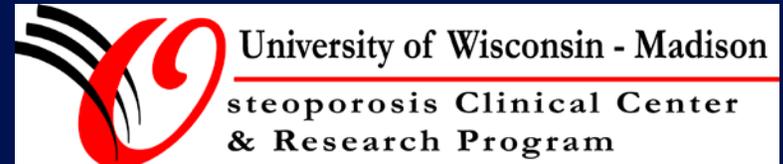


Lack of Standardization: Clinical Impact

Nov 14, 2013

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Madison, WI, USA



Disclosures: None

Note: Orange Font = My Opinion



The Clinical Impact = Confusion

Vitamin D prevents heart disease

Can Vitamin D Replace Flu Shots?

Vitamin D increases skin cancer risk

New Study Warns Against Excessive Vitamin D Intake

Component Results			
Component	Result	Flag	Reference Range
Vitamin D3, 25-Hydroxy	28		
Vitamin D2, 25-Hydroxy	<5		
Vitamin D, 25-Hydroxy	28	L	30 - 80
Comment			
Vitamin D status in a patient is judged by Total 25-OH Vitamin D.			
Total 25-OH Vitamin D clinical reference values:			
< 10 ng/mL	Severe deficiency		
10-29 ng/mL	Mild to moderate deficiency		
30-80 ng/mL	Optimum levels		
> 80 ng/mL	Toxicity possible		

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The Clinical Impact = Confusion



There is Controversy in the Field

IOM Endorsed 25(OH)D of 20 ng/mL as Adequate, But....

Ross, et. al., J Clin Endocrinol Metab, 96; 53-58, 2011

The IOM report ...makes a positive contribution by grounding its recommendations on the available evidence base....(we are) generally in agreement with these conclusions.”

Reid IR & Avenell A, JBMR, 26;452-454, 2011

“The IOM recommendations for vitamin D fail in a major way on logic, on science and on effective public health guidance....our recommendation to the American public is that the IOM report should be taken with a grain of salt...”

Heaney RP & Holick MF, JBMR, 26;455-457, 2011



Respected Groups Have Differing Daily Intake Recommendations



Nutrient Reference Values
for Australia and New Zealand

200-600 IU



COMITÉ PERMANENT DES MÉDECINS EUROPÉENS
STANDING COMMITTEE OF EUROPEAN DOCTORS

600-800 IU



INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

600-800 IU

Food and Nutrition Board



International
Osteoporosis
Foundation

800-1,000 IU



THE
ENDOCRINE
SOCIETY®

1,500-2,000 IU

Respected Groups Have Recommendations That Directly Conflict

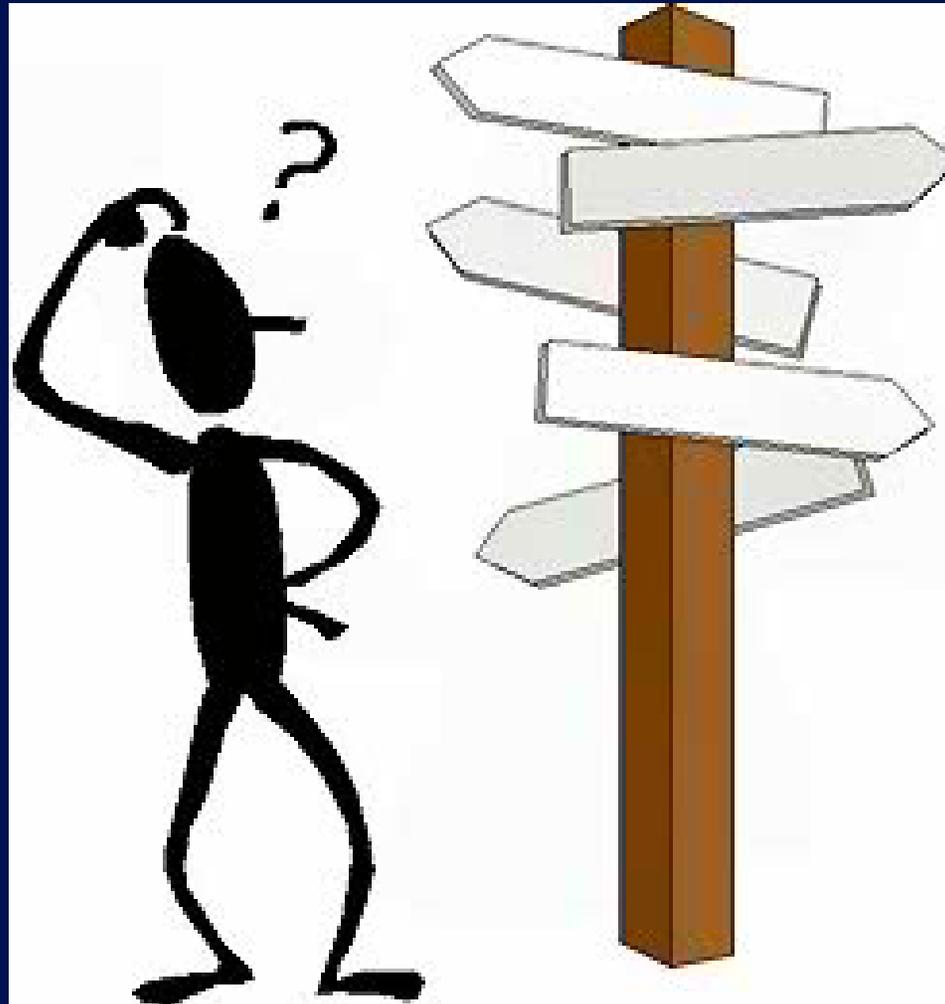
- ❑ The USPSTF **recommends** exercise or physical therapy and **vitamin D supplementation to prevent falls** in community-dwelling adults aged 65 years or older who are at increased risk for falls
- ❑ The USPSTF **recommends against daily supplementation with 400 IU or less of vitamin D₃ and 1,000 mg or less of calcium for the primary prevention of fractures** in non-institutionalized postmenopausal women

* The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D₃ and 1,000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.
Grade: D Recommendation.

