Are we really all vitamin D deficient?

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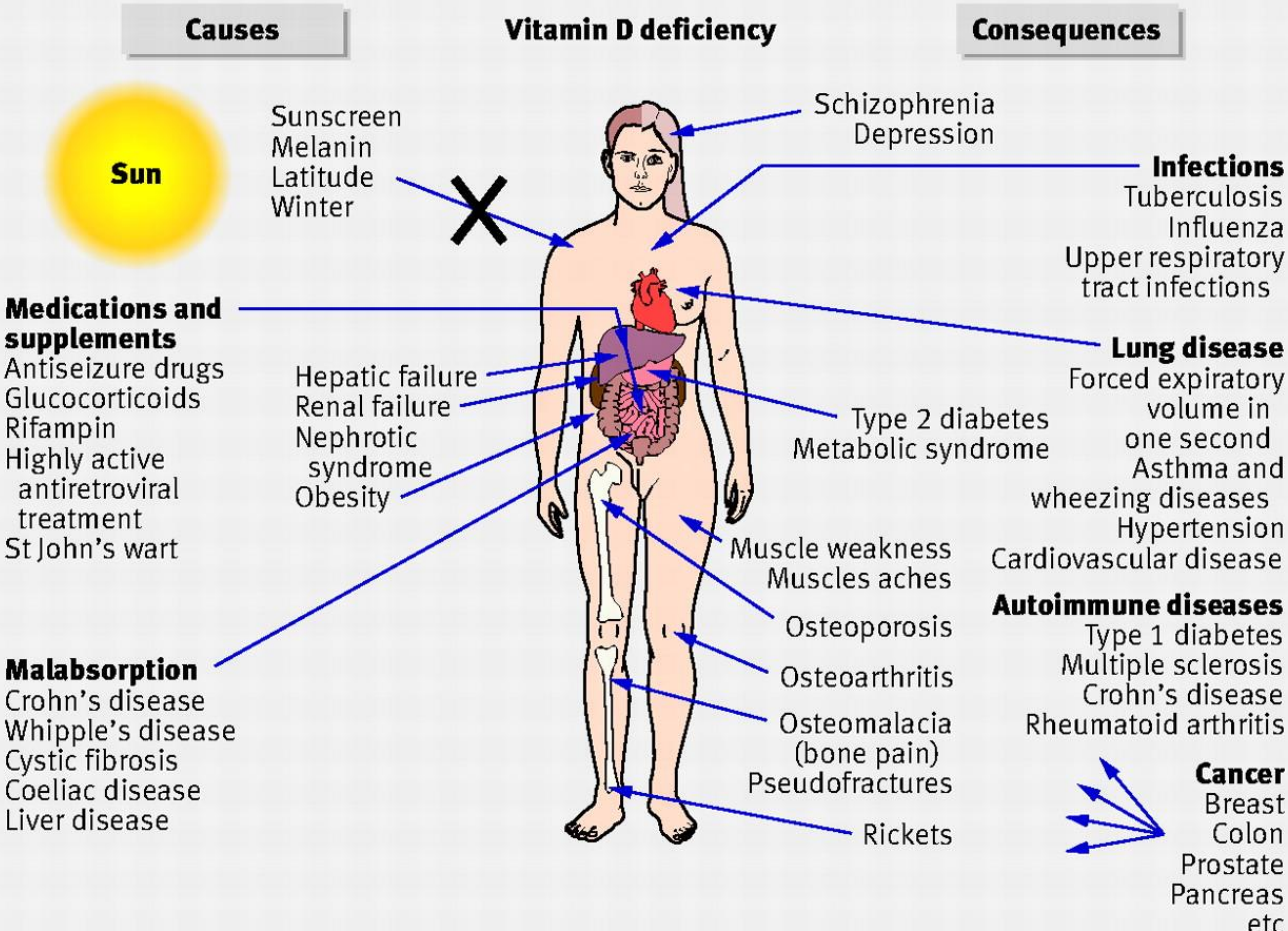
Harvard Medical School
Assistant Director of Clinical Chemistry
Beth Israel Deaconess Medical Center

- Grant support from NIH,
- Consultant to AB Sciex

True vitamin D deficiency does exist…

Rickets & Vitamin D deficiency



http://www.progressive-charlestown.com

Cross Sectional

Study	N	Male (%)	Age (Years)	Primary Outcome	Baseline 25(OH)D (ng/mL)	Systolic blood pressure	Diastolic blood pressure
Zagura et al.	152	100	62	Aortic pulse wave velocity	17	↓	↓
Almirall et al.	237	47	72	Blood pressure	16	↓	↓
Burgaz et al.	833	100	71	Hypertension	27	↓	↓
Bhandari et al.	2,722	31	59	Hypertension	48	↓	↓
Martins et al.	15,088	48	Stratified	Cardiovascular risk factors	30	↓	↓
Williams et al.	5,609	~50	NR	Cardiovascular risk factors	20	↓	✗
Fraser et al.	3,958	NR	NR	Cardiovascular risk factors	24	↓	✗
Forrest et al.	4,495	48	Stratified	Cardiovascular risk factors	20	↓	↓
Hintzpeter et al.	4,030	44	Stratified	Health correlates	18	↓	↓
Zhao et al.	7,228	49	48	Blood pressure	Stratified	↓	↓
Fiscella et al.	7,140	50	45	Systolic blood pressure	Stratified	↓	--
Snijder et al.	1,205	50	75	Blood pressure	22	✗	✗
Reis et al.	1,070	38	75	Metabolic syndrome	42	↓	✗
Chan et al.	939	100	73	Osteoporotic fractures	31	✗	✗

Prospective Observational

Study	N	Male (%)	Age (Years)	Follow up	Primary Outcome	Baseline 25(OH)D (ng/mL)	Systolic blood pressure	Diastolic blood pressure
Forman et al.	1,484	0	43	7 years	Hypertension	27	↓	↓
Griffin et al.	559	0	37	14 years	Metabolism and bone health	24	↓	↓
Forman et al.	1,811	34	Stratified	4 years	Hypertension	NR	↓	↓
Forman et al.	209,313	18	44	≥8 years	Cardiovascular disease	NR	✗	✗
Jorde et al.	4,125	37	59	14 years	Blood pressure	23	↓	✗
Margolis et al.	2,153	0	66	7 years	Blood pressure	NR	✗	✗

Randomized Trials

Study	N	Male (%)	Age (Years)	Intervention	Vitamin D dose	Follow up	Primary Outcome	Baseline 25(OH)D (ng/mL)	Systolic blood pressure	Diastolic blood pressure
Sugden et al.	34	53	54	Ergocalciferol	100,000 IU once	8 weeks	Endothelial function and blood pressure	15	↓	✗
Judd et al.	9	NR	45	Cholecalciferol or calcitriol	200,000 IU weekly; 0.5 µg twice a day	4 weeks	Blood pressure	13	↓	--
Nagpal et al.	71	100	37	Cholecalciferol	120,000 IU every other week	6 weeks	Insulin sensitivity	13	✗	✗
Krause et al.	18	56	26 - 66	Ultraviolet B	6 minutes 0.5 MED three times a week	6 weeks	Blood pressure	19	↓	↓
Jorde et al.	438	35	48	Cholecalciferol	40,000 IU weekly; 20,000 IU weekly	1 year	Lipids and blood pressure	23	✗	✗
Pfeifer et al.	148		75	Cholecalciferol and calcium	800 IU daily	8 weeks	Blood pressure	25	↓	✗
Margolis et al.	36,282	0	62	Cholecalciferol	400 IU daily	7 years	Hip fracture	NR	✗	✗
Major et al.	63	0	43	Cholecalciferol and calcium	400 IU daily	15 weeks	Lipids and blood pressure	NR	↓	↓
Orwoll et al.	65	100	57	Cholecalciferol	1000 IU daily	3 years	Blood pressure	NR	↓	✗
de Zeeuw et al.	281	70	64	Paricalcitol	1 µg or 2 µg daily	24 weeks	Albuminuria	17	↓	--
Liu et al.	25	58	36	Calcitriol	0.5 µg twice per week	48 weeks	Proteinuria	29	✗	✗
Thadhani et al.	227	70	64	Paricalcitol	2 µg daily	48 weeks	Left ventricular mass index	NR	✗	✗

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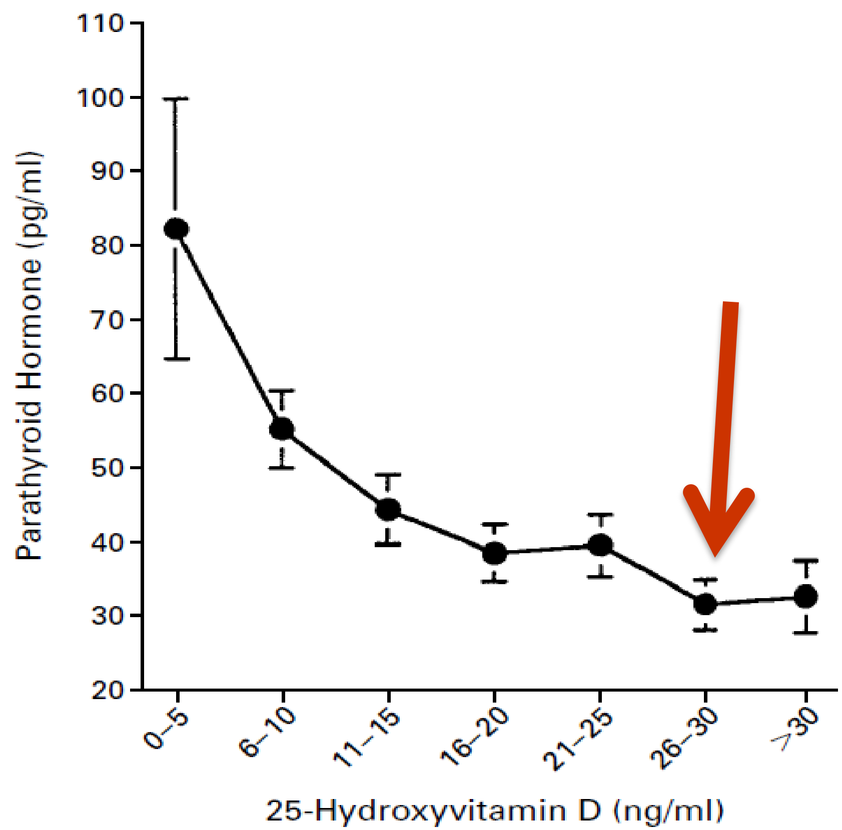
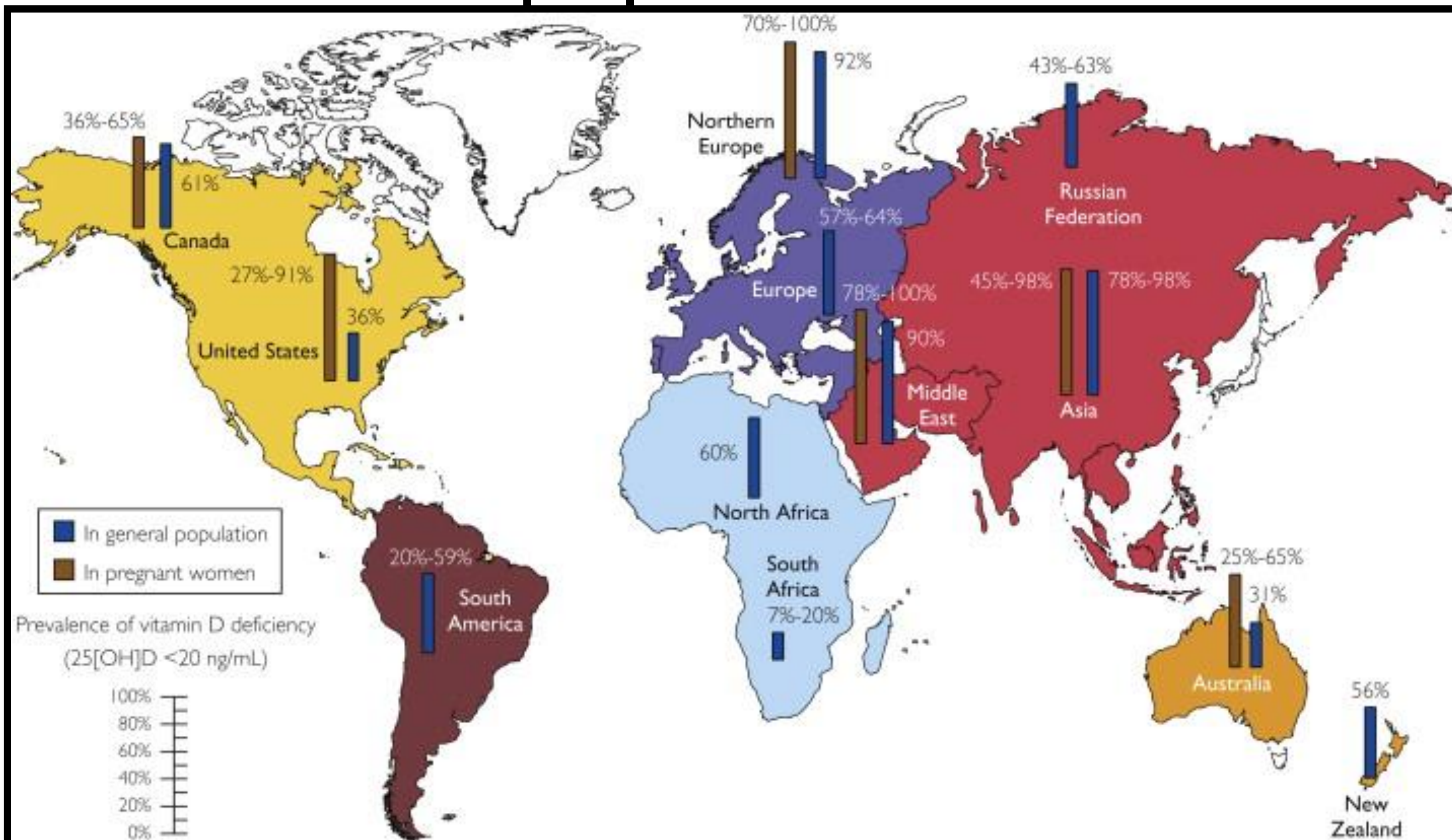
VOLUME 338 MARCH 19, 1998 NUMBER 12

HYPOVITAMINOSIS D IN MEDICAL INPATIENTS

MELISSA K. THOMAS, M.D., PH.D., DONALD M. LLOYD-JONES, M.D., RAVI I. THADHANI, M.D., M.P.H., ALBERT C. SHAW, M.D., PH.D., DONALD J. DERASKA, M.D., BARRETT T. KITCH, M.D., ELEFTHERIOS C. VAMVAKAS, M.D., PH.D., IAN M. DICK, M.SC., RICHARD L. PRINCE, M.D., AND JOEL S. FINKELSTEIN, M.D.



But does it exist for > 50% of the population?



