Vitamin D testing

Quo vadis?

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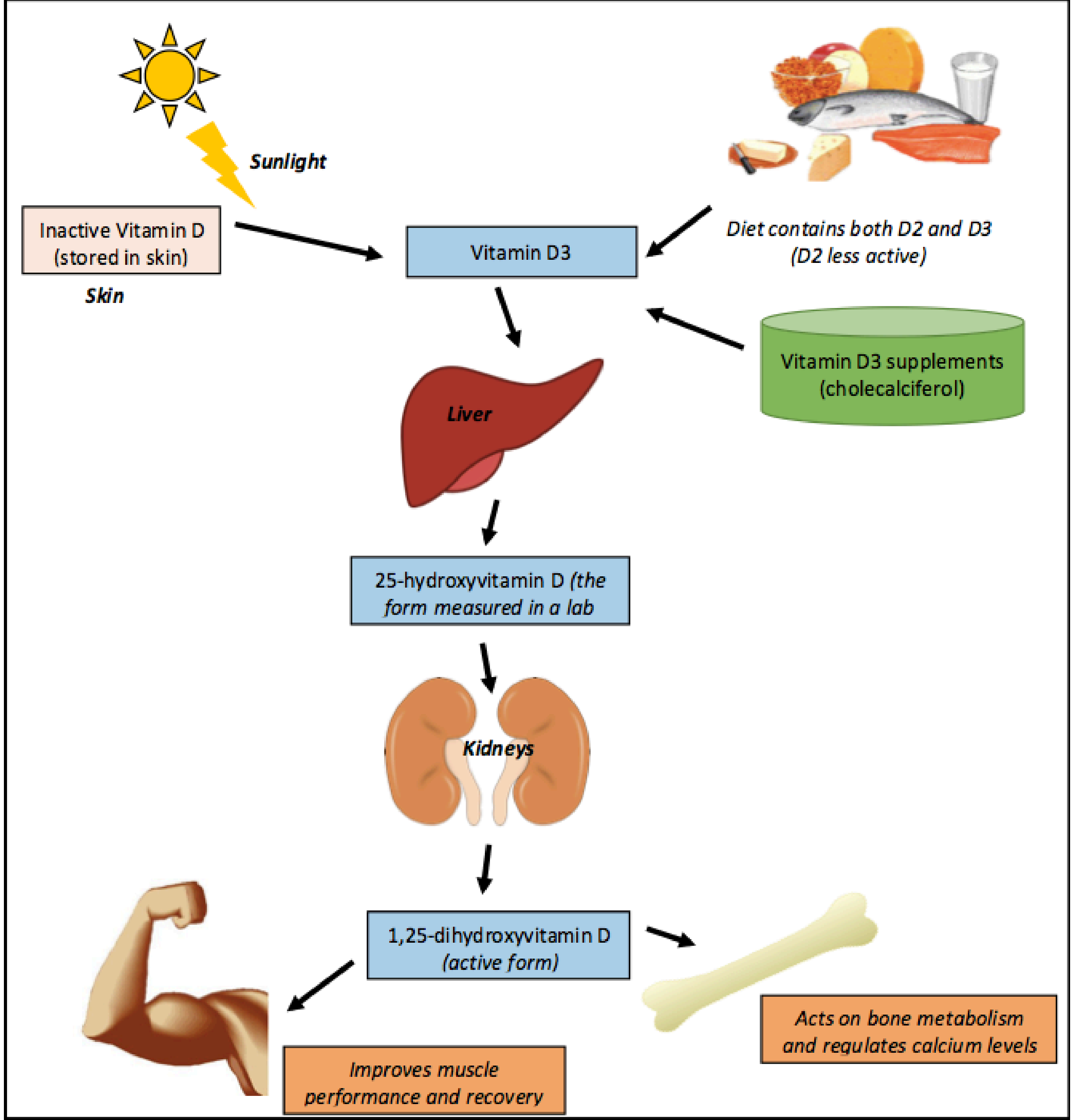
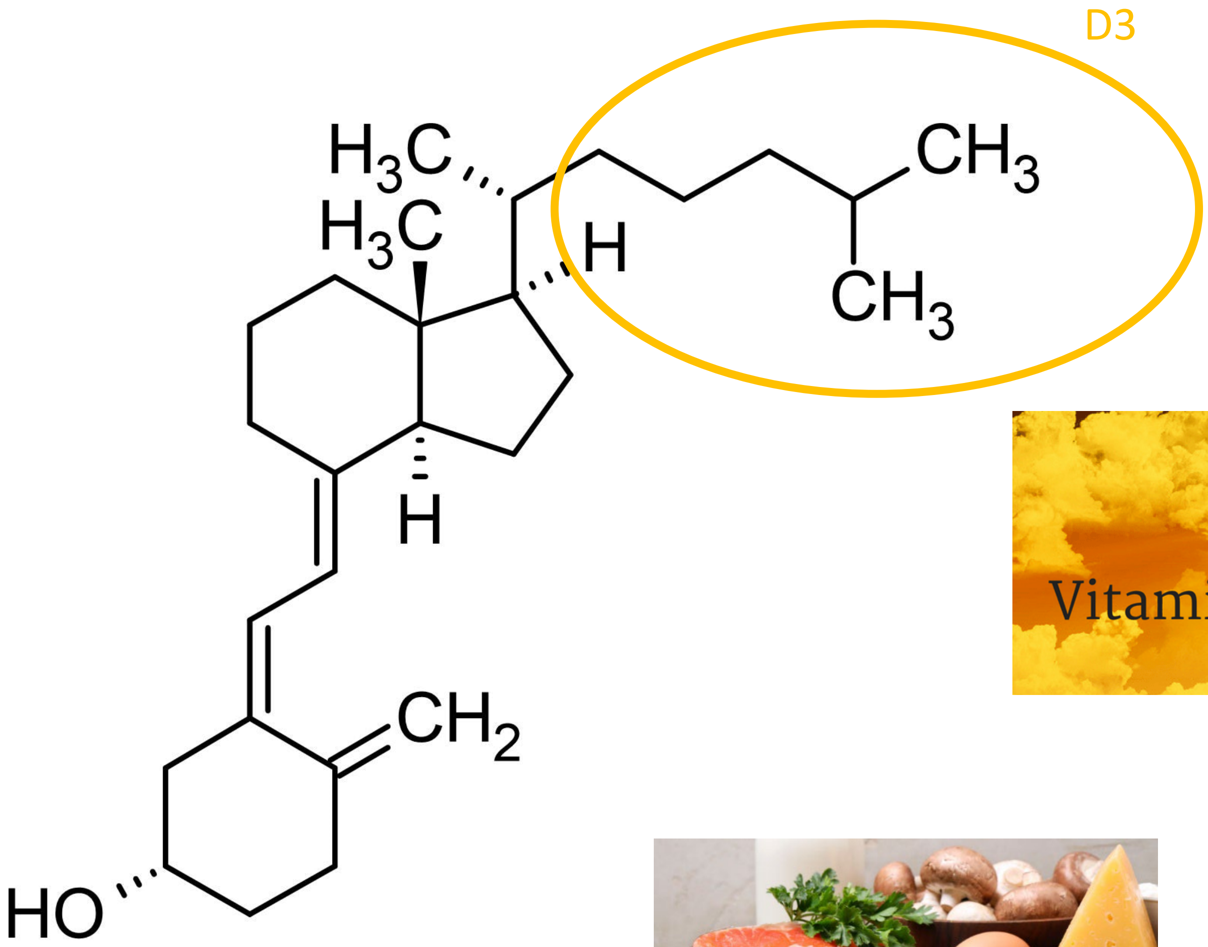
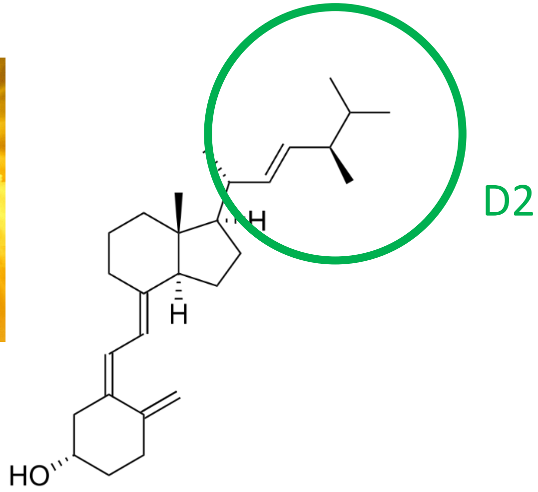
Klinische Biologie
UZ Leuven


Sunlight
Inactive Vitamin D (stored in skin)
Skin
Vitamin D3
Diet contains both D2 and D3 (D2 less active)
Vitamin D3 supplements (cholecalciferol)
Liver
25-hydroxyvitamin D (the form measured in a lab
Kidneys
1,25-dihydroxyvitamin D (active form)
Improves muscle performance and recovery
Acts on bone metabolism and regulates calcium levels