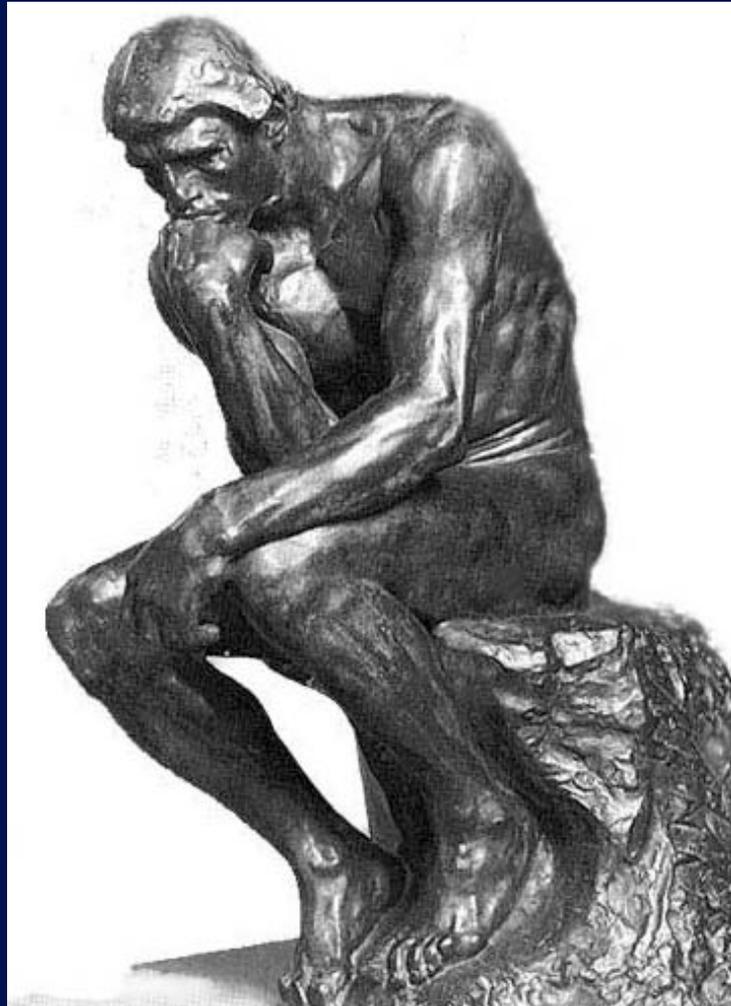
<http://www.uspreventiveservicestaskforce.org/uspstf/uspsfalls.htm>
<http://www.uspreventiveservicestaskforce.org/uspstf/uspsvitd.htm>



How Can Patients and Clinicians NOT be Confused?



What's a Clinician to Do?





Recognize That Diagnostic Cutpoints Are Used in Clinical Care, but Human Physiology is Rarely Black and White

Consider Osteoporosis....

65 yo female, BMI 25 with no other clinical risk factors

- T-score = -2.4: Dx = **Osteopenia**, 10 yr Fx risk = **13%**
- T-score = -2.6: Dx = **Osteoporosis**, 10 yr Fx risk = **14%**

