Why Should We Use Mass Spectrometry to Measure Vitamin D Metabolites?

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VDSP
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Disclosures

Grant funding
Waters

Equipment
Waters
Thermo

The Changing Clinical Landscape

Indications for measuring 25(OH)D [from Medicare]:

- chronic kidney disease (stage ≥3)
- cirrhosis
- hypocalcemia
- hypercalcemia
- hypercalciuria
- hypervitaminosis D
- parathyroid disorders
- vitamin D deficiency on replacement therapy related to a condition listed above
- malabsorption states
- obstructive jaundice
- osteomalacia
- osteoporosis (certain instances)
- osteosclerosis/petrosis
- rickets

Testing may not be used for routine or other screening

General Thoughts

We need accuracy

We need consistency

We need selectivity

We can do it!

How to Measure Vitamin D?

Immunoassay, Protein binding assay

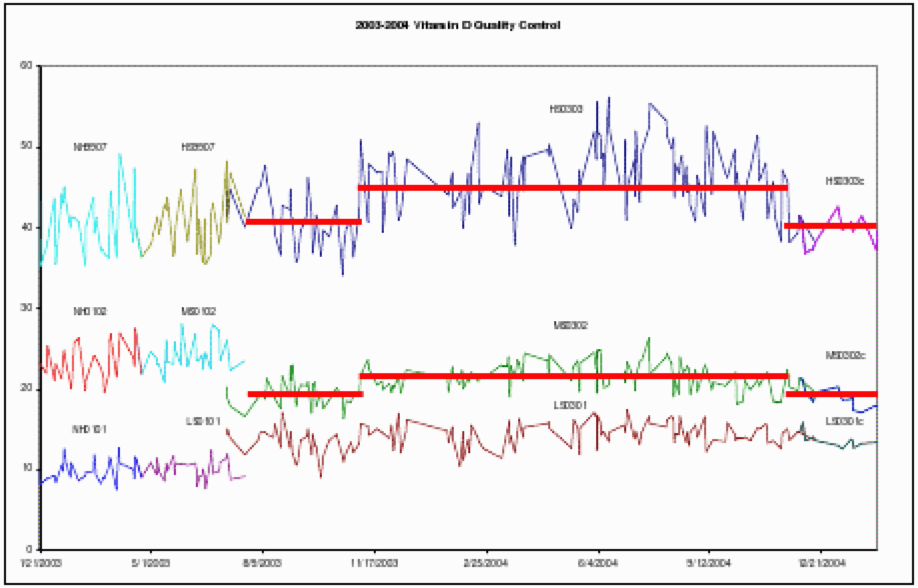
- RIA
- Chemiluminescent
  - Competitive assays with radioactive or chemiluminescent tracer

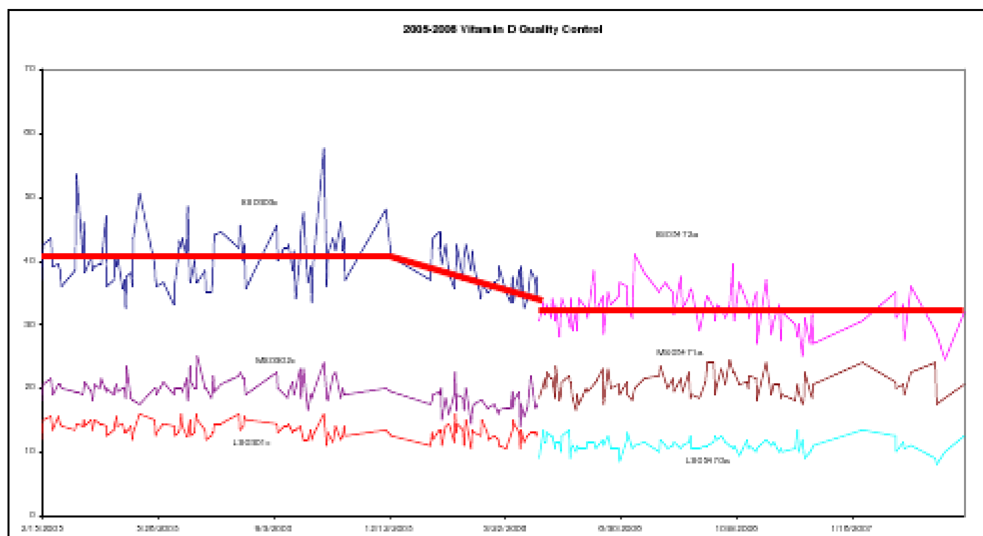
HPLC,
HPLC-Mass spectrometry

- Extraction with solvent
- Detection with uv absorption or mass spectrometry

Historical perspective: all early studies done with RIA

Sadly, All Early Experiments Done with RIA





Cliff Johnson presentation to IOM
August, 2009

Surprised? No Two Assays Are The Same

One *RIA, HPLC and LC-MS very similar*

Table 1. Method means and ALTM for the 5 samples distributed by DEQAS in October 2008.

	Mean 25-OH-D concentration, nmol/L (CV)				
Sample no.	341	342	343	344	345
Method					
DiaSorin RIA (n = 40)	52.0 (18%)	80.4 (18%)	106.5 (16%)	37.8 (21%)	62.3 (17%)
DiaSorin Liaison T[a] (n = 144)	52.2 (15%)	75.8 (15%)	103.7 (14%)	31.0 (17%)	58.6 (15%)
IDS RIA (n = 29)	56.9 (15%)	89.6 (15%)	128.8 (15%)	39.1 (14%)	67.3 (14%)
IDS EIA (n = 84)	55.1 (13%)	83.6 (15%)	111.4 (17%)	34.8 (13%)	62.4 (16%)
IDS EIA, automated (n = 32)	56.8 (12%)	85.9 (15%)	113.6 (16%)	36.4 (13%)	63.1 (12%)
Roche 25-OH-D_3 (n = 26)	53.0 (14%)	75.0 (11%)	94.3 (12%)	43.4 (15%)	57.2 (15%)
HPLC (n = 16)	58.7 (25%)	94.3 (20%)	124.4 (21%)	38.9 (17%)	66.6 (18%)
LC-MS/MS (n = 39)	56.5 (15%)	94.5 (13%)	125.4 (13%)	39.6 (14%)	66.3 (18%)
ALTM (n = 437)	54.2 (15%)	81.8 (17%)	109.9 (17%)	35.2 (20%)	61.6 (16%)

[a] DiaSorin Liaison Total; EIA, enzyme immunoassay.

Carter, 2009, Clin Chem

But Who is Right?

American Journal of Clinical Nutrition

Development of a standard reference material for vitamin D in serum[1–4]

Karen W Phinney

ABSTRACT
The most widely used indicator of vitamin D status is the measurement of 25-hydroxyvitamin D [25(OH)D] in either serum or plasma. Several studies have reported discrepancies between the results of assays used to measure 25(OH)D, however, which calls into question the ability of 25(OH)D assays to reflect accurately the vitamin D status of individuals. The National Institute of Standards and Technology has been working with the National Institutes of Health's Office of Dietary Supplements to develop a standard reference material for circulating vitamin D analysis. This standard reference material will provide a material with stable, well-defined levels of the analytes of interest. Investigators will be able to use the standard reference material to validate new analytic methods as they are developed and to assign values to in-house quality-control materials. *Am J Clin Nutr* 2008;88(suppl):511S–2S.

STANDARD REFERENCE MATERIAL FOR VITAMIN D

might complicate the ability to define optimal levels of circulating 25(OH)D (3). For these reasons, investigators have called for international standardization of vitamin D measurements.

The National Institute of Standards and Technology (NIST) has been working with the National Institutes of Health's Office of Dietary Supplements to develop a standard reference material (SRM) for circulating vitamin D analysis. NIST has a long history of providing SRMs for the clinical chemistry community to support accuracy in clinical laboratory measurements.

The reference material currently in development at NIST, SRM 972 Vitamin D in Human Serum, consists of 4 pools of fresh-frozen serum. Each pool has a different level of $25(OH)D_2$, $25(OH)D_3$, or both. One pool also contains 3-epi-$25(OH)D_3$. NIST designed the SRM to pose similar analytic challenges to those encountered in patient samples. NIST will assign values for each of the analytes through measurements at NIST and collaborating laboratories. NIST will perform its measurements by isotope-dilution liquid chromatography-mass spectrometry and tandem mass spectrometry methodology. The certificate of anal-

Phinney, 2008, AJCN

NIST Standard Reference Material

Four levels of control material

Level 1
Normal human plasma

Level 2
Normal human plasma diluted with horse serum

Level 3
Normal human plasma spiked with vitamin D_2

Level 4
Normal human plasma spiked with C-3 epimer vitamin D_3

Comparison Using NIST controls

Sample ID	Immunoassay		HPLC		LC-MS	
Baseline	43.7		48.3			
Vitamin D2	81.1		80			
Baseline + 25(OH)D2	51	23%	79.7	98%		
Baseline + 25(OH)D3	63.7	63%	80	99%		
Horse Serum	12.7		4.7			
NIST Level 1	24.4	106%	26	113%	24.6	103%
NIST Level 2	19.8	152%	15.9	122%	15.1	108%
NIST Level 3	27.2	62%	48.1	109%	46.2	103%
NIST Level 4	Not analyzed		Not analyzed		35.6	101%

"Do not use spiked samples to validate direct immunoassays"

Why not use gold standard reference methods?

Bruce Hollis presentation to IOM
August, 2009

We Need Selectivity

Use the Right Assay to Measure Vitamin D in Infants

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(8):3055–3061

doi: 10.1210/jc.2006-0710

C-3 Epimers Can Account for a Significant Proportion of Total Circulating 25-Hydroxyvitamin D in Infants, Complicating Accurate Measurement and Interpretation of Vitamin D Status

Ravinder J. Singh, Robert L. Taylor, G. Satyanarayana Reddy, and Stefan K. G. Grebe

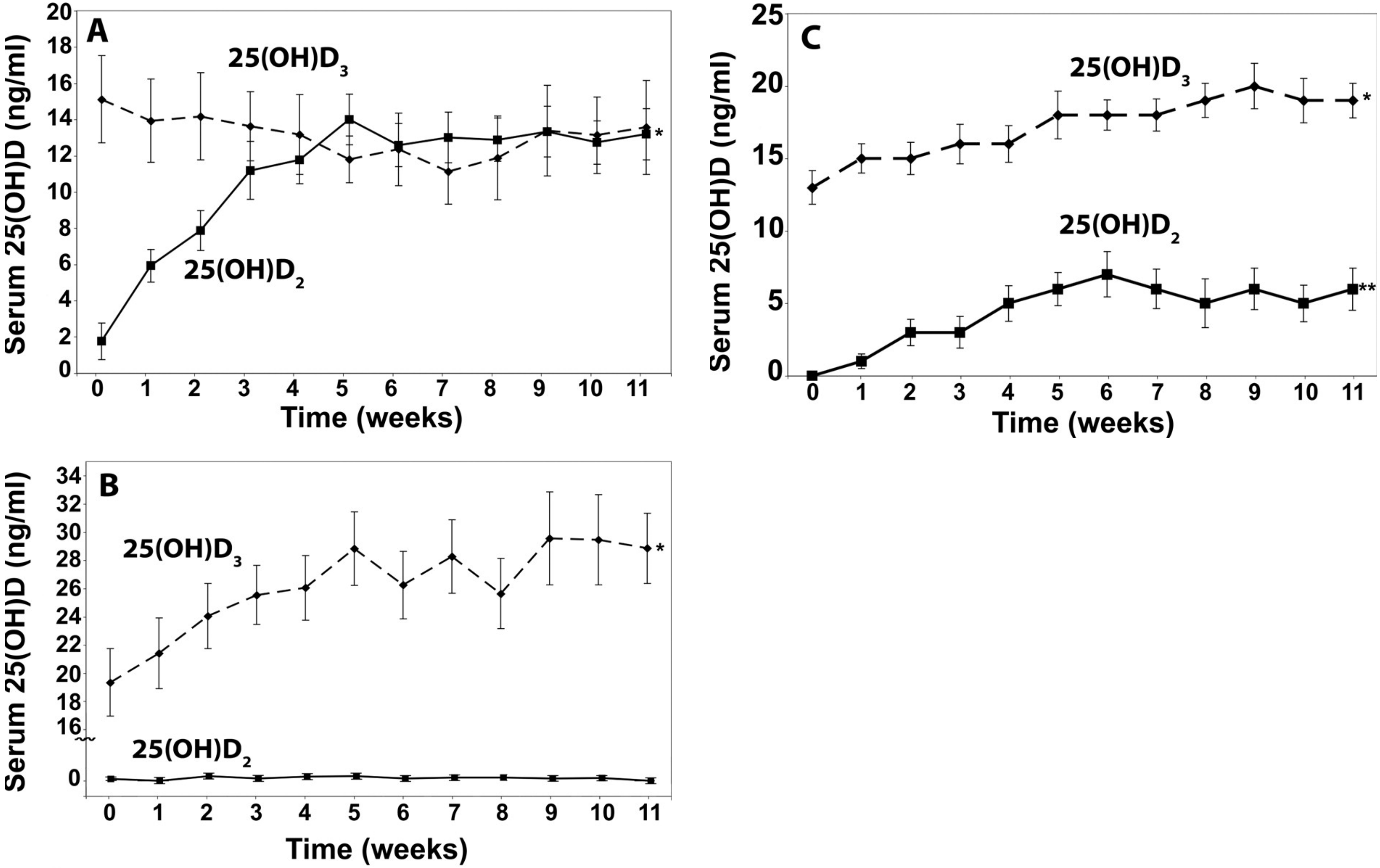
Departments of Laboratory Medicine and Pathology (R.J.S., R.L.T., S.K.G.G.) and Medicine (S.K.G.G.), Mayo Clinic, Rochester, Minnesota 55905; and Epimer, LLC (G.S.R.), Providence, Rhode Island 02906

Context: We have recently introduced liquid chromatography-tandem mass spectrometry (LC-MS/MS) for 25-hydroxyvitamin D_2 ($25OHD_2$) and $25OHD_3$ testing. During subsequent clinical use, we identified significantly elevated results in some infants. We hypothesized this might represent assay interference caused by C-3 epimers of $25OHD_2$ or $25OHD_3$.