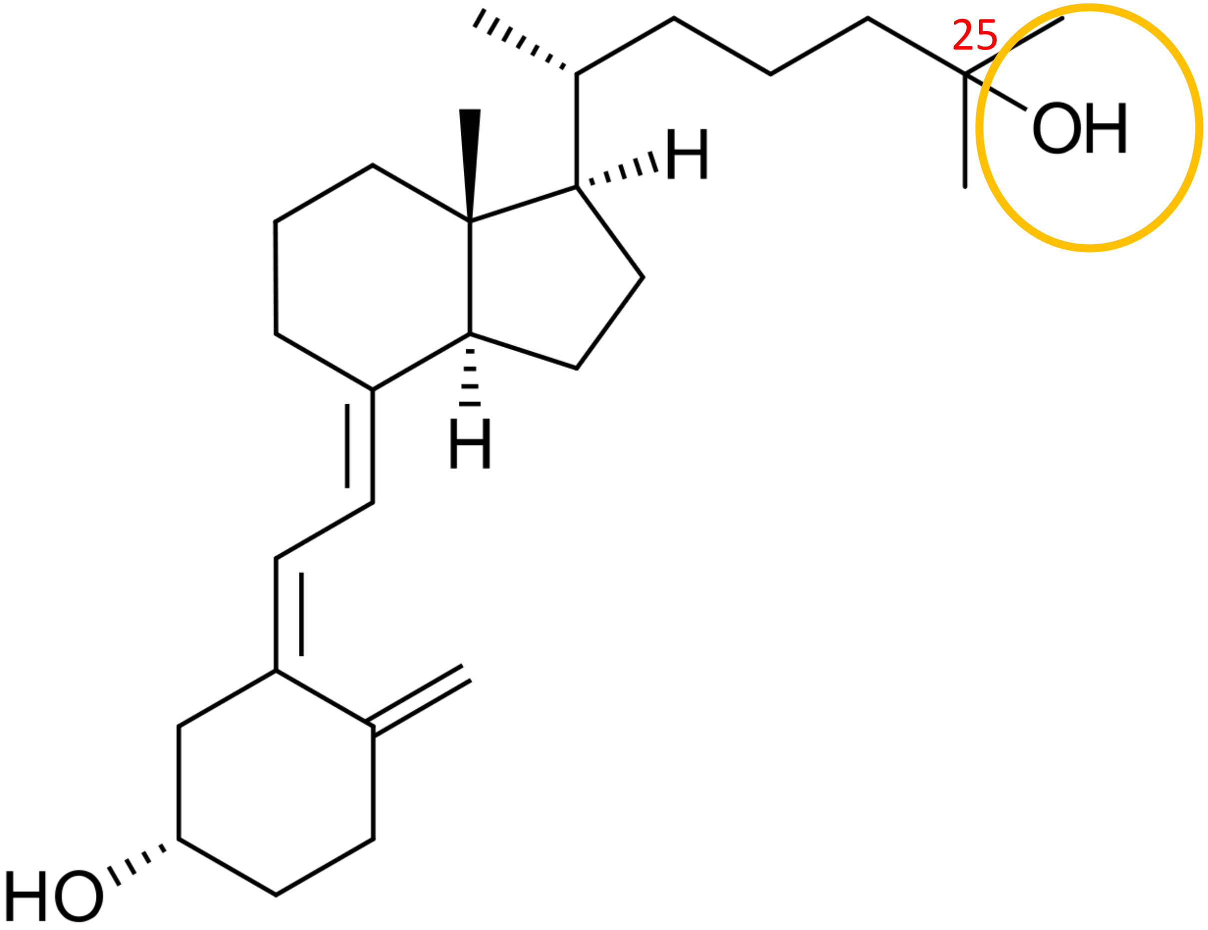
Vit D: metabolites



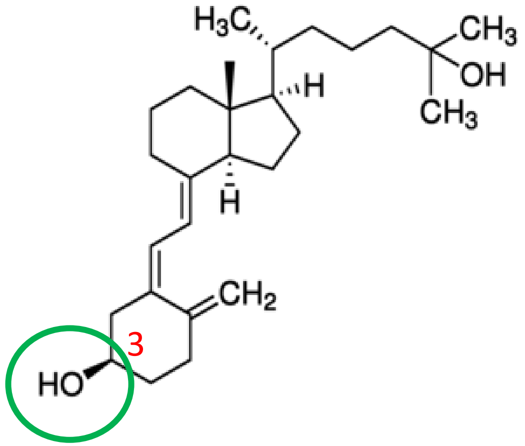


Ergocalciferol
Vitamine D2

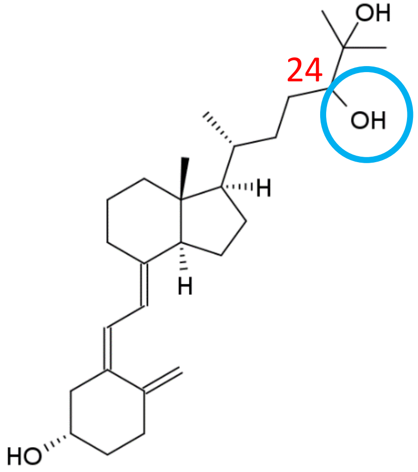
Cholecalciferol
Vitaminde D3



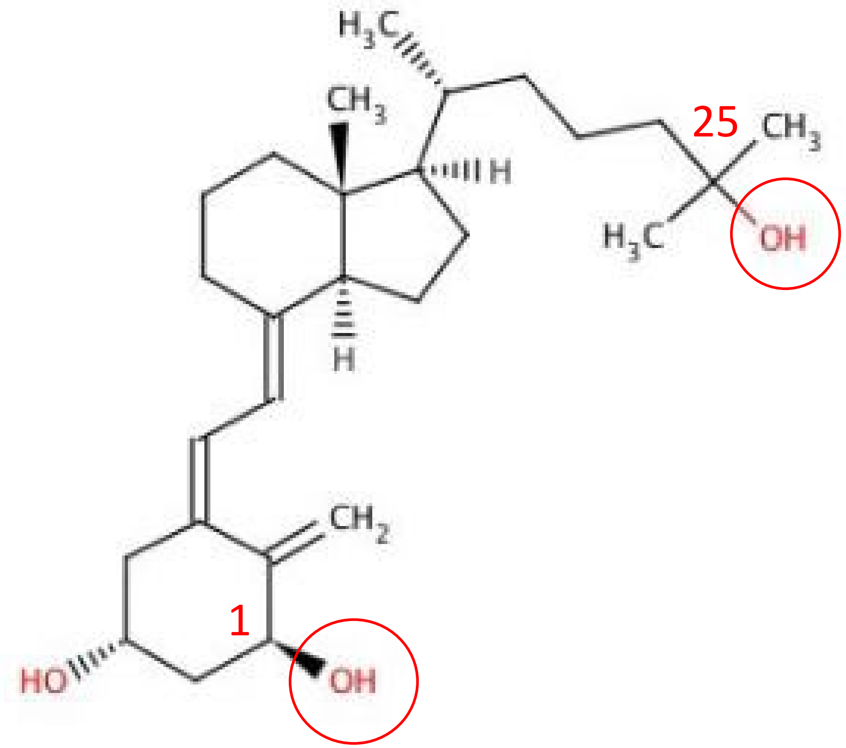
25-hydroxyvitamin D_3
calcifediol



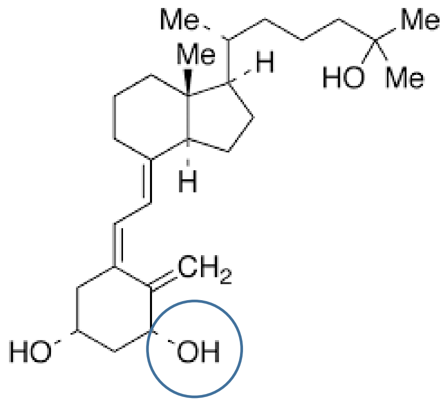
3-epi,25-hydroxyvitamin D_3



24,25-dihydroxyvitamin D_3



1alfa,25-dihydroxyvitamin D
calcitriol



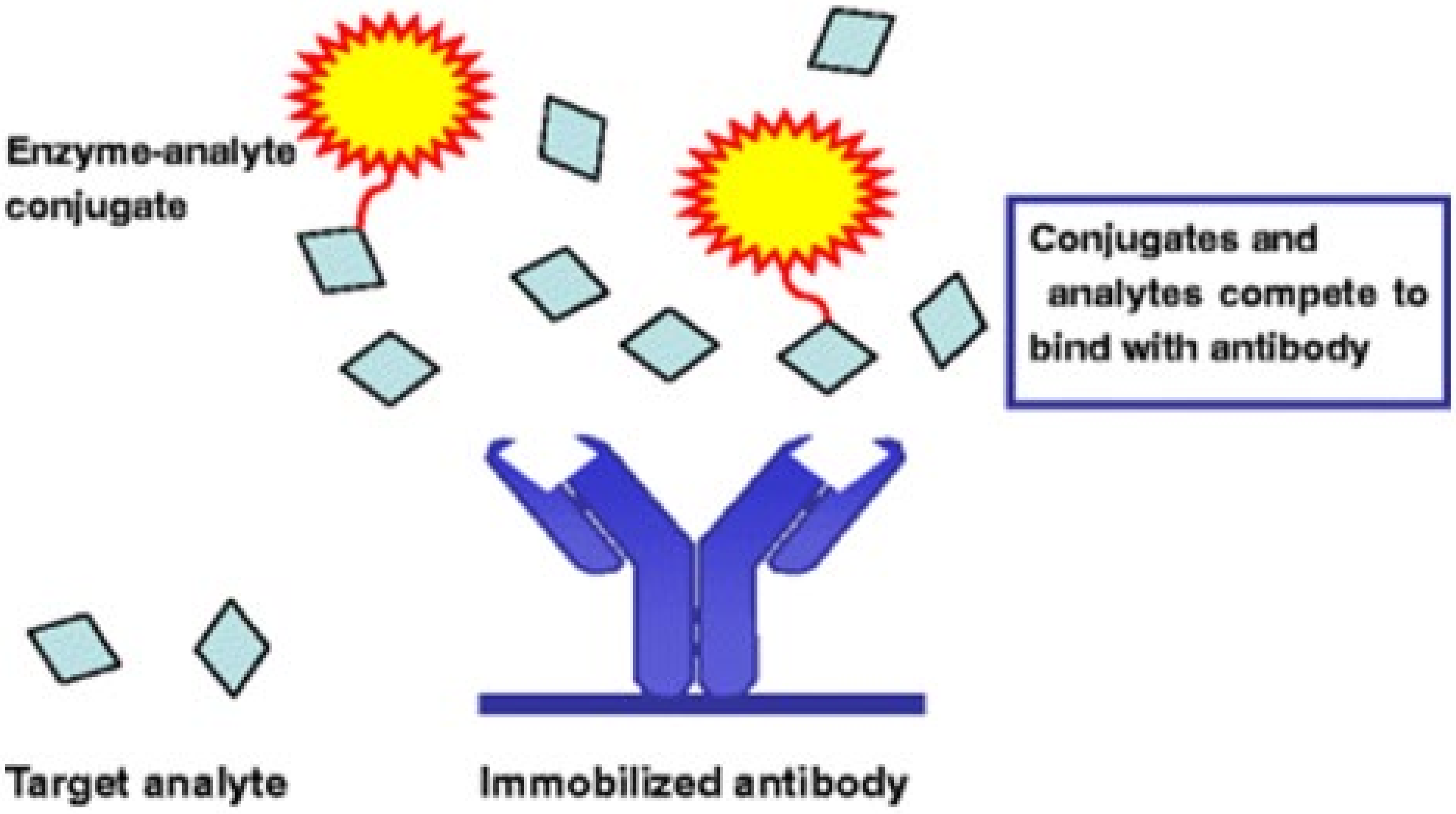
1beta,25 vit D

Vit D: assays

Immunoassays

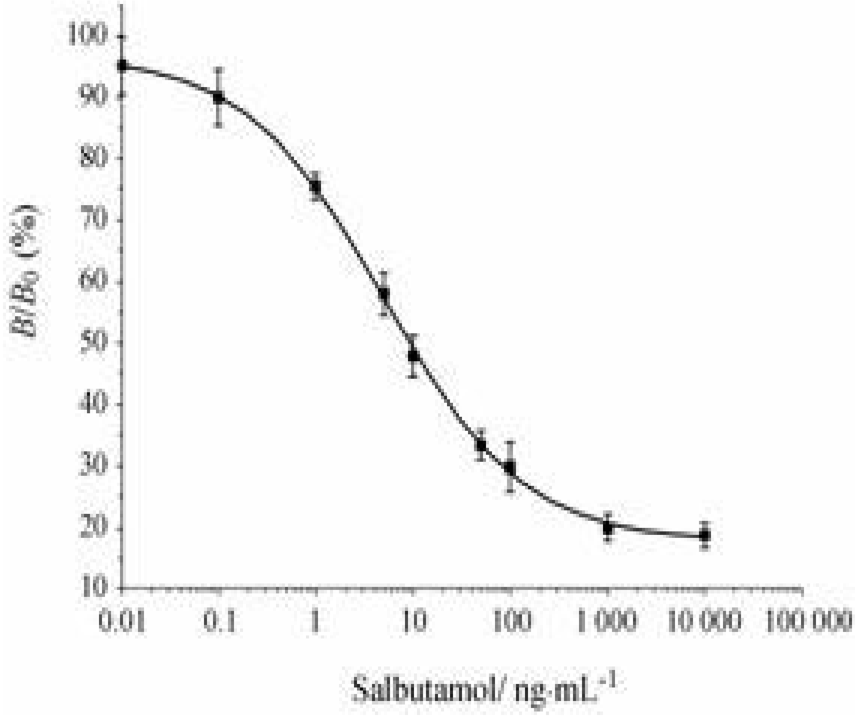
LC-MS/MS

