Washington State Health Care Authority
Health Technology Assessment

Vitamin D Screening and Testing

Scheduled Presentations

	Name / Representing
1	Eugene F. May, MD / NW Alliance of Multiple Sclerosis Centers Nesanet Mitku, MD / NW Alliance of Multiple Sclerosis Centers

Disclosure

Any unmarked topic will be considered a "Yes"

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

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

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

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 Oct 12 Eugene F. May

Signature *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"

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

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7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		x

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X _____ 10/18/12 Nesanet Mitiku

Signature *Date* *Print Name*

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X Susan Ott 10/29/2012 Susan Ott

Signature *Date* *Print Name*

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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

8. Licensure: California (1975-1984), Washington (1979-present)

9. Professional Organizations:

1983	American Society of Bone and Mineral Research (Council, 1988 - 1991)
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)

11. Editorial Boards: Journal of Bone and Mineral Research (1993-7)
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

KDIGO (Kidney Disease: Improving Global Outcomes) international committee for guideline development for treatment of chronic kidney disease - mineral and bone disorder (2007-2010)

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

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10. Ott SM. Aluminum accumulation in individuals with normal renal function. Am J Kidney Dis 1985;6:297-301.

11. Sherrard DJ, Ott SM, Andress DL, Pseudohyperparathyroidism: A syndrome associated with aluminum intoxication in patients with renal failure. Am J Med 1985;79:127-30.

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13. Ott SM, Kilcoyne RF, Chesnut CH. Longitudinal changes in bone mass after one year as measured by different techniques in patients with osteoporosis. Calcif Tissue Int 1986;39:133-8.

14. Ott SM, Andress DL, Sherrard DJ. Bone oxalate in a long-term hemodialysis patient who ingested high doses of vitamin C. Am J Kidney Dis 1986;8:450-4.

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16. Ott SM, Kilcoyne RF, Chesnut CH. Ability of four different techniques of measuring bone mass to diagnose vertebral fractures in postmenopausal women. J Bone Mineral Res 1987;2:201-10.

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18. Lipkin EW, Ott SM, Klein GL. Heterogeneity of bone histology in parenteral nutrition patients. Am J Clin Nutr 1987;46:673-80.

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a(2) Reviews or editorials in peer review journals

73. Ott SM. Should women get screening bone mass measurements? (editorial) Ann Intern Med 1986;104:874-6.

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b) Book chapters

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2. Sherrard DJ, Ott SM, Coburn JW. Bone disease due to aluminum: A comparison between uremia and total parenteral nutrition. in: Coburn JW and Klein GL, eds. *Metabolic Bone Disease in Total Parenteral Nutrition*. Urban & Schwarzenberg,Baltimore-Munich. 1985:63-72.

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Washington State Health Care Authority

Vitamin D Screening and Testing

State Agency Utilization & Outcomes

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

Vitamin D Screening & Testing

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.

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Washington State Health Care Authority

Vitamin D Screening & Testing

Background, cont'd

- 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?

Washington State Health Care Authority

Vitamin D Screening & Testing

Background, cont'd

- 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

Washington State Health Care Authority

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

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Washington State Health Care Authority

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.

Washington State Health Care Authority

Vitamin D Screening & Testing

Medicare Policies

National Coverage Decision - None

CMS Local Coverage Decisions - None

Washington State Health Care Authority

Vitamin D Screening & Testing

Agency Utilization

Agency	2008	2009	2010	2011	4-Yr Total	%Change
PEB: Population	204,804	210,501	213,487	212,596		1.3%
Patients	14,042	24,892	30,794	27,884		
(% agency pop.)	(6.9%)	(11.8%)	(14.4%)	(13.1%)	**62,537[1]**	*28.5%
Amount Paid	$794K	$1.4M	$1.5M	$1.0M	**$4.8M**	*15.7%
Avg Tests/Patient	1.3	1.3	1.2	1.2	**1.9**	
(95% upper limit/pt)	(2.7)	(2.6)	(2.4)	(2.3)	**(5.0)**	
Average Paid/Test	$44	$44	$40	$31	**$39**	-10.3%
Medicaid: Pop.	392,808	416,871	424,230	435,187		3.5%
Patients	6,849	14,874	21,450	21,432		
(% agency pop.)	(1.7%)	(3.6%)	(5.1%)	(4.9%)	**48,870[1]**	*47.90%
Amount Paid	$341K	$707K	$975K	$898K	**$2.9M**	*40.3%
Avg Tests/Patient	1.3	1.3	1.3	1.3	**1.7**	
(95% upper limit/pt)	(2.7)	(2.7)	(2.7)	(2.7)	**(4.7)**	
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.