www.shef.ac.uk/frax

A 25(OH)D of 29 ng/mL is Not Different than 31 ng/mL

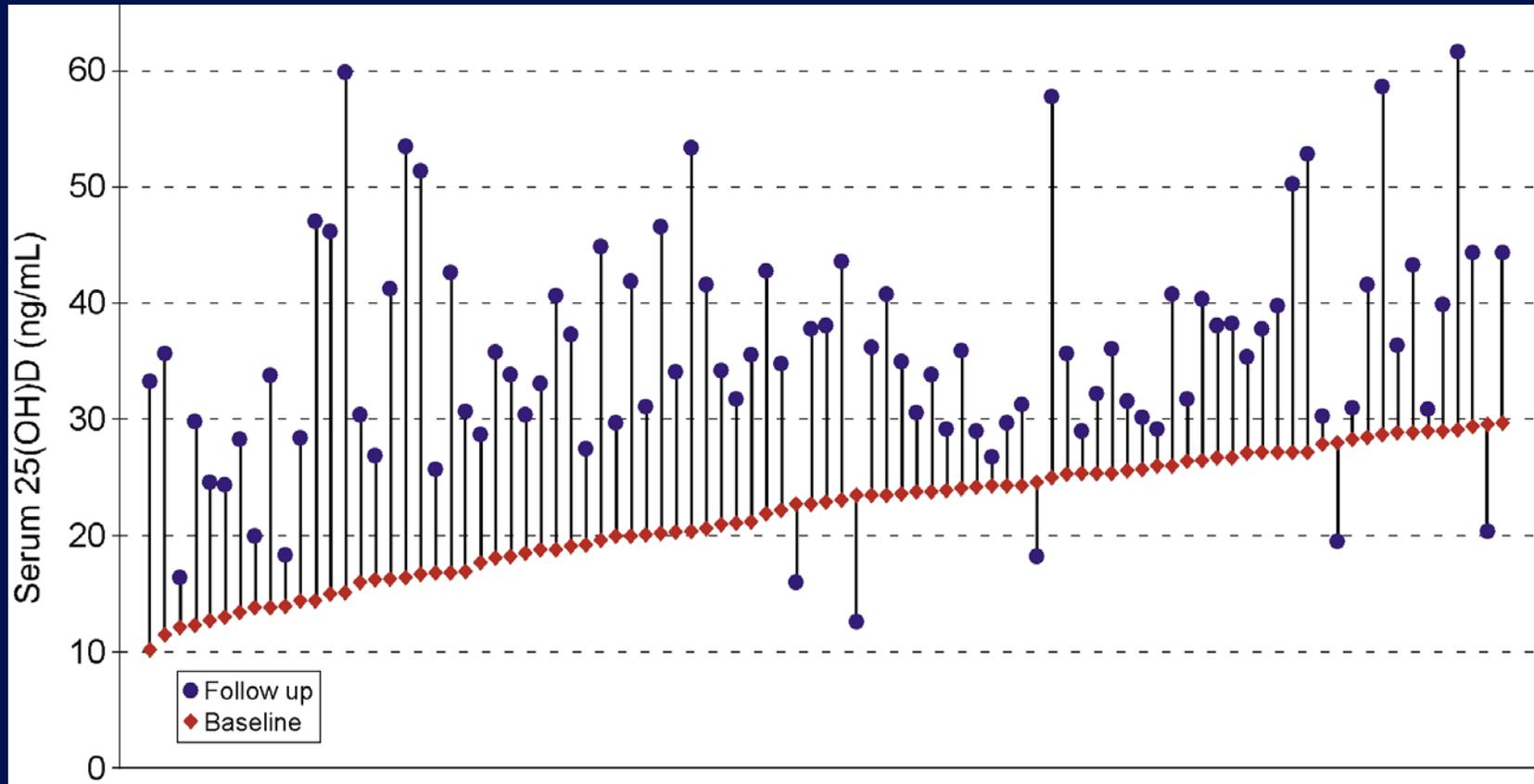


Remember the Obvious: We Are Not All The Same....



We Are Not All The Same.....

Dramatic Differences in 25(OH)D Response to Oral Vitamin D



Postmenopausal women receiving cholecalciferol 2300-2500 IU daily for 4-6 months



Unpublished data; Binkley, et al.

Recognize Assay Variability and Ask...

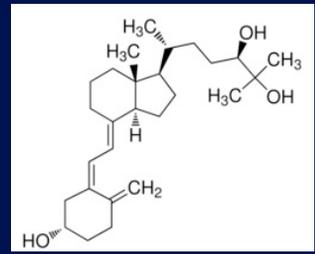


One Confounder is 3-Epi-25(OH)D

- Given the identical structure (and therefore identical MW) seems likely that epimers of 25(OH)D might lead to higher 25(OH)D values
 - Reports exist that the C-3 epimer may confound 25(OH)D measurement by some liquid chromatography-tandem mass spectrometry methods
- Historically felt to occur only in infants
 - Present at generally low levels in virtually all human sera
- Source, and physiologic importance (if any) remain to be clarified