Mayoclinicproceedings.com

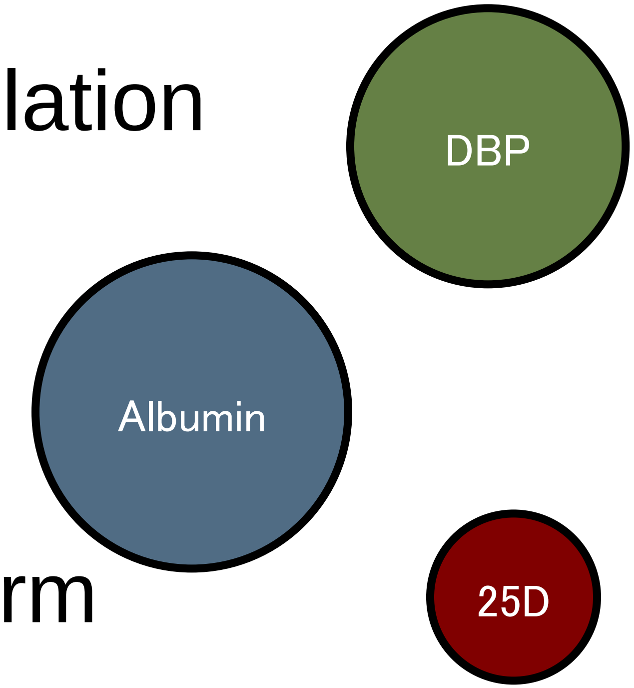
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

IOM on Calcium & Vitamin D

- Assessed >1,000 studies/reports plus expert testimony related to various health outcomes:
  - cancer, CVD, hypertension, diabetes/metabolic syndrome, falls, immune response, neuropsychologic function, physical performance, preeclampsia and reproductive function
  - found evidence to be mixed and inconclusive
- "Current evidence supports a role in <u>bone health</u> but not in other health conditions"

25D and Circulating Proteins

- 25D binds to DBP in circulation
- 25D binds to Albumin
- 25D circulates in a free form

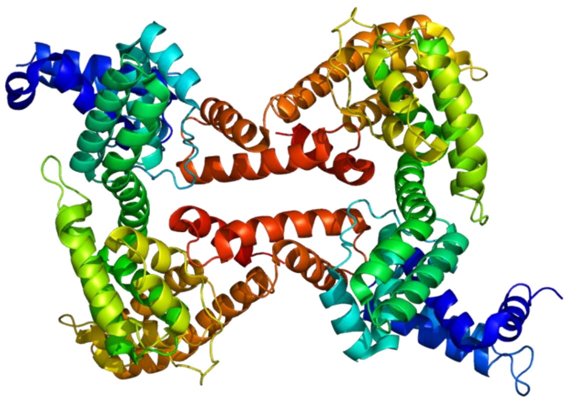


- [Total] = [D] + [DAlb] + [DDBP]

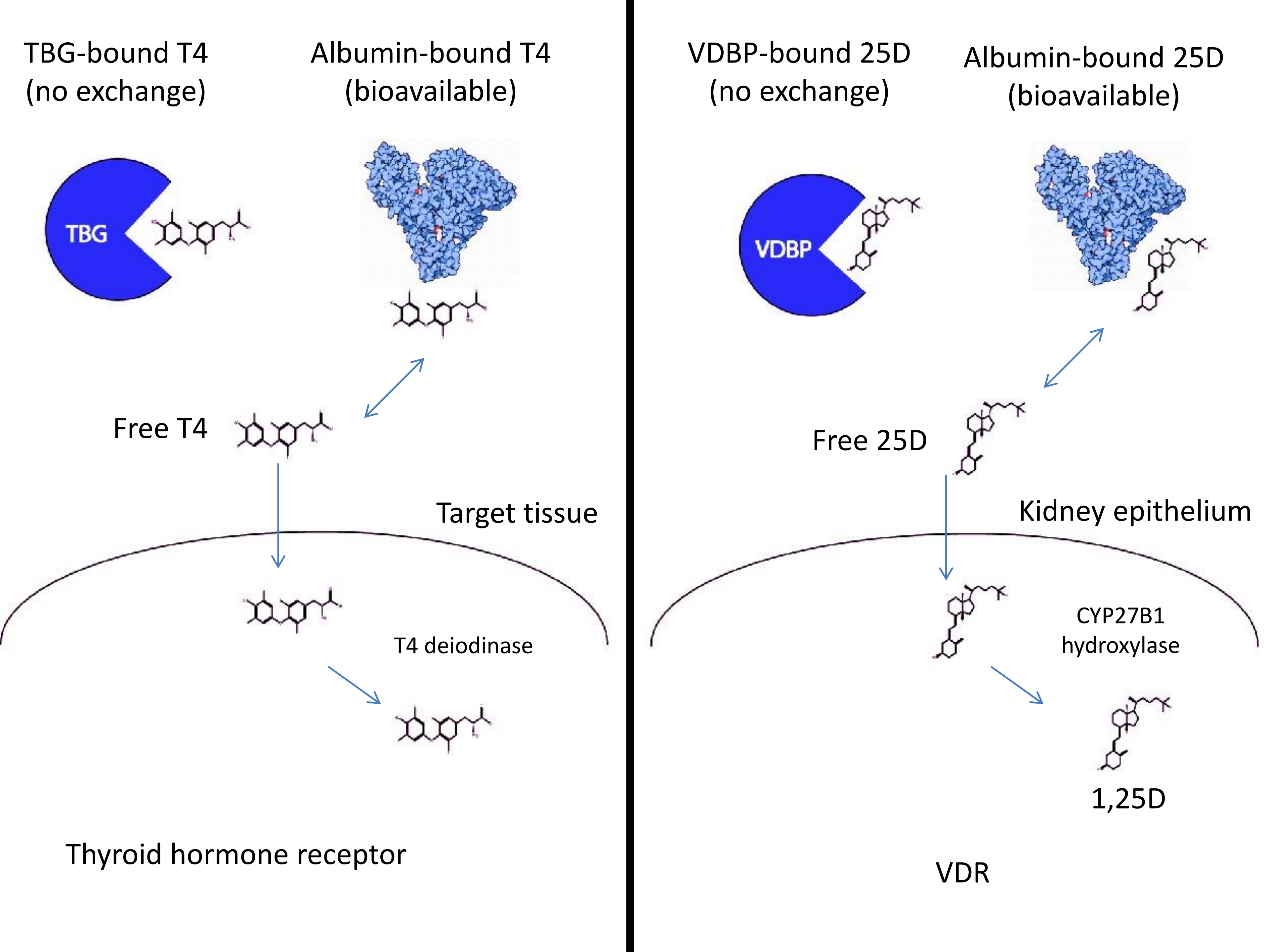
What is measured and reported today.

Vitamin D Binding Protein

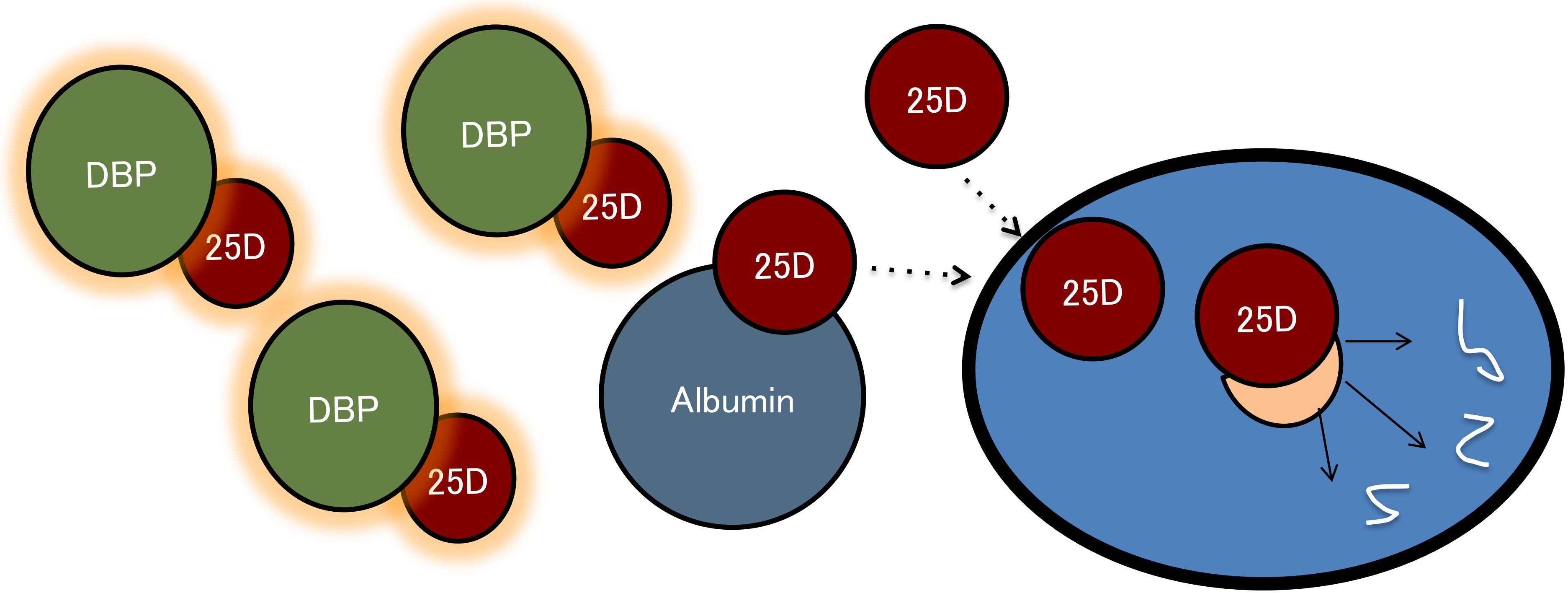
- ~ 55kd protein that is glycosylated
- 458 AA, 13 exons
- t ½ ~ 2-3 days
  - 25D t ½ is ~2 weeks, ligand recycling
- Produced in the Liver
- Negative acute phase reactant
  - binds actin in tissue damage
  - DBP-actin is rapidly cleared



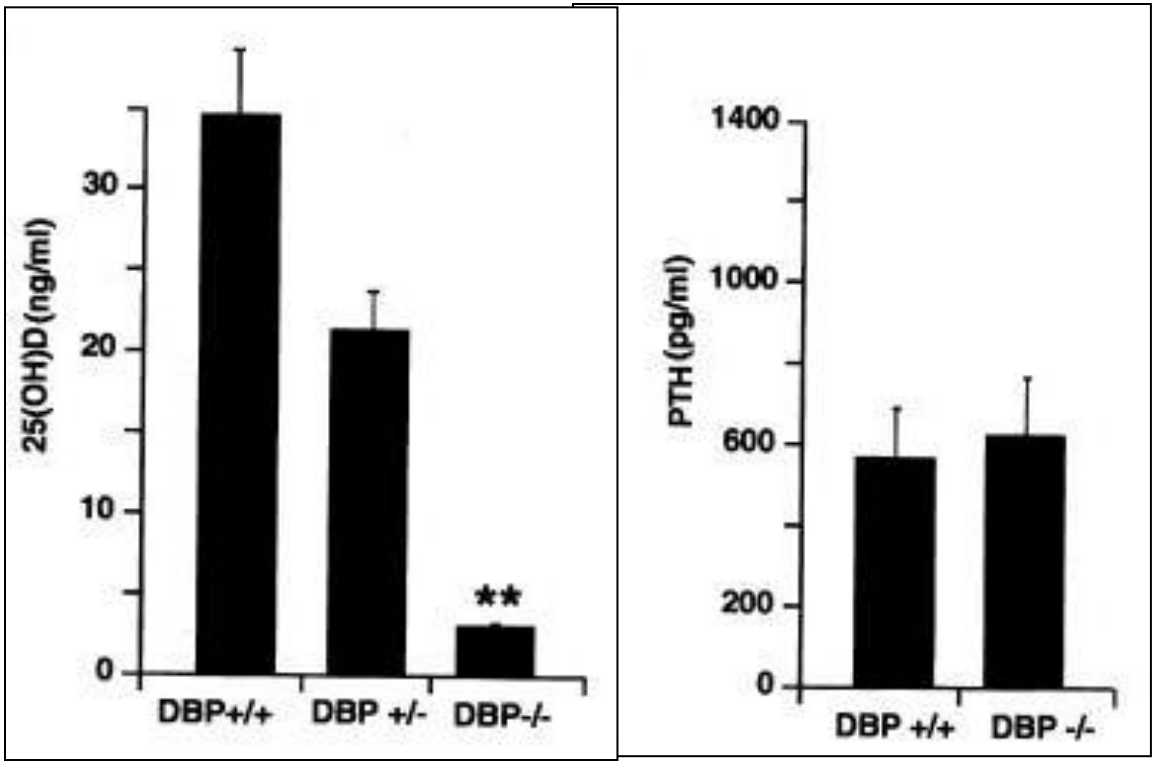
Bioavailable Vitamin D


TBG-bound T4
(no exchange)
Albumin-bound T4
(bioavailable)
TBG
Free T4
Target tissue
T4 deiodinase
Thyroid hormone receptor
VDBP-bound 25D
(no exchange)
Albumin-bound 25D
(bioavailable)
VDBP
Free 25D
Kidney epithelium
CYP27B1
hydroxylase
1,25D
VDR

Hormones circulating bound to albumin or circulating in a free form (collectively known as *Bioavailable Vitamin D)* are more readily available to enter cells than hormones bound to their traditional binding proteins



Without vitamin D binding protein, Vitamin D serum levels are very low, but mice have normal bones, normal calcium, normal PTH



	Ca (mg/dl)	Phos (mg/dl)	AlkPhos (U/l)
DBP +/+	8.0 ± 0.3	11.4 ± 1.0	74 ± 28
DBP -/-	7.9 ± 0.8	10.3 ± 1.5	94 ± 26

Safadi et al. JCI 1999

Patients with nephrotic syndrome (gross proteinuria) develop vitamin D deficiency because DBP proteinuria leeches vitamin D in urine

VITAMIN-D METABOLISM IN NEPHROTIC SYNDROME

J. M. Barragry M. W. France
N. D. Carter J. A. Auton

DATA FROM PATIENTS WITH NEPHROTIC SYNDROME

Case no.	Sex	Age	Serum: Albumin (g/l) (36–52)	Serum: Calcium (mmol/l) (2·15–2·60)	Serum: Alkaline phosphatase (I.U./l) (20–85)	Serum: 25-OHD$_3$ (nmol/l) (20–173·5)	Urine: Total protein (g/24 h) (0–0·15)	Urine: V.D.B.G. (mg/24 h)
1	M	52	24	1·95	112	2·25	8·2	80·0
2	M	33	25	2·00	128	0	9·0	106·0
3	F	27	26	2·04	204	1·25	8·7	130·0
4	M	68	29	2·07	80	0	5·9	28·5
5	M	72	19	1·98	205	3·75	9·3	117·0
6	F	65	22	1·98	66	1·25	13·0	170·0
7	F	54	27	1·91	121	9·75	19·6	41·8
8	M	46	28	2·04	22	0	6·9	51·9
9	F	26	18	1·81	51	3·5	7·2	50·0
10	M	49	28	2·09	47	16·5	3·4	20·5
Mean±S.E.M.			24·6±1·2	1·98±0·02	103·6±19·9	3·83±1·69	9·1±1·4	79·5±15·6

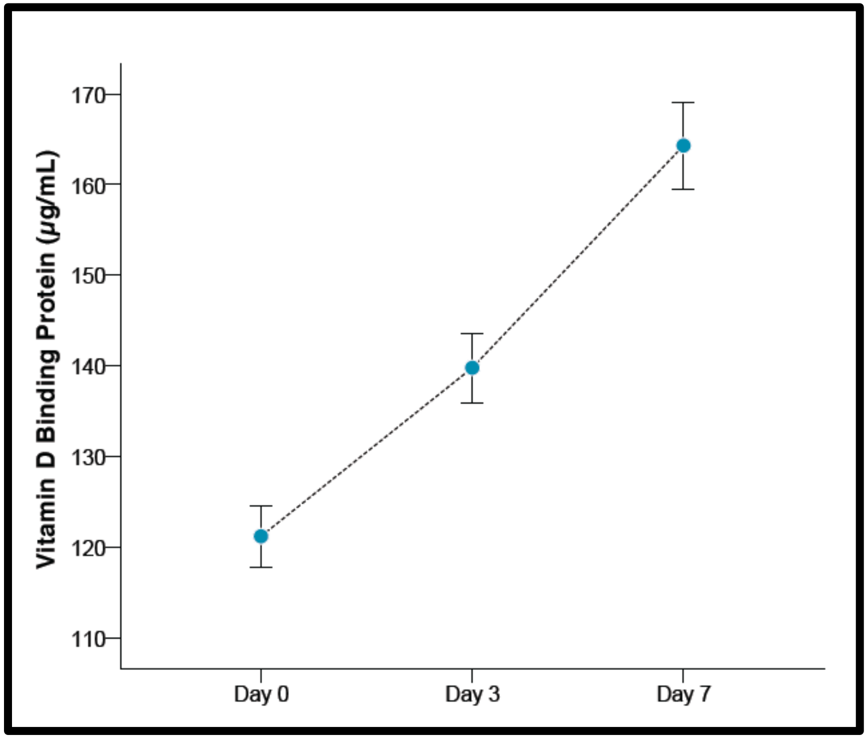
Control ranges are shown in parentheses.

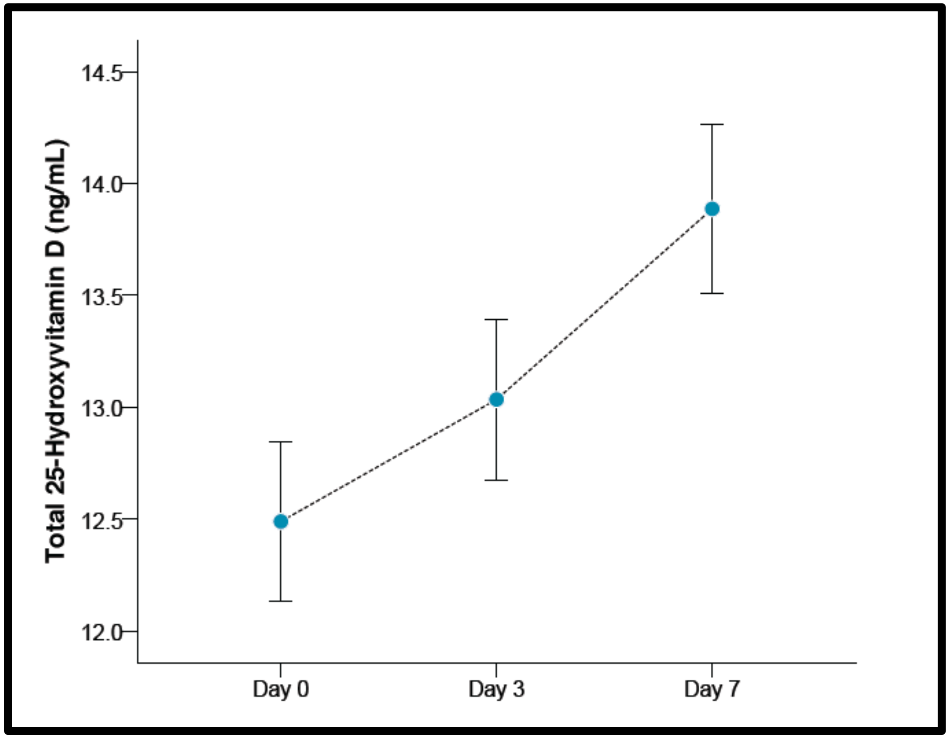
25-OHD$_3$ was substantially reduced in the nephrotic syndrome.