Results: In 172 children from group 1 with detectable $25OHD_2$ or $25OHD_3$, we identified C-3 epimers in 39 (22.7%). The epimers contributed 8.7–61.1% of the total 25-OHD. There was an inverse relationship between patient age and epimer percentage ($r = 0.48$; $P < 0.002$). The RIA gave accurate 25-OHD results that correlated with the modified LC-MS/MS method. No C-3 epimers were detected in any of the other groups.

C-3 epimer of Vitamin D is inactive and is high in some infants…formula?

Vitamin D_2 is Used to Treat Low Vitamin D in Patients



Holick, 2008, JCEM

One Assay Wasn't Able to Reliably Detect Vitamin D_2

Underestimation of Serum 25-Hydroxyvitamin D by the Nichols Advantage Assay in Patients Receiving Vitamin D Replacement Therapy

To the Editor:

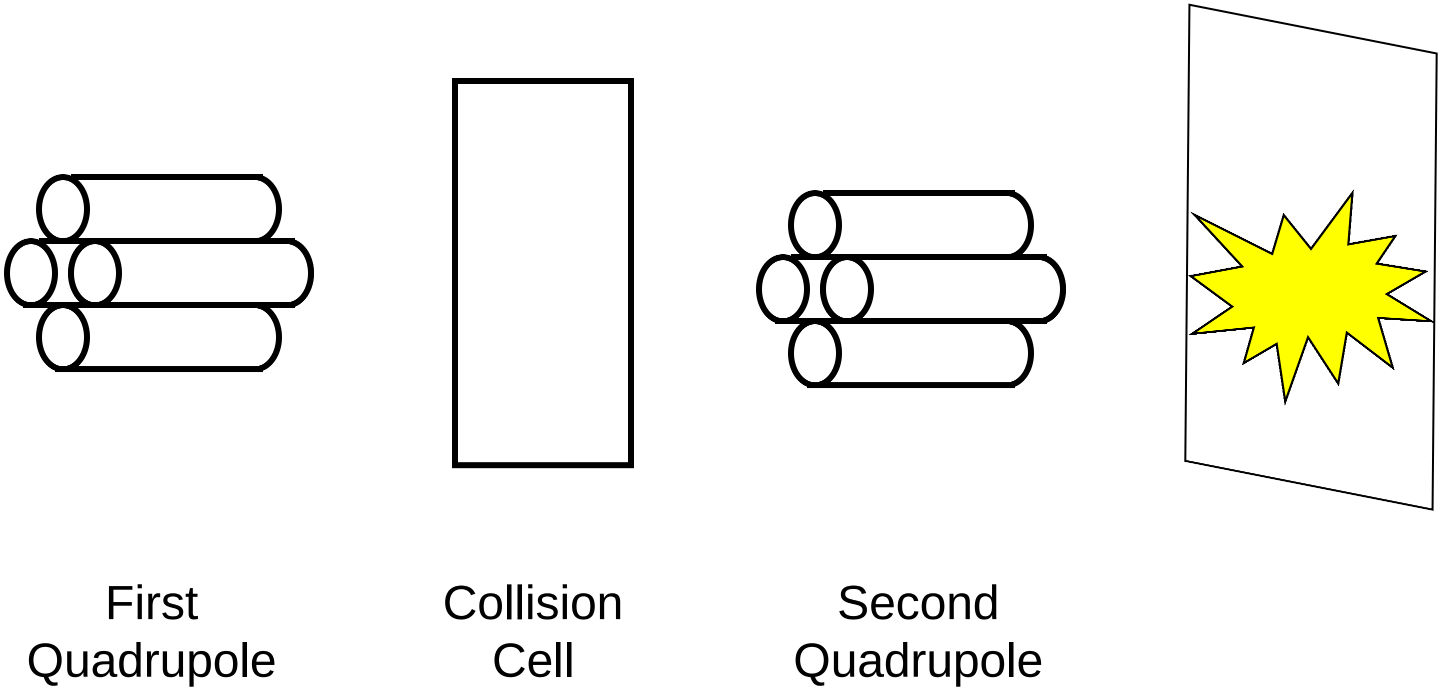
Measurement of 25-hydroxyvitamin D (25OHD) is used to assess both vitamin D status and the response to

Now it's gone…

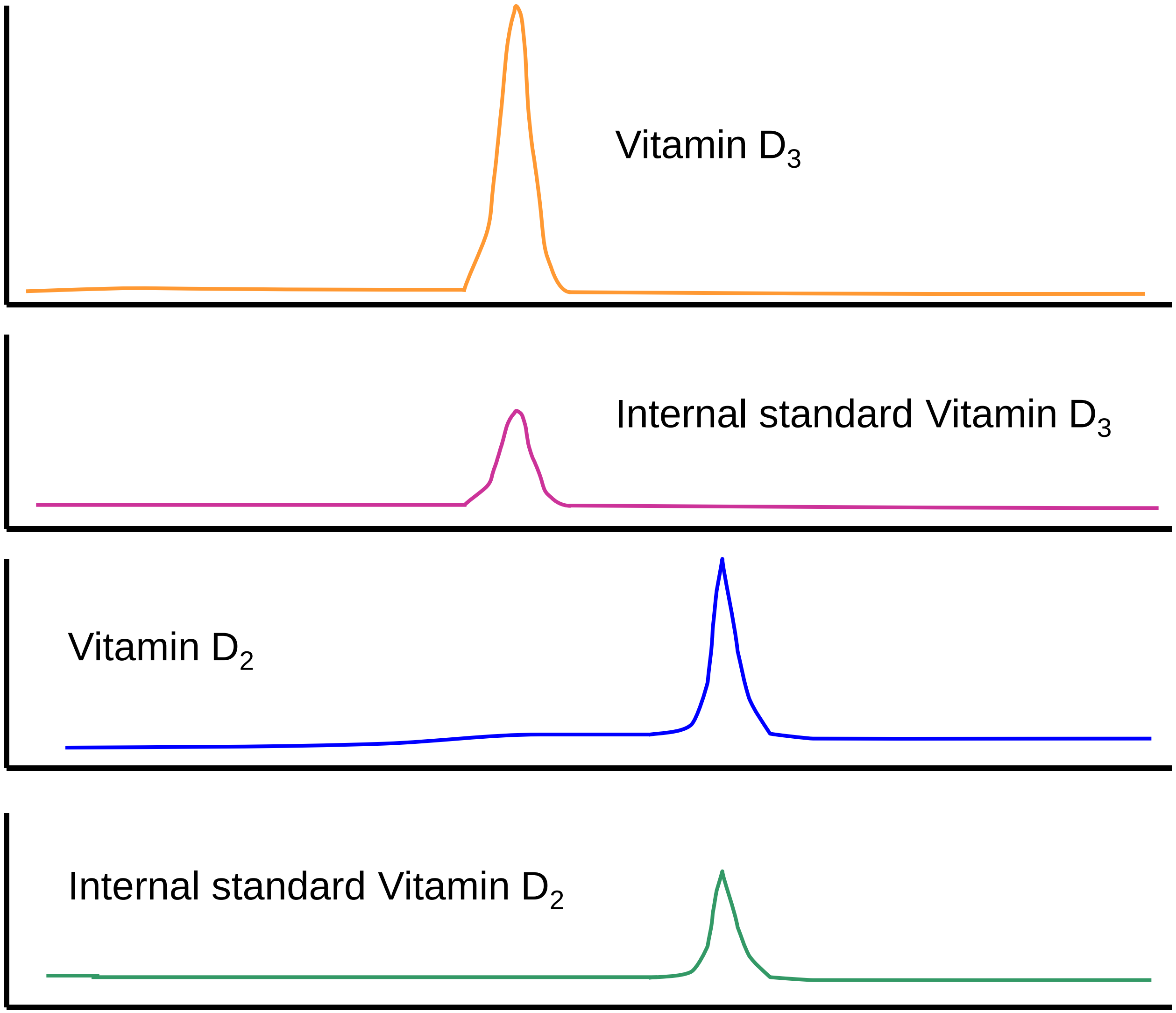
Mass Spectrometry as a Method

Selected Reaction Monitoring

Measuring Four Things At Once



Measuring Many Things at Once



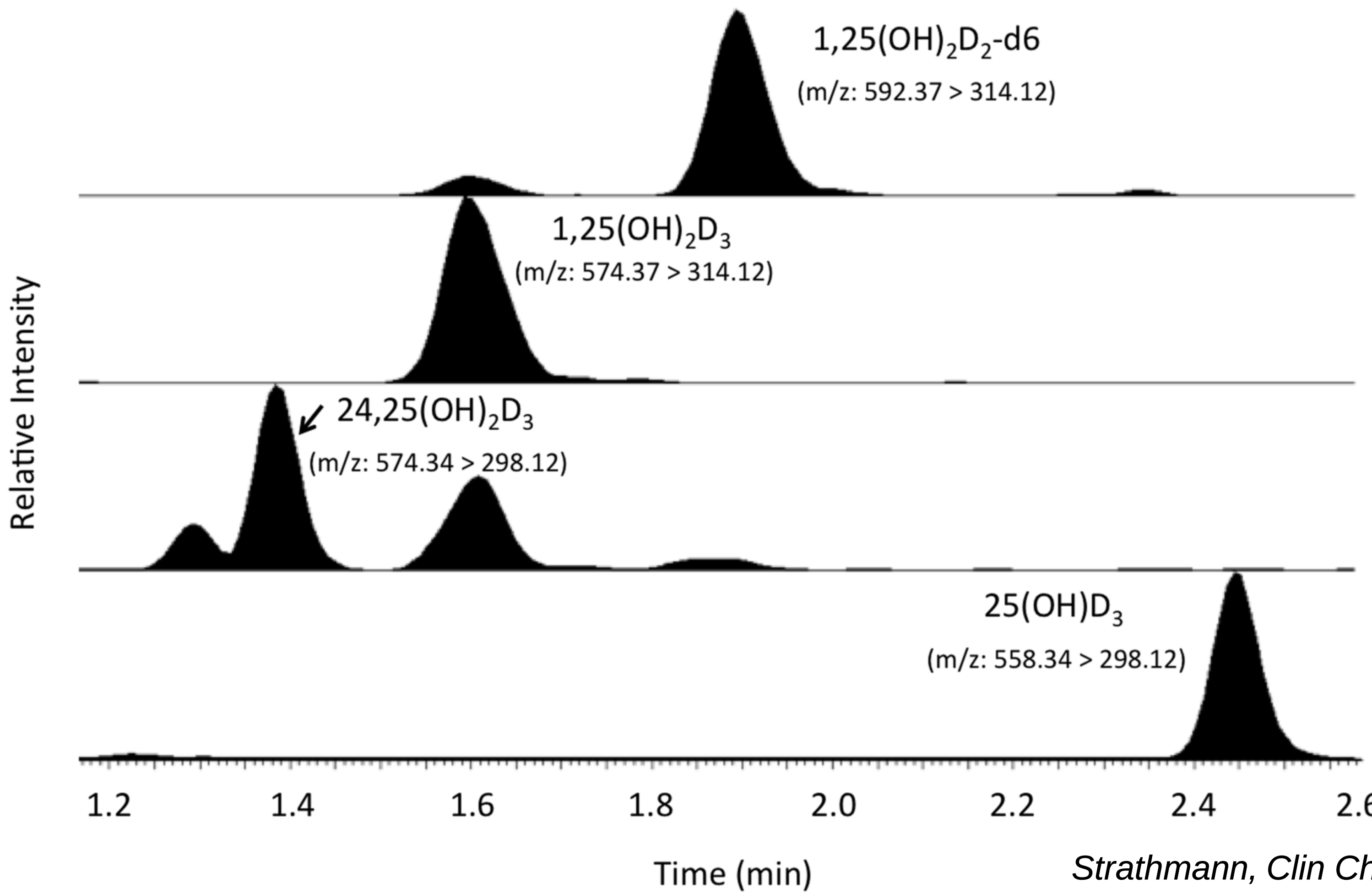
Why Should I Use Mass Spectrometry?