Another Confounder is 24, 25(OH)₂D₃

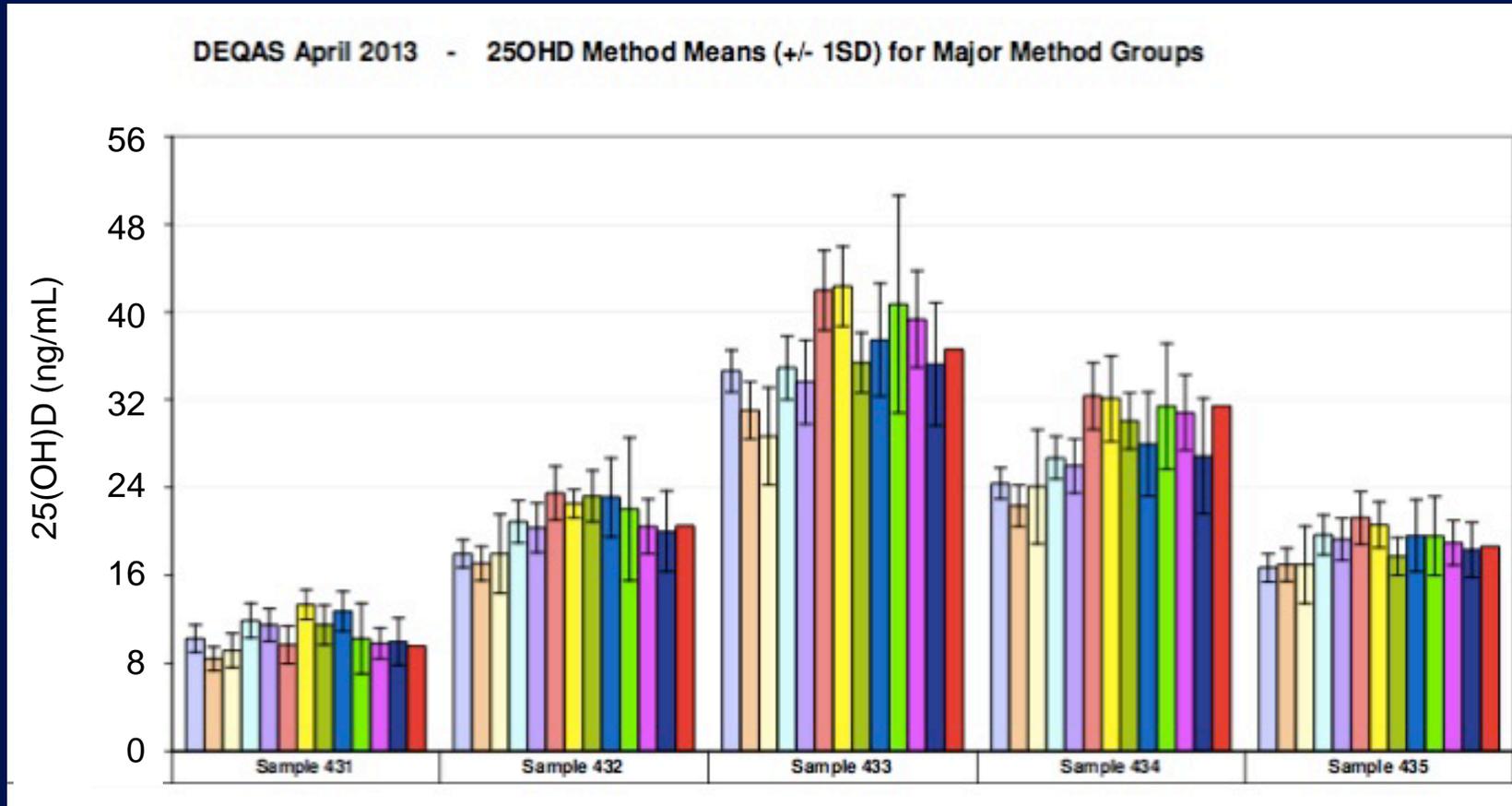


- Often considered to be simply an inactivating step of 25(OH)D; i.e., a degradation product ultimately leading to calcitroic acid
 - Not surprising that some have found no rationale for 24, 25(OH)₂D₃ measurement
- Some work finds 24, 25 (OH)₂D₃ to possess physiologic effects on cartilage and bone
 - 24, 25(OH)₂D₃ supplementation reduces PTH in humans with X-linked hypophosphatemic rickets