Liver disease patients have low “total” but preserved “free” 1,25$(OH)_2$D in the setting of low DBP

	Normal	**Liver disease**
Total 25D (ng/ml)	**19.2**	**9.7**
Total 1,25D (pg/ml)	**41.5**	**22.6**
% Free	**0.42**	**1.09**
Free	**174**	**209**
DBP (ug/dl)	**404**	**188**

Bikle et al, JCI 1984



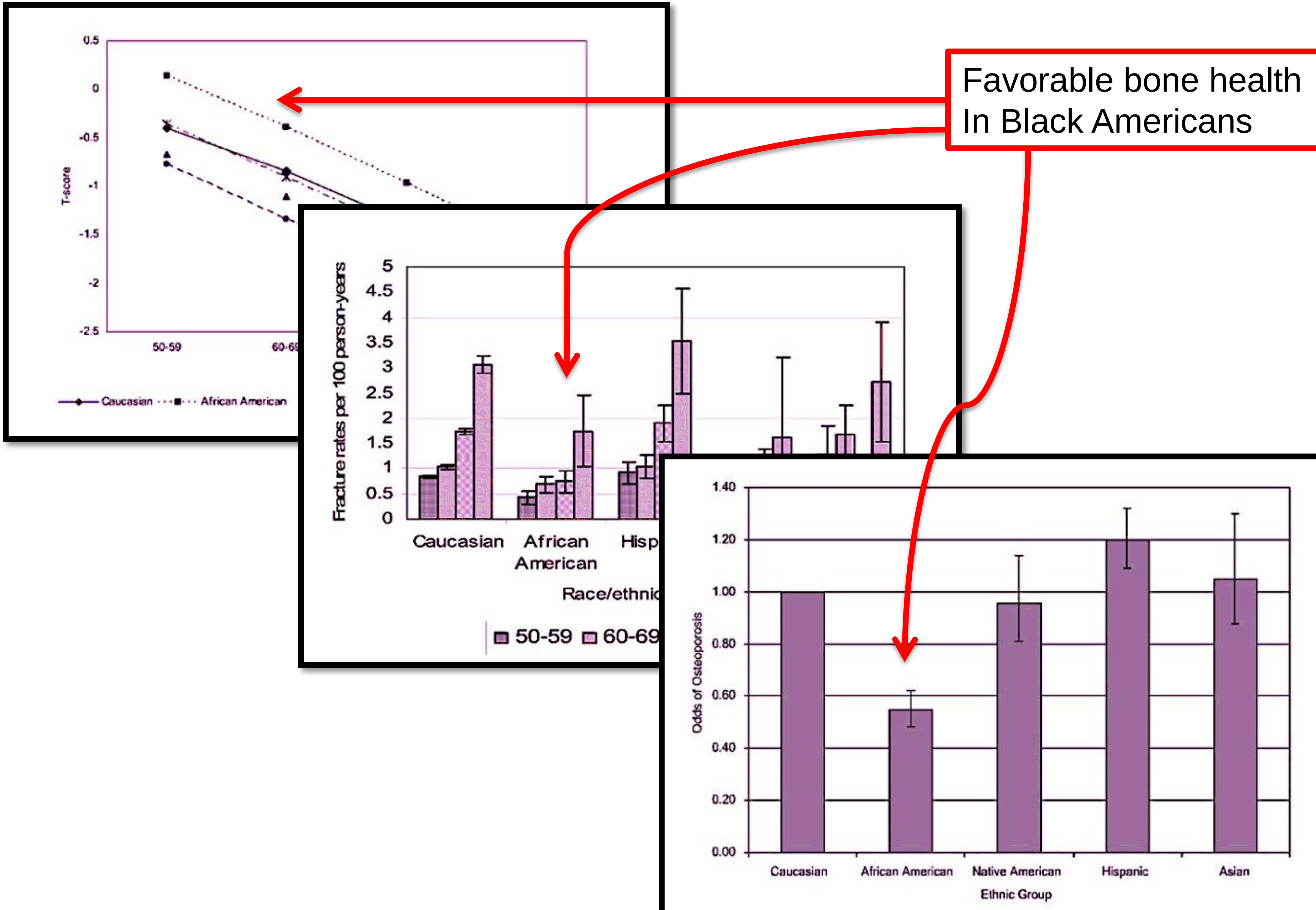


~ 550 MGH ICU patients
Bajwa, Bhan – Unpublished

DBP levels rise and Total 25D levels rise as illness subsides

THE RACIAL PARADOX

	WHITES	BLACKS
25(OH)D	**High**	**Low**
PTH	**Low**	**High(er)**
Bone Mineral Density	**Low**	**High**
Osteoporosis/Fracture	**High**	**Low**



Barrett-Conner JMBR 2004

RESEARCH Open Access

Vitamin D status in cord blood and newborns: ethnic differences

Francesco Cadario[1,2*], Silvia Savastio[1],
Mauro Zaffaroni[1] and Gianni Bona[1]

American journal of human biology : the official journal of the Human Biology Council

Author Manuscript NIH Public Access

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Luke

American Journal of Epidemiology

Oxford University Press

A Prospective Study of Serum 25-Hydroxyvitamin D Levels and Mortality Among African Americans and Non-African Americans

Lisa B. Signorello, Xijing Han,

Nutrition, metabolism, and cardiovascular diseases : NMCD

Author Manuscript NIH Public Access

Relationship of vitamin D levels to blood pressure in a biethnic population

R. Sakamoto, K. Jaceldo-Siegl, [...], and S. Tonstad

Factors associated with circulating levels of 25(OH)D

- Diet
- Season
- Race
- BMI
- Genetics

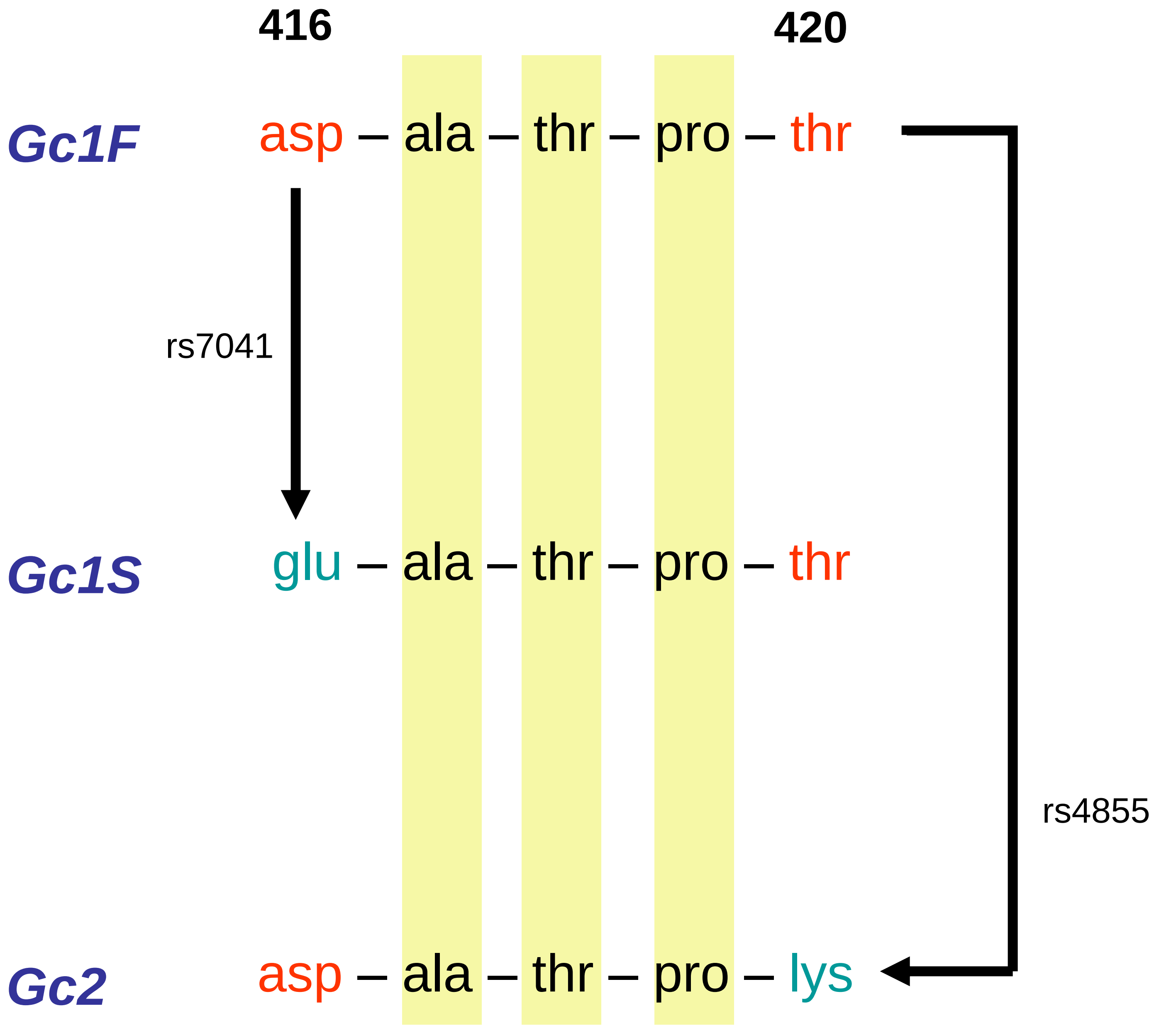
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

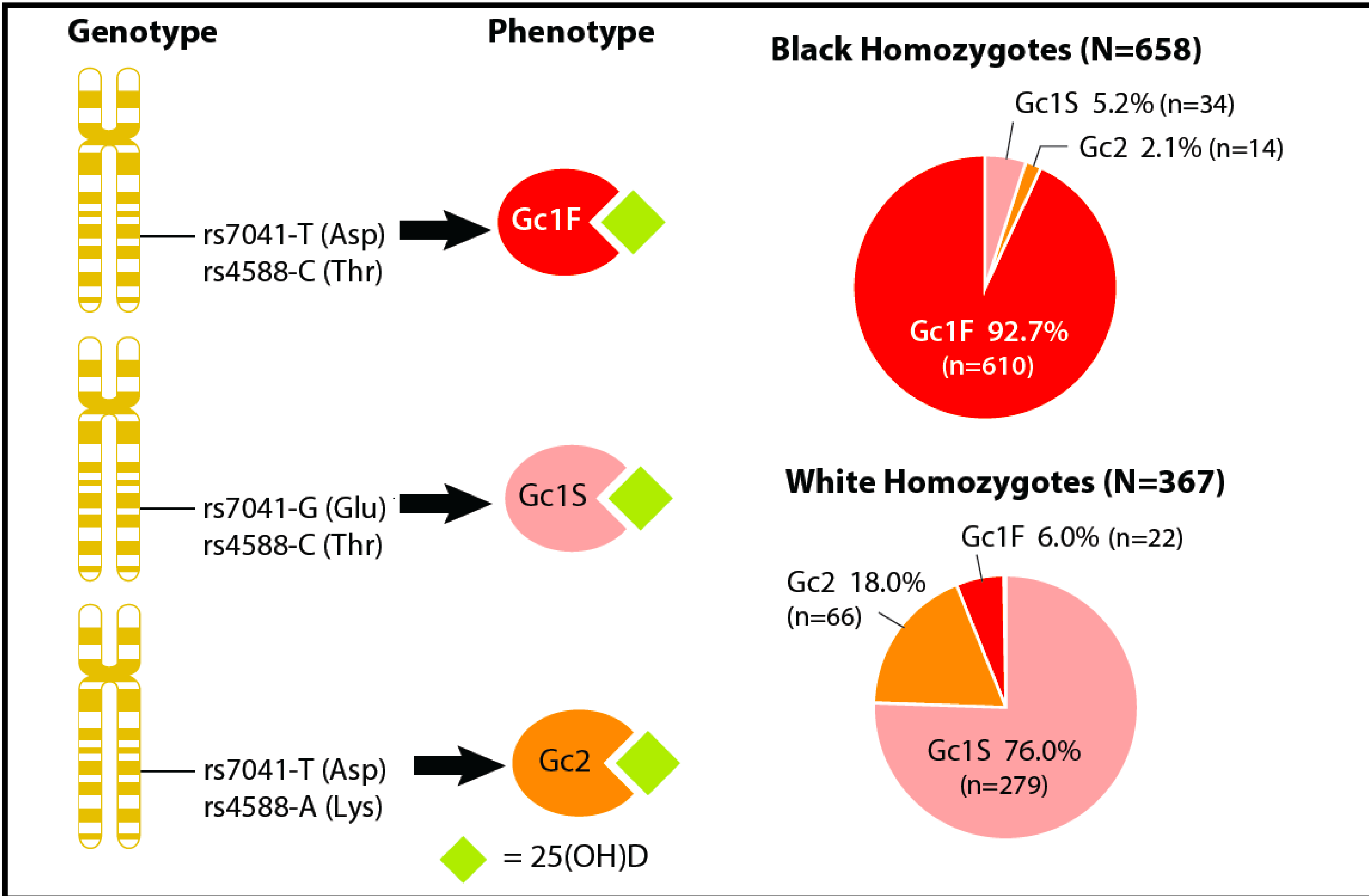
Vitamin D–Binding Protein and Vitamin D Status of Black Americans and White Americans

Camille E. Powe, M.D., Michele K. Evans, M.D., Julia Wenger, M.P.H.,
Alan B. Zonderman, Ph.D., Anders H. Berg, M.D., Ph.D., Michael Nalls, Ph.D.,
Hector Tamez, M.D., M.P.H., Dongsheng Zhang, Ph.D.,
Ishir Bhan, M.D., M.P.H., S. Ananth Karumanchi, M.D.,
Neil R. Powe, M.D., M.P.H., M.B.A., and Ravi Thadhani, M.D., M.P.H.

