>
<td>69%</td>
<td>71%</td>
</tr>
<tr>
<td>80+</td>
<td>75%</td>
<td>70%</td>
<td>69%</td>
<td>69%</td>
<td>71%</td>
</tr>
</tbody>
</table>

1 Patients who receive tests in multiple years are counted once in the 4-year overall total.

### Vitamin D Screening & Testing

**Agency Utilization**

**Average Cost of Vitamin D Test - 2008-2011**

<table>
<thead>
<tr>
<th>Overall Average</th>
<th>PEB Primary</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td>$55</td>
<td>$36</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>$67 (29%)</td>
<td>$40 (30%)</td>
</tr>
<tr>
<td>Independent Lab</td>
<td>$50 (53%)</td>
<td>$34 (64%)</td>
</tr>
<tr>
<td>Office</td>
<td>$54 (17%)</td>
<td>$40 (4%)</td>
</tr>
</tbody>
</table>

**2012 Maximum Payments for Vitamin D Tests**

<table>
<thead>
<tr>
<th>Agency</th>
<th>CPT 82306</th>
<th>CPT 82652</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicaid</td>
<td>$32.29</td>
<td>$41.99</td>
</tr>
<tr>
<td>L&amp;I</td>
<td>$58.72</td>
<td>$75.29</td>
</tr>
</tbody>
</table>

1 Medicaid Fee Schedule
2 L&I Fee Schedule
### PEB

**Top 10* Diagnoses For Vitamin D Tests**  
By Frequency, (2008-2011)

<table>
<thead>
<tr>
<th>Dx Code &amp; Description</th>
<th>Allowed Amount</th>
<th>Count</th>
<th>Cumulative % Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tests</td>
<td>$6,677,275</td>
<td>121,788</td>
<td></td>
</tr>
<tr>
<td>V70.0  Routine Medical Exam</td>
<td>$1,041,581</td>
<td>20,924</td>
<td>17.2%</td>
</tr>
<tr>
<td>268.9  Vitamin D Deficiency, NOS</td>
<td>$625,897</td>
<td>11,545</td>
<td>26.7%</td>
</tr>
<tr>
<td>780.79 Malaise &amp; Fatigue, NEC</td>
<td>$454,822</td>
<td>8,331</td>
<td>33.5%</td>
</tr>
<tr>
<td>272.4  Hyperlipidemia, NEC/NOS</td>
<td>$344,657</td>
<td>6,137</td>
<td>38.5%</td>
</tr>
<tr>
<td>244.9  Hypothyroidism, NOS</td>
<td>$288,744</td>
<td>5,337</td>
<td>42.9%</td>
</tr>
<tr>
<td>V72.31 Routine GYN Exam</td>
<td>$210,201</td>
<td>4,159</td>
<td>46.3%</td>
</tr>
<tr>
<td>250    Diabetes Type II</td>
<td>$162,638</td>
<td>2,938</td>
<td>48.7%</td>
</tr>
<tr>
<td>401.1  Benign Hypertension</td>
<td>$156,608</td>
<td>2,895</td>
<td>51.1%</td>
</tr>
<tr>
<td>272    Hyperlipidemia</td>
<td>$124,533</td>
<td>2,314</td>
<td>53.0%</td>
</tr>
<tr>
<td>401.9  Hypertension, NOS</td>
<td>$116,982</td>
<td>2,132</td>
<td>54.8%</td>
</tr>
</tbody>
</table>

* 2503 diagnosis codes were used on PEB claims during 2008-2011.