Despite Standardization Efforts; 25(OH)D Variability Persists

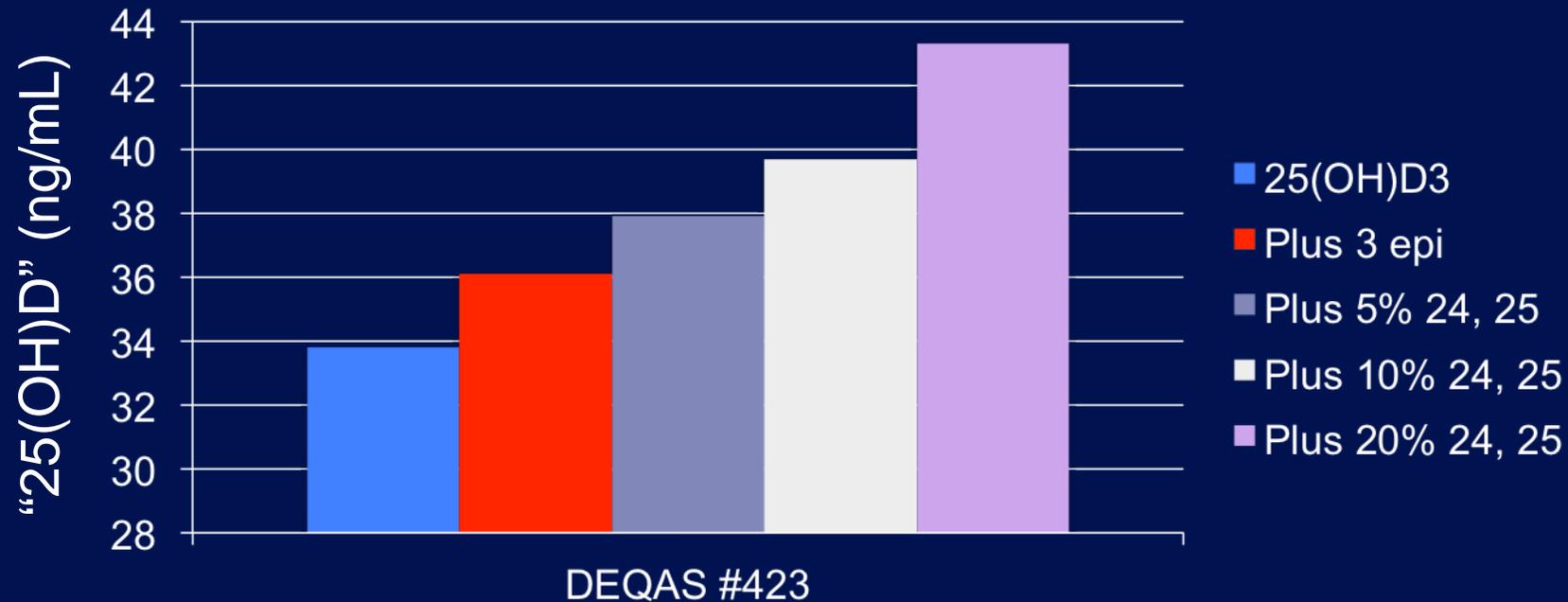
Mean 25(OH)D Values for Various Methods



Data from DEQAS April 2013 distribution



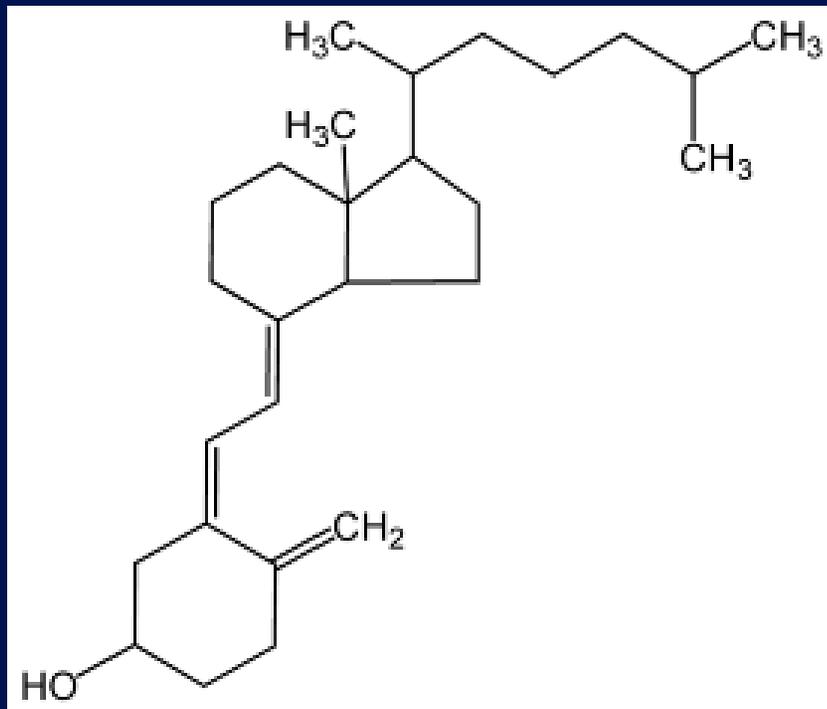
Example of Potential Effect of Confounders on Total 25(OH)D Measurement



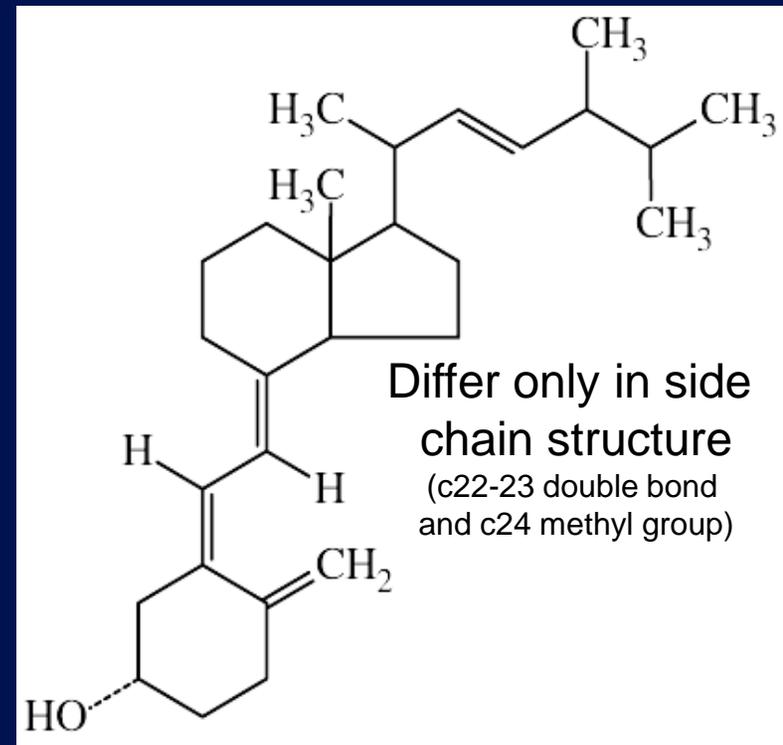
It is my bias that we need to standardize measurement of at least 25(OH)D, 3-epi 25(OH)D and 24, 25(OH)₂D AND understand the physiologic role(s) if any



Yet Another Confounder May be The Presence of Metabolites of Both Ergocalciferol and Cholecalciferol



Cholecalciferol
Vitamin D₃



Ergocalciferol
Vitamin D₂



Vitamin D₂ and D₃ Appear to be Equally Effective in Treating Rickets

THE PHARMACOPEIA AND THE
PHYSICIAN

—
THE THERAPY OF RICKETS

EDWARDS A. PARK, M.D.

BALTIMORE

“More than forty studies have been made in order to determine whether the two forms of vitamin D are equally effective....”

“Only generalizations of an uncertain nature can be drawn from the conflicting and confusing data obtained. For practical purposes the vitamin D in viosterol may be regarded as being equal to the vitamin D of cod liver oil.”