Direct Competitive ELISA

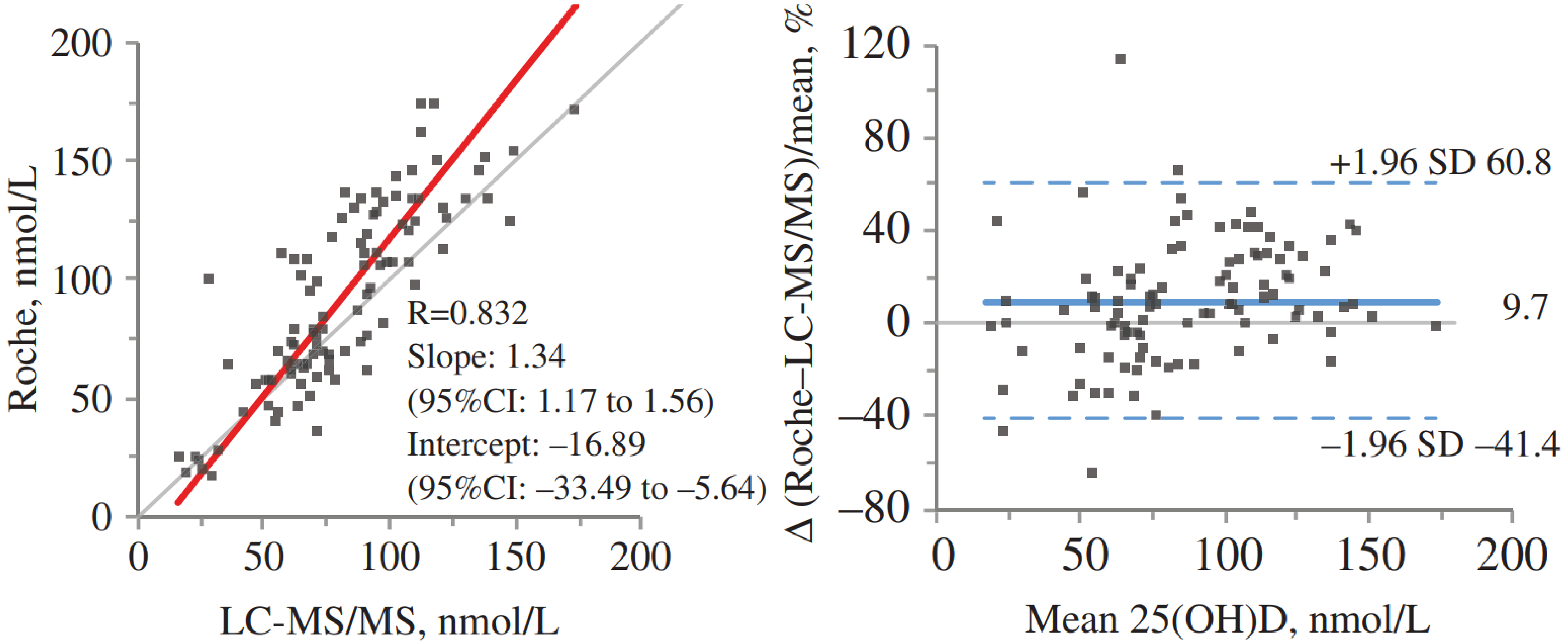


Competitive immunoassay

- Only one epitope
- One antibody
- Competion for antibody

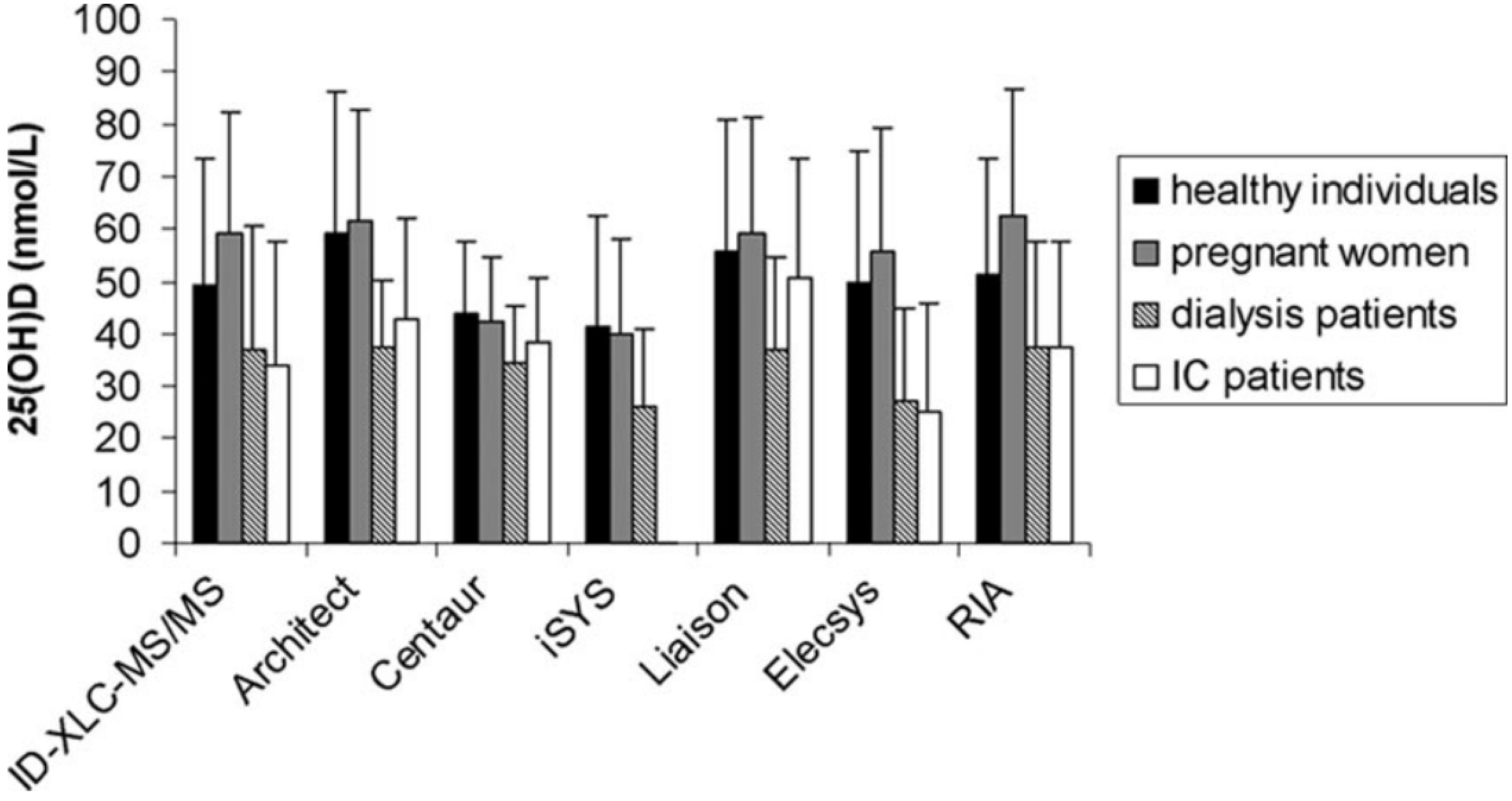


- Not very sensitive
- Not very specific
- Small dynamic range

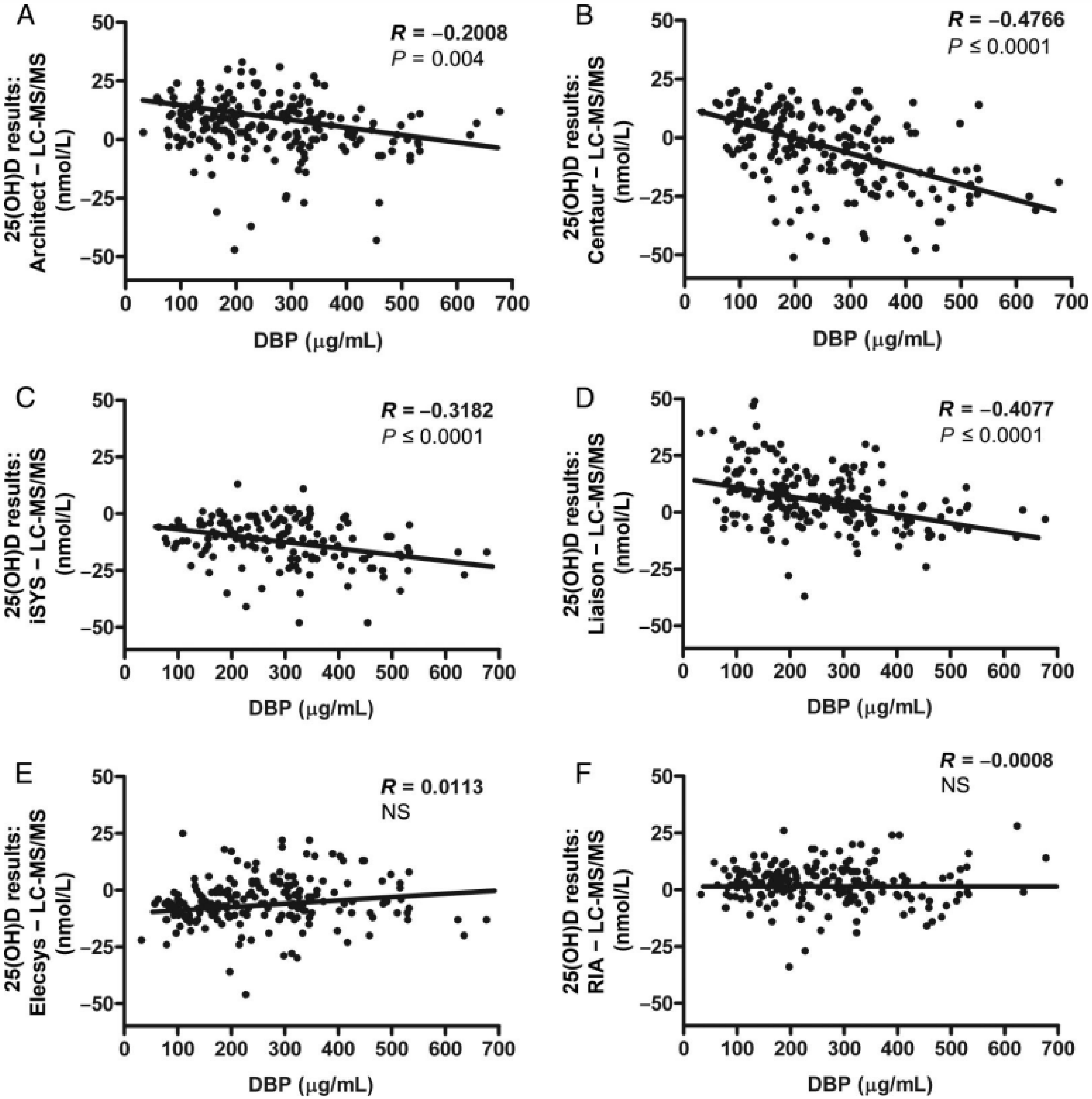


Roche, nmol/L
200
150
100
50
0
0
50
100
150
200
LC-MS/MS, nmol/L
R=0.832
Slope: 1.34
(95%CI: 1.17 to 1.56)
Intercept: –16.89
(95%CI: –33.49 to –5.64)
Δ (Roche–LC-MS/MS)/mean, %
120
80
40
0
–40
–80
+1.96 SD 60.8
9.7
–1.96 SD –41.4
0
50
100
150
200
Mean 25(OH)D, nmol/L