---

### Medicaid

**Top 10* Diagnoses For Vitamin D Tests**  
By Frequency, (2008-2011)

<table>
<thead>
<tr>
<th>Dx Code &amp; Description</th>
<th>Allowed Amount</th>
<th>Count</th>
<th>Cumulative % Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tests</td>
<td>$3,024,254</td>
<td>84,278</td>
<td></td>
</tr>
<tr>
<td>268.89 Vitamin D Deficiency, NOS</td>
<td>$270,031</td>
<td>7,768</td>
<td>8.9%</td>
</tr>
<tr>
<td>780.79 Malaise &amp; Fatigue, NEC</td>
<td>$194,619</td>
<td>5,109</td>
<td>15.4%</td>
</tr>
<tr>
<td>250.00 Diabetes Type II</td>
<td>$136,482</td>
<td>3,844</td>
<td>19.9%</td>
</tr>
<tr>
<td>272.24 Hyperlipidemia, NEC/NOS</td>
<td>$102,576</td>
<td>2,807</td>
<td>23.3%</td>
</tr>
<tr>
<td>585.56 End-Stage Renal Disease</td>
<td>$94,842</td>
<td>2,465</td>
<td>26.4%</td>
</tr>
<tr>
<td>401.19 Hypertension, NOS</td>
<td>$72,799</td>
<td>2,068</td>
<td>28.8%</td>
</tr>
<tr>
<td>401.11 Benign Hypertension</td>
<td>$69,116</td>
<td>2,004</td>
<td>31.1%</td>
</tr>
<tr>
<td>244.49 Hypothyroidism, NOS</td>
<td>$66,321</td>
<td>1,853</td>
<td>33.3%</td>
</tr>
<tr>
<td>V58.69 Long-term Use Meds, NEC</td>
<td>$60,863</td>
<td>1,709</td>
<td>35.3%</td>
</tr>
<tr>
<td>V22.21 Supervise Other Normal Preg.</td>
<td>$54,875</td>
<td>1,617</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

* 2806 diagnosis codes used for Medicaid claims during 2008-2011.
Vitamin D Screening & Testing

Agency Considerations

– Vitamin D testing is widespread in clinical practice.
  • Due to volume, total costs are significant.

– Usually not associated with a clinical diagnosis indicating a specific disorder of vitamin D metabolism.

– After review of agency utilization data and evidence report, revised primary criteria ranking:
  • Safety – Low
  • Efficacy – High
  • Cost - High

Vitamin D Screening & Testing

Agency Considerations

– No evidence that routine screening or testing of vitamin D levels improves health outcomes.

– Testing is appropriate in clinical settings in which vitamin D plays a well-defined role.
  • E.g., Rickets/osteomalacia; secondary hyperparathyroidism; intestinal malabsorption; hypo- and hypercalcemia

– For conditions in which vitamin D supplementation is known to be beneficial (osteoporosis and in elderly individuals), there is no evidence that testing aids clinical management.
Vitamin D Screening & Testing

Agency Recommendations

Cover with conditions:
– For evaluation and management of:
  • Rickets/ Osteomalacia
  • Secondary hyperparathyroidism
    (Including chronic kidney disease stage G3 or higher)
  • Intestinal malabsorption
  • Hypo- or hypercalcemia, otherwise unexplained
– Other conditions, Not covered

Questions?

For More Information: HTA Program
Vitamin D Screening and Testing

Teresa Rogstad, MPH
Senior Medical Research Analyst
Louisville, KY

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Medical Research Analyst

Karen Crotty, PhD
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Internal Primary Care Consultant
Presentation Overview

- Challenges
- Background
- Policy Context
- Review Objectives
- Methods
- Findings
- Evidence-Based Conclusions
- Gaps in the Evidence

CHALLENGES
Vitamin D Screening/Testing

- Several causal relationships, different directions
- Many tissues/diseases
- Not a diagnostic test
- Minor prognostic contribution to most outcomes
- Screening versus testing
- Healthy versus disease-defined populations
- Accuracy (clinical validity) versus effectiveness (clinical utility)
Biggest Problem

No clinical trials evaluating the effectiveness of screening/testing

Solution

• Evaluate evidence for effectiveness of vitamin D supplementation
• *Potential, plausible* clinical utility of testing/screening
• Especially important
  – Differential effectiveness of supplementation by baseline serum level
BACKGROUND: Risk Factors for and Signs of Low Vitamin D