25(OH)D Measurement

- Progress in 25(OH)D measurement has been made
- Well-organized international standardization efforts are in place and moving forward
- Issues persist regarding potential confounders and other analytes including, but potentially not limited to:
 - 3-epi 25(OH)D
 - 24, 25 (OH)₂D
 - Need to measure both D₂ and D₃ metabolites
 - D binding protein
 - Free/bioavailable 25(OH)D
 - Etc, etc.....



Is Vitamin D Status Assessment Where Lipid Measurement Was Many Years Ago??

ANGINA PECTORIS IN HEREDITARY XANTHOMATOSIS

CARL MÜLLER, M.D.

Arch Intern Med. 1939;64(4):675-700.

The Role of Lipids and Lipoproteins in Atherosclerosis

John W. Gofman, Frank Lindgren, Harold Elliott, William Mantz,
John Hewitt, Beverly Strisower, and Virgil Herring

Gofman, J, et. al., *Science*, 111: 166-171, 1950



**The “What Are We Measuring?”
Question Substantially Flaws Systematic
Reviews/Meta-Analyses**

Additionally, but importantly.....



Need to Link Outcome to Blood Level Achieved

“An identical nutrient intake (i.e., prescribed dose) may or may not produce a measurable response.”

Heaney, RP, NEJM, 2012, 367, 77-78

Until we link outcomes to blood levels achieved, and understand what analytes to measure, meta-analyses will not answer the “how much is enough” question



We Can't Meta-Analyze Our Way Out of This, But Need to Care for Patients Today...

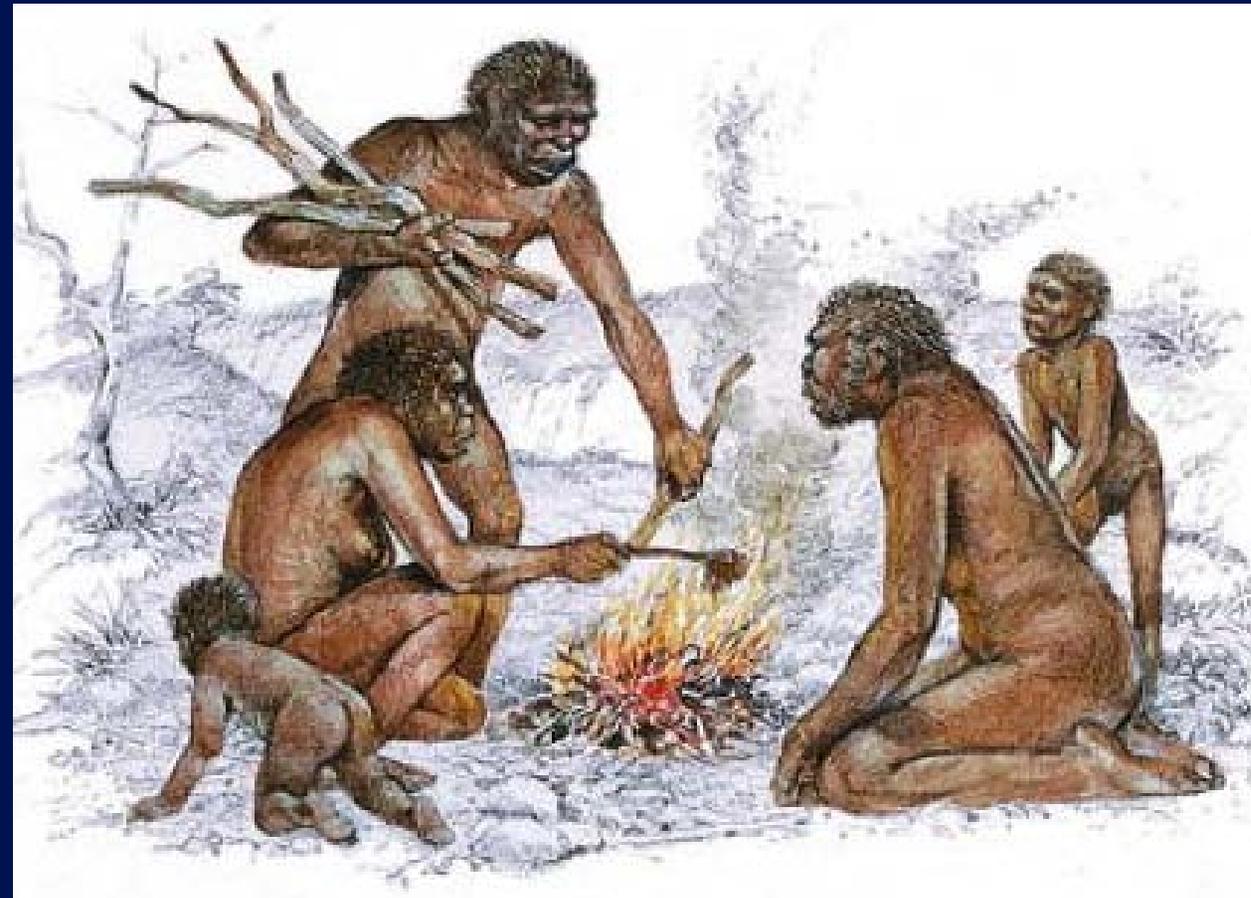
What Do I Do Clinically??