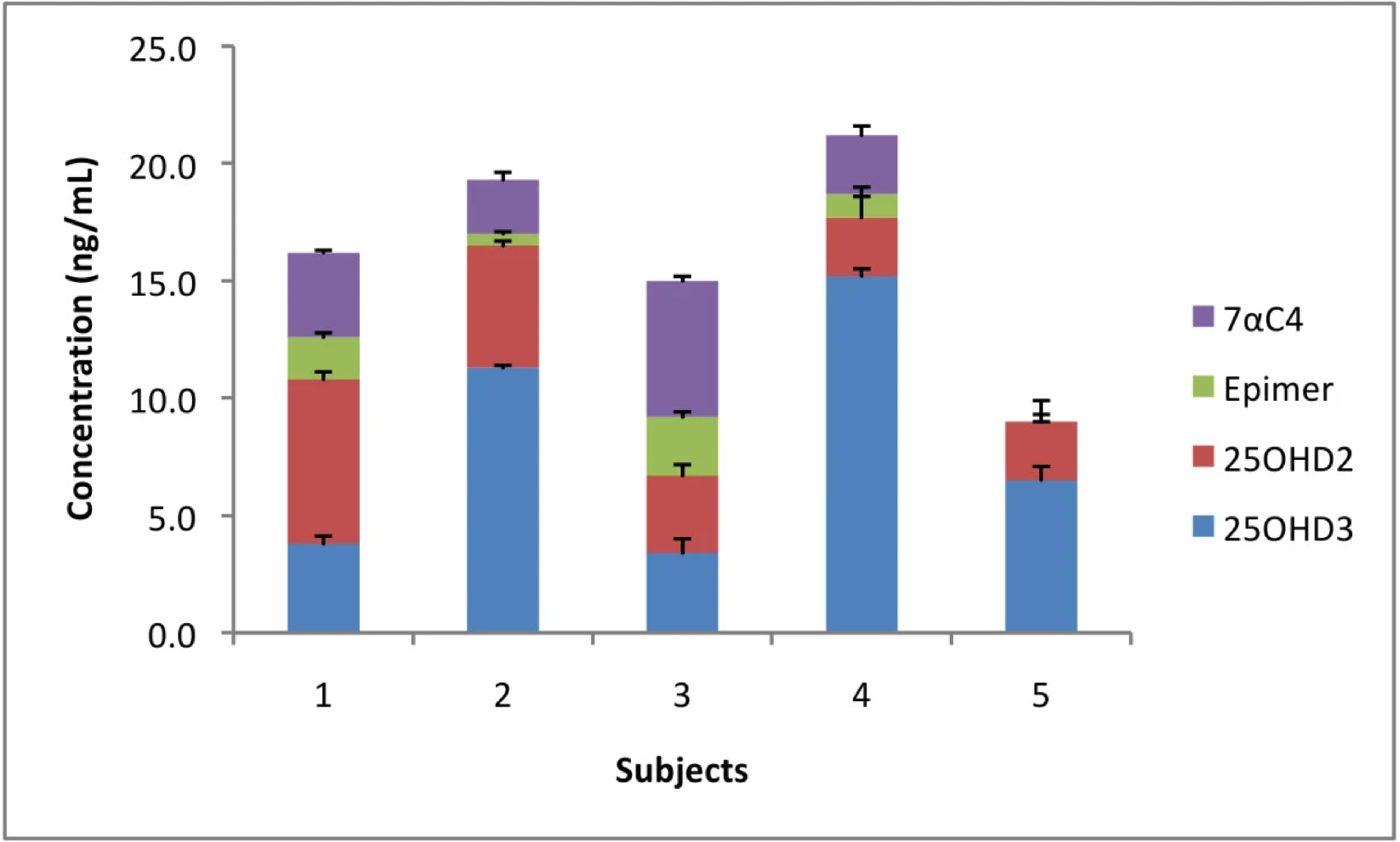
Immuno-assay = D2 + D3



100
90
80
70
60
50
40
30
20
10
0
25(OH)D (nmol/L)
ID-XLC-MS/MS
Architect
Centaur
iSYS
Liaison
Elecsys
RIA
healthy individuals
pregnant women
dialysis patients
IC patients

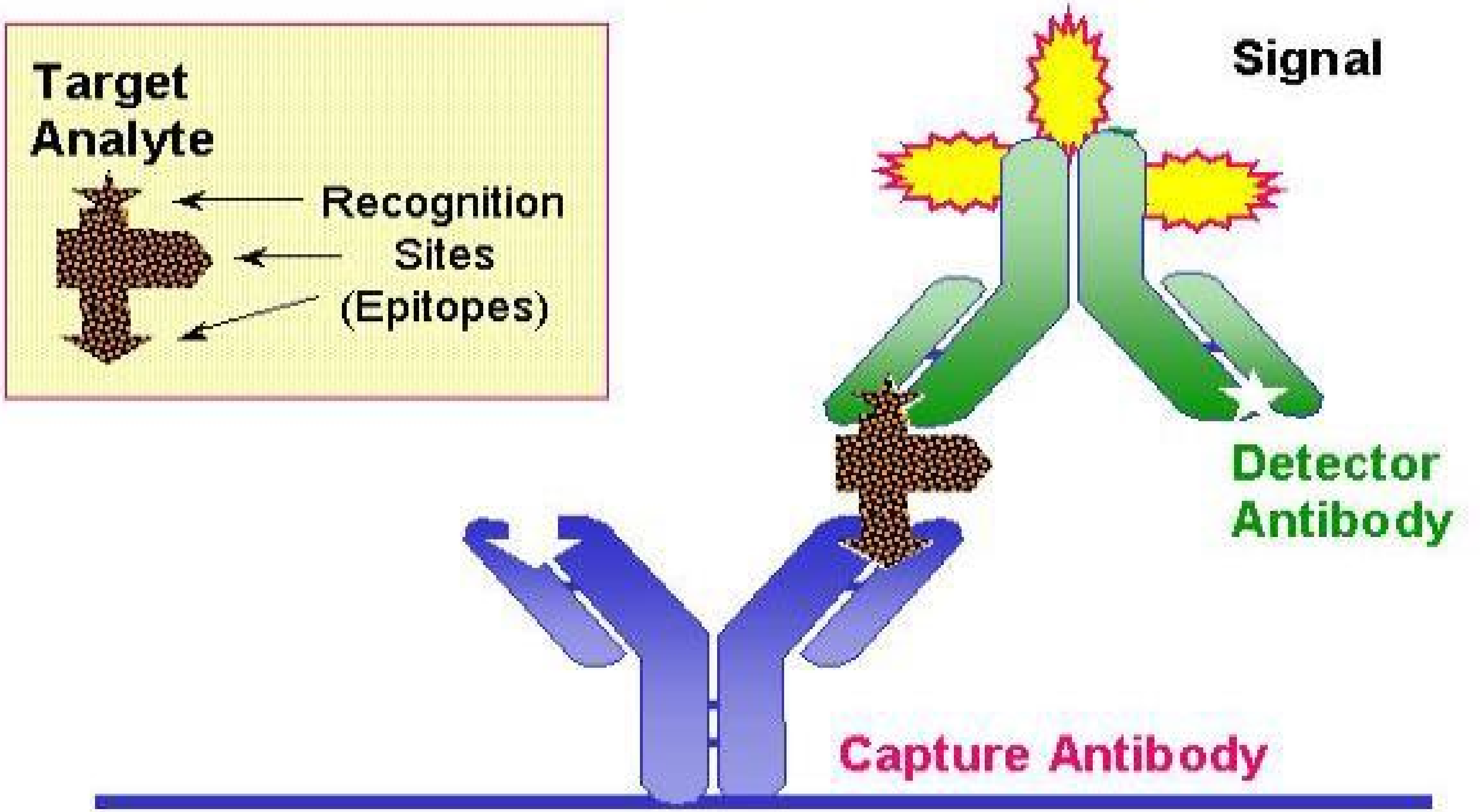

A
R = −0.2008
P = 0.004
25(OH)D results: Architect – LC-MS/MS (nmol/L)
DBP (μg/mL)
B
R = −0.4766
P ≤ 0.0001
25(OH)D results: Centaur – LC-MS/MS (nmol/L)
DBP (μg/mL)
C
R = −0.3182
P ≤ 0.0001
25(OH)D results: iSYS – LC-MS/MS (nmol/L)
DBP (μg/mL)
D
R = −0.4077
P ≤ 0.0001
25(OH)D results: Liaison – LC-MS/MS (nmol/L)
DBP (μg/mL)
E
R = 0.0113
NS
25(OH)D results: Elecsys – LC-MS/MS (nmol/L)
DBP (μg/mL)
F
R = −0.0008
NS
25(OH)D results: RIA – LC-MS/MS (nmol/L)
DBP (μg/mL)

Metabolites	ADVIA (Siemens)	ARCHITECT (Abbott)	COBAS (Roche)
25-hydroxy-vitamin D_2	106.2%	82.0%	92.0%
25-hydroxy-vitamin D_3	97.4%	105.0%	100.0%
3-epi-25-hydroxy-vitamin D^3	1.0%	2.7%	91.0%



Vitamin D levels and co-eluting epimers and isobars in five volunteers.