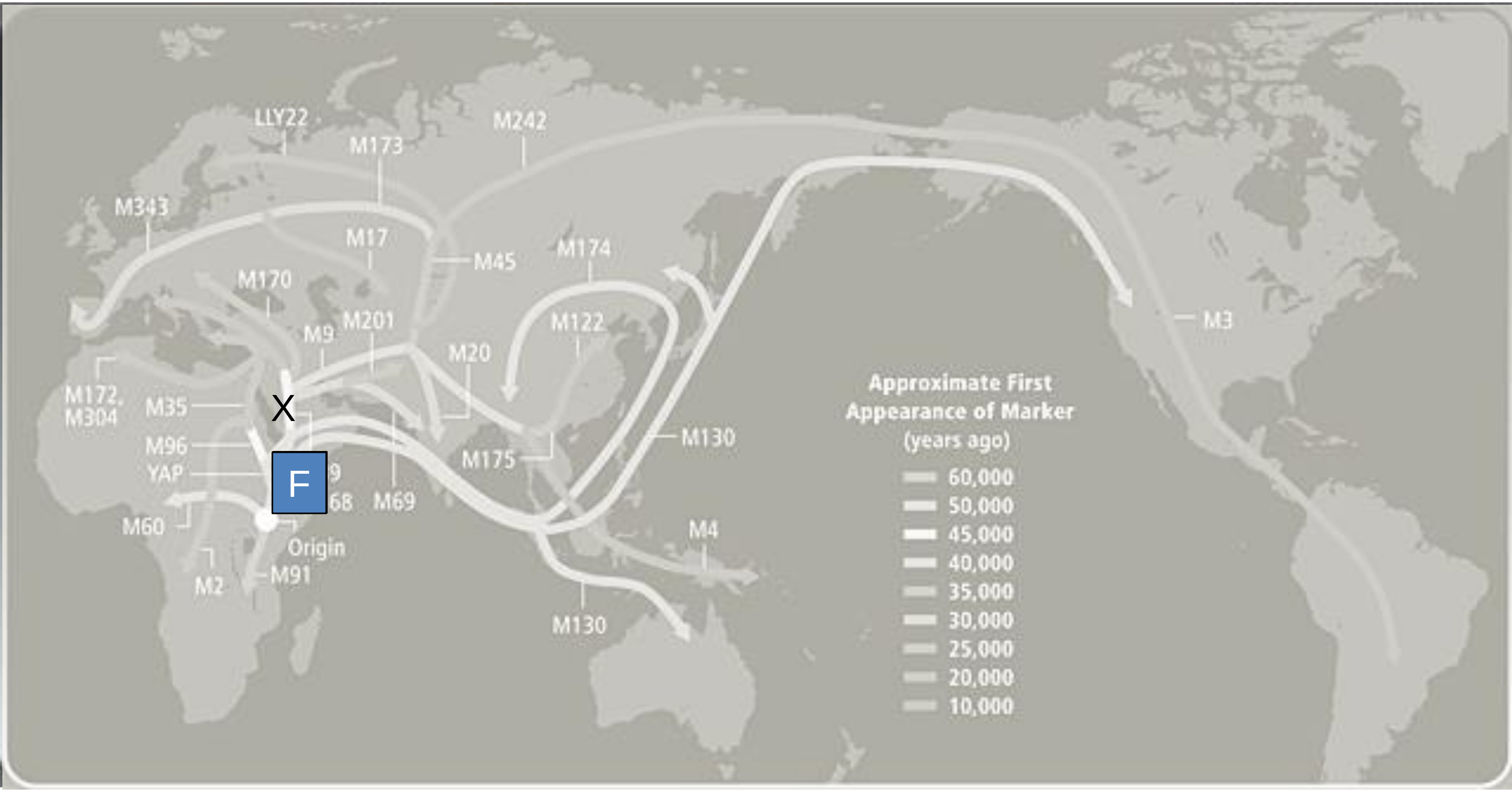
Nov 2013



416
420
Gc1F
asp – ala – thr – pro – thr
rs7041
Gc1S
glu – ala – thr – pro – thr
rs4855
Gc2
asp – ala – thr – pro – lys


Genotype
Phenotype
rs7041-T (Asp)
rs4588-C (Thr)
Gc1F
rs7041-G (Glu)
rs4588-C (Thr)
Gc1S
rs7041-T (Asp)
rs4588-A (Lys)
Gc2
= 25(OH)D
Black Homozygotes (N=658)
Gc1S 5.2% (n=34)
Gc2 2.1% (n=14)
Gc1F 92.7%
(n=610)
White Homozygotes (N=367)
Gc1F 6.0% (n=22)
Gc2 18.0%
(n=66)
Gc1S 76.0%
(n=279)

Human Migration Patterns out of Africa



Scientific American 2008

Healthy **A**ging in **N**eighborhoods of **D**iversity across the **L**ife **S**pan

- NIH-supported population-based cohort

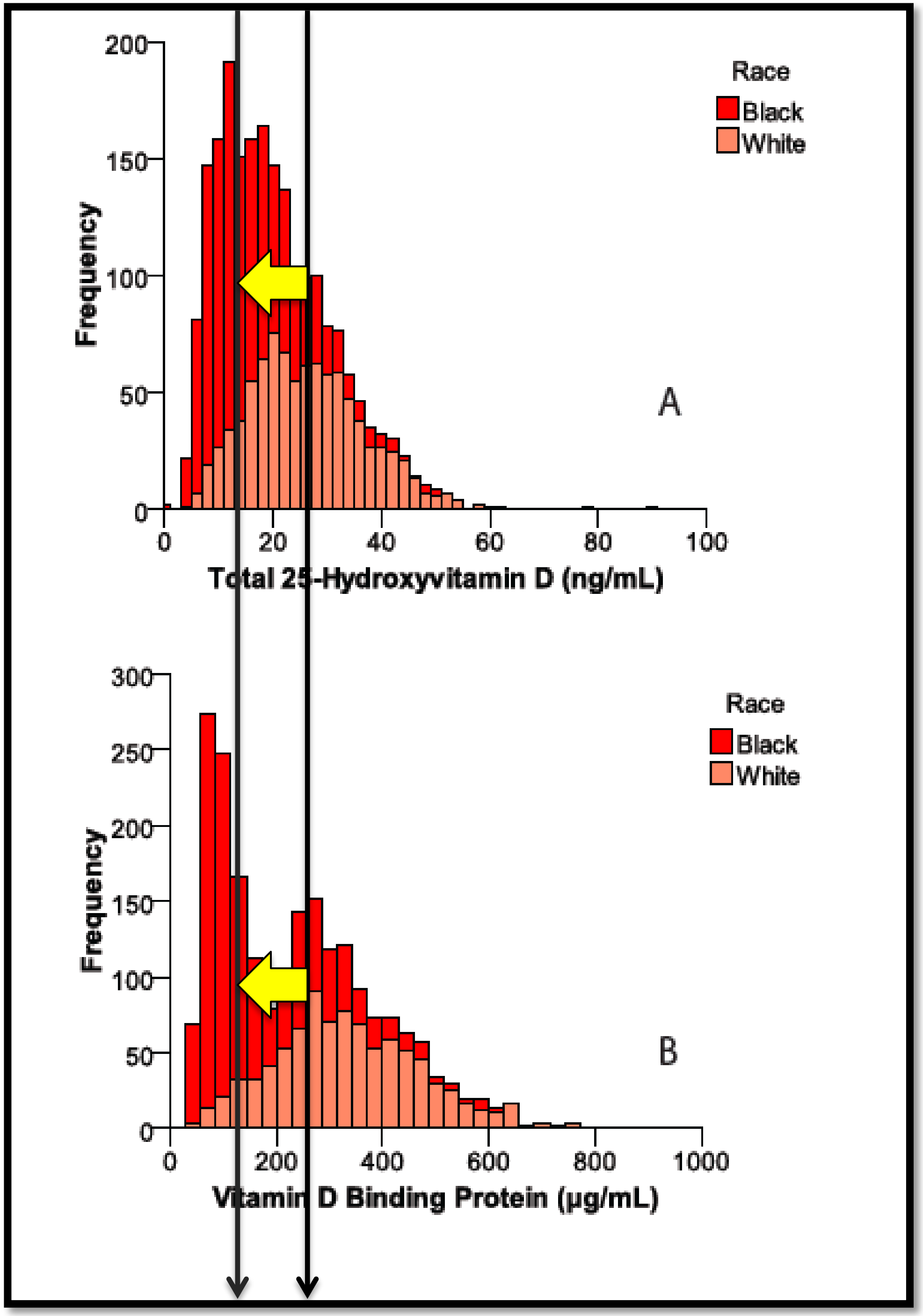
- White and African-American adults (30-64 years old) from Baltimore (~ 48 years of age, BMI ~ 29)

- 3,720 patients enrolled (2004 – 2008)

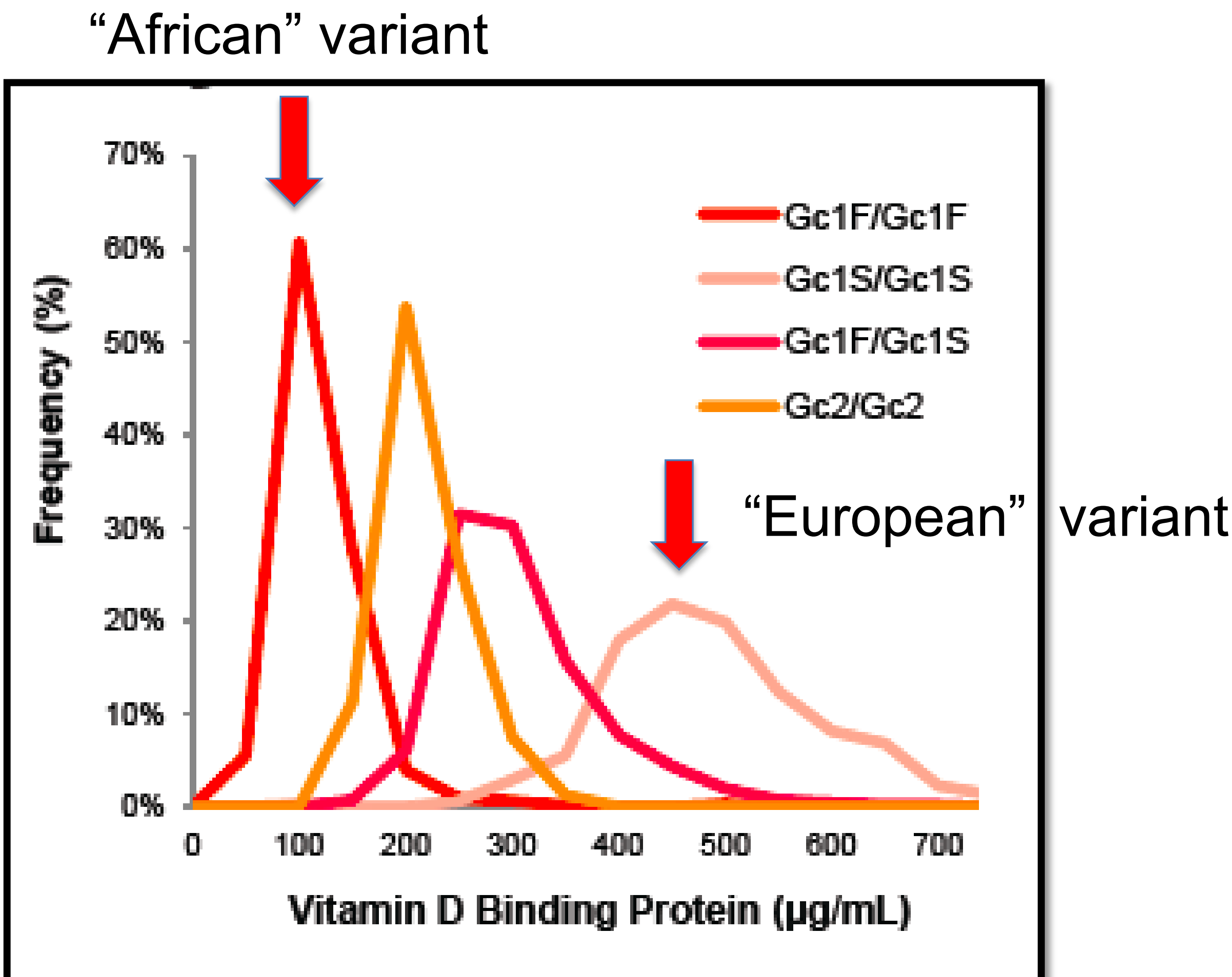
- Randomly samples within age, race, gender, and socioeconomic status

Total 25D Levels
“Left Shifted” in Blacks

D Binding Protein Levels
“Left Shifted” in Blacks

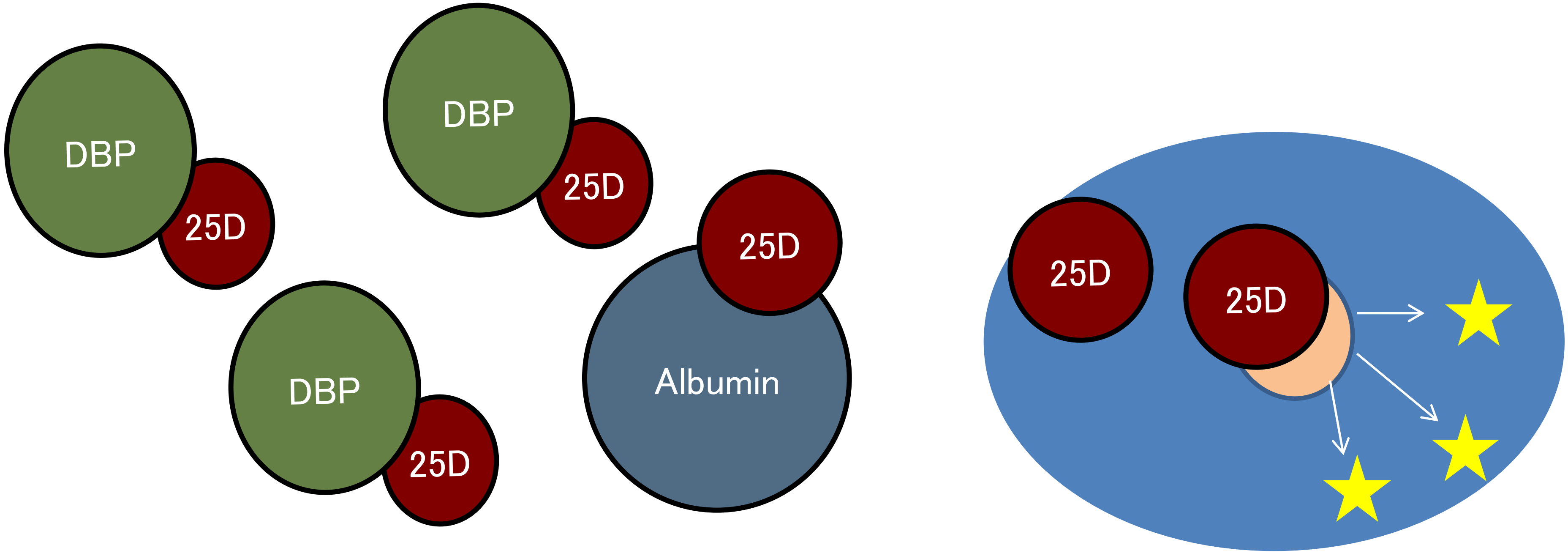


Serum DBP concentrations are influenced by Vitamin D binding protein genotype



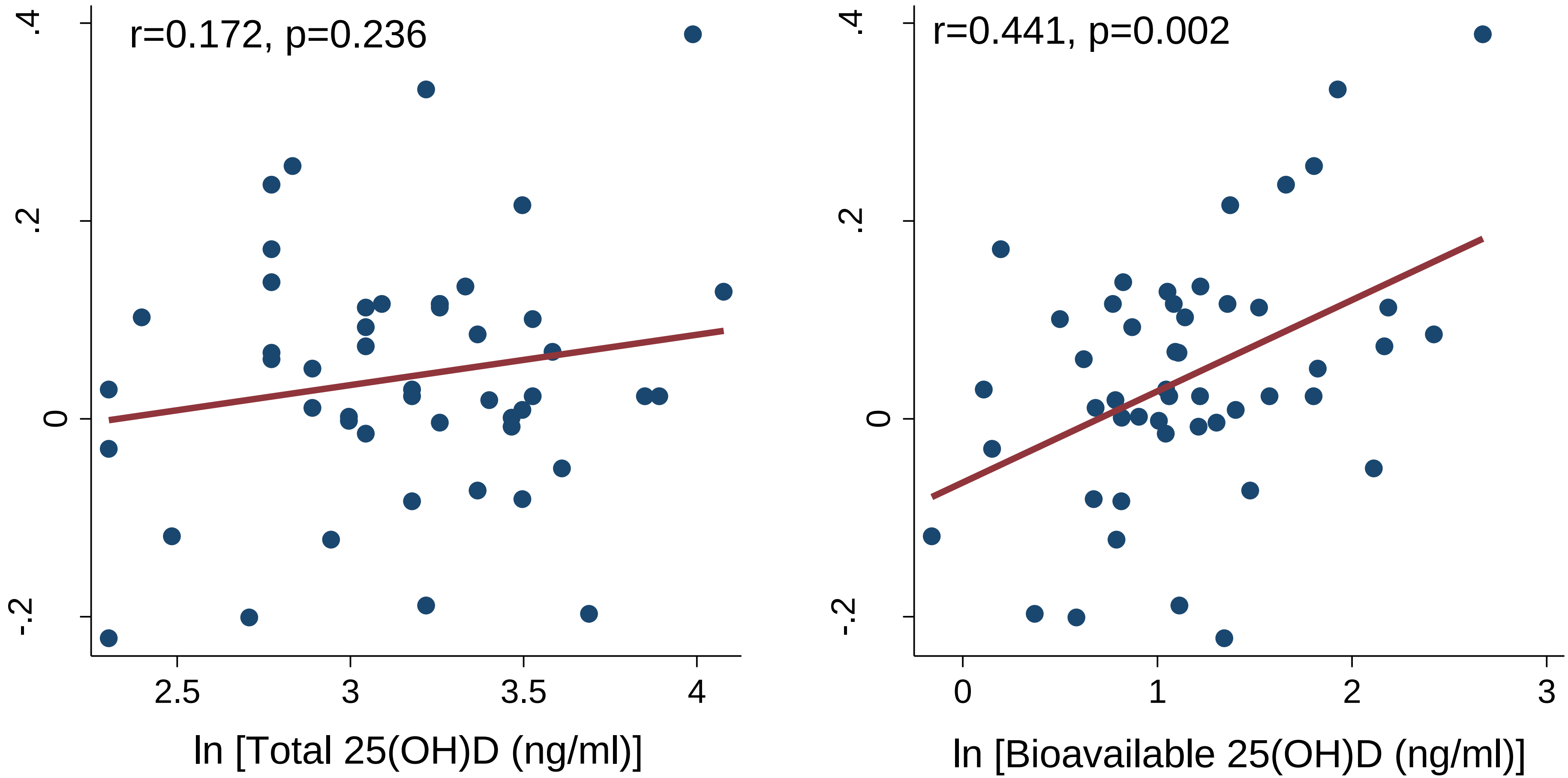
Free Hormone Hypothesis may be answer to racial paradox

Only UNBOUND hormones cross cell membranes and have biological action.