- Female sex
- Obesity
- Age
- Dark skin
- Low sun exposure
- Infants breastfed
- Osteoporosis
- Non-traumatic fracture
- Hyperparathyroidism
- Low serum calcium
- Low phosphorus
- Infants breastfed

Vitamin D and Health

- Chronic kidney disease (CKD), sarcoidosis
- Malabsorptive disease, e.g., celiac
- Vit D depletion
- Secondary malabsorption
- Bariatric surgery
- Demographic risk factors
- Rickets, osteomalacia, osteoporosis
- Fractures
- Muscle weakness
- Falls
- Impaired regulation in multiple tissues and systems
- Obesity, cancer, CVD, MS, . . .
- Disease-related outcomes
**Vitamin D Toxicity**

- Hypercalcemia
- Hypercalciuria
- Kidney stones

**HIGH Vit D**

**Vitamin D Deficiency**

- Vitamin D thresholds defined for good *bone health* by the Institute of Medicine (IOM)
  - Possibly harmful: $> 125$ nmol/L (50 ng/mL)
  - Sufficient: $\geq 50$ nmol/L (20 ng/mL)
  - At risk of insufficiency: $< 50$ nmol/L (20 ng/mL)
  - At risk of deficiency: $< 30$ nmol/L (12 ng/mL)

- Prevalence of insufficiency/deficiency (NHANES III, 2001-2006)
  - At risk of insufficiency: 33%
  - At risk of deficiency: Females, 10%; males, 6%

NHANES = National Health and Nutrition Examination Survey
Measuring Vitamin D Status

- 25-hydroxyvitamin D (25-OHD)
  - 1,25-dihydroxyvitamin D (1,25-[OH]2-D) (calcitriol)
- Assays
- Screening
  - Universal
  - Based on risk factors, e.g., age or ethnicity
- Testing
  - Presence of known cause, e.g., chronic kidney disease
  - Presence of known marker, e.g., osteoporosis, hyperparathyroidism
- Monitoring

Intake

- IOM recommendations for bone health in healthy populations
  - Infants, 400 IU/day
  - Children, 600 IU/day
  - Adults, 600 IU/day
  - Adults > 70 years of age, 800 IU/day
  - Upper tolerable limit, 4000 IU/day
- Forms of non-dietary vitamin D intake
  - D3 (cholecalciferol) (inactive)
  - D2 (ergocalciferol, or calciferol) (inactive)
  - 1,25-(OH)2-D (calcitriol) (active, “pharmaceutical”)
  - Synthetic analogs (active, “pharmaceutical”)
POLICY CONTEXT

• Wide range of health outcomes, purported but unproven relationship with vitamin D
  – Potential for overutilization of tests
• Key U.S. and Canadian organizations
  – No definitive cutoff values for specific outcomes
  – Routine testing is not warranted

Practice Guidelines

• 17 generally good-quality guidelines were rated
• Routine screening is not recommended (5 guidelines; very poor to good)
  – Except in individuals who are at general high risk (not well-defined)
• Testing recommended for individuals with known poor bone health (3 guidelines; fair to good)
• Monitoring (1 guideline; good)
  – Not necessary at doses < 2000 IU/day
  – Every 3 to 4 months for pharmaceutical supplementation
• Other rated guidelines addressed supplementation but not screening/testing
Payer Policies

- Centers for Medicare & Medicaid (CMS) and GroupHealth
  - No policy for screening, testing, or supplementation
- Aetna
  - Injections of active vitamin D
- Regence
  - Testing in individuals with: (1) a disease or condition known to cause vitamin D depletion; or (2) radiologic or laboratory findings that are positive for markers for insufficiency

REVIEW OBJECTIVES: PICO

Populations:

Healthy populations: Generally healthy adults, including pregnant women, and children without symptoms or findings of the outcome of interest.