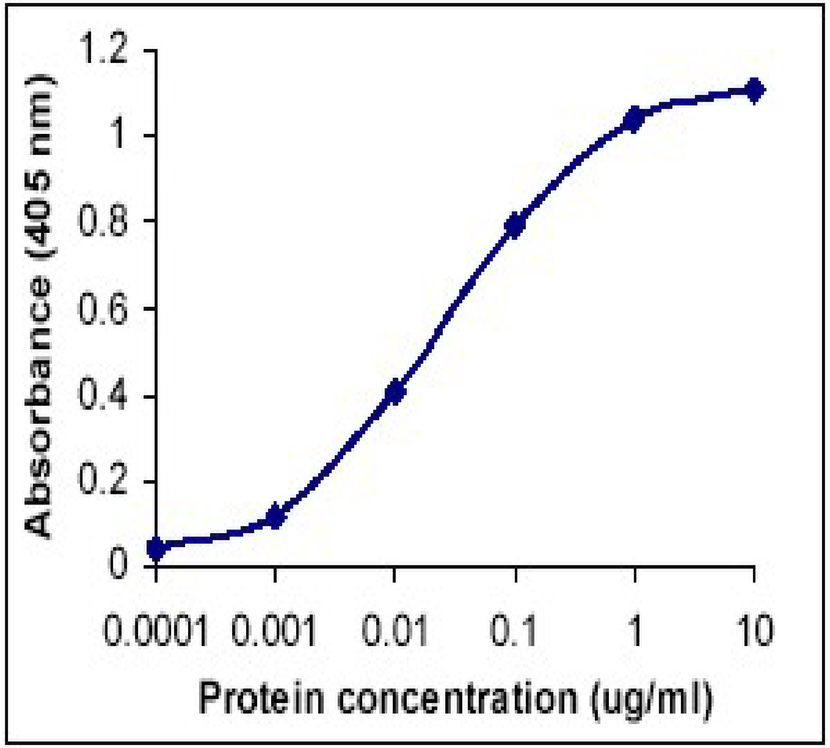
Double Antibody Sandwich Immunoassay

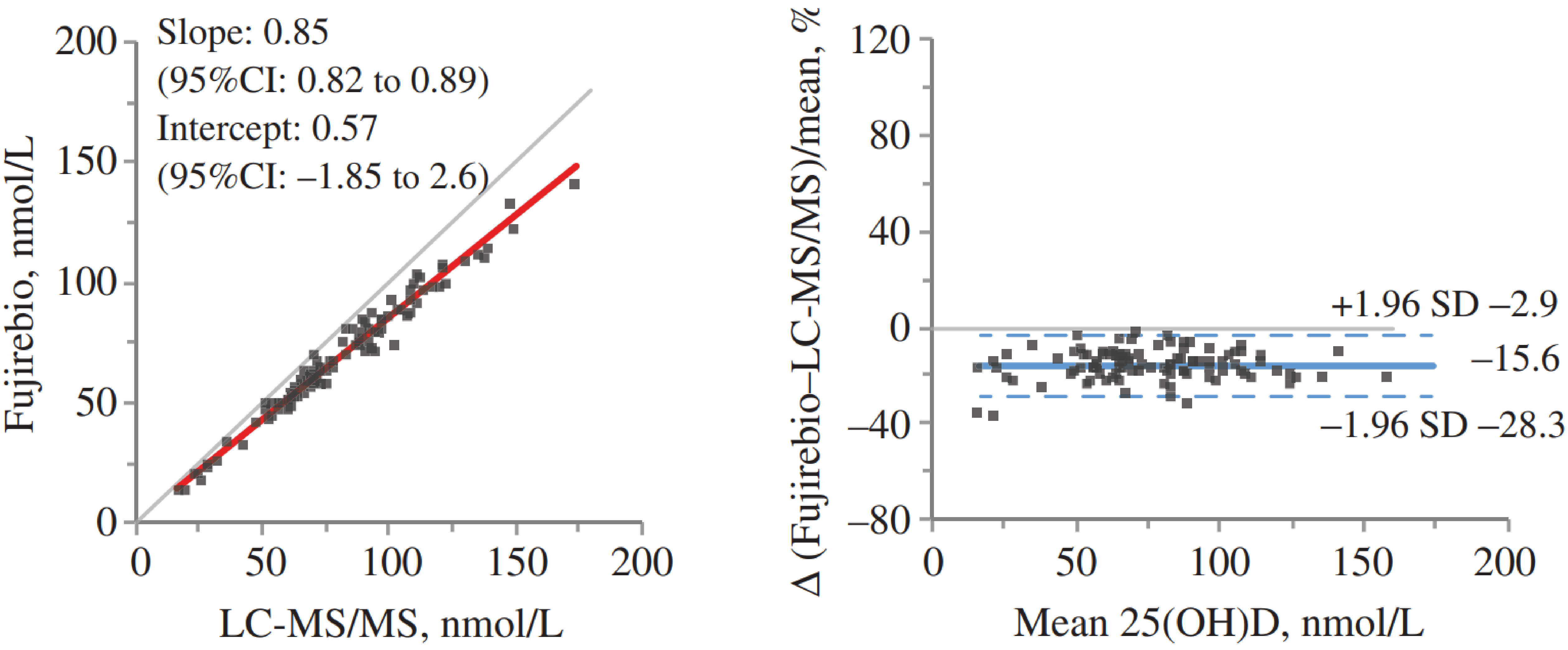


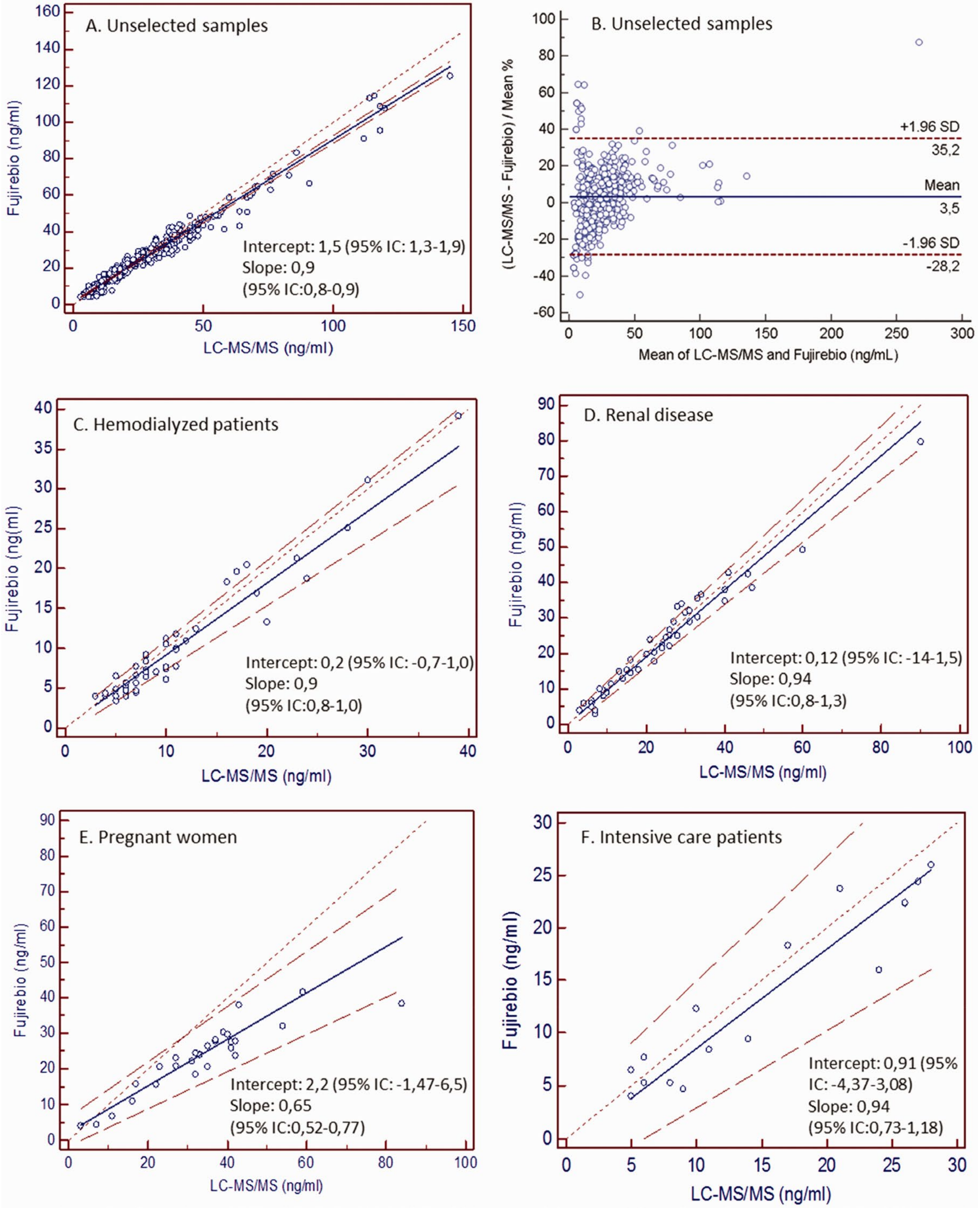
Sandwich assay

- Two epitopes
- Excess capture antibody
- Excess detection antibody

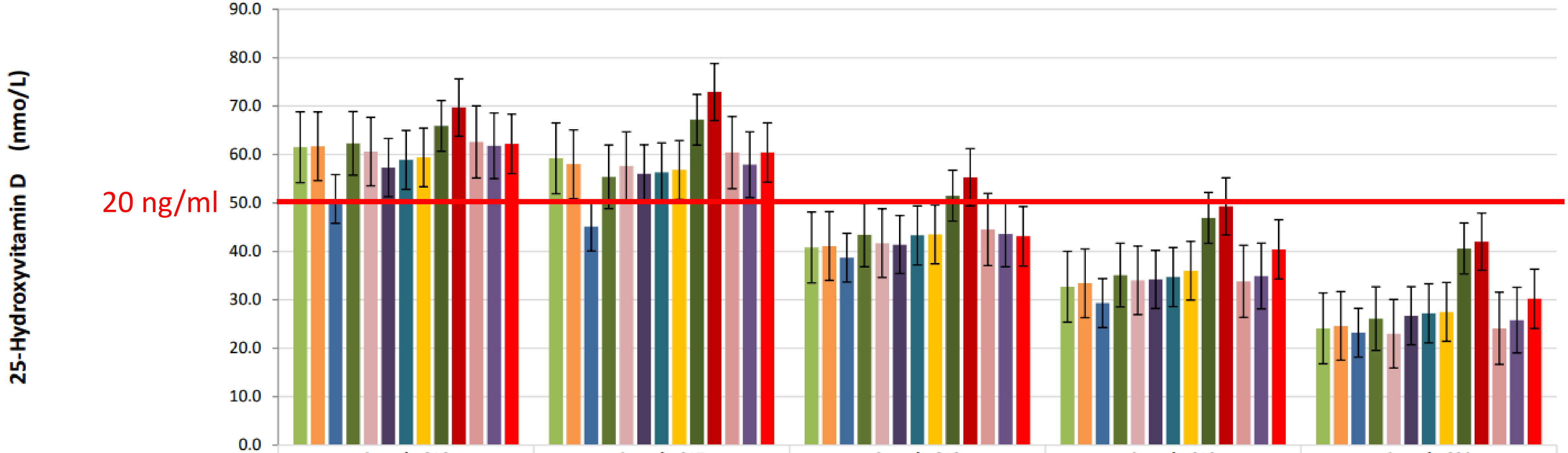
- Most sensitive immunoassays
- Large dynamic range
- High specificity




Slope: 0.85
(95%CI: 0.82 to 0.89)
Intercept: 0.57
(95%CI: –1.85 to 2.6)
Fujirebio, nmol/L
LC-MS/MS, nmol/L
0
50
100
150
200
Δ (Fujirebio–LC-MS/MS)/mean, %
Mean 25(OH)D, nmol/L
120
80
40
0
–40
–80
+1.96 SD –2.9
–15.6
–1.96 SD –28.3