“I suggest that the 25(OH)D levels in the lifeguards are normal.”

Hollis, J Nutr, 135:317-325, 2005

IF we use highly sun exposed people to define a goal 25(OH)D concentration what is our target?



Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l

Martine F. Luxwolda*†, Remko S. Kuipers†, Ido P. Kema, D. A. Janneke Dijck-Brouwer and Frits A. J. Muskiet

“We studied two traditional tribes. Both live 2-4° south of the equator in Tanzania, have skin type VI and neither uses sunscreen.”

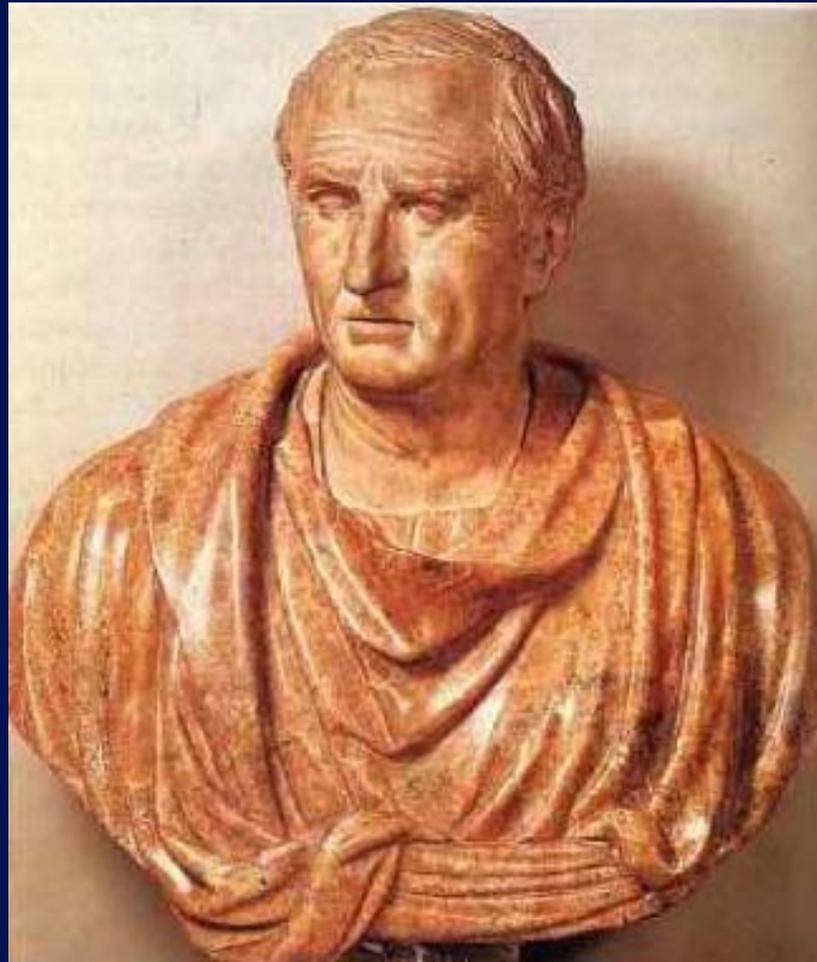
“Maasi spend most of their days in the sun wearing clothes that cover mainly their upper body and upper legs. Whenever possible they avoid direct exposure to the sun and prefer a shady place...”

Hadzabe are traditional hunter-gatherers. They live in small bands of 10-30 in arid bush lands. They have no personal belongings... shelters are only used during the rain or night. Similar to the Maasai, they avoid direct exposure to the sun whenever possible... spending the middle part of the day sleeping, eating or talking in a cooler place under a tree or rock.”

Mean 25(OH)D
46 ng/mL



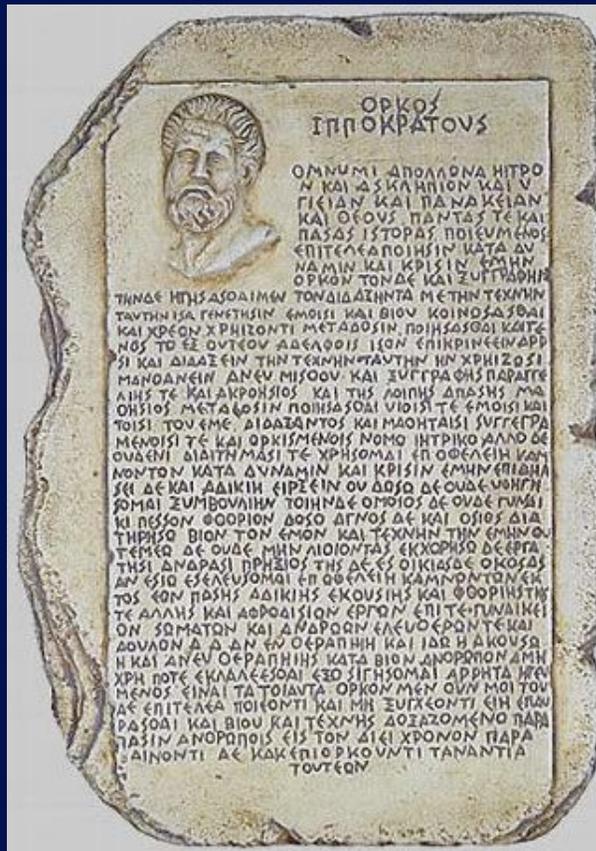
“Never go to excess, but let moderation be your guide.”