CPT 82652 tests		
Agency	**% Total Tests**	**% Total Payments**
PEB	4.2%	3.5%
Medicaid	4.1%	3.6%
L&I	16.9%	19.5%

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PEB

Vitamin D Testing – Utilization by Age & Gender

Age	2008	2009	2010	2011	4-Yr Overall[1]
Total	**14,042**	**24,892**	**30,794**	**27,884**	**62,537**
0-17	277	464	736	735	**1,774**
18-34	1,221	2,518	3,148	3,229	**7,513**
35-49	3,303	6,421	8,065	7,223	**15,946**
50-64	7,854	13,126	15,946	13,636	**30,183**
65-79	1,252	2,115	2,626	2,716	**6,322**
80+	135	248	273	345	**799**
% Female	**78%**	**76%**	**72%**	**72%**	**72%**
0-17	57%	60%	58%	56%	**57%**
18-34	81%	82%	79%	78%	**78%**
35-49	81%	79%	76%	75%	**76%**
50-64	79%	76%	72%	71%	**72%**
65-79	67%	62%	59%	61%	**61%**
80+	70%	63%	64%	64%	**65%**

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

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Medicaid

Vitamin D Testing – Utilization by Age & Gender

Age	2008	2009	2010	2011	4-Yr Overall[1]
Total	**6,849**	**14,875**	**21,450**	**21,432**	**48,870**
0-17	632	1,385	1,963	2,370	**4,995**
18-34	1,106	2,855	4,557	4,344	**10,854**
35-49	1,795	3,934	5,711	5,318	**12,464**
50-64	2,751	5,791	8,116	7,940	**17,209**
65-79	476	752	907	1,161	**2,713**
80+	89	158	196	299	**635**
% Female	**74%**	**71%**	**70%**	**68%**	**69%**
0-17	47%	54%	52%	51%	**52%**
18-34	76%	75%	74%	74%	**75%**
35-49	76%	73%	70%	70%	**70%**
50-64	77%	71%	70%	69%	**69%**
65-79	78%	74%	70%	69%	**71%**
80+	75%	70%	69%	69%	**71%**

[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

	PEB Primary	Medicaid
Overall Average	**$55**	**$36**
Hospital	$67 (29%)	$40 (30%)
Independent Lab	$50 (53%)	$34 (64%)
Office	$54 (17%)	$40 (4%)

2012 Maximum Payments for Vitamin D Tests

Agency	CPT 82306	CPT 82652
Medicaid[1]	$32.29	$41.99
L&I[2]	$58.72	$75.29

[1] Medicaid Fee Schedule
[2] L&I Fee Schedule

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PEB

Top 10* Diagnoses For Vitamin D Tests

By Frequency, (2008-2011)

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

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

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Medicaid

Top 10* Diagnoses For Vitamin D Tests

By Frequency, (2008-2011)

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

* 2806 diagnosis codes used for Medicaid claims during 2008-2011.

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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**

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Washington State Health Care Authority

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.

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Washington State Health Care Authority

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**

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Washington State Health Care Authority

Questions?

For More Information: HTA Program

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Washington State Health Care Authority

Vitamin D Screening and Testing

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Hayes

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Presentation Overview

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

Hayes

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)

Hayes

Biggest Problem

No clinical trials evaluating the effectiveness of screening/testing

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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

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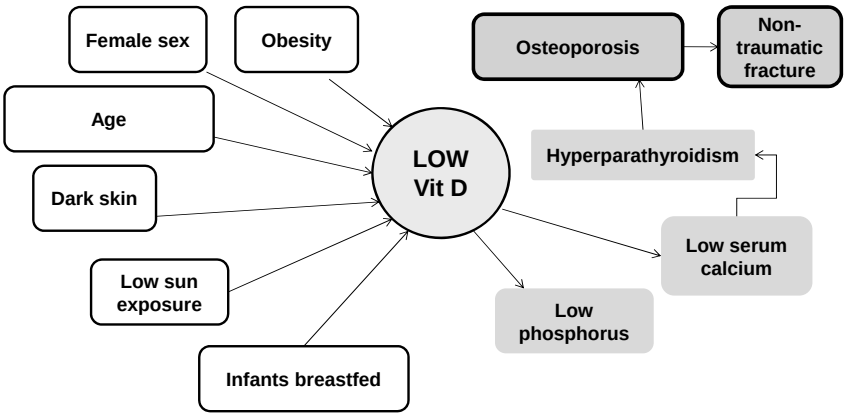
BACKGROUND: Risk Factors for and Signs of Low Vitamin D