Yet, vitamin D deficiency is clinically defined as low TOTAL 25(OH)D levels

MACS Study: bioavailable 25D correlates with bone mineral density, total 25D does NOT



Powe et. al., J Bone Miner Res. 2011 PMID: 21416506

Calculating Bioavailable D

[Total D] = concentration of total 25-hydroxyvitamin D = $[D_{DBP}] + [D_{Alb}] + [D_{Free}]$

[Bio D] = concentration of bioavailable 25-hydroxyvitamin D = $[D_{Free}] + [D_{Alb}]$

$[D_{Alb}]$ = concentration of albumin-bound 25-hydroxyvitamin D

$[D_{DBP}]$ = concentration of D-binding protein-bound 25-hydroxyvitamin D

$[D_{Free}]$ = concentration of free (unbound) 25-hydroxyvitamin D

DBP_{1F} = Gc1F variant of the D-binding protein

DBP_{1S} = Gc1S variant of the D-binding protein

DBP_{2} = Gc2 variant of the D-binding protein

K_{alb} = affinity constant between 25-hydroxyvitamin D and albumin = $6 \times 10^5\ M^{-1}$

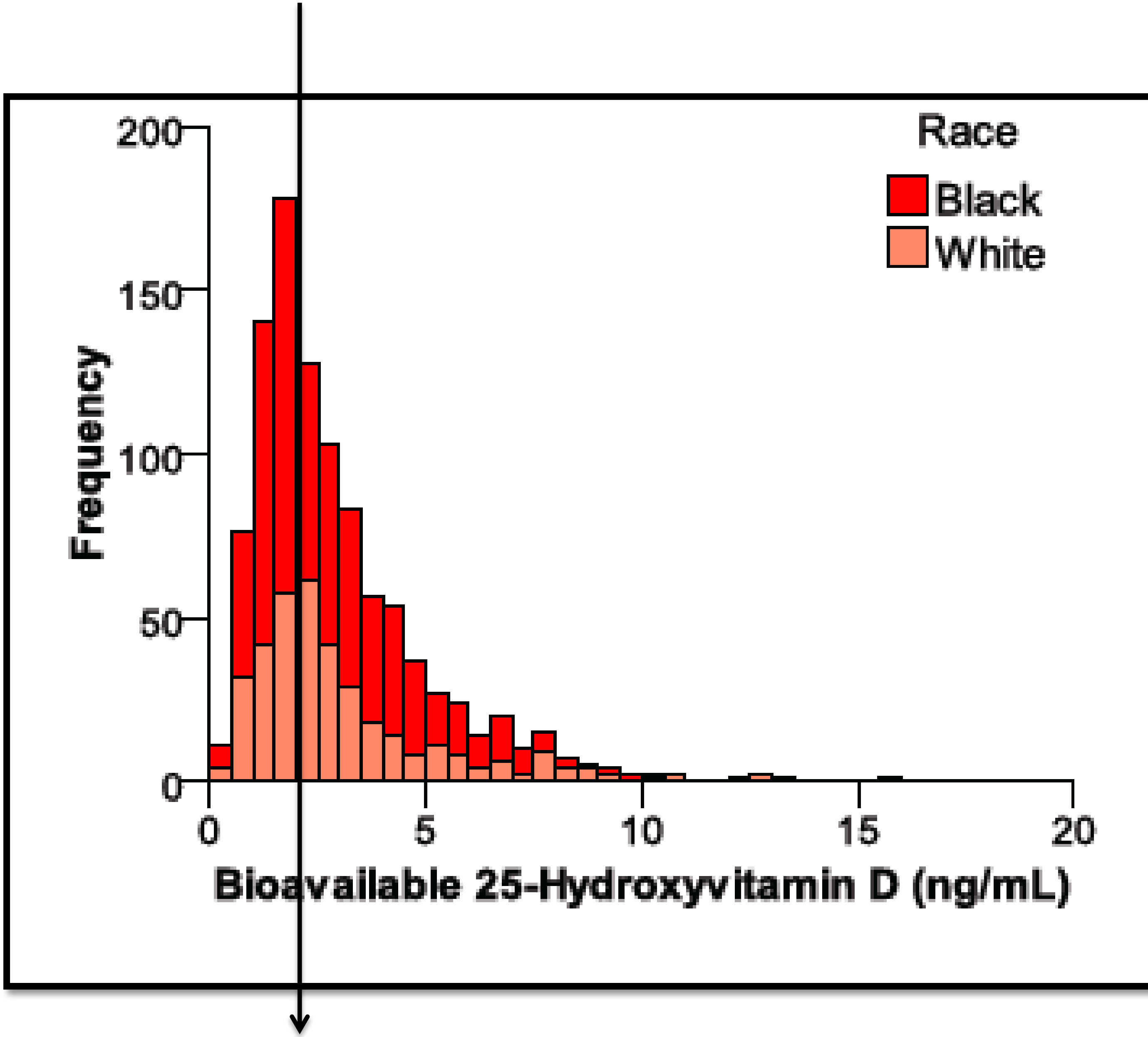
$KDBP_{1S}$ = affinity constant between 25-hydroxyvitamin D and DBP_{1S} = $0.6 \times 10^9\ M^{-1}$

$KDBP_{1F}$ = affinity constant between 25-hydroxyvitamin D and DBP_{1F} = $1.12 \times 10^9\ M^{-1}$

$KDBP_{2}$ = affinity constant between 25-hydroxyvitamin D and DBP_{2} = $0.36 \times 10^9\ M^{-1}$

Calculating Bioavailable D

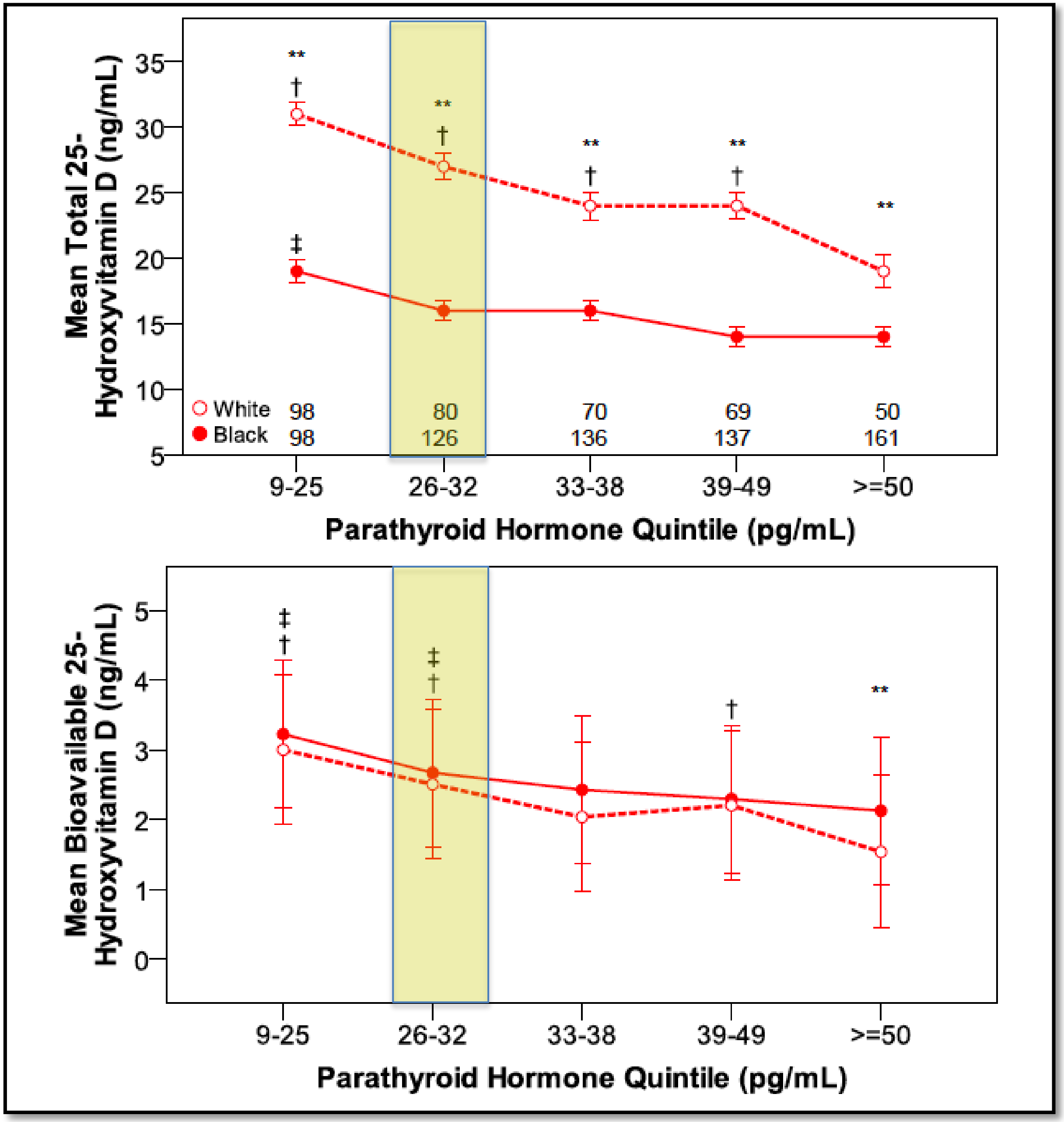
- 25(OH)D3 was measured by isotope dilutional LC-MS/MS in a CLIA-certified lab.
- Vitamin D binding protein was measured by RUO sandwich immunoassay (R&D Systems).
- Albumin was measured colorimetrically (Roche).
- Vitamin D binding protein genotyping was performed by TaqMan 5'-nuclease assay on ABI PRISM analyzers.



Bioavailable D levels similar in Blacks and Whites
(calculated, and in a subset directly measured)

For the same level of PTH, Blacks have lower Total 25 D levels compared with Whites

For the same level of PTH, Blacks and Whites have similar Bioavailable D levels



Scandinavian Journal of Clinical & Laboratory Investigation, 2013; Early Online: 1–7

informa
healthcare

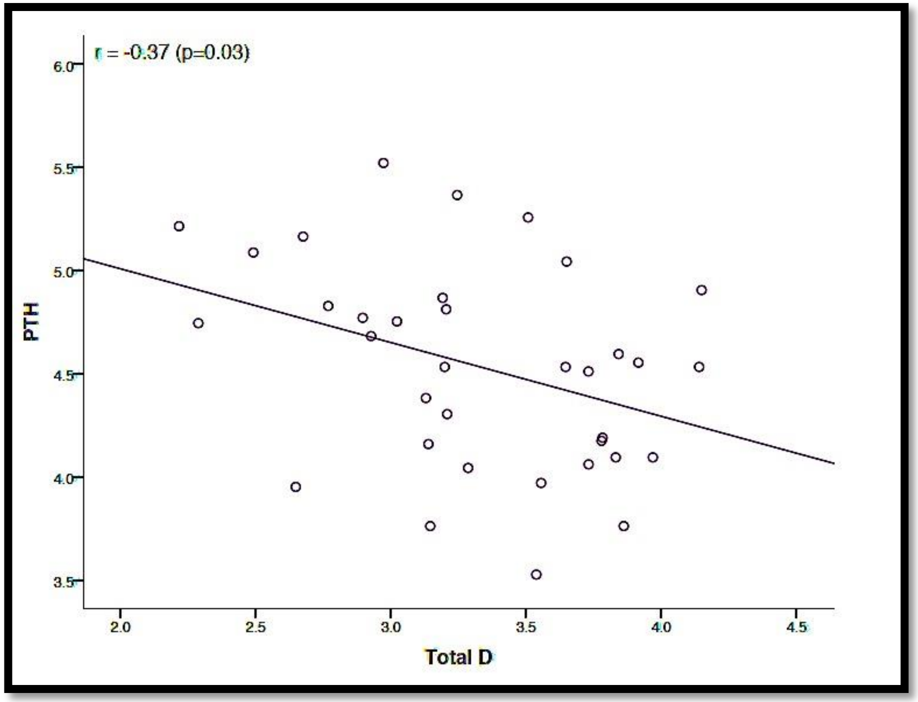
ORIGINAL ARTICLE

Serum free and bio-available 25-hydroxyvitamin D correlate better with bone density than serum total 25-hydroxyvitamin D

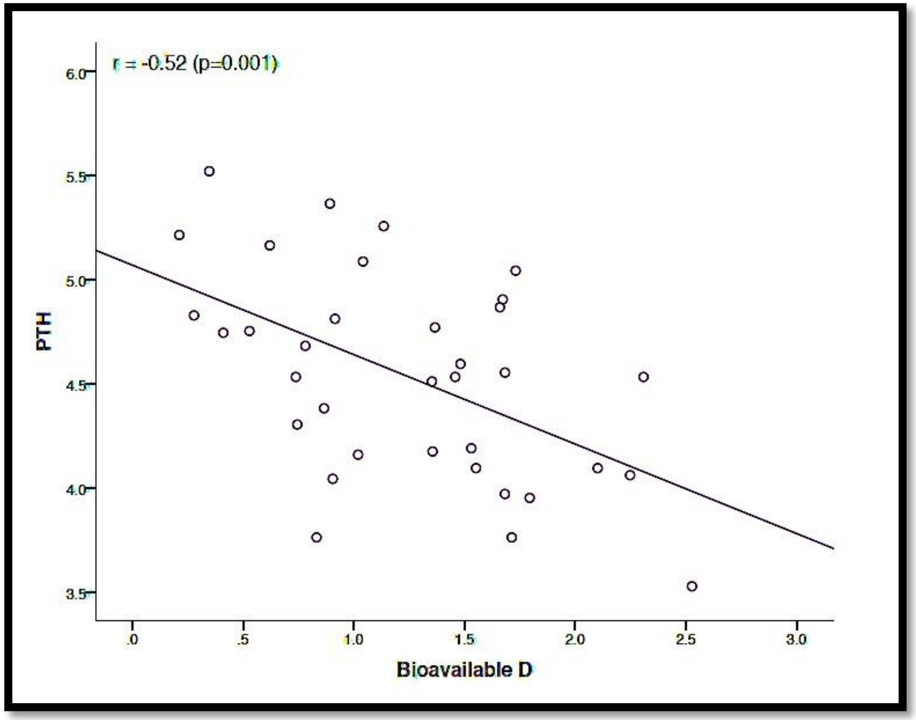
MARTIN S. JOHNSEN[1], GURI GRIMNES[1,2], YNGVE FIGENSCHAU[3], PETER A. TORJESEN[4], BJØRG ALMÅS[5] & ROLF JORDE[1,2]

[1]*Tromsø Endocrine Research Group, Department of Clinical Medicine, University of Tromsø, Tromsø,* [2]*Division of Internal Medicine, University Hospital of North Norway, Tromsø,* [3]*Institute of Medical Biochemistry, University of Tromsø and Department of Laboratory Medicine, University Hospital of North Norway, Tromsø,* [4]*Hormone Laboratory, Department of Endocrinology, Oslo University Hospital, Oslo, and* [5]*Hormone Laboratory, Haukeland University Hospital, Bergen, Norway*