Problems with clinical immunoassays

Single-plex
Poor standardization
Specificity
Autoantibodies
Anti-reagent antibodies
Microclots*

Hoofnagle and Wener, J Immunol Methods (2009)
** Strathmann, et al., AJCP (2011)*

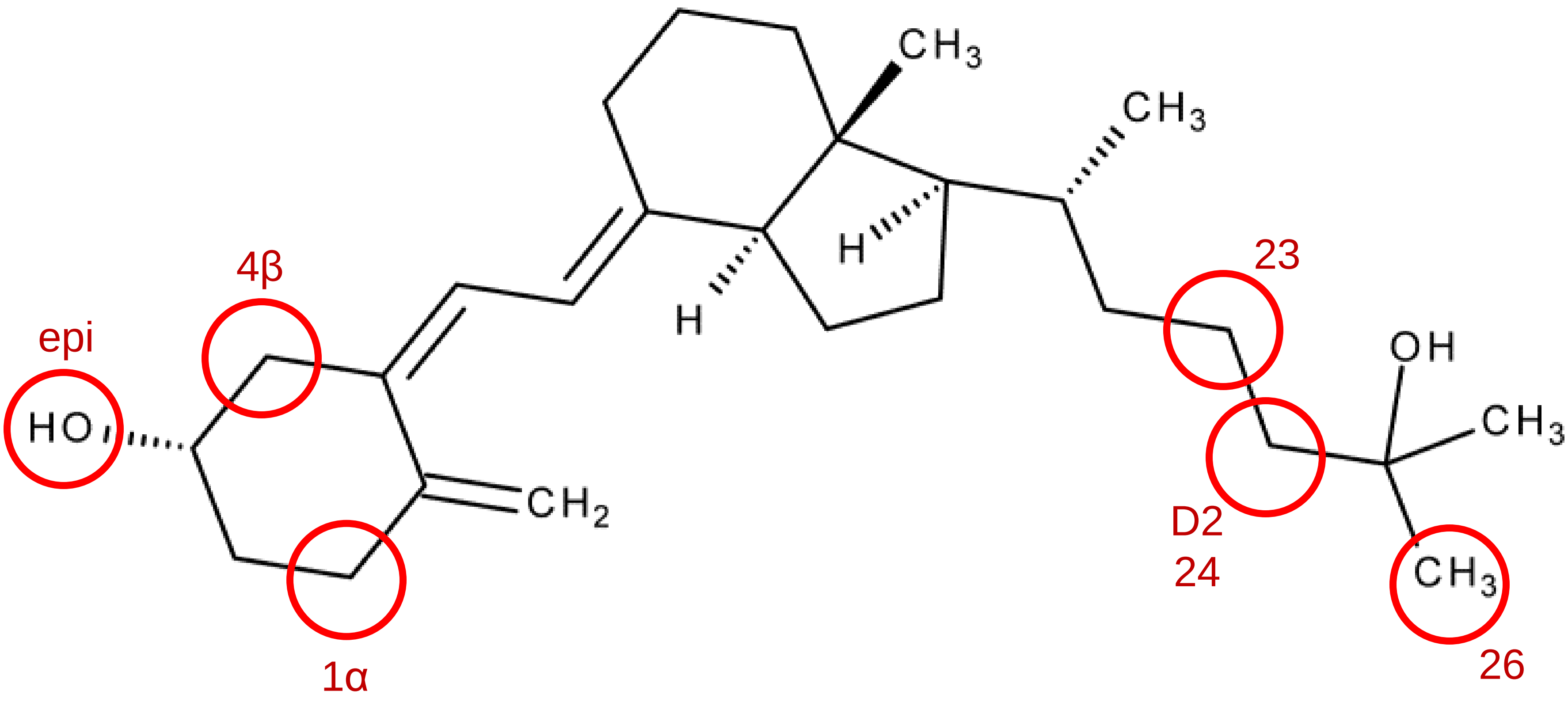
Antibodies are Not Perfect



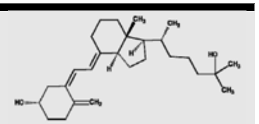
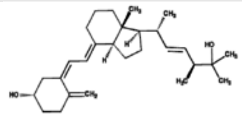
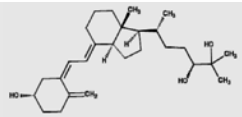
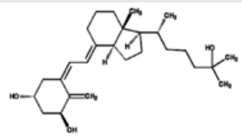
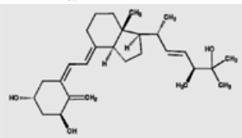
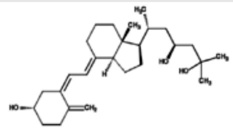
Strathmann, Clin Chem, 2010

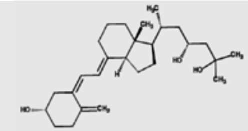
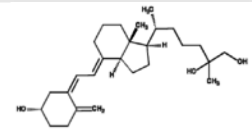
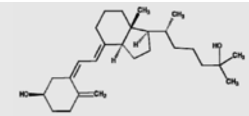
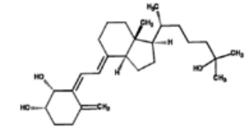
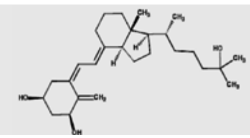
1,25 Vitamin D antibody has an affinity for several metabolites

Identifying the Interferences



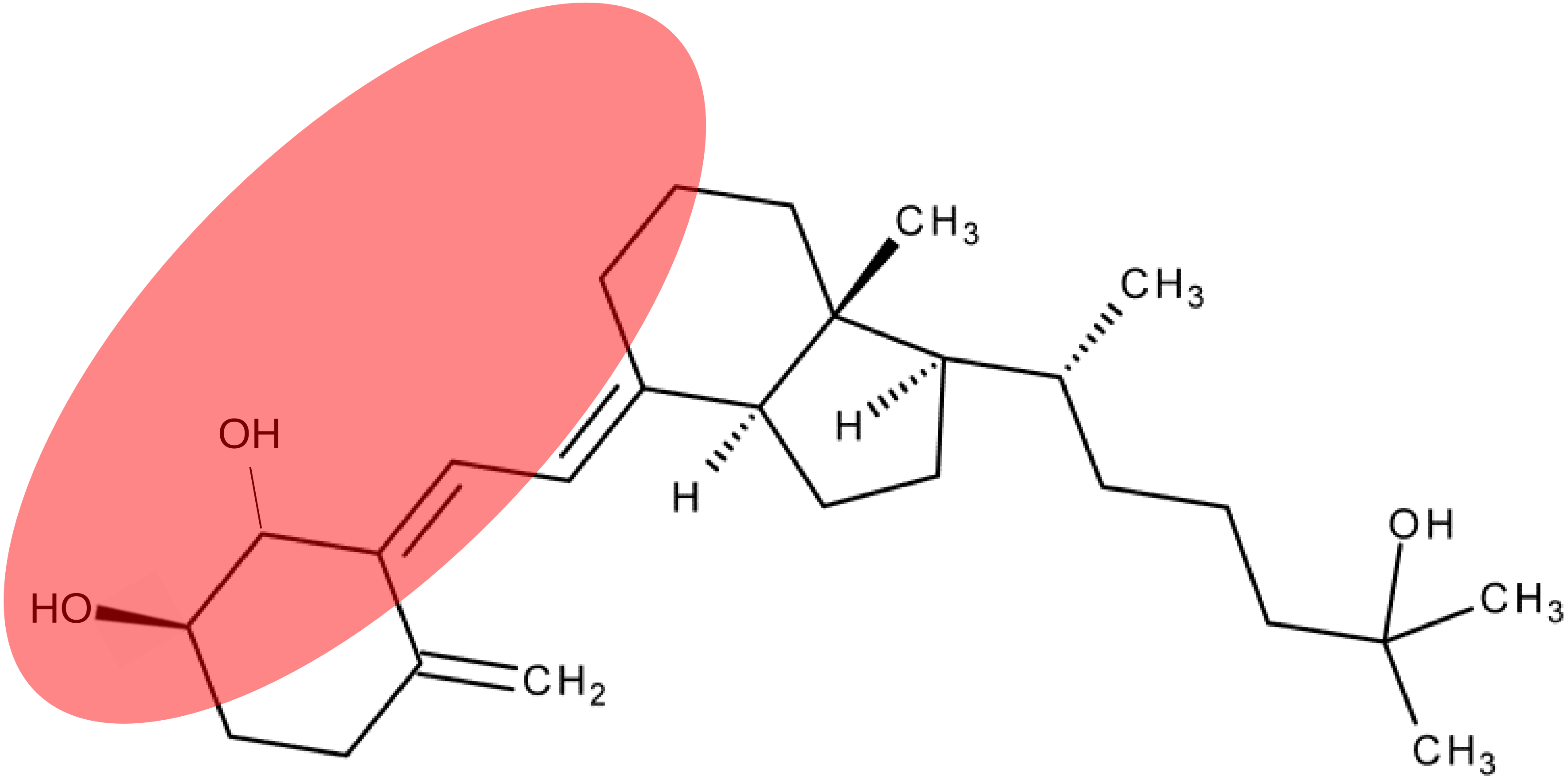
Identifying the Immunoassay Interferences

Compound	% Recovery (SD)[d]	Structure
25$(OH)D_3$	43.3 (2.1)	
25$(OH)D_2$	32.2 (3.3)	
24,25$(OH)_2D_3$	70.8 (9.8)	
1α,25$(OH)_2D_3$	79.4 (3.5)	
1α,25$(OH)_2D_2$	78.2 (12.4)	
23(S),25$(OH)_2D_3$	64.0 (2.1)	

Compound	% Recovery (SD)[d]	Structure
23(R),25$(OH)_2D_3$	67.0 (3.2)	
25,26$(OH)_2D_3$	69.2 (4.0)	
3-epi-25$(OH)D_3$	3.2 (1.0)	
4β,25$(OH)_2D_3$	3.0 (0.01)	
3-epi-1α,25$(OH)_2D_3$	15.0 (0.4)	

Laha, 2012, *Clin Chem*

Mapping the Hapten



Determinants of antibody "specificity":
1) Overall Polarity
2) 3,4-carbon face of the molecule

Taking Advantage of Promiscuous Antibodies

Compound	Regression[a]	r^2 [a]	Conc	Intra-assay[b] %CV	Total[b] %CV	LLOQ[c]
$25(OH)D_3$	Y=1.04x+0.08	0.955	12.3 ng/mL	3.0	3.7	1.0
$25(OH)D_2$	y=0.94x-1.00	0.981	10.6 ng/mL	4.7	10.2	0.2
$24,25(OH)_2D_3$	Y=0.96x-0.23	0.922	1.6 ng/mL	2.6	6.4	0.06
$1\alpha,25(OH)_2D_3$	y=0.96x-2.97	0.901	14.6 pg/mL	10.0	15.6	3.4
$1\alpha,25(OH)_2D_2$	y=0.89x-0.54	0.976	12.8 pg/mL	10.9	17.1	2.8

Laha, 2012, *Clin Chem*

Mass Spectrometry is Not Infallible

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Quest Acknowledges Errors in Vitamin D Tests

By ANDREW POLLACK
Published: January 7, 2009

The nation's largest medical laboratory company provided possibly erroneous results to thousands of people who had their vitamin D levels tested in the last two years, the company has acknowledged.

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Quest Diagnostics Inc

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The company, Quest Diagnostics, has already sent letters to thousands of doctors listing the patients who might have received "questionable" test results and is offering free retests. The company said it had fixed the problems.