Marcus Cicero
(Roman philosopher and
Statesman; 106-43 BC)



Whether You Wish to Aim for 20 ng/mL or 30 ng/mL, Clinical Judgment Needs to Consider Assay Variability



What's a Clinician to Do? Aim High!

To Maintain Serum 25(OH)D of ≥ 20 ng/mL or ≥ 30 ng/mL

	Measured	“True” Value	Maintain	Maximum
25(OH)D	20 ng/mL	~10 to ~ 35 ng/mL	~35 ng/mL	~50 ng/mL
25(OH)D	30 ng/mL	~15 to ~45 ng/mL	~45 ng/mL	~60 ng/mL

Recognize that the reported value may be low:
with this approach, the maximum is likely to be ~50
to ~60 ng/mL, below that attainable by UV exposure



If I Were King...



- Acknowledge That We Don't Know the "Right" Answer
- Target ≥ 30 ng/mL (Aim High)



Call a Halt to the Battling

(March 2012)



IOM Committee Members Respond to Endocrine Society Vitamin D Guideline

Clifford J. Rosen, Steven A. Abrams, John F. Aloia, Patsy M. Brannon, Steven K. Clinton, Ramon A. Durazo-Arvizu, J. Christopher Gallagher, Richard L. Gallo, Glenville Jones, Christopher S. Kovacs, JoAnn E. Manson, Susan T. Mayne, A. Catharine Ross, Sue A. Shapses, and Christine L. Taylor

Maine Medical Center Research Institute, Scarborough, Maine 04074; Baylor College of Medicine, Houston, Texas 77030; State University of New York at Stony Brook and Winthrop-University Hospital, Mineola, New York, 11501; Cornell University, Ithaca, New York 14853; The Ohio State University, Columbus, Ohio 43210; Loyola University Chicago, Maywood, Illinois 60153; Creighton University Medical Center, Omaha, Nebraska 68131; University of California, San Diego, San Diego, California 92161; Queens University, Kingston, Ontario, Canada K7L 3N6; Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X6; Harvard Medical School, Boston, Massachusetts 02215; Yale School of Public Health, New Haven, Connecticut 06520; The Pennsylvania State University, University Park, Pennsylvania 16802; and Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08901; and Office of Dietary Supplements (C.L.T.), The National Institutes of Health, Bethesda, Maryland 20892

In early 2011, a committee convened by the Institute of Medicine issued a report on the Dietary Reference Intakes for calcium and vitamin D. The Endocrine Society Task Force in July 2011 published a guideline for the evaluation, treatment, and prevention of vitamin D deficiency. Although these reports are intended for different purposes, the disagreements concerning the nature of the available data and the resulting conclusions have caused confusion for clinicians, researchers, and the public. In this commentary, members of the Institute of Medicine committee respond to aspects of The Endocrine Society guideline that are not well supported and in need of reconsideration. These concerns focus on target serum 25-hydroxyvitamin D levels, the definition of vitamin D deficiency, and the question of who constitutes a population at risk vs. the general population. (*J Clin Endocrinol Metab* 97: 1146–1152, 2012)

“The current guideline fails in both respects and therefore is in need of reexamination.”

SPECIAL FEATURE

Controversy in Clinical Endocrinology

Guidelines for Preventing and Treating Vitamin D Deficiency and Insufficiency Revisited

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

Boston University School of Medicine (M.F.H.), Boston, Massachusetts 02118-2526; Osteoporosis Research Program (N.C.B.), University of Wisconsin, Madison, Wisconsin 53706; Department of Rheumatology and Institute for Physical Medicine (H.A.B.-F.), University Hospital Zurich, 8091 Zurich, Switzerland; Divisions of Adolescent Medicine and Endocrinology (C.M.G.), Childrens Hospital, Boston, Massachusetts 02115; Division of Endocrinology and Metabolism (D.A.H.), Health Science Centre, University of Calgary Faculty of Medicine (R.P.H.), Calgary, Canada AB T2N 4N1; Creighton University (R.P.H.), Omaha, Nebraska 68131; Division of Preventative, Occupational, and Aerospace Medicine Mayo Clinic (M.H.M.), Rochester, Minnesota 55905; and Department of Foods and Nutrition (C.M.W.), Purdue University, West Lafayette, Indiana 47907

“At this time, the existing guidelines provide reasonable recommendations for clinical care. It is to be expected that these guidelines, as well as the IOM recommendations will require reconsideration in the future...”



Require Laboratory Traceability of 25(OH)D Measurements to the NIST Standards





**Demand Additional
Research to Define
Which Vitamin D
Metabolites Have
Physiologic Effect(s)
and How Best to
Evaluate Vitamin D
Status in a Given
Individual**



Summary; Clinical Vitamin D Assessment

November 2013

- Vitamin D inadequacy (however defined) is common
 - Fixing this is cheap and virtually side effect free
- Little need to utilize D₂ (ergocalciferol); this unnecessarily confounds assay methodologies
- Ancestral human 25(OH)D mean is ~ 40 ng/mL
- Recognize that our current “25(OH)D” measurements are imperfect, standardization is needed and that improved knowledge and perhaps “D assay panels” are coming
 - Much more work is needed

“We know an insufficient amount about vitamin D insufficiency.”



Thank You