35 CKD patients GFR ~ 35-40 ml/min, PTH ~ 2x normal



PTH and Total D
r= - 0.37, p= 0.03



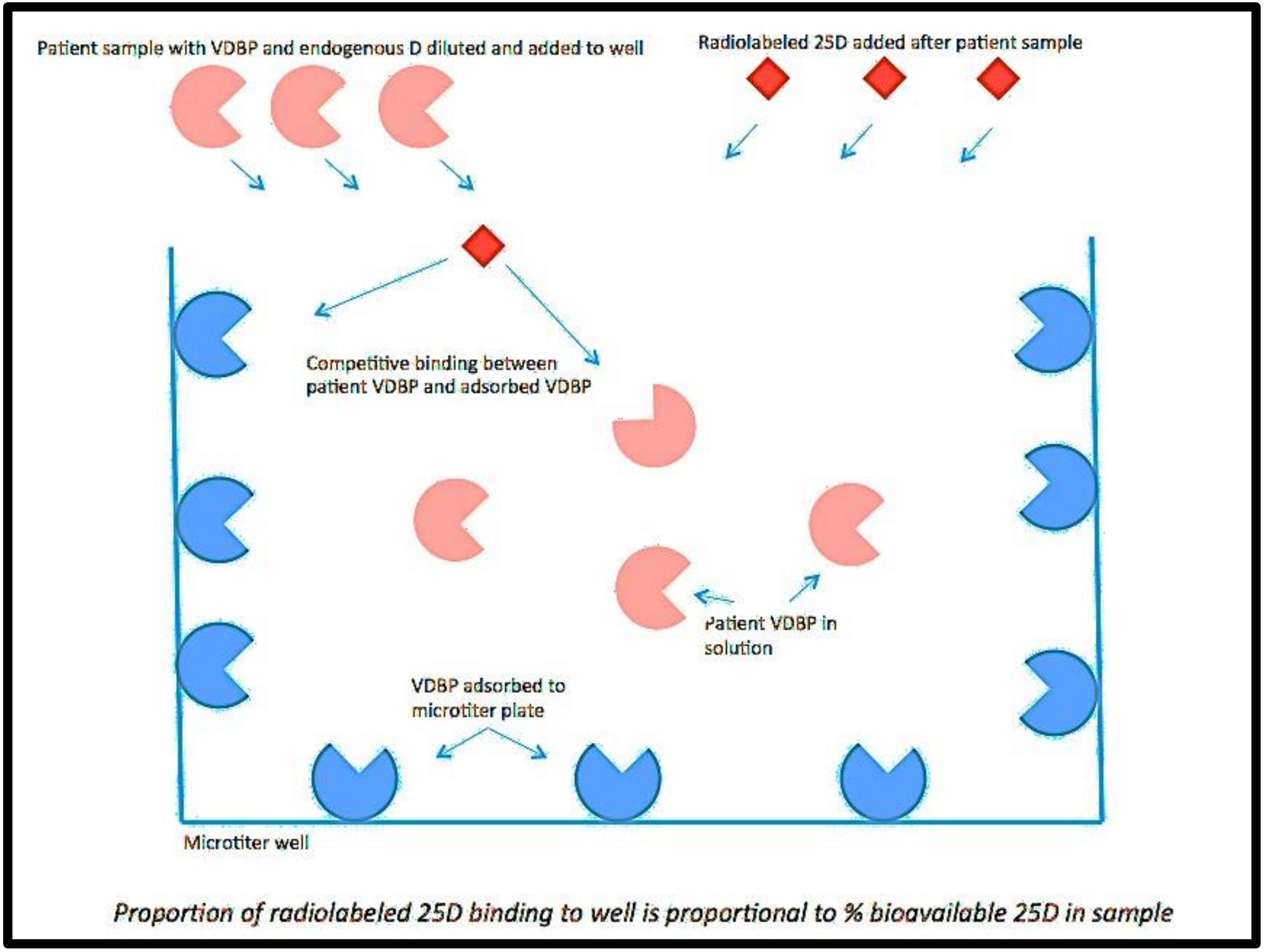
PTH and Bioavailable D
r= - 0.52, p= 0.001

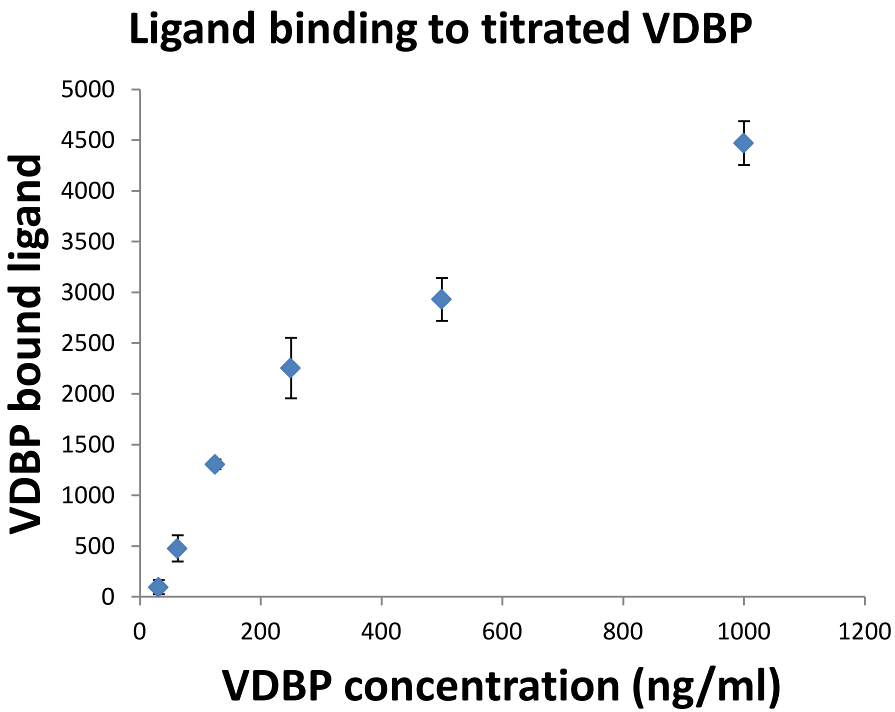
Unpublished

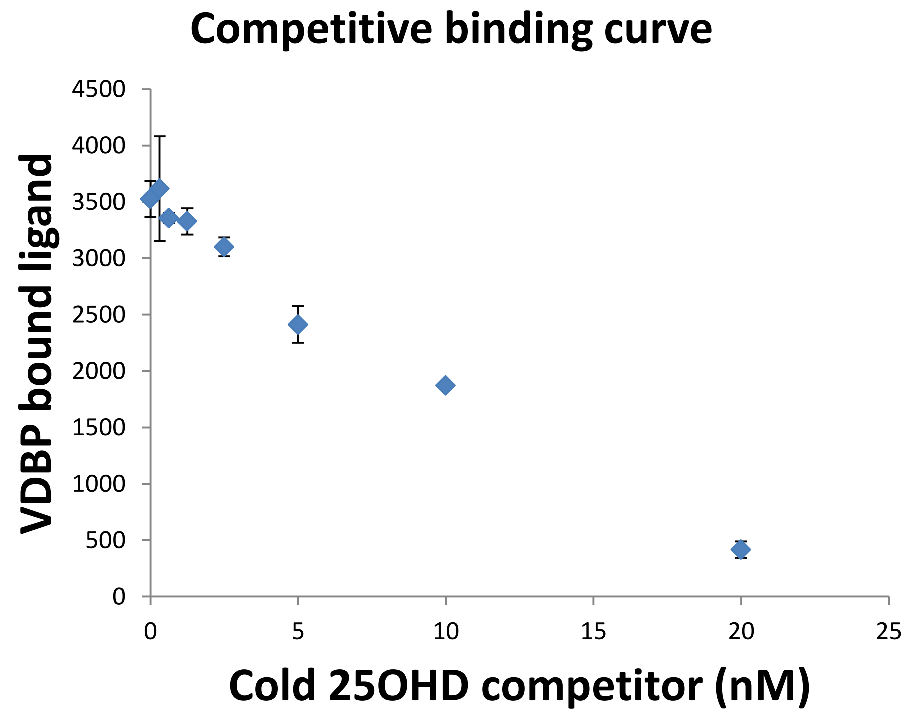
Summary

- Numerous therapeutic trials show benefits of vitamin D supplementation on bone mineral and cardiovascular health.
- Evidence that measurements of total serum 25-hydroxyvitamin D levels are predictive of disease is less consistent, especially in African Americans and other populations.
- Bioavailable 25D may be a better indicator of vitamin D sufficiency.
- Calculated bioavailable 25D assays are clinically impractical because of need for VDBP genotyping.
- Direct measurement of bioavailable 25D is needed.

Bioavailable Vitamin D Radioligand Competitive Binding Assay




Ligand binding to titrated VDBP
VDBP bound ligand
VDBP concentration (ng/ml)
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
0
200
400
600
800
1000
1200


Competitive binding curve
VDBP bound ligand
Cold 25OHD competitor (nM)
0
500
1000
1500
2000
2500
3000
3500
4000
4500
0
5
10
15
20
25

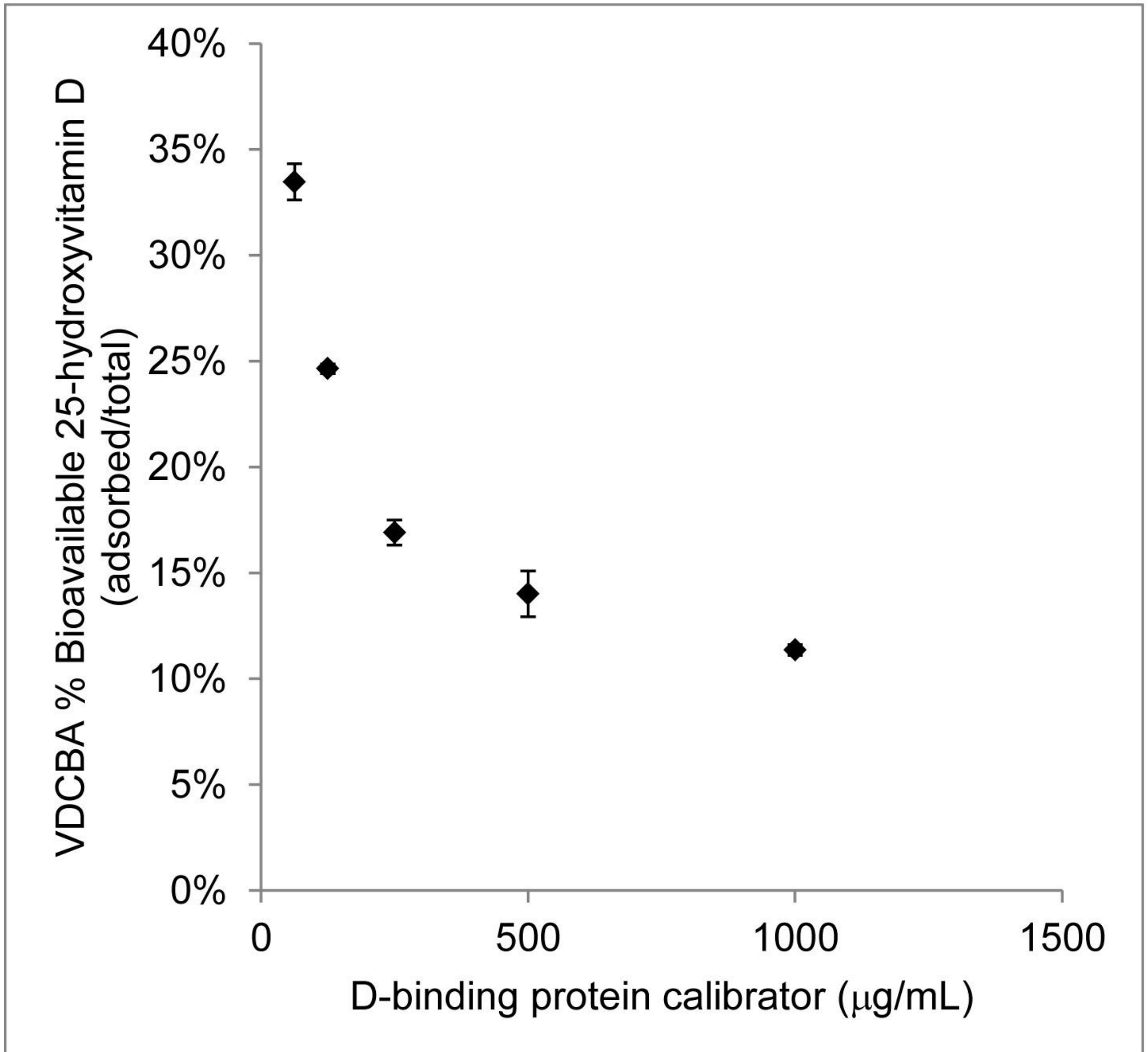


Figure S2. *Direct measurement of % bioavailable 25*-hydroxyvitamin *D in presence of increasing concentrations of purified* D-binding protein *calibrator*. Reactions contained fixed amount of 25-hydroxyvitamin D radioligand, 5% serum albumin, and increasing concentrations of purified D-binding protein calibrator (as indicated on x-axis). Y-axis shows % bioavailable 25-hydroxyvitamin D calculated from amount of adsorbed radioligand as a percentage of the total radioligand added to reaction. Each data point represents the average of triplicate measurements; error bars indicate standard deviation of replicates.

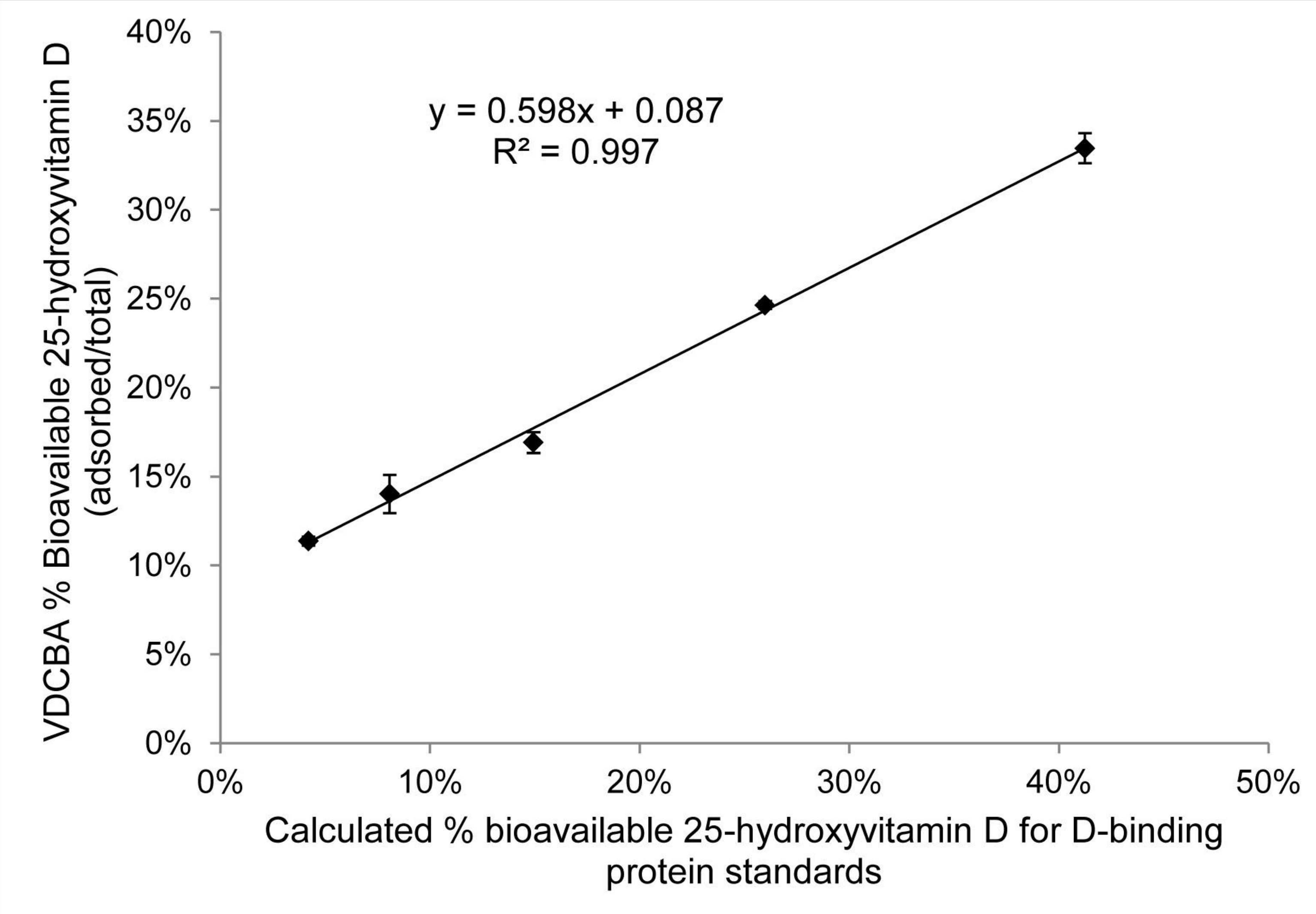


Figure S3. *Vitamin D radioligand competitive binding assay standard curve for conversion of radioligand binding measurements into equivalent calculated bioavailable 25*-hydroxyvitamin *D values*. % bioavailable 25-hydroxyvitamin D values for the D-binding protein calibrator mixtures shown in Fig. S2 were calculated based upon these solutions' known concentrations of serum albumin, 25-hydroxyvitamin D radioligand, and purified D-binding protein. Calculated % bioavailable 25-hydroxyvitamin D values were plotted against the directly measured % bioavailable 25-hydroxyvitamin D values shown in Fig. S2. Each data point represents the average of triplicate measurements; error bars indicate standard deviation of replicates.