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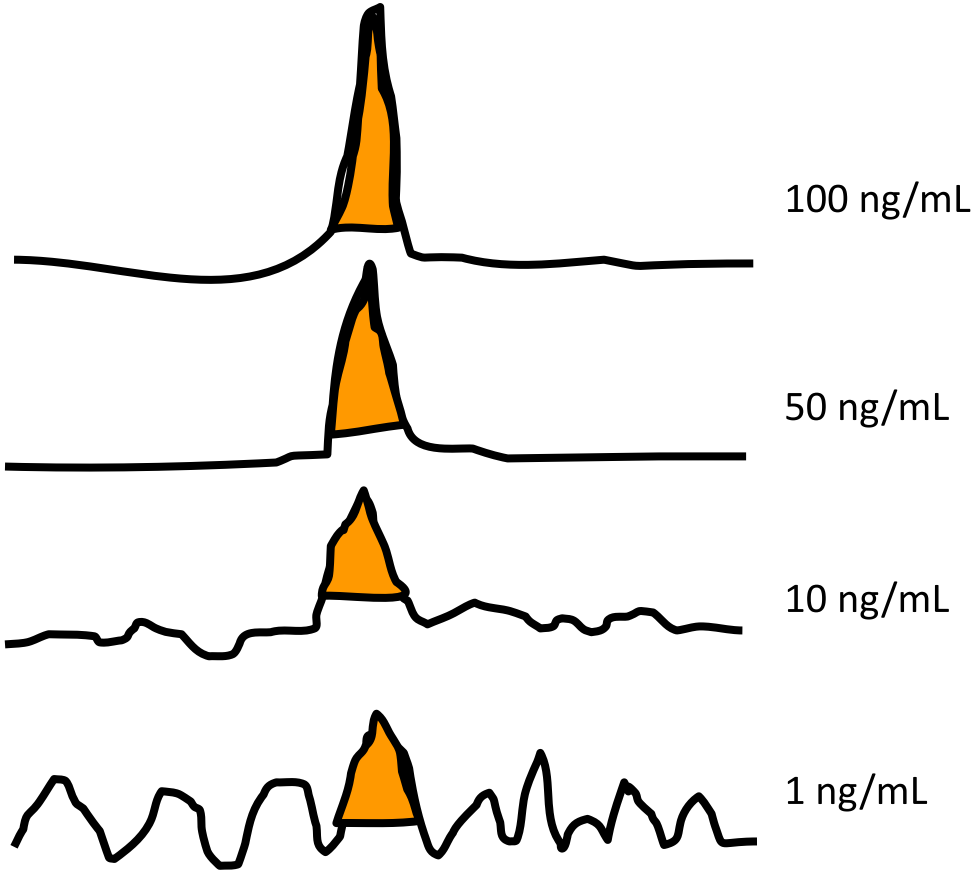
Good Quality Control of Mass Spectrometry is Vitally Important

Quality Control for LC-MS/MS: Reading the Signs

Proper Quality Control

Checking Instrument Sensitivity



Integrating noise!

Solution:

Ensure that lowest standard has an acceptable peak area or signal-to-noise.

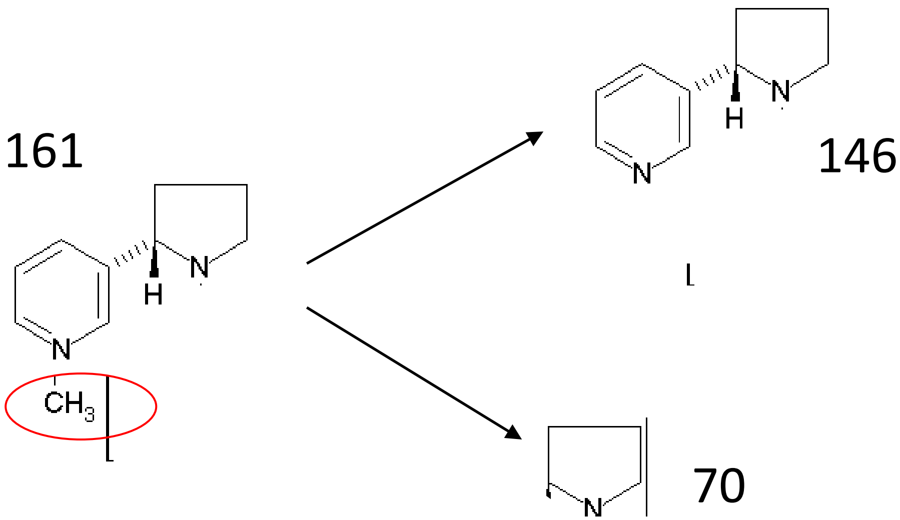
Proper Quality Control

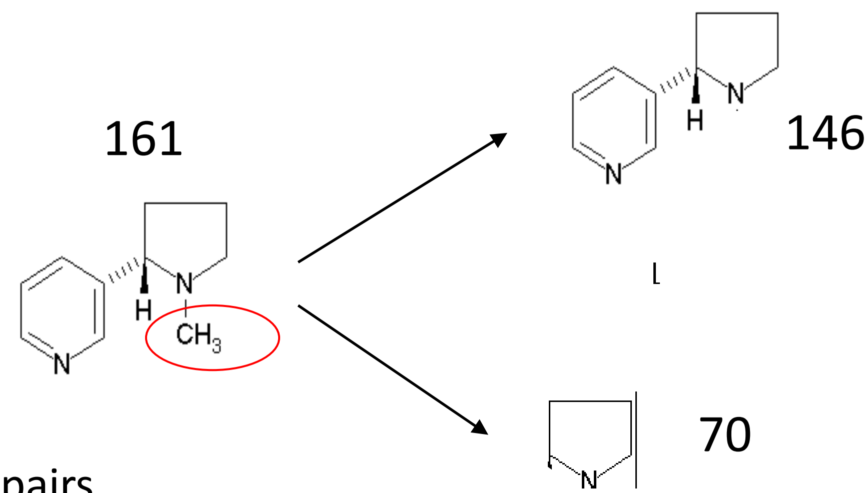
Checking Instrument Sensitivity

Date	Unextract A D2	Unextract A D3	Std A D2	IS A D2	Std A D3	IS A D3
1/2/2008			300	12495	435	15744
1/4/2008	2015	2467	258	12828	374	16164
1/6/2008			292	13820	424	17413
1/8/2008			305	12584	442	15856
1/9/2008			284	13391	412	16873
1/11/2008	2410	2943	307	12664	445	15957
1/13/2008			296	13804	430	17393
1/15/2008			289	12706	419	16010
1/16/2008			245	13454	355	16952
1/18/2008	1913	2312	234	10090	339	12713
1/20/2008			198	9034	287	11383
1/22/2008	1208	1315	130	7023	189	8849
1/23/2008			98	5012	142	6315

Proper Quality Control

Checking for Specificity



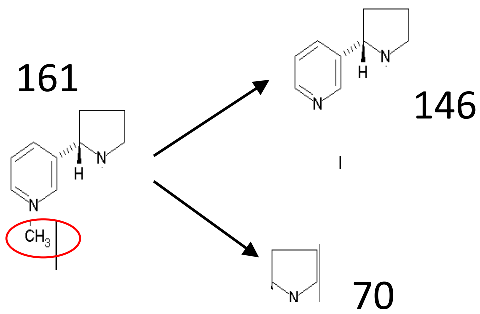


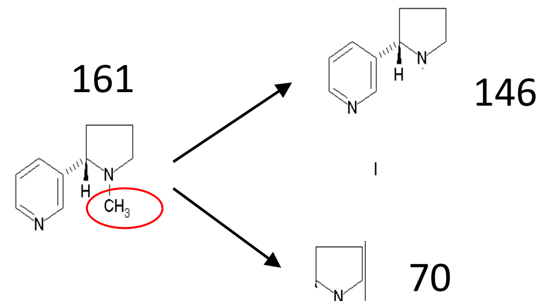
Isobaric interference

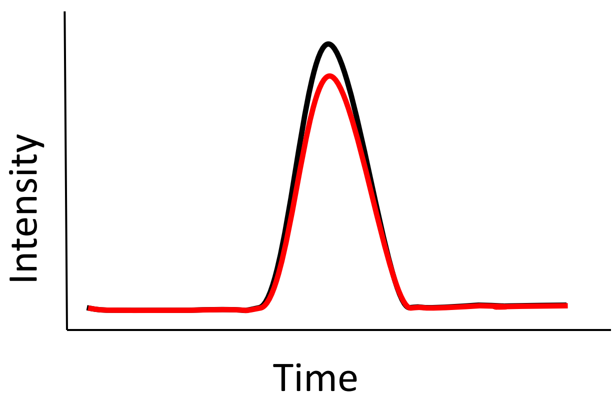
Different molecules, same Q1 and Q3 m/z pairs

Proper Quality Control

Checking for Specificity

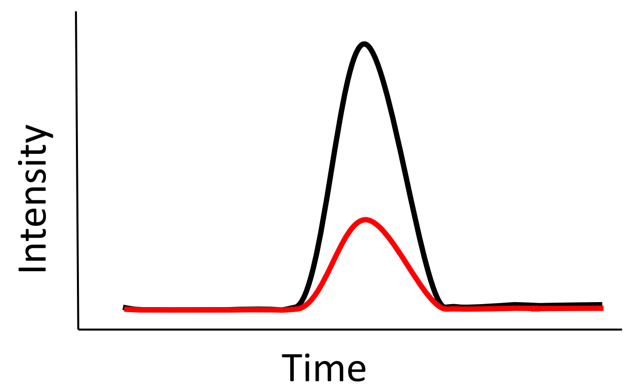






161 → 146

161 → 70



Ratio: 0.96

Ratio: 0.28 Wrong!!

Isobaric interference

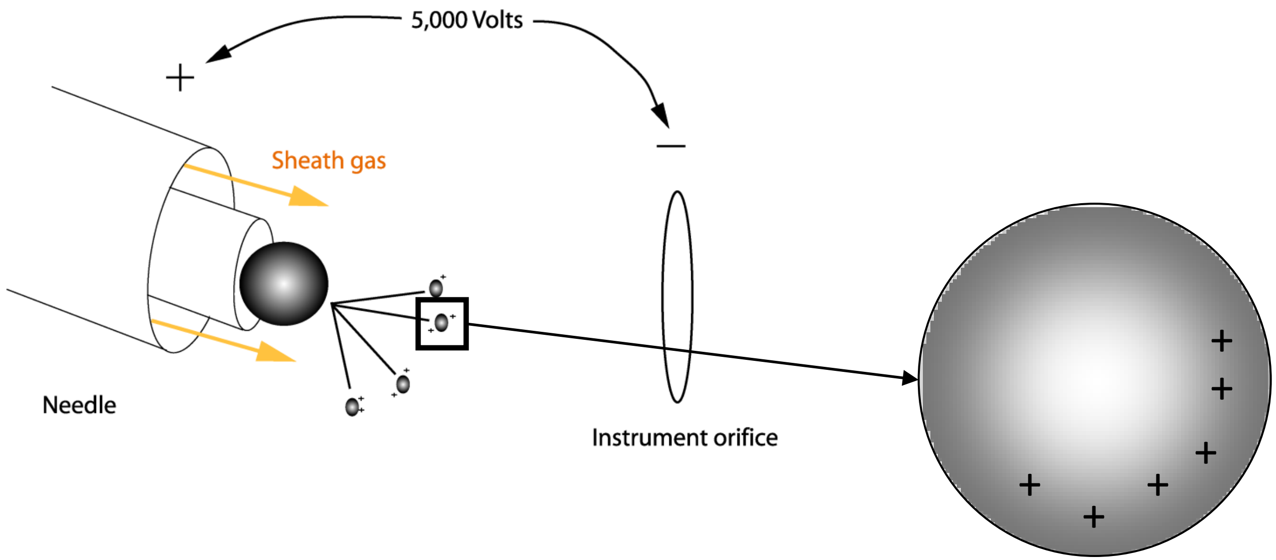
Same Q1 and Q3 m/z pairs, different ratio of the pairs