Populations with known disease that may be linked with but does not cause vitamin D insufficiency: Adults and children with chronic diseases such as poor bone health, obesity, cardiovascular disease (CVD) (e.g., hypertension, heart failure, coronary artery disease), cancer, diabetes, multiple sclerosis (MS), or depression.

Intervention: Serum vitamin D testing
PICO (cont.)

Comparator: No testing

Outcomes:

Healthy populations: Growth, obesity, bone health, and fractures or falls; all-cause mortality; and the incidence of other chronic diseases such as of CVD, cancer, diabetes, MS, and depression, as well as related mortality.

Populations with known disease that may be linked with but does not cause vitamin D insufficiency: Health outcomes related to the indication disease.

Key Questions

1. 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)?
   a. In healthy populations?
   b. In patients with chronic disease?

2. Is there evidence that testing for serum vitamin D levels improves health outcomes (clinical utility)?
   a. As a routine screening test in healthy patients?
   b. In patients who already have chronic disease thought to be associated with low serum vitamin D?
Key Questions (cont)

3. Are harms associated with vitamin D testing or with subsequent supplementation?

4. 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 and (b) populations who already have chronic disease, according to factors such as:
   - Patient characteristics (e.g., age, baseline serum vitamin D level)
   - Testing parameters

5. What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?

Analytic Framework

- Accurate serum values
- Low serum vitamin D
- Higher serum levels
- Testing in population of interest
- Harms
- Falls
- Cancer
- Mortality
- Dietary intake or Supplementation
- Examples
- 1
- 2
- 3
- 4
- 5
- 6
- 7
METHODS: Evidence Sources

- MEDLINE
- Systematic review/guideline databases
- National Health Service Economic Evaluation Database (NHS EED)
- Relevant professional associations

Evidence Selection

- Key Question #1
  - Representative systematic/narrative reviews, recent trials
  - Descriptive, no critical appraisal

- Focus on Key Questions #2 through #4
Evidence Selection (cont.)

- Effectiveness of supplementation as indicator of the potential utility of and safety of screening/testing (KQs #2 through #4)
  - Healthy populations, musculoskeletal outcomes: Systematic reviews of RCTs
  - Healthy populations, other outcomes: RCTs
  - Disease populations: Systematic reviews of RCTs where possible

---

FINDINGS: KQ #1a (clinical validity of serum 25-OHD in healthy populations)

<table>
<thead>
<tr>
<th>BENEFICIAL ASSOCIATION</th>
<th>HARMFUL ASSOCIATION</th>
<th>UNCLEAR</th>
<th>INSUFFICIENT EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Cancer mortality in men</td>
<td>Cancer other than CRC or ovarian</td>
<td>Obesity</td>
</tr>
<tr>
<td>Colorectal cancer (CRC)</td>
<td></td>
<td></td>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td>Multiple sclerosis (MS)</td>
</tr>
<tr>
<td>Cardiovascular disease (CVD)</td>
<td></td>
<td></td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td>Depression and mood disorders</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cutoff values: No definitive values; vary by outcome

Association ≠ causation
KQ #1b (clinical validity of serum 25-OHD in disease populations)

<table>
<thead>
<tr>
<th>BENEFICIAL ASSOCIATION</th>
<th>INSUFFICIENT EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Some types of cancer (survival or recurrence)</td>
<td>• Obesity (weight control, metabolic outcomes)</td>
</tr>
<tr>
<td>• Colon cancer</td>
<td>• Multiple sclerosis (relapses)</td>
</tr>
<tr>
<td>• Prostate cancer</td>
<td>• Depression (symptoms)</td>
</tr>
<tr>
<td>• Melanoma</td>
<td></td>
</tr>
<tr>
<td>• Hypertension (cardiovascular events)</td>
<td></td>
</tr>
<tr>
<td>• Diabetes (complications)</td>
<td></td>
</tr>
</tbody>
</table>