A. Unselected samples
Fujirebio (ng/ml)
LC-MS/MS (ng/ml)
Intercept: 1,5 (95% IC: 1,3-1,9)
Slope: 0,9
(95% IC:0,8-0,9)
B. Unselected samples
(LC-MS/MS - Fujirebio) / Mean %
Mean of LC-MS/MS and Fujirebio (ng/mL)
+1.96 SD
35,2
Mean
3,5
-1.96 SD
-28,2
C. Hemodialyzed patients
Fujirebio (ng(ml)
LC-MS/MS (ng/ml)
Intercept: 0,2 (95% IC: -0,7-1,0)
Slope: 0,9
(95% IC:0,8-1,0)
D. Renal disease
Fujirebio (ng/ml)
LC-MS/MS (ng/ml)
Intercept: 0,12 (95% IC: -14-1,5)
Slope: 0,94
(95% IC:0,8-1,3)
E. Pregnant women
Fujirebio (ng/ml)
LC-MS/MS (ng/ml)
Intercept: 2,2 (95% IC: -1,47-6,5)
Slope: 0,65
(95% IC:0,52-0,77)
F. Intensive care patients
Fujirebio (ng/ml)
LC-MS/MS (ng/ml)
Intercept: 0,91 (95%
IC: -4,37-3,08)
Slope: 0,94
(95% IC:0,73-1,18)

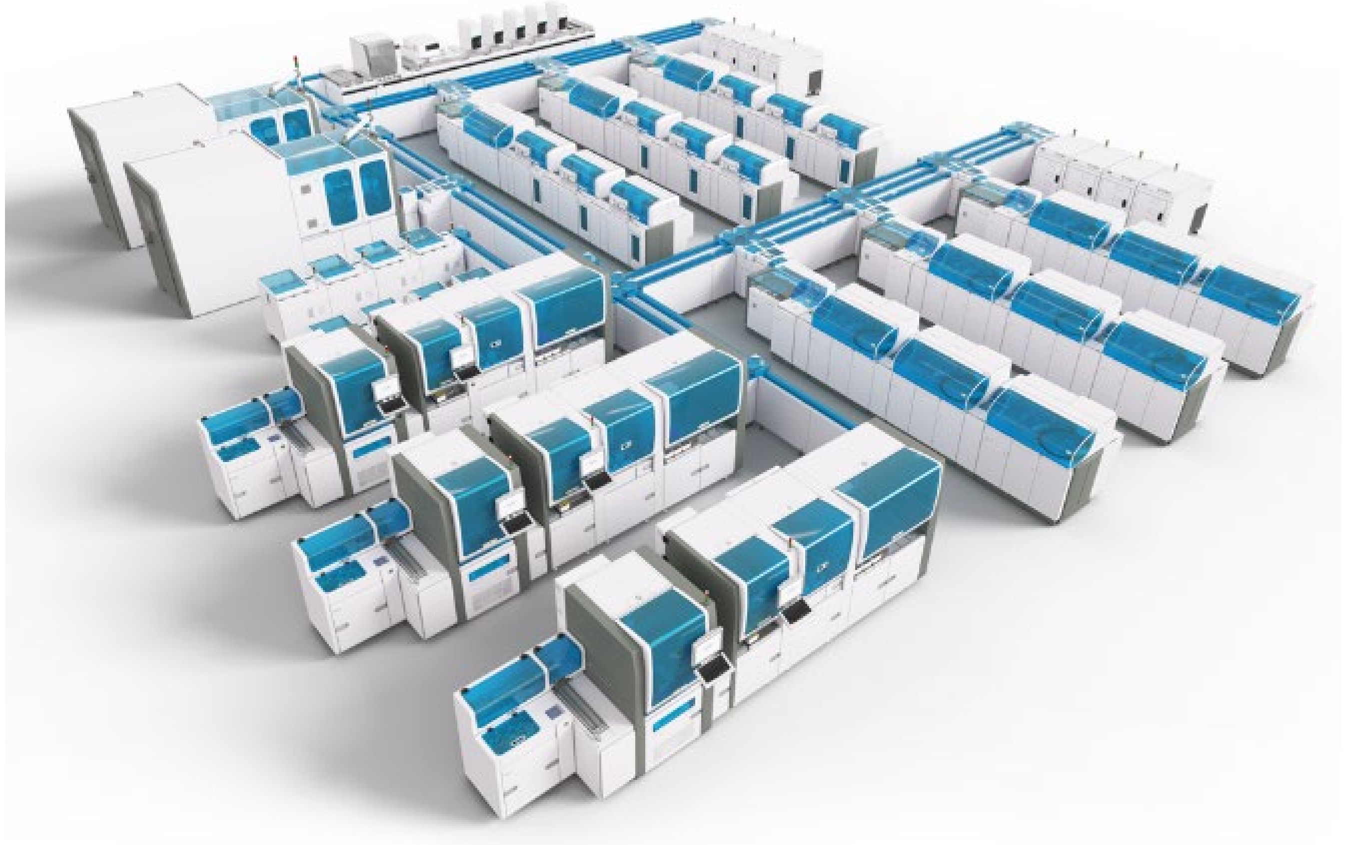
DEQAS July 2022 - 25-OHD Method Means (+/-1SD) for Major Method Groups*



	Sample 616	Sample 617	Sample 618	Sample 619	Sample 620
Abbott Alinity i (n=32)	61.5	59.2	40.8	32.7	24.1
Abbott Architect New Kit (n=21)	61.7	58.0	41.1	33.4	24.6
Beckman Unicel Dxi (n=12)	50.8	45.1	38.7	29.3	23.2
DiaSorin Liaison (n=138)	62.3	55.4	43.4	35.1	26.1
IDS Automated (n=23)	60.6	57.6	41.7	34.0	23.0
Roche Total (n=17)	57.3	56.0	41.4	34.2	26.7
Roche Vitamin D total II (n=27)	58.9	56.3	43.3	34.7	27.2
Roche Vitamin D total III (n=26)	59.4	56.8	43.5	36.0	27.5
Siemens Centaur (n=14)	65.9	67.2	51.5	46.9	40.6
Siemens Atellica (n=13)	69.7	72.9	55.3	49.3	42.0
LC-MS/MS (n=112)	62.6	60.4	44.5	33.8	24.1
ALTM (n=469)	61.8	57.9	43.6	34.9	25.8
TARGET VALUE	62.2	60.4	43.1	40.4	30.2

* Methods with 10 or more results returned

Grote platformen:



+ SNELHEID
- Monopolie Roche/Abbott/Beckman

Middelgroot platform: ABBOTT

Niche parameters (bv. BOT)

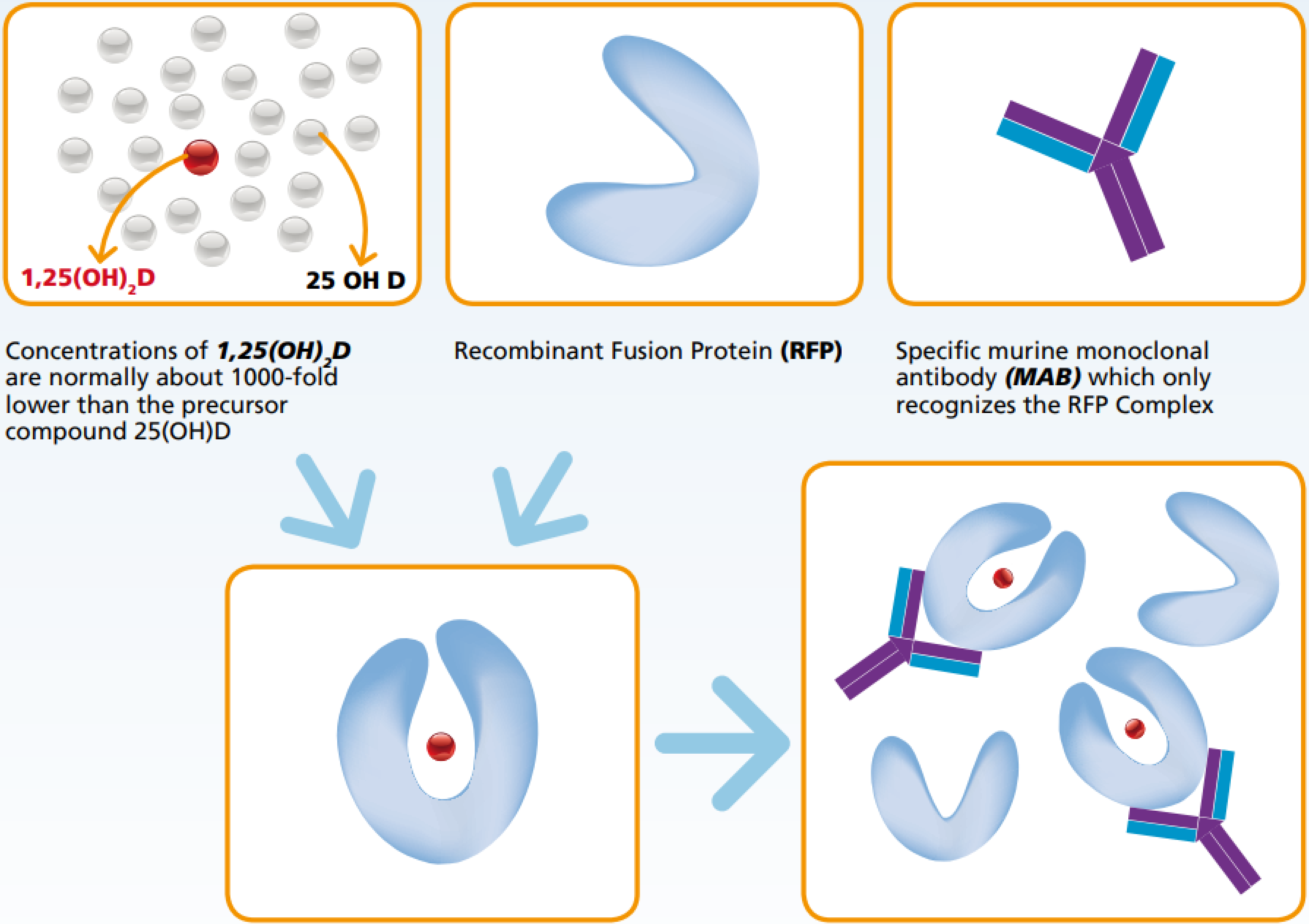
25 vit D
1,25 vit D

(Diasorin, IDS iSys, Fujerebio…)