Proper Quality Control

Checking for Specificity

Sample	Analyte	Conc	RT	Analyte Peak Area	IS	Response	Calc conc	Ion Ratio	Ratio Flag?
Std D	D3	200	2.81	12870	12370	1.04	198.9	1.5	NO
Std C	D3	100	2.82	5990	12335	0.49	100.1	1.5	NO
Std B	D3	30	2.88	2288	13237	0.17	32.9	1.5	NO
Std A	D3	1	2.88	252	13704	0.02	0.9	1.4	NO
Ctrl HI	D3		2.90	780	13109	0.06	11.6	1.4	NO
Ctrl LO	D3		2.86	3501	13932	0.25	48.7	1.5	NO
W54634	D3		2.83	1650	13081	0.13	24.5	1.5	NO
W58132	D3		2.86	1249	12703	0.10	19.1	1.5	NO
W66023	D3		2.89	1641	13211	0.12	24.1	1.5	NO
W62743	D3		2.81	2423	12636	0.19	37.2	1.5	NO
W66817	D3		2.86	2208	13543	0.16	31.6	1.5	NO
H66438	D3		2.83	2359	12163	0.19	37.6	1.4	NO
H62633	D3		2.81	2057	13559	0.15	29.4	1.5	NO
H78948	D3		2.82	1593	12762	0.12	24.2	1.4	NO
H78388	D3		2.82	2836	12824	0.22	42.9	1.4	NO
H74054	D3		2.87	1257	12469	0.10	19.6	1.5	NO
H87727	D3		2.67	1362	12944	0.11	20.4	1.9	YES
H89927	D3		2.85	1851	12528	0.15	28.7	1.4	NO
H88721	D3		2.89	2731	13284	0.21	39.9	1.4	NO

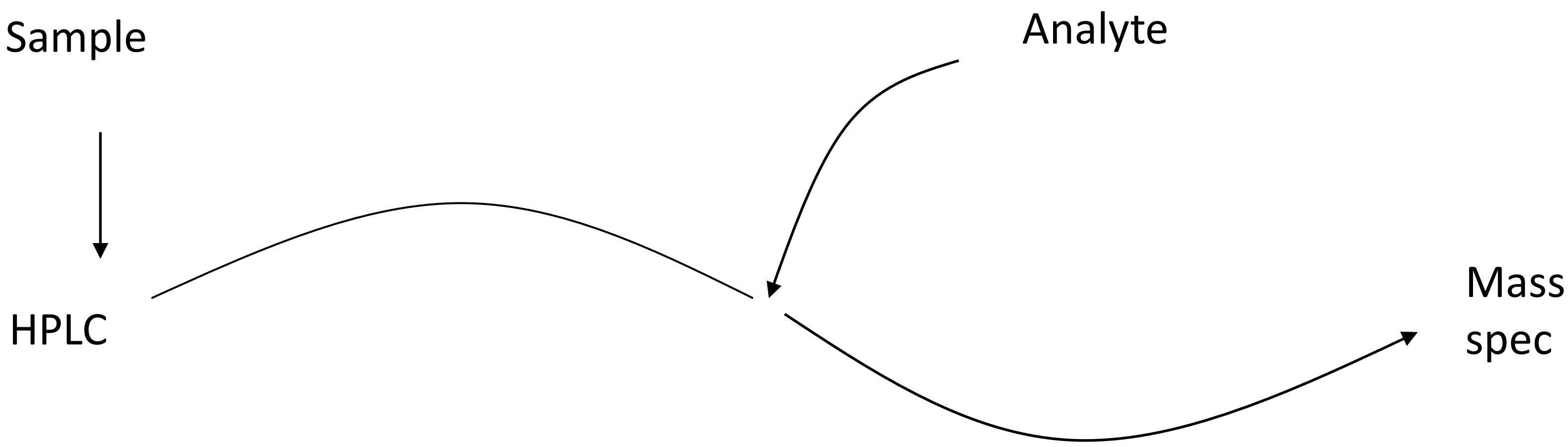
Interferences

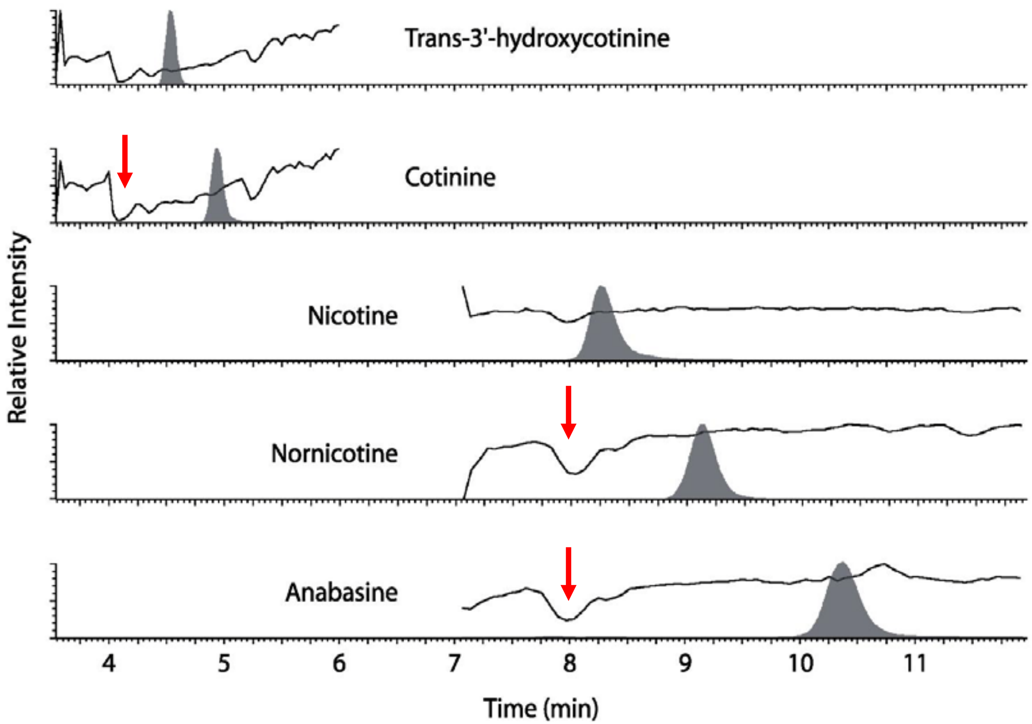


Ion suppression — any molecule will compete for charge namely, phospholipids, proteins, salts

Isobaric interference — molecules with the same mass that elute at the same time

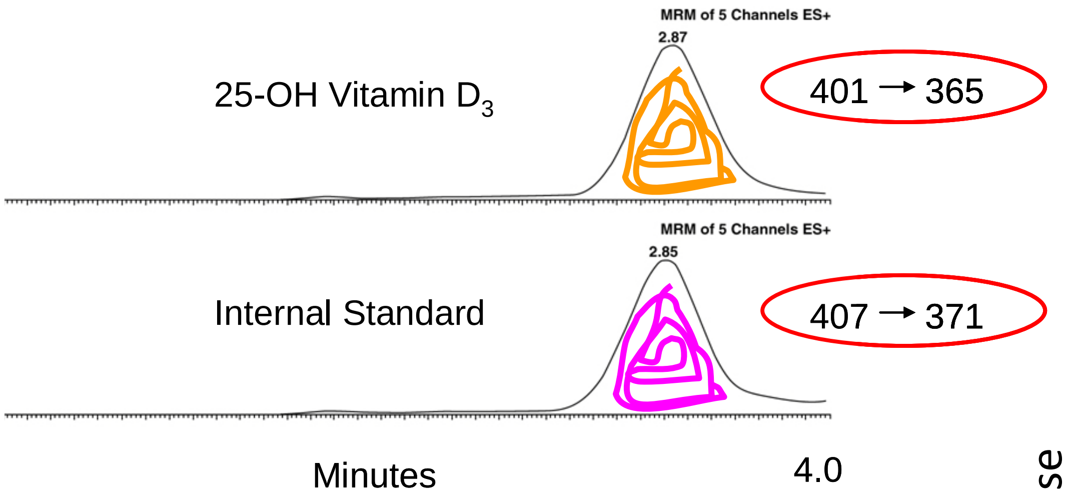
Ion Suppression

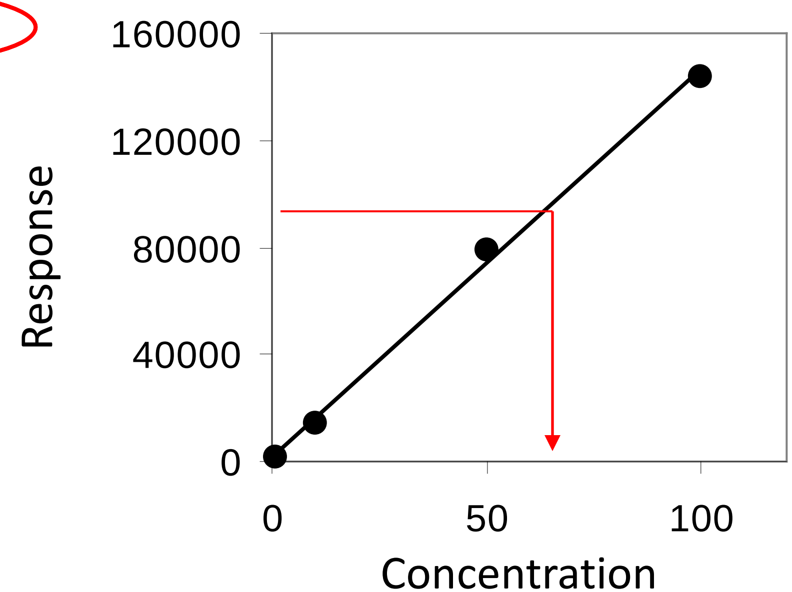




↓ Ion suppression

Internal Standard





$$\text{Response} = \frac{\text{Vitamin } D_3}{\text{Internal Standard}}$$

We can correct for some amount of ion suppression…

Proper Quality Control

Checking for Ion Suppression

Ion suppression	Recovery
10%	104%
25%	98%
50%	107%
75%	80%
95%	12%

But, too much ion suppression is BAD!!

Solution: *In every sample, check internal standard must meet minimum peak area to accept sample quantification*

Proper Quality Control

Checking for Ion Suppression

Sample	Analyte	Conc	RT	Analyte Peak Area	IS	Response	Calc conc	Ion Ratio	Ratio Flag?
Std D	D3	200	2.84	13902	12597	1.10	201.1	1.4	NO
Std C	D3	100	2.82	5210	10349	0.50	99.8	1.3	NO
Std B	D3	30	2.88	2128	11640	0.18	33.3	1.4	NO
Std A	D3	1	2.87	249	10274	0.02	1.1	1.4	NO
Ctrl HI	D3		2.88	808	13878	0.06	10.7	1.4	NO
Ctrl LO	D3		2.88	3190	12186	0.26	48.4	1.4	NO
M64598	D3		2.89	2809	8234	0.34	63.0	1.3	NO
M67899	D3		2.86	1408	13192	0.11	19.7	1.5	NO
M70133	D3		2.84	1504	13469	0.11	20.6	1.5	NO
M70134	D3		2.82	1443	10960	0.13	24.3	1.2	NO
M70135	D3		2.90	1703	12058	0.14	26.1	1.3	NO
M71222	D3		2.80	1774	13004	0.14	25.2	1.4	NO
M72090	D3		2.84	1932	11747	0.16	30.4	1.4	NO
T80031	D3		2.83	2034	2312	0.88	162.6	1.4	NO
T80100	D3		2.83	2178	13075	0.17	30.8	1.3	NO
T81070	D3		2.89	4508	12678	0.36	65.7	1.2	NO
T90909	D3		2.83	3488	11378	0.31	56.7	1.4	NO
T91002	D3		2.80	2912	12790	0.23	42.1	1.4	NO
T91114	D3		2.84	2600	12610	0.21	38.1	1.5	NO

Proficiency Testing

25-OH Vitamin D, total – ng/mL

ABVD-06

METHOD	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
Abbott Architect I System	29	25.41	2.31	9.1	25.7	20.0	29.7
Diasorin Liaison	53	23.55	2.37	10.1	23.5	18.2	29.8
Diasorin RIA	6	-	-	-	25.2	21.0	35.0
Immunodiagnostic Systems (IDS) Ltd.	17	34.20	5.55	16.2	33.0	25.7	49.0
Liquid Chromatography-Mass Spectrometry-Mass Spectrometry (LC-MS-MS)	61	29.32	3.46	11.8	29.6	20.7	38.7
Siemens Diagnostics ADVIA Centaur, Centaur XP	59	15.10	2.25	14.9	15.5	9.1	21.1
All Methods	**245**	**24.27**	**6.71**	**27.6**	**24.4**	**9.1**	**49.0**
Reference Target*		**29.4**					