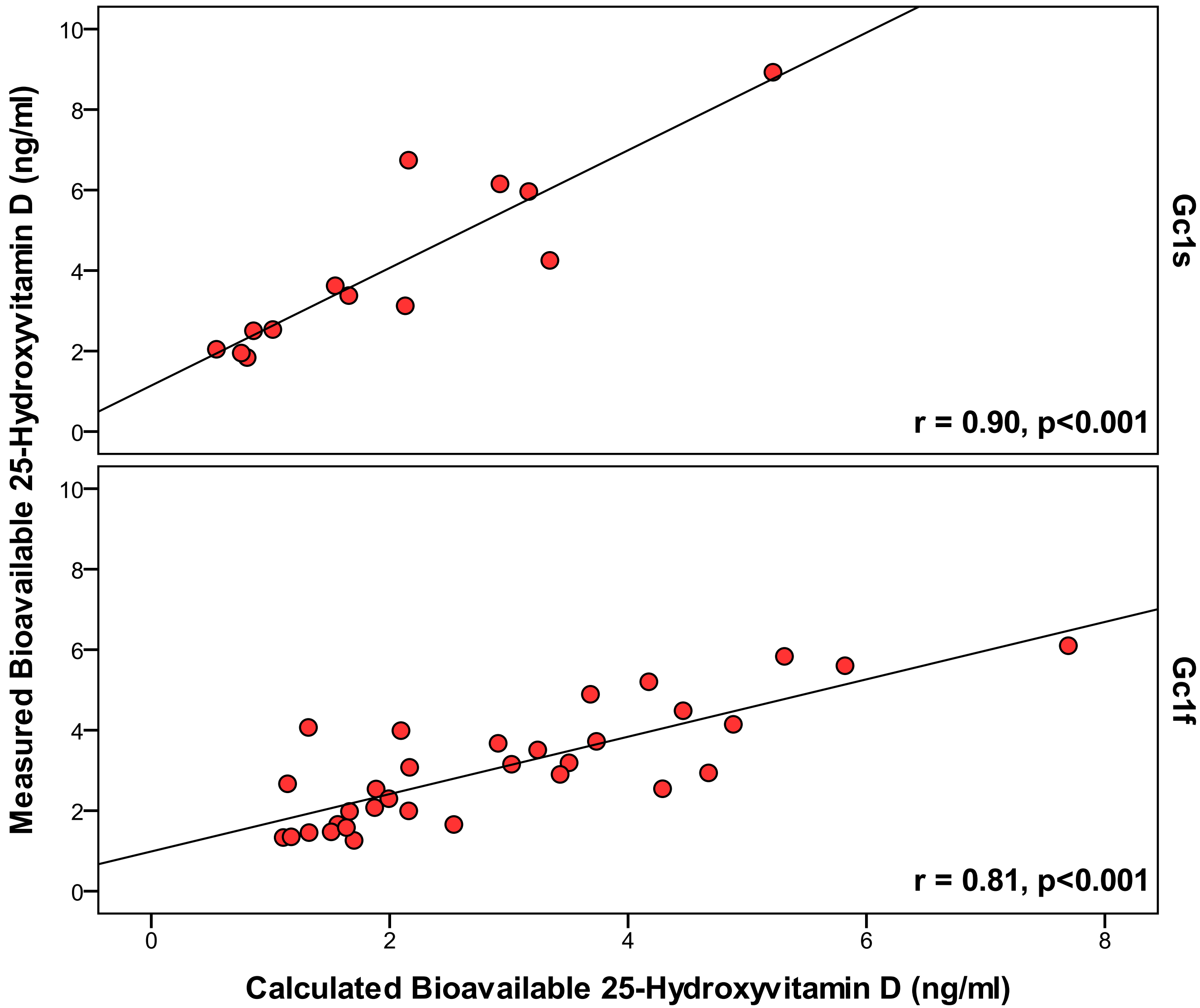
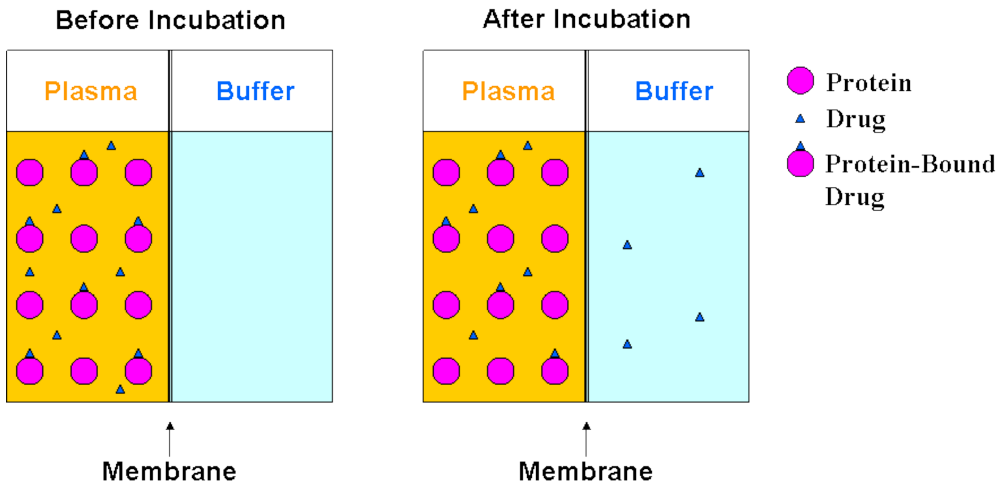


Figure S4*. Correlations between calculated bioavailable 25-*hydroxyvitamin *D concentrations in homozygous subjects compared to measurements by radioligand competitive binding assay*. Direct measurement of % bioavailable 25-hydroxyvitamin D concentrations were performed using radioligand binding assay on a subset of 46 HANDLS subjects homozygous for Gc1F or Gc1S. Direct measurements were transformed into their calculated bioavailable 25-hydroxyvitamin D equivalents using the calibrator curve obtained in Fig. S2 ($y = 0.598x + 0.087$). Absolute concentrations of bioavailable 25-hydroxyvitamin D (in ng/mL) were obtained by multiplying % bioavailable 25-hydroxyvitamin D values by the subjects' LC-MS/MS measured serum total 25-hydroxyvitamin D concentrations. The directly measured bioavailable 25-hydroxyvitamin D concentrations (y-axis) were then plotted against their corresponding calculated bioavailable 25-hydroxyvitamin D values (x-axis).

Future of Bioavailable Vitamin D

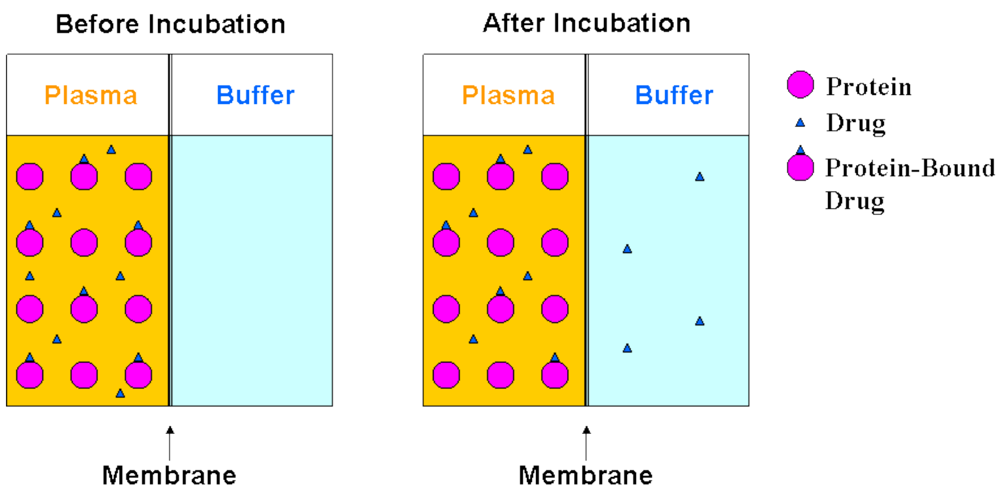
- Evidence is growing that bioavailable 25D may be better indicator of vitamin D sufficiency.
- Direct assay for bioavailable 25D needed because calculated methods impractical/biased
- Although radioligand binding assays may work, clinical labs are unlikely to bring this technology back.
- We are continuing to work on this!

Bioavailable 25D separation techniques



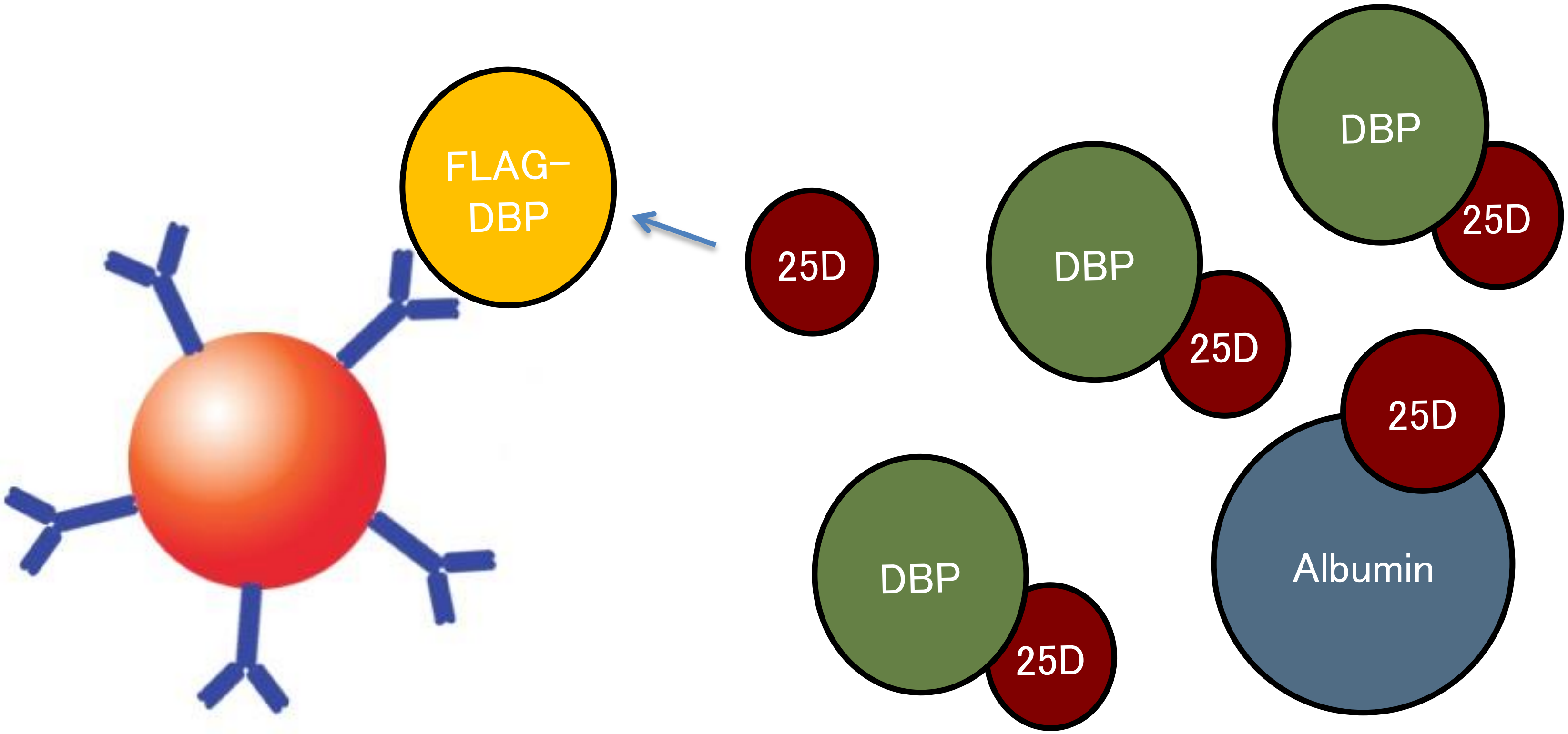
Equilibrium dialysis

Bioavailable 25D separation techniques



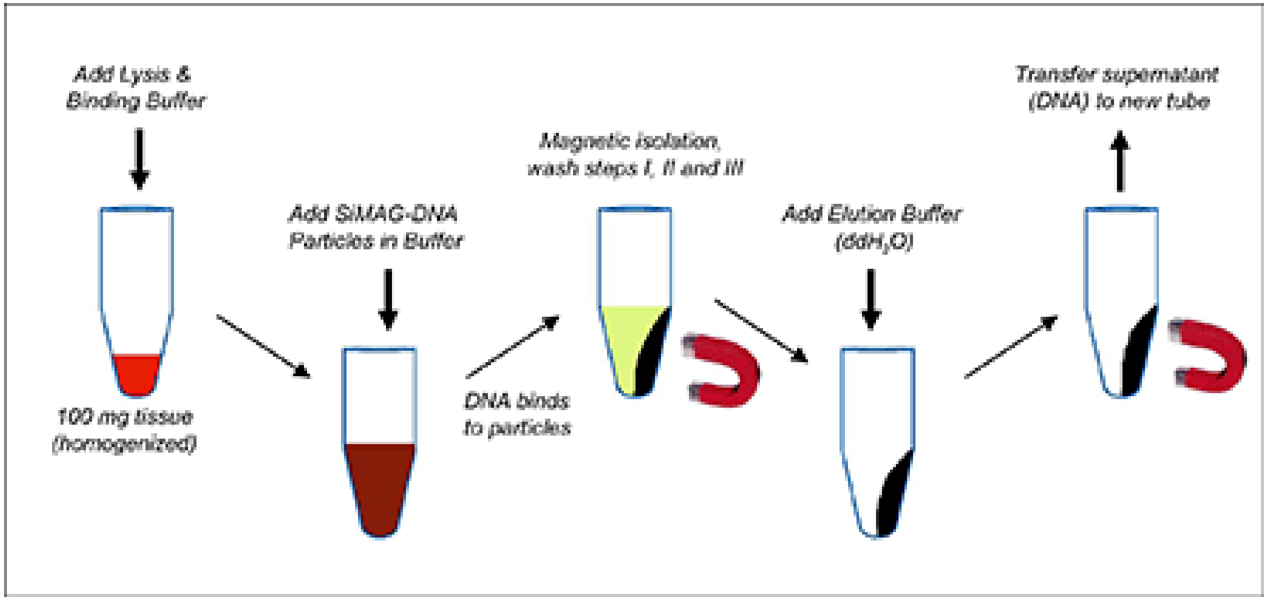
Centrifugal ultrafiltration
(Steve Soldin – NIH)