Hayes

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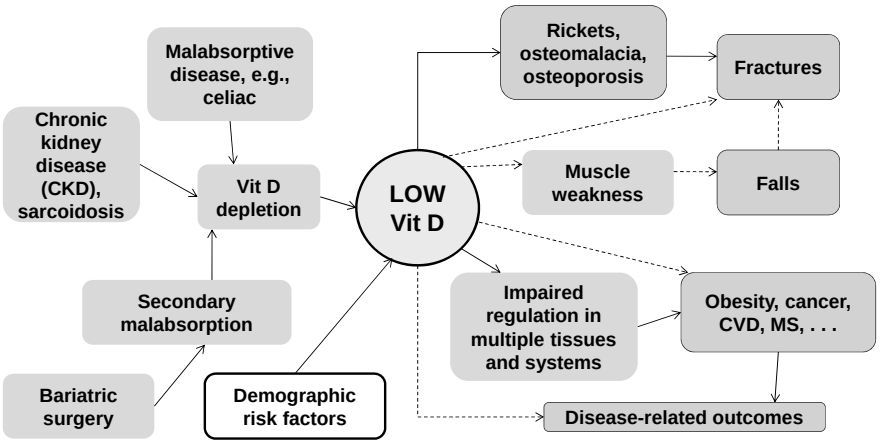
Vitamin D and Health



Hayes

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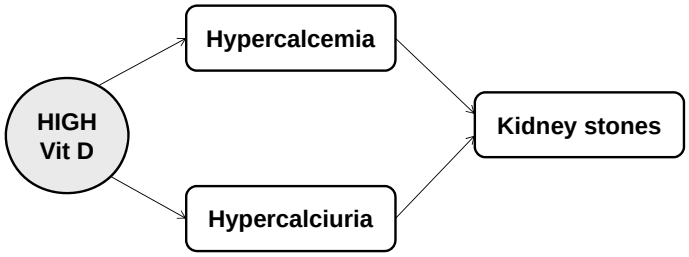
Vitamin D Toxicity



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: ≥ 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

Hayes

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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"*)

Hayes

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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

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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

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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

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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

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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.

Hayes

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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?

Hayes

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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?

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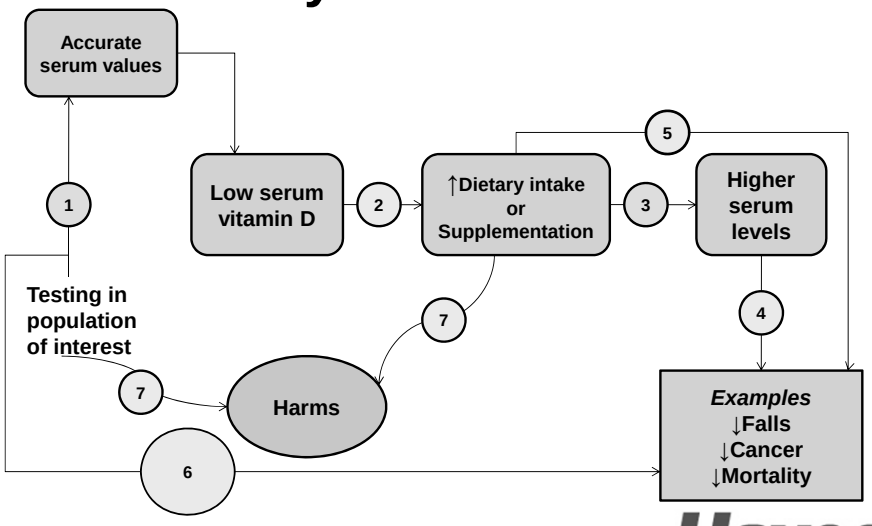
Analytic Framework



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METHODS: Evidence Sources

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

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Evidence Selection

- Key Question #1
  - Representative systematic/narrative reviews, recent trials
  - Descriptive, no critical appraisal
- Focus on Key Questions #2 through #4

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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

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

BENEFICIAL ASSOCIATION	HARMFUL ASSOCIATION	UNCLEAR	INSUFFICIENT EVIDENCE
•Osteoporosis •Colorectal cancer (CRC) •Ovarian cancer •Cardiovascular disease (CVD) •Type 2 diabetes •All-cause mortality	Cancer mortality in men	Cancer other than CRC or ovarian	•Obesity •Gestational diabetes •Multiple sclerosis (MS) •Type 1 diabetes •Depression and mood disorders
Cutoff values: **No definitive values; vary by outcome** ***Association ≠ causation***			