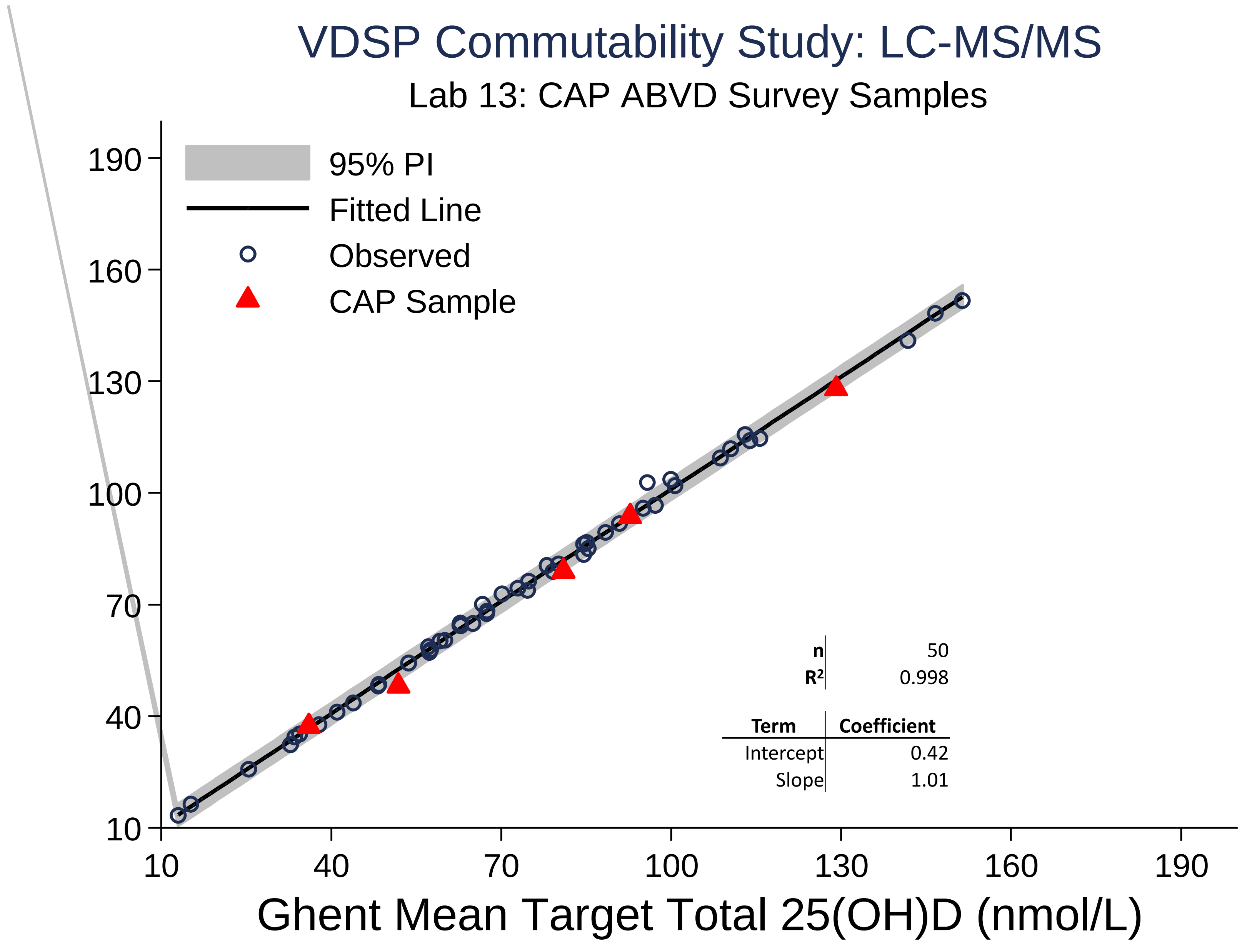
ABVD-07

METHOD	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
Abbott Architect I System	29	18.47	1.55	8.4	18.3	15.6	21.2
Diasorin Liaison	52	20.75	1.58	7.6	20.9	15.8	24.3
Diasorin RIA	6	-	-	-	22.2	18.5	30.3
Immunodiagnostic Systems (IDS) Ltd.	17	24.31	2.88	11.9	24.3	18.7	31.0
Liquid Chromatography-Mass Spectrometry-Mass Spectrometry (LC-MS-MS)	63	23.59	3.03	12.8	24.0	15.6	30.0
Siemens Diagnostics ADVIA Centaur, Centaur XP	59	17.88	2.61	14.6	17.7	12.0	24.0
All Methods	**246**	**20.63**	**3.51**	**17.0**	**20.6**	**12.0**	**31.0**
Reference Target*		**22.2**					

ABVD-08

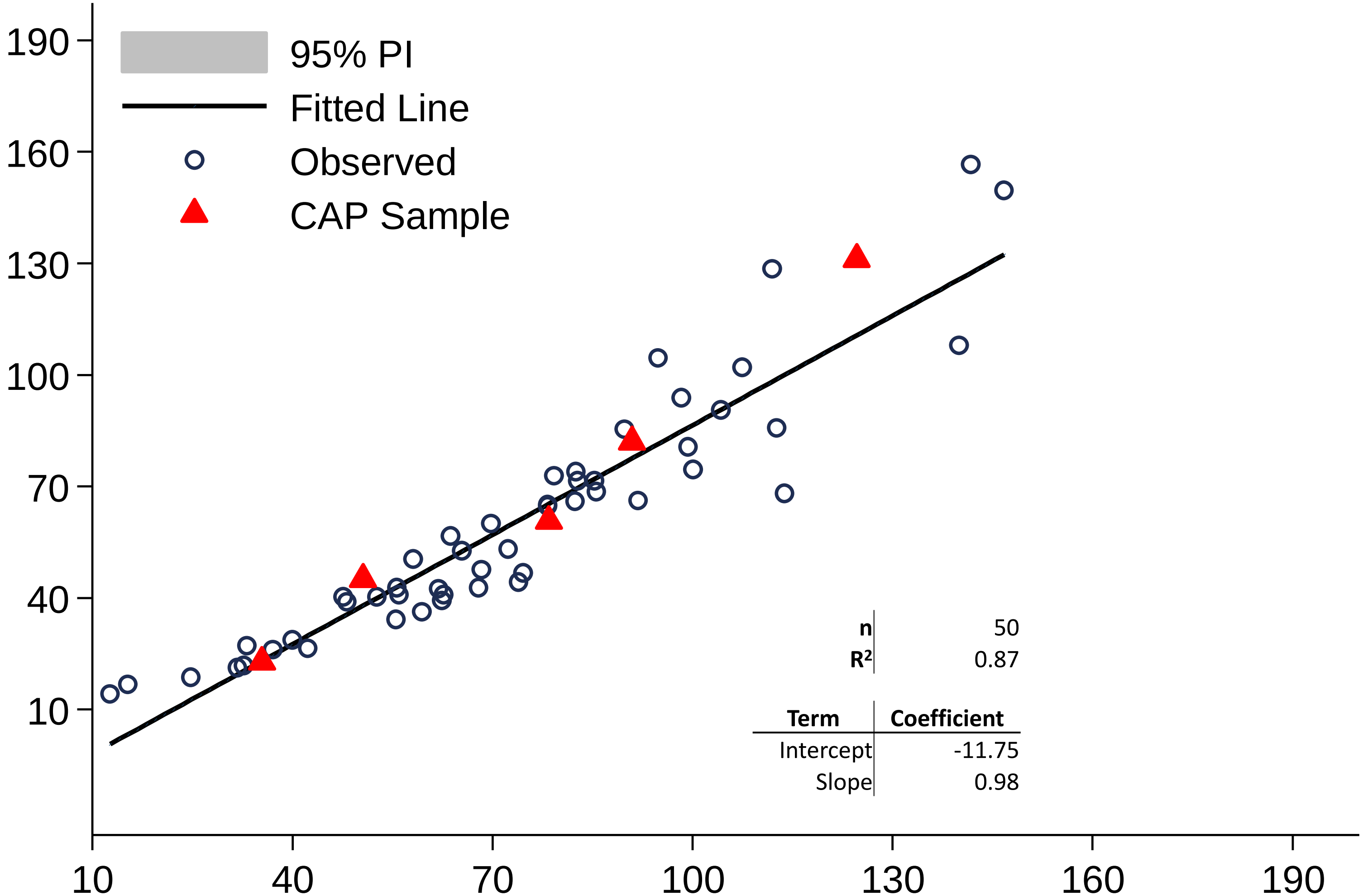
METHOD	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
Abbott Architect I System	29	37.90	2.97	7.8	37.5	32.4	42.5
Diasorin Liaison	54	37.02	3.33	9.0	36.9	29.8	43.9
Diasorin RIA	5	-	-	-	31.8	25.3	39.3
Immunodiagnostic Systems (IDS) Ltd.	16	42.69	3.67	8.6	43.6	35.9	48.0
Liquid Chromatography-Mass Spectrometry-Mass Spectrometry (LC-MS-MS)	62	33.76	3.59	10.6	33.5	26.0	44.5
Siemens Diagnostics ADVIA Centaur, Centaur XP	59	28.25	3.99	14.1	28.1	18.2	38.1
All Methods	**245**	**34.43**	**5.67**	**16.5**	**35.0**	**18.2**	**48.0**
Reference Target*		**34.7**					

Shifting to accuracy-based standards is a great step forward...


VDSP Commutability Study: LC-MS/MS
Lab 13: CAP ABVD Survey Samples
95% PI
Fitted Line
Observed
CAP Sample
190
160
130
100
70
40
10
10
40
70
100
130
160
190
Ghent Mean Target Total 25(OH)D (nmol/L)
n 50
R² 0.998
Term Coefficient
Intercept 0.42
Slope 1.01

VDSP Commutability Study: Immunoassay

Lab 12: CAP ABVD Survey Samples

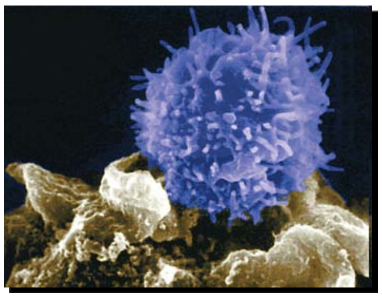


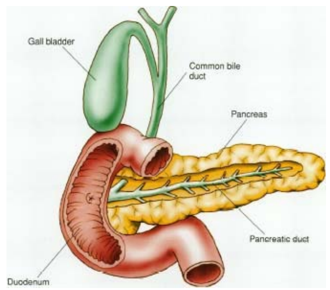
n	50
R^2	0.87

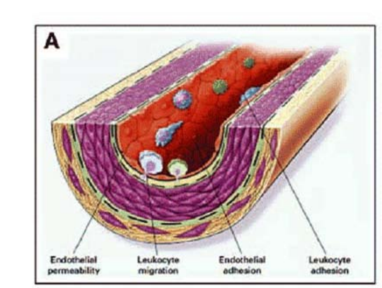
Term	Coefficient
Intercept	-11.75
Slope	0.98

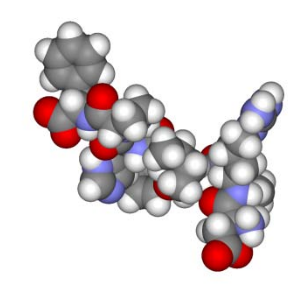
LC-MS Assays Enable the Clinical Research Community

Pleitropic Actions of 1,25-dihydroxyvitamin D









Immune cell function

Glucose homeostasis

VSMC

↓RAAS

Cardio-myocytes

Atherosclerosis prevention

↓LVH

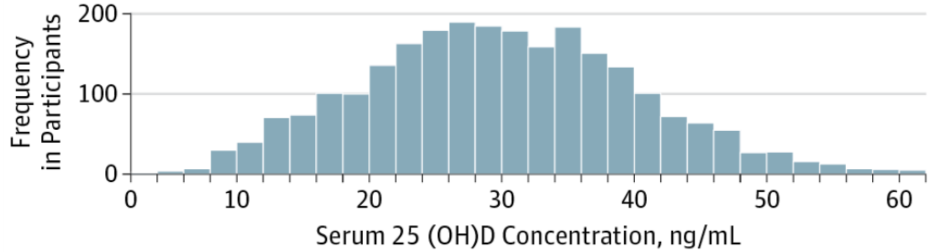
Multi-Ethnic Study of Atherosclerosis (MESA)

A large, representative group accrued throughout the US that includes four races and incredible follow-up