1,25 vit D

fully automated

DIASORIN patent



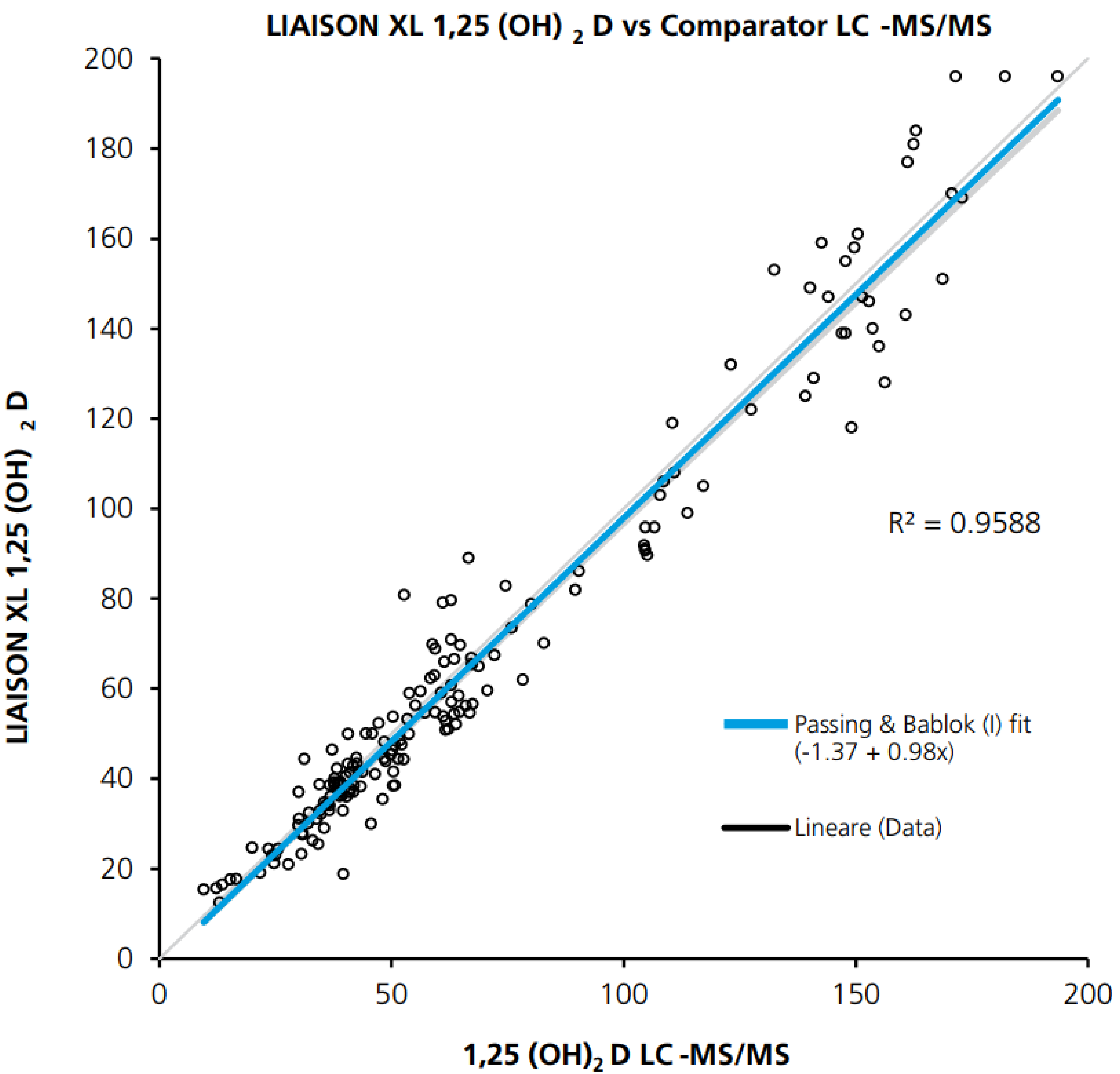
Concentrations of ***$1,25(OH)_2D$*** are normally about 1000-fold lower than the precursor compound 25(OH)D

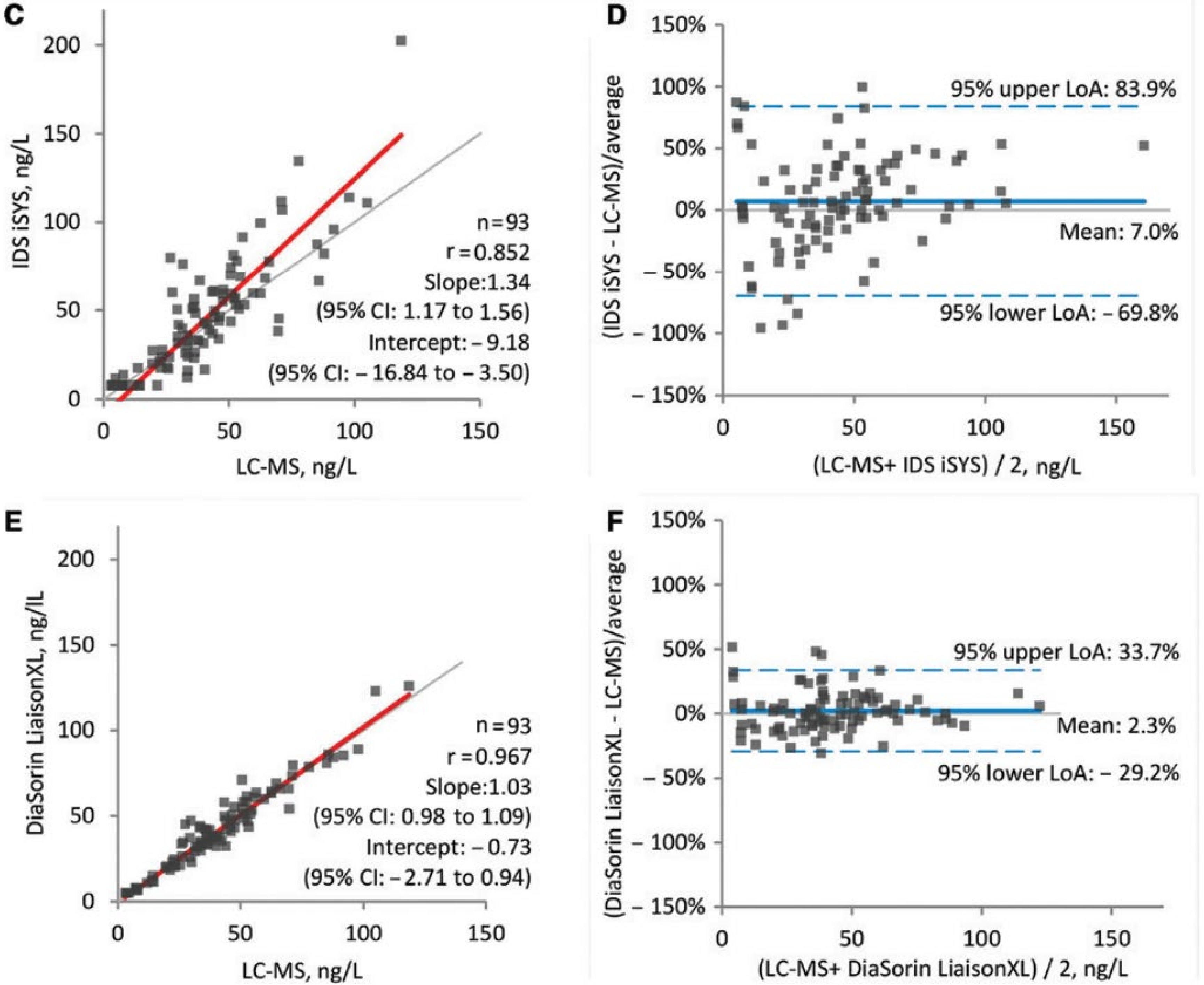
Recombinant Fusion Protein **(RFP)**

Specific murine monoclonal antibody ***(MAB)*** which only recognizes the RFP Complex

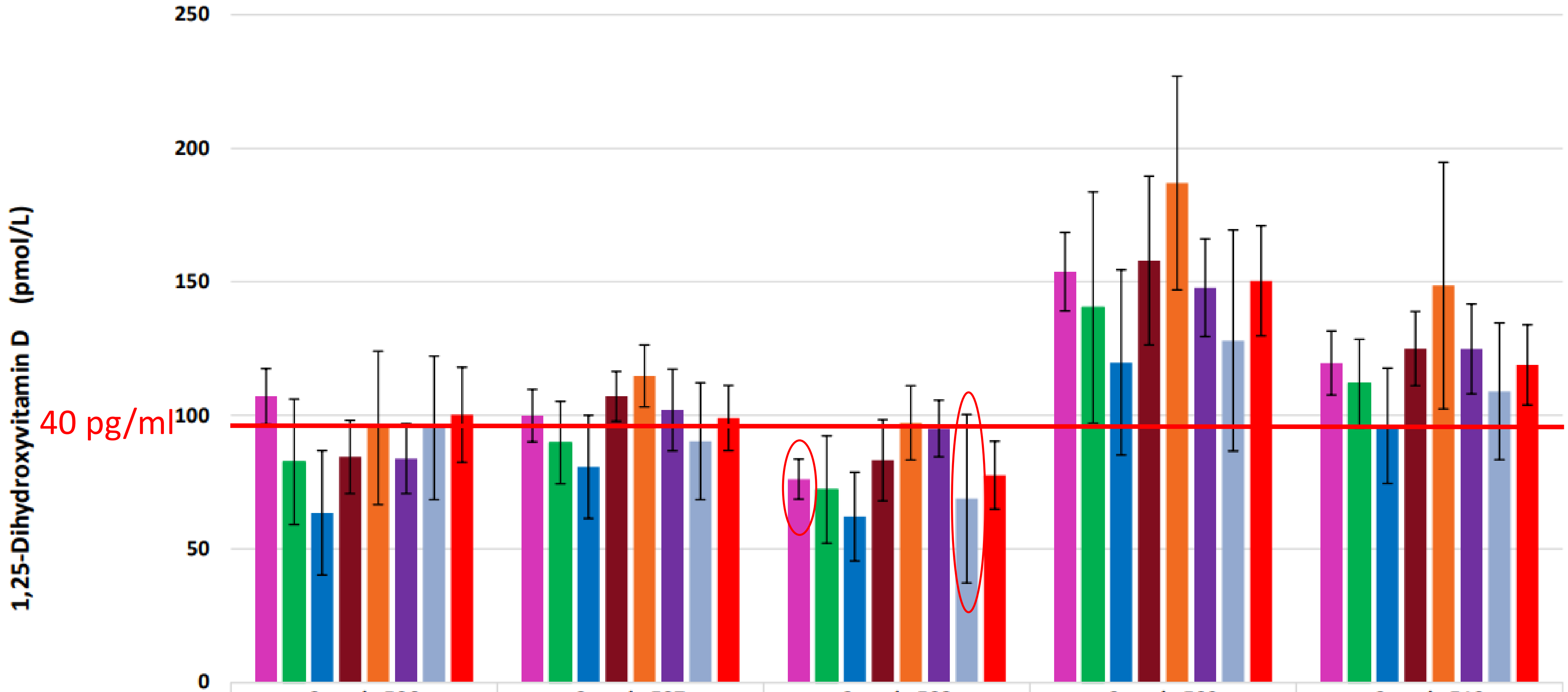
RFP changes conformation after capturing $1,25(OH)_2D$ and forms the ***RFP Complex***

RFP Complex is selectively recognized by the MAB


LIAISON XL 1,25 (OH) 2 D vs Comparator LC -MS/MS
LIAISON XL 1,25 (OH) 2 D
1,25 (OH)2 D LC -MS/MS
R² = 0.9588
Passing & Bablok (I) fit
(-1.37 + 0.98x)
Lineare (Data)
0
20
40
60
80
100
120
140
160
180
200
0
50
100
150
200


C
IDS iSYS, ng/L
LC-MS, ng/L
n=93
r=0.852
Slope:1.34
(95% CI: 1.17 to 1.56)
Intercept: −9.18
(95% CI: −16.84 to −3.50)
D
(IDS iSYS - LC-MS)/average
(LC-MS+ IDS iSYS) / 2, ng/L
95% upper LoA: 83.9%
Mean: 7.0%
95% lower LoA: −69.8%
E
DiaSorin LiaisonXL, ng/lL
LC-MS, ng/L
n=93
r=0.967
Slope:1.03
(95% CI: 0.98 to 1.09)
Intercept: −0.73
(95% CI: −2.71 to 0.94)
F
(DiaSorin LiaisonXL - LC-MS)/average
(LC-MS+ DiaSorin LiaisonXL) / 2, ng/L
95% upper LoA: 33.7%
Mean: 2.3%
95% lower LoA: −29.2%