Bioavailable 25D separation techniques

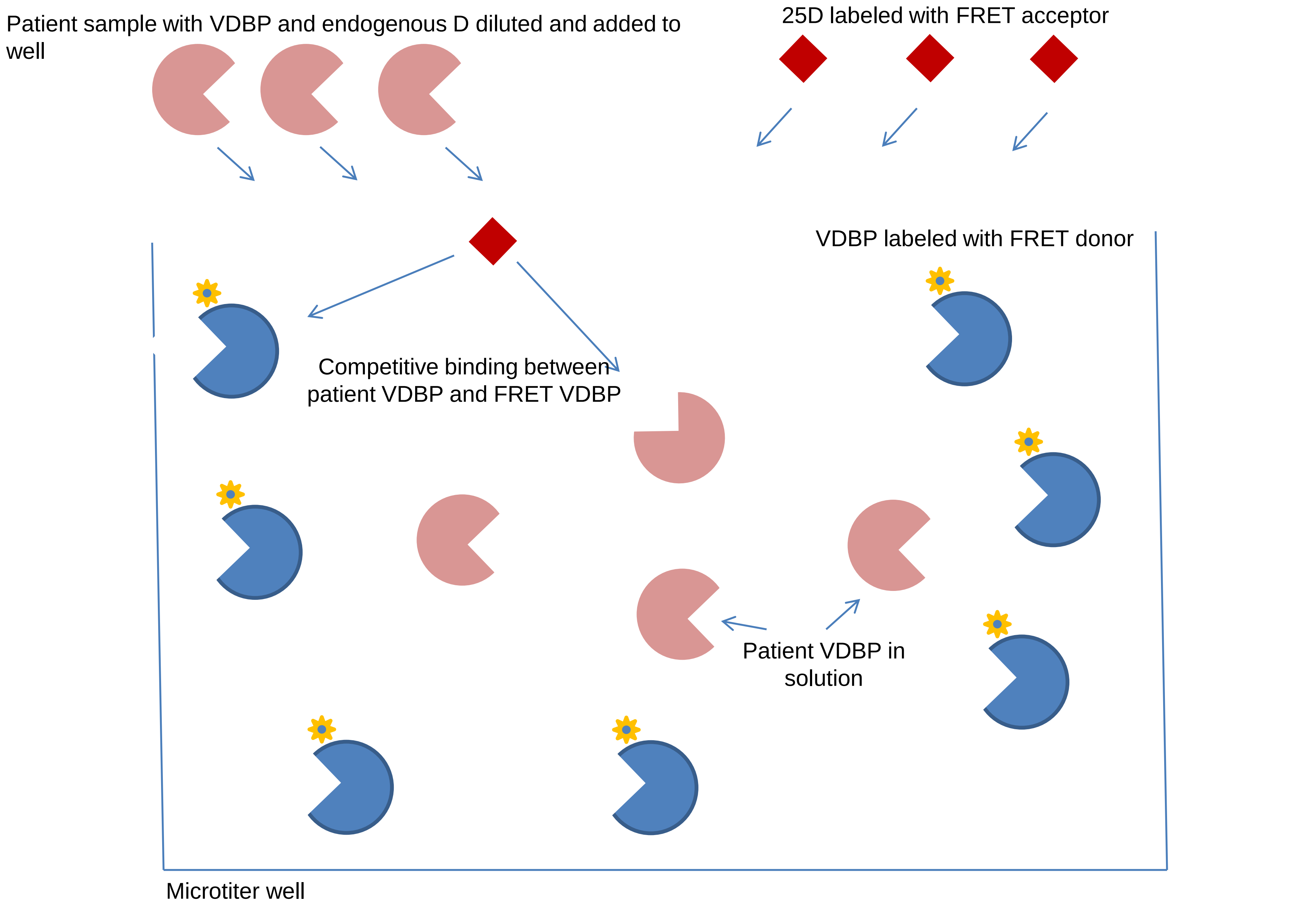


Extraction with beads coated with FLAG-tagged recombinant DBP

Bioavailable 25D separation techniques

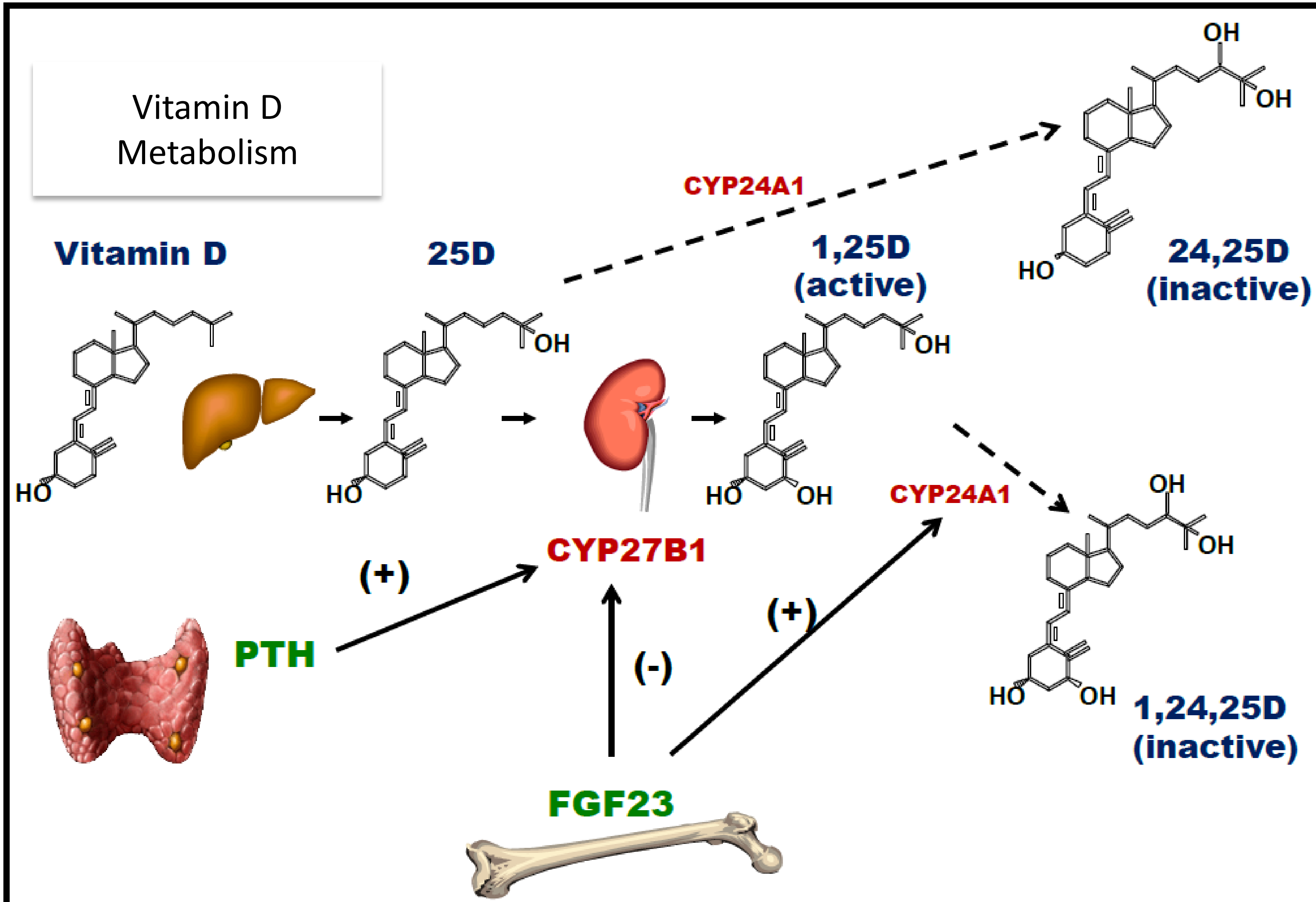


Extraction with magnetized charcoal



Proportion of FRET-25D binding to FRET-VDBP is proportional to % bioavailable 25D

Are levels of 24,25D3 or the ratio of 24,25D3-to-25D3 another marker of vitamin D adequacy?

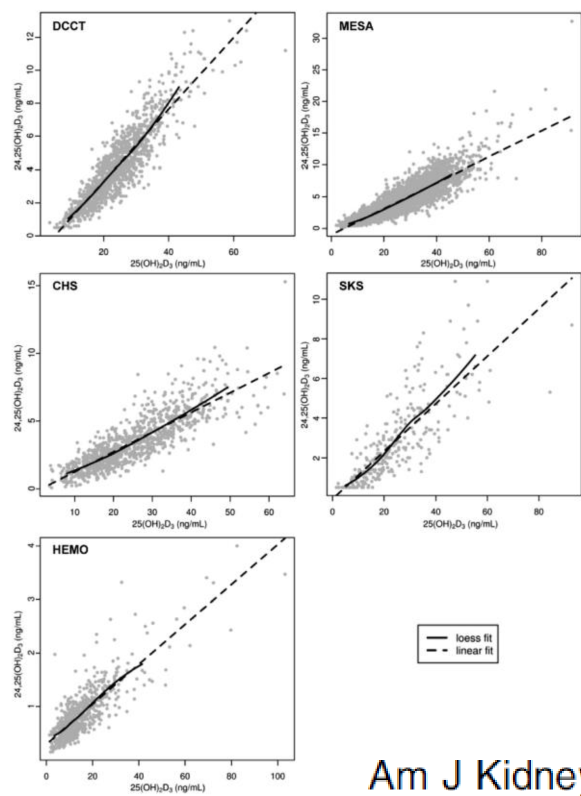


Patients with functional deficiency of active 1,25D3 have decreased ratio of 24,25D3 to 25D3

Table 1. LC-MS/MS Analysis of Vitamin D Metabolites in Patients With Hypercalcemia

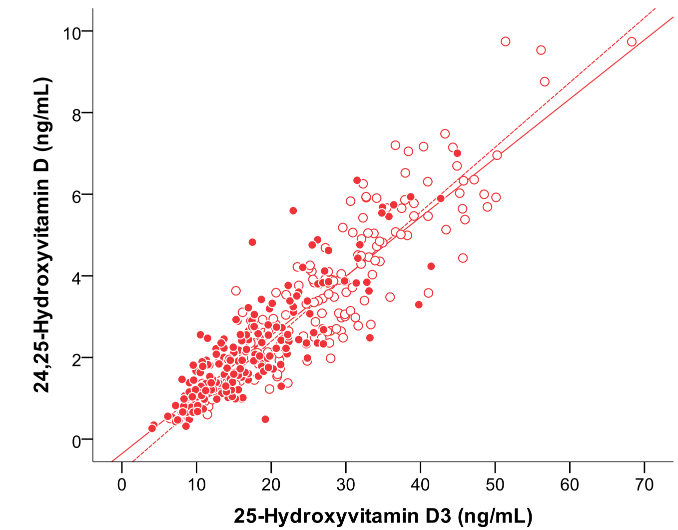
Patient	25-OH-D_3, nmol/L	24,25-$(OH)_2D_3$, nmol/L	25-OH-D_3 to 24,25-$(OH)_2D_3$ ratio
IIH1	94.8	0.9	98.7
IIH2	81.2	0.7	112.8
Hypervitaminosis D	420.0	34.0	12.35
Control	53.5	5.0	10.6

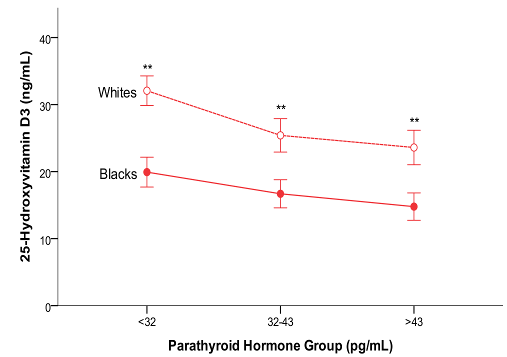
Kaufmann et al Clinical Utility of Simultaneous Vitamin D Assays J Clin Endocrinol Metab, July 2014, 99(7):2567–2574

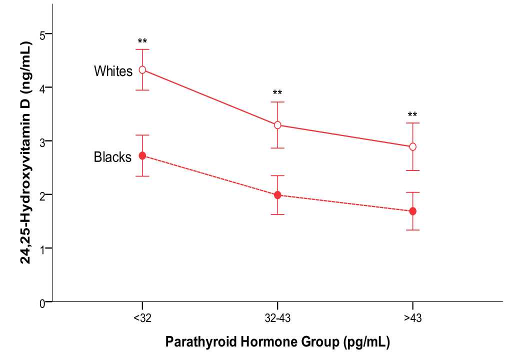


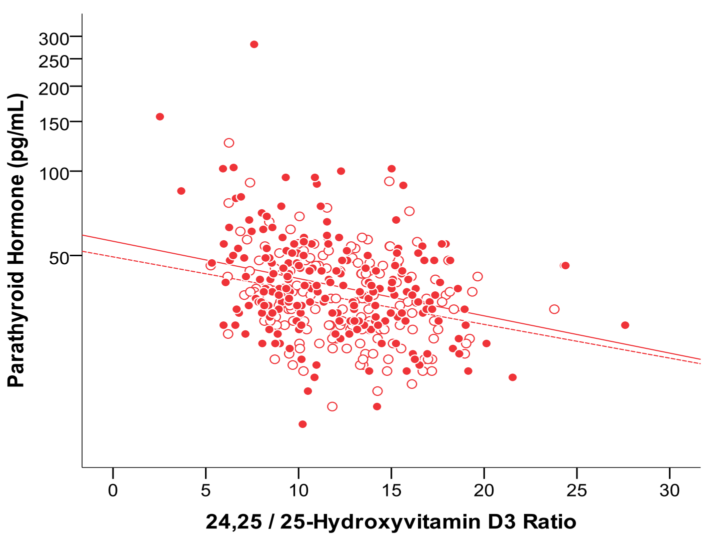
Am J Kidney Dis. 2014;64(2):187-197

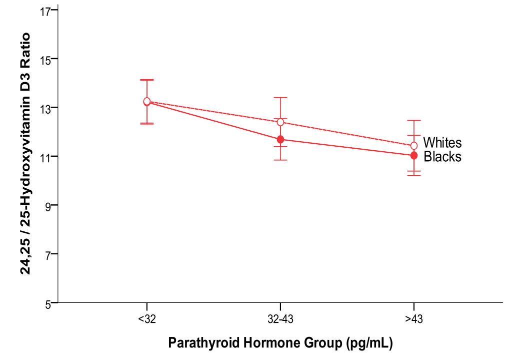
Although Black Americans have much lower serum 25D concentrations, their 24/25D ratios are same as whites











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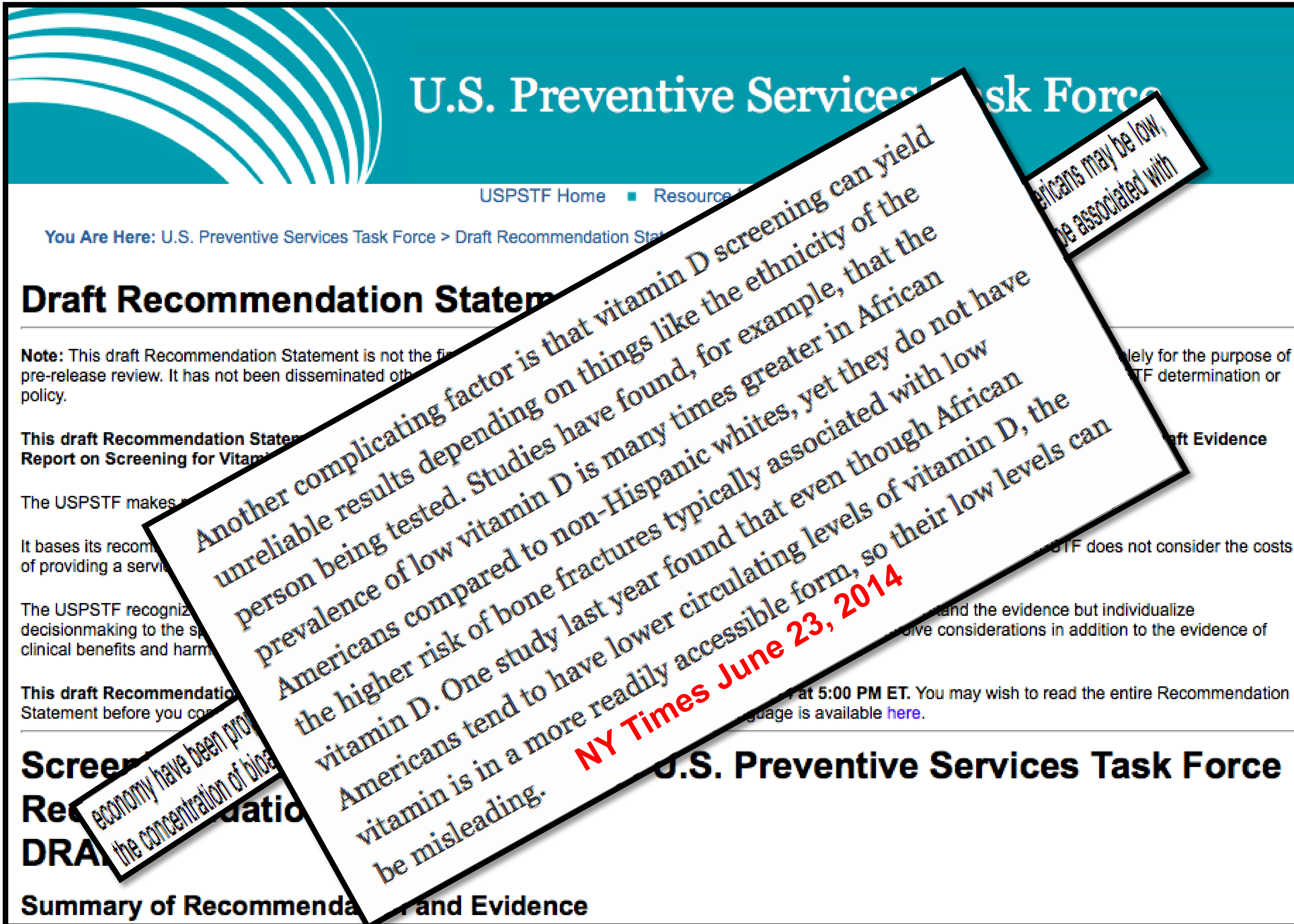
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Another complicating factor is that vitamin D screening can yield unreliable results depending on things like the ethnicity of the person being tested. Studies have found, for example, that the prevalence of low vitamin D is many times greater in African Americans compared to non-Hispanic whites, yet they do not have the higher risk of bone fractures typically associated with low vitamin D. One study last year found that even though African Americans tend to have lower circulating levels of vitamin D, the vitamin is in a more readily accessible form, so their low levels can be misleading.
NY Times June 23, 2014

Summary (cont.)

- Vitamin D supplements are beneficial for health.
- Measurement of total serum 25-hydroxyvitamin D levels may not predict vitamin D deficiency
- Bioavailable 25D may be a better indicator of vitamin D sufficiency.
- Calculated bioavailable 25D assays are clinically impractical because of need for VDBP genotyping.
- Direct measurement of bioavailable 25D are needed.
- Measurement of 24/25D ratio may be alternative functional marker for Vitamin D deficiency

Summary of **clinical** implications

- Vitamin D supplements are beneficial for health.
- Measurement of total serum 25-hydroxyvitamin D levels may not predict vitamin D deficiency *in all populations*.
- Bioavailable 25D or other vitamin D metabolite measurements *may* be better indicators of vitamin sufficiency.
- In light of new evidence, especially with regards to patients with African ancestry, ***we need to reconsider the significance of our reference intervals – but further investigation is needed before clinical recommendations can be made.***

How do we answer these questions, how do we advance this field?

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