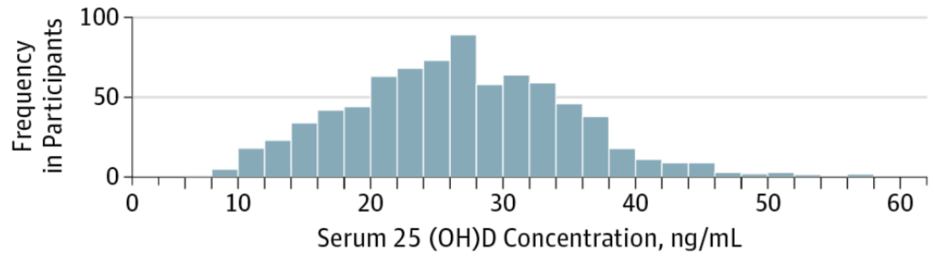
- 6,814 people
- 45-84 years of age
- 53% female
- Sites: NC, NY, MD, MN, IL, CA
- African Americans, Chinese Americans, Whites, and Hispanics
- ≥8 years follow-up

Racial Differences in 25(OH)D Concentrations

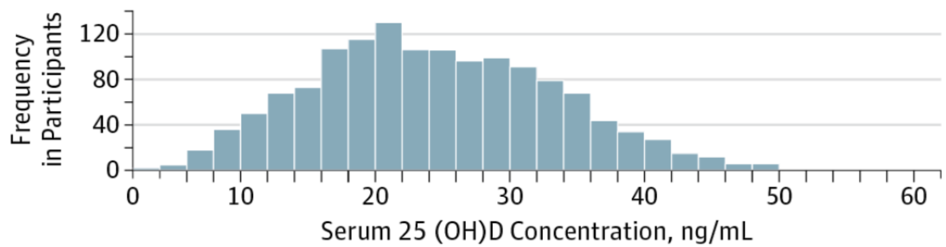
White



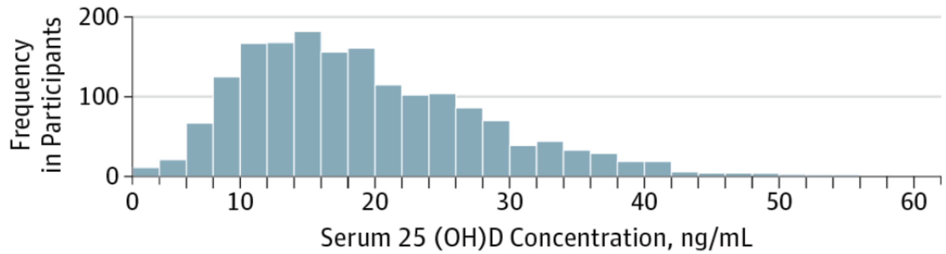
Chinese



Hispanic

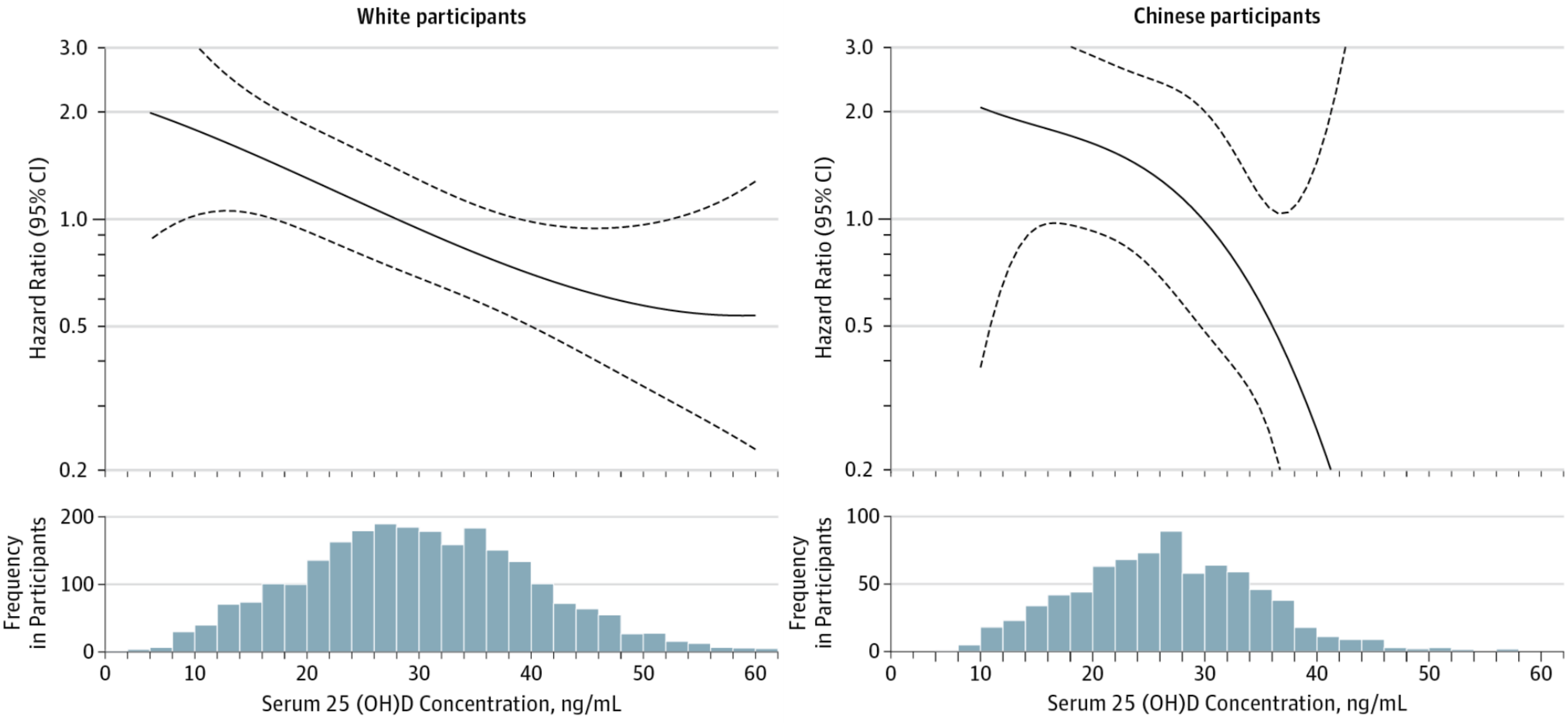


Black



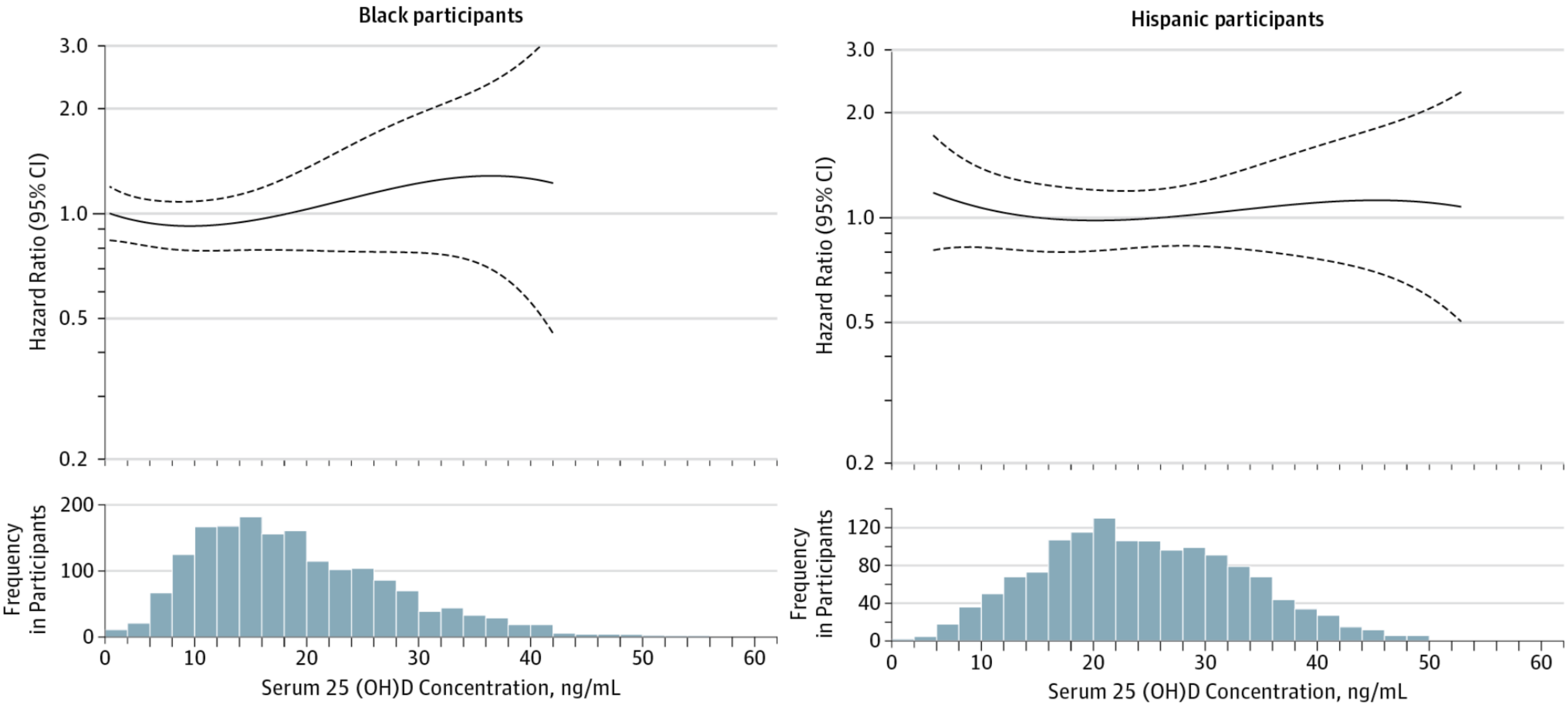
Robinson-Cohen, 2013, JAMA

Racial Differences in CVD Outcomes



Robinson-Cohen, 2013, JAMA

Racial Differences in CVD Outcomes



Robinson-Cohen, 2013, JAMA

National Health and Nutrition Examination Survey

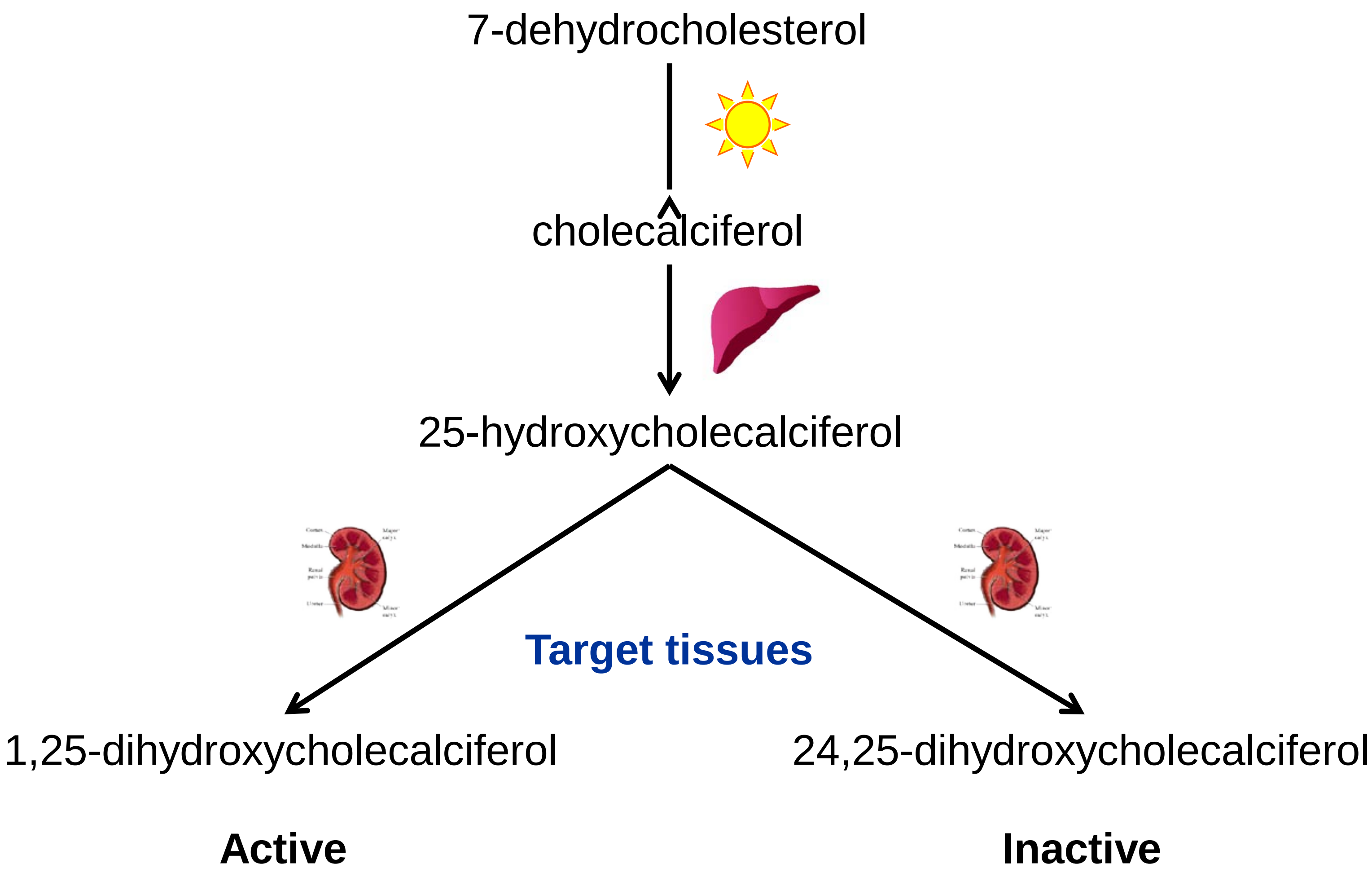
A New Perspective

Male	ng/mL	Female	ng/mL
12–29 y		**12–29 y**	
White	33.4	White	29.9
Black	20.0	Black	16.9
Mexican American	27.6	Mexican American	23.1
30–59 y		**30–59 y**	
White	30.0	White	26.4
Black	19.5	Black	16.7
Mexican American	25.4	Mexican American	21.4
>59 y		**>59 y**	
White	30.3	White	25.8
Black	21.3	Black	18.8
Mexican American	26.3	Mexican American	23.5