*Cutoff values: No definitive values; vary by outcome

Association ≠ causation

KQ #2a (effectiveness of vitamin D screening in healthy populations)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone mineral density (BMD), older adults*</td>
<td>9 RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>Falls, older adults*</td>
<td>1 M-A (26 RCTs)</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures, older adults*</td>
<td>1 M-A (11 RCTs)</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality, older adults*</td>
<td>2 RCTs (n=38,968)</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes, adults</td>
<td>2 RCTs (n=34,293)</td>
<td>Low</td>
</tr>
<tr>
<td>Mood disorders, adults</td>
<td>3 RCTs (n=4625)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*Predominantly postmenopausal women.
KQ #2a (effectiveness of vitamin D screening in healthy populations) (cont)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNCERTAIN BENEFIT (inconsistent results)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone health, infants/children/adolescents</td>
<td>3 SRs</td>
<td>Low</td>
</tr>
<tr>
<td>Obesity, adults</td>
<td>3 RCTs (n=36,687)</td>
<td>Low</td>
</tr>
<tr>
<td>Cancer, older adults*</td>
<td>3 RCTs (n=40,165)</td>
<td>Low</td>
</tr>
<tr>
<td>CVD, older adults*</td>
<td>2 RCTs (n=38,968)</td>
<td>Low</td>
</tr>
<tr>
<td>Birth size and weight, maternal supplementation in late pregnancy</td>
<td>3 RCTs (n=422)</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Predominantly postmenopausal women.

KQ #2a (effectiveness of vitamin D screening in healthy populations) (cont)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNKNOWN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>Nonskeletal outcomes; younger adults, lactating women, infants, children, adolescents</td>
<td>Insufficient evidence</td>
<td></td>
</tr>
</tbody>
</table>
KQ #2b (effectiveness of vitamin D screening in disease populations)

Supplementation trials, \textit{potential} utility of screening.

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis (musculoskeletal health) (\textit{active} vitamin D)</td>
<td>15 RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>CVD, adults</td>
<td>8 RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>Abnormal blood glucose, adults</td>
<td>12 RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>Osteoporosis (\textit{inactive} vitamin D at ordinary doses)</td>
<td>4 RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obesity, adults</td>
<td>5 RCTs</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

KQ #2b (effectiveness of vitamin D screening in disease populations) (cont)

Supplementation trials, \textit{potential} utility of screening.

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced prostate cancer (survival)</td>
<td>3 RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>MS (relapse, functional outcomes)</td>
<td>4 RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>Cancer other than prostate cancer</td>
<td>Insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>Depression, mood disorder</td>
<td>Insufficient evidence</td>
<td></td>
</tr>
</tbody>
</table>
KQ #3 (safety)

- Vitamin D testing
  - Safe (blood test)
- Inactive vitamin D (D3, D2)
  - Moderate increase in risk of hypercalcemia and kidney stones
- Active (pharmaceutical) vitamin D
  - Threefold increase in risk of hypercalcemia

KQ #4a (differential effects in healthy populations – by baseline 25-OHD)

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>QUANTITY OF EVIDENCE</th>
<th>DIRECTION OF TREND</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls, adults overall (not in community-only)</td>
<td>2 M-A</td>
<td>↓ serum value, ↑ effect</td>
<td>Low</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>1 M-A</td>
<td>↑ serum value, ↑ effect</td>
<td>Low</td>
</tr>
<tr>
<td>*CRC risk</td>
<td>1 RCT (n&gt;36,000)</td>
<td>↓ serum value, ↑ effect</td>
<td>Low</td>
</tr>
<tr>
<td>*Hypertension</td>
<td>1 RCT (n&gt;36,000)</td>
<td>↑ serum value, ↑ effect</td>
<td>Low</td>
</tr>
<tr>
<td>*All-cause mortality</td>
<td>1 RCT (n&gt;36,000)</td>
<td>↓ serum value, ↑ effect</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Postmenopausal women.
KQ #4a (differential effects in healthy populations – by baseline 25-OHD) (cont)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>Type 2 diabetes</td>
<td>1 RCT (n&gt;36,000)</td>
</tr>
<tr>
<td>UNCLEAR</td>
<td>BMD, children</td>
<td>1 M-A</td>
</tr>
</tbody>
</table>