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

BENEFICIAL ASSOCIATION	INSUFFICIENT EVIDENCE
•Some types of cancer (survival or recurrence) •Colon cancer •Prostate cancer •Melanoma •Hypertension (cardiovascular events) •Diabetes (complications)	•Obesity (weight control, metabolic outcomes) •Multiple sclerosis (relapses) •Depression (symptoms)
Cutoff values: **No definitive values; vary by outcome** ***Association ≠ causation***	

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

Supplementation trials, *potential* utility of screening.

	OUTCOME	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
BENEFIT	Bone mineral density (BMD), older adults*	9 RCTs	Low
	Falls, older adults*	1 M-A (26 RCTs)	Low
	Fractures, older adults*	1 M-A (11 RCTs)	Low
	Mortality, older adults*	2 RCTs (n=38,968)	Low
NO BENEFIT	Diabetes, adults	2 RCTs (n=34,293)	Low
	Mood disorders, adults	3 RCTs (n=4625)	Moderate
*Predominantly postmenopausal women.			

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

Supplementation trials, *potential* utility of screening.

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

*Predominantly postmenopausal women.

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

Supplementation trials, *potential* utility of screening.

	OUTCOME	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
UNKNOWN	Multiple sclerosis	Insufficient evidence	
	Nonskeletal outcomes; younger adults, lactating women, infants, children, adolescents	Insufficient evidence	

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

Supplementation trials, *potential* utility of screening.

	INDICATION	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
BENEFIT	Osteoporosis (musculoskeletal health) (active vitamin D)	15 RCTs	Moderate
	CVD, adults	8 RCTs	Moderate
	Abnormal blood glucose, adults	12 RCTs	Moderate
NO BENEFIT	Osteoporosis (inactive vitamin D at ordinary doses)	4 RCTs	Moderate
	Obesity, adults	5 RCTs	Moderate

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

Supplementation trials, *potential* utility of screening.

	INDICATION	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
UNCERTAIN BENEFIT (inconsistent results)	Advanced prostate cancer (survival)	3 RCTs	Low
	MS (relapse, functional outcomes)	4 RCTs	Low
UNKNOWN	Cancer other than prostate cancer	Insufficient evidence	
	Depression, mood disorder	Insufficient evidence	

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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

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

Supplementation trials, *potential* utility of screening.

	OUTCOME	QUANTITY OF EVIDENCE	DIRECTION OF TREND	QUALITY OF EVIDENCE
EFFECT MAY DIFFER	Falls, adults overall (not in community-only)	2 M-A	↓ serum value, ↑ effect	Low
	Nonvertebral fractures	1 M-A	↑serum value, ↑effect	Low
	*CRC risk	1 RCT (n>36,000)	↓ serum value, ↑ effect	Low
	*Hypertension	1 RCT (n>36,000)	↑serum value, ↑effect	Low
	*All-cause mortality	1 RCT (n>36,000)	↓ serum value, ↑ effect	Low

*Postmenopausal women.

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

Supplementation trials, *potential* utility of screening.

	OUTCOME	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
NONE	Type 2 diabetes	1 RCT (n>36,000)	Low (single trial)
UNCLEAR	BMD, children	1 M-A	Low (metaregression)

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

Supplementation trials, *potential* utility of screening.

	OUTCOME, FACTOR	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
NONE	Falls, weight control, cancer, CVD, diabetes, mortality; all other factors of interest; older adults, primarily postmenopausal women	1 RCT (n>36,000) 1 M-A	Low (single trial or meta-regression)
	BMD, age, children and adolescents	1 M-A	Low (meta-regression)
UNKNOWN	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		

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KQ #4b (differential effects in disease populations)

Supplementation trials, *potential* utility of screening.

	INDICATION, FACTOR	QUANTITY OF EVIDENCE	QUALITY OF EVIDENCE
NONE	Adults at high glycemic risk (obesity or abnormal glucose control), baseline serum 25-OHD	1 RCT (obesity) 11 RCTs (abnormal glucose control)	Low (single trial or qualitative analysis)
UNKNOWN	Other indications and factors	Insufficient evidence	

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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

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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)

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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

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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*

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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

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Too Early to Tell

- Screening
  - *Theoretical* value for reducing risk of disease (some cancers, CVD) and mortality in <u>postmenopausal women</u>
- *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

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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**.

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