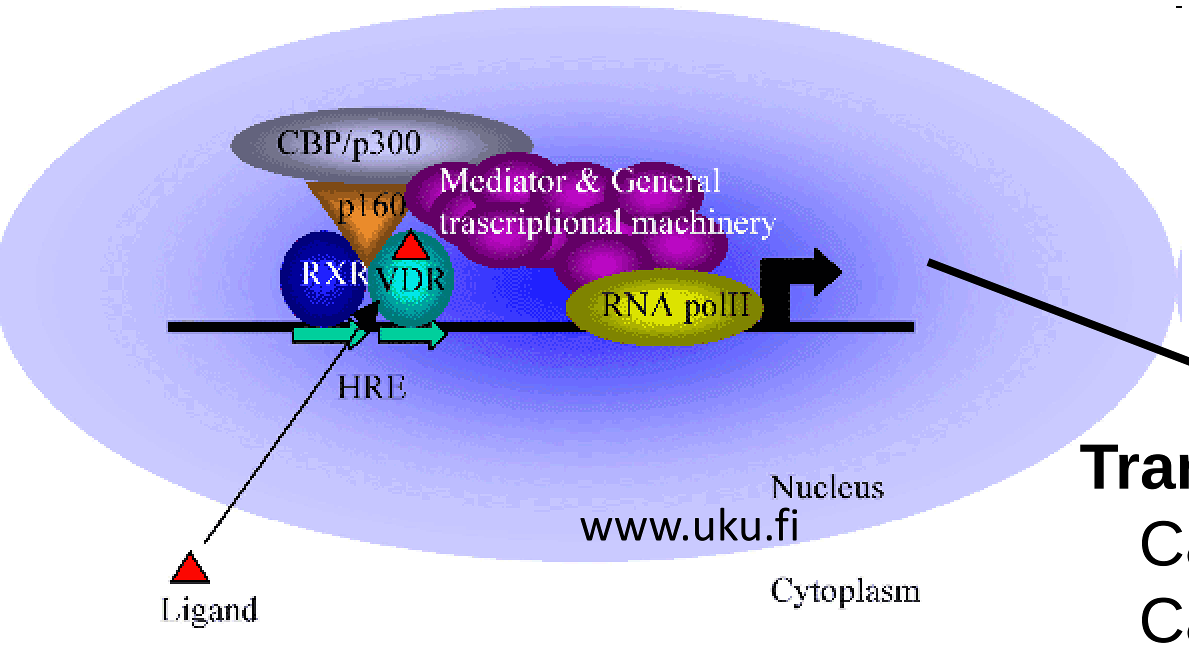
Data collected in the South during the winter

Weaver and Fleet, AJCN, 2004

Vitamin D Metabolism: Making the Active Hormone



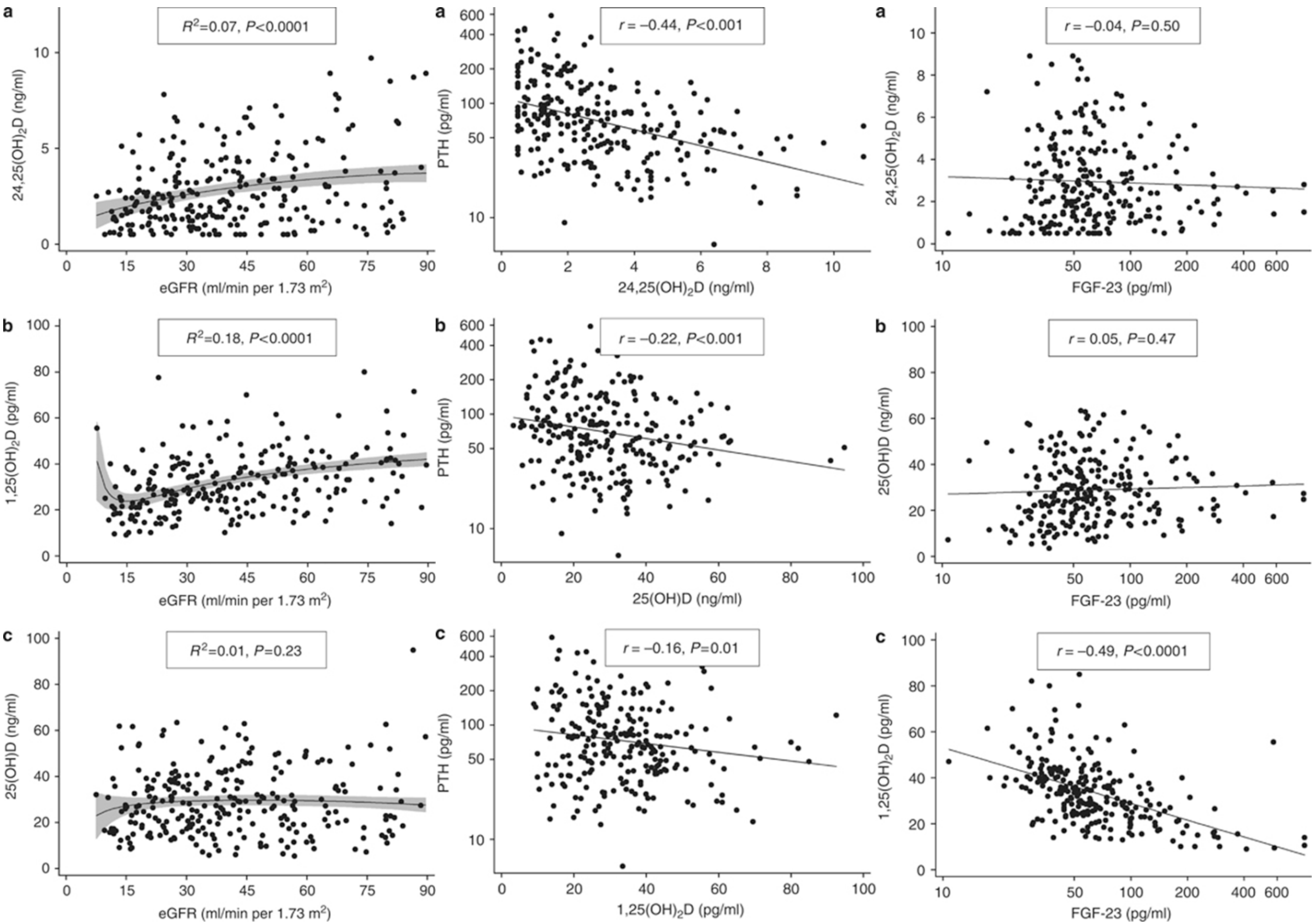
Vitamin D Action in the Cell



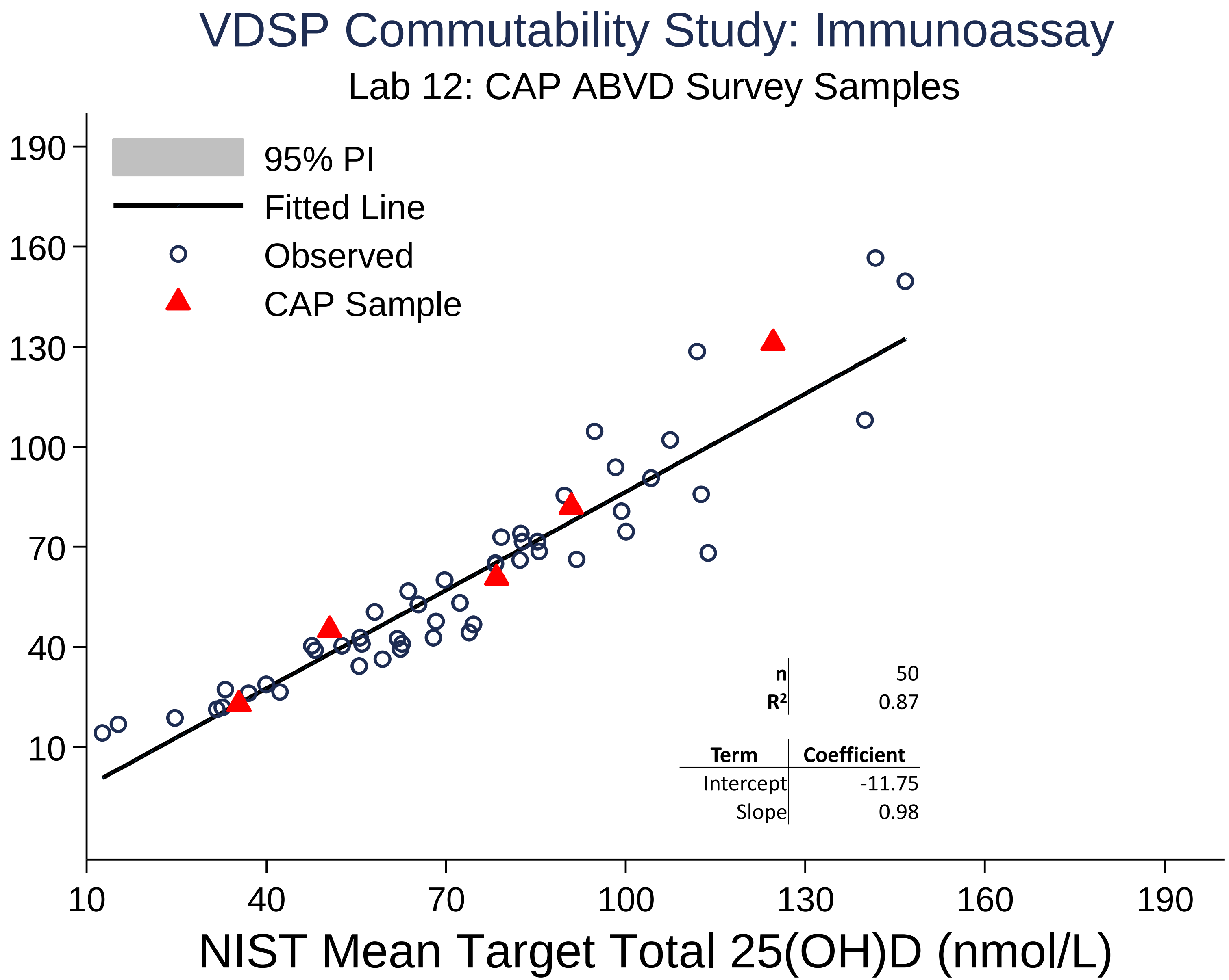
Transcription:

Calcium channels
Calbindin
Osteopontin
Osteocalcin
Cathelicidin
Integrin $_3$
Renin
Vitamin D 24-hydroxylase

Multiplexed Panels and Epidemiological Studies



Bosworth, 2012, *Kidney Int*



VDSP Commutability Study: Immunoassay
Lab 12: CAP ABVD Survey Samples
95% PI
Fitted Line
Observed
CAP Sample
190
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100
130
160
190
NIST Mean Target Total 25(OH)D (nmol/L)
n 50
R² 0.87
Term Coefficient
Intercept -11.75
Slope 0.98

Summary

Accuracy

Important for clinical care

Reference ranges are target concentrations

Consistency

Comparison of research studies

International epidemiology

Selectivity

Vitamin D metabolism is complex

A lot to learn about the biology (still)

We can do it

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