KQ #4a (differential effects in healthy populations – other factors)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>OUTCOME, FACTOR</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>Falls, weight control, cancer, CVD, diabetes, mortality; all other factors of interest; older adults, primarily postmenopausal women</td>
<td>1 RCT (n&gt;36,000) 1 M-A</td>
</tr>
<tr>
<td></td>
<td>BMD, age, children and adolescents</td>
<td>1 M-A</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>Safety for any population Effectiveness, testing parameters, any population Effectiveness; any factor in younger adults, pregnant women, or lactating women Effectiveness for prevention of obesity, MS, or depression</td>
<td></td>
</tr>
</tbody>
</table>
## KQ #4b (differential effects in disease populations)

Supplementation trials, potential utility of screening.

<table>
<thead>
<tr>
<th>INDICATION, FACTOR</th>
<th>QUANTITY OF EVIDENCE</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>Adults at high glycemic risk (obesity or abnormal glucose control), baseline serum 25-OHD</td>
<td>1 RCT (obesity) 11 RCTs (abnormal glucose control)</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>Other indications and factors</td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>

## Costs

- $39 to $250, vitamin D test
- < $40, 1-year supply of vitamin D supplements at 800 IU/day
- < $80, 1-year supply of vitamin D supplements at 50,000 IU/week
- No information on cost of megadose injections
Cost-Effectiveness

- 3 studies
  - Cost-effectiveness of supplementation for prevention of fracture, older populations
  - Payer perspective, Canada and Europe
  - Assume universal (no testing) 800 IU/day plus calcium
- Supplementation is cost-saving or reasonably cost-effective compared with no treatment (2 studies)
- Supplementation is less effective than hip protector for nursing home residents (1 study)

EVIDENCE-BASED CONCLUSIONS

- Definitive conclusions about screening/testing not possible
- Potential effectiveness for some populations/outcomes
  - Association between serum levels and outcomes
  - Positive effect of supplementation on outcomes
- Testing and treatment reasonably safe
Factors Determining Value

- Association, serum 25-OHD with outcomes
- Effectiveness of screening/testing (no evidence)
- *Effectiveness of supplementation
- *Differential effectiveness of supplementation, especially according to baseline serum values
- Safety
  *Direction of results, quality of evidence

Possible Value
(evidence across Key Questions)

- **Testing and monitoring**
  - In adults with known or highly suspected osteoporosis, when active or megadose inactive vitamin D is used
  - To prevent toxicity
- **Moderate level of confidence in conclusion**
  - Demonstrated association, serum levels and BMD
  - Moderate-quality positive evidence: Active vitamin D
  - Low-quality negative evidence: Inactive vitamin D at ≤ 1400 IU/day (follow-up 3 to 18 months)
  - Greater toxicity risk, active or megadose inactive vitamin D
  - No data on differential effectiveness or cost-effectiveness
Too Early to Tell

- Screening
  - *Theoretical* value for reducing risk of disease (some cancers, CVD) and mortality in postmenopausal women
- Very low confidence in this conclusion
  - Low-quality evidence of serum-disease association and effect of supplementation
  - Low-quality evidence for differential effect of supplementation by baseline 25-OHD, *but conflicting trends*
  - No evidence for other populations; no cost-effectiveness data
- More research is needed

GAPS IN THE EVIDENCE

- No direct evidence, *utility of screening/testing*.
- *Definitive cutoffs* for serum values lacking.
- Missing data, *differential effectiveness* of supplementation by baseline serum 25-OHD.
- Few supplementation trials in healthy older populations using *current doses* and representing a *wide range of baseline values*.
- Little epidemiological evidence and few supplementation trials: *populations other than healthy older adults*. 
Thank you.