DEQAS July 2022 - 1,25-dihydroxyvitamin D Method Means * (+/- 1 SD)



	Sample 506	Sample 507	Sample 508	Sample 509	Sample 510
DiaSorin Liaison XL (n=90)	107.1	99.9	76.1	153.8	119.6
DIASource CT (n=4)	82.6	89.8	72.2	140.4	112
IDS EIA (n=6)	63.5	80.7	62.1	119.8	96.1
IDS RIA (n=5)	84.4	107.1	83.2	158	125.0
IDS (n=4)	95.3	114.8	97.2	187	148.6
IDS XP (n=15)	83.8	102	95.1	147.8	124.9
LC-MS/MS (n=16)	95.3	90.3	68.8	128	109
ALTM (n=140)	100.2	99	77.6	150.4	118.9

Mass spectrometry

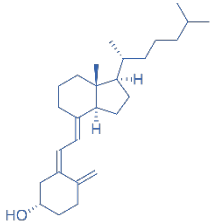
Mass spectrometry (MS)

Theoretical concepts: 19th century

1919 First mass spectrometer

Discovery & identification of isotopes

Proteins
Peptides



Hormones

Small
molecules

Biological matrix

→ Identify (qualitative analysis)

→ Quantify (quantitative analysis)

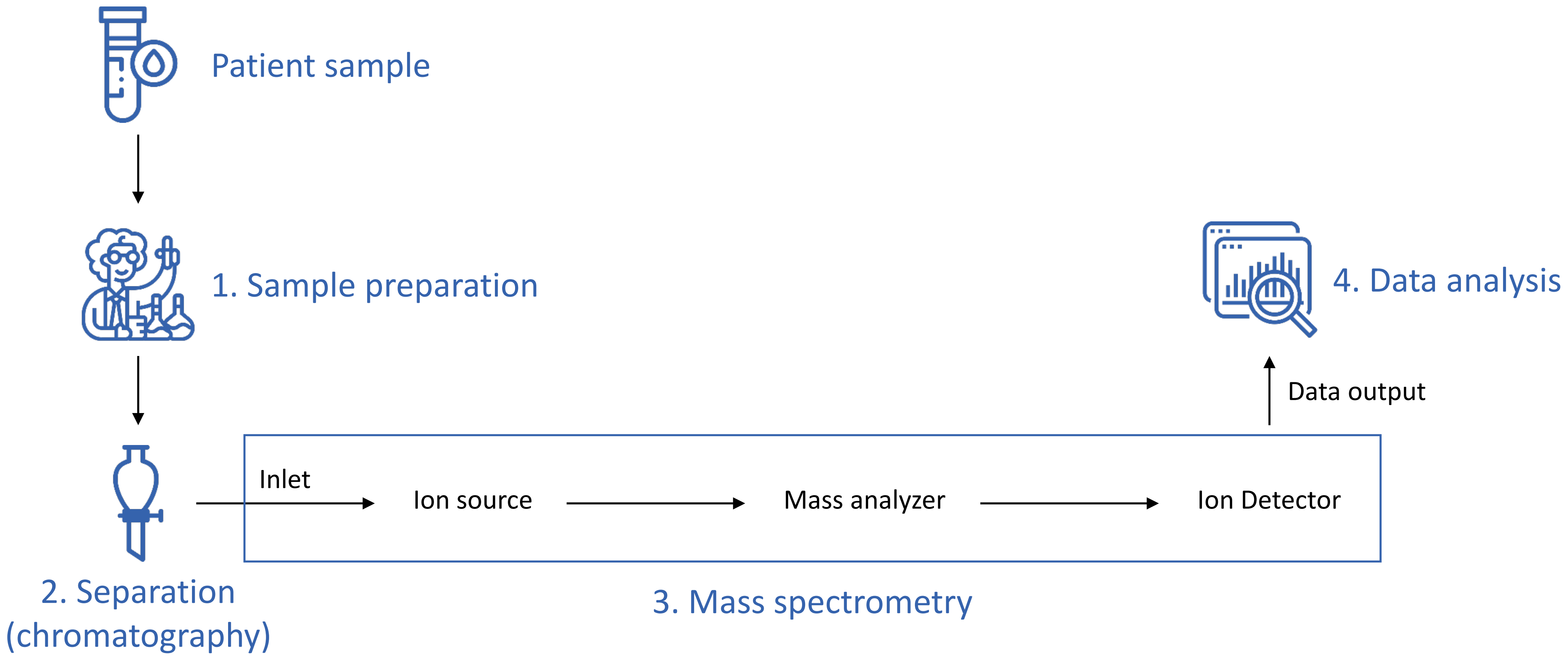
<u>Applications</u>

Scientific

Industrial

Clinical

MS technique overview



Sample preparation

Removal of contaminants

Isolate analyte of interest

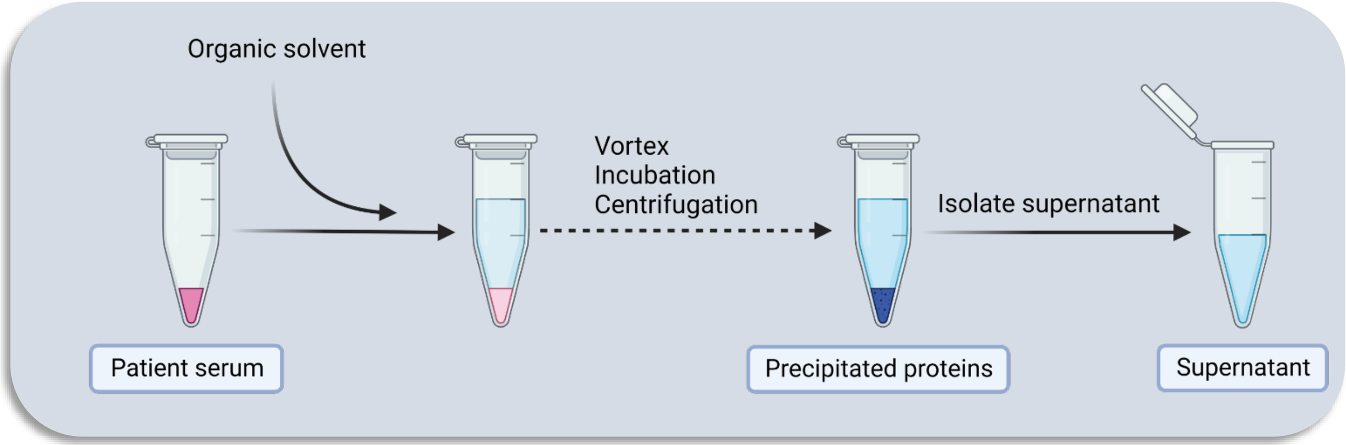
→ Increase method performance

Dilution, centrifugation

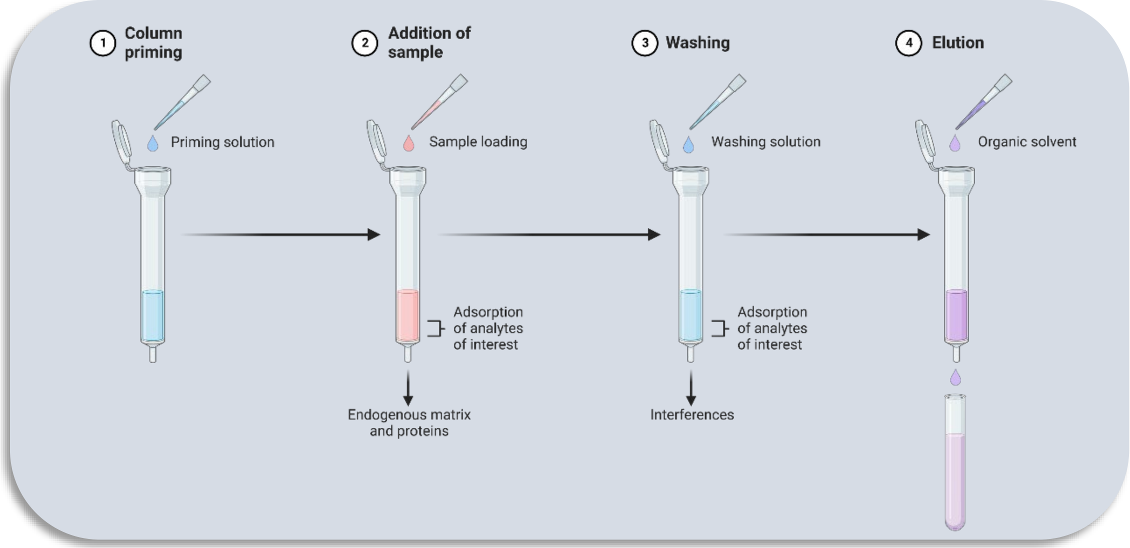
Homogenization, filtration

Dialysis, desalting, buffer exchange

Protein precipitation



Solid phase extraction



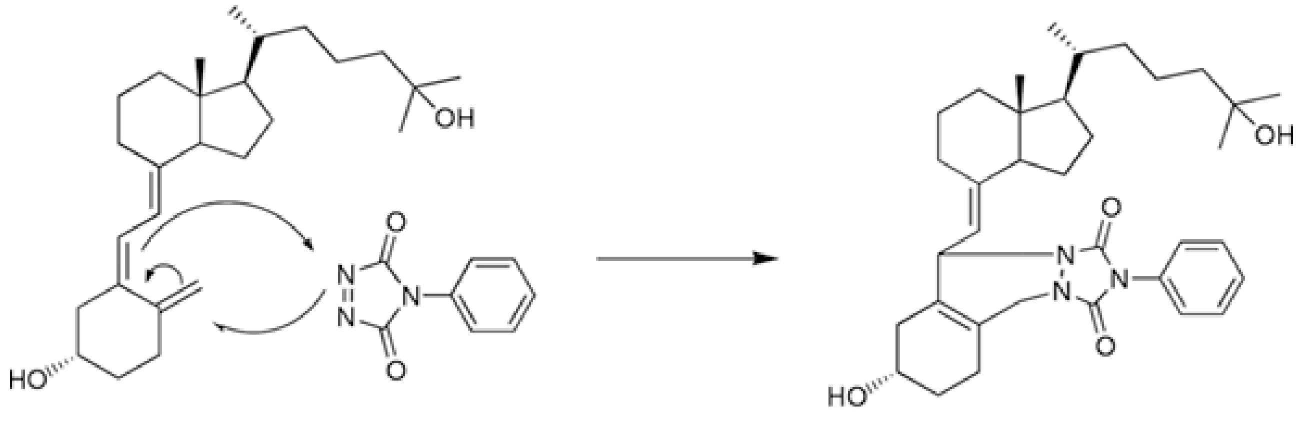
Liquid-liquid extraction

Sample preparation

Derivatization → Attachment of functional group

→ Improvement of selectivity
Enhancing ionization efficiency
Removal of endogenous interference

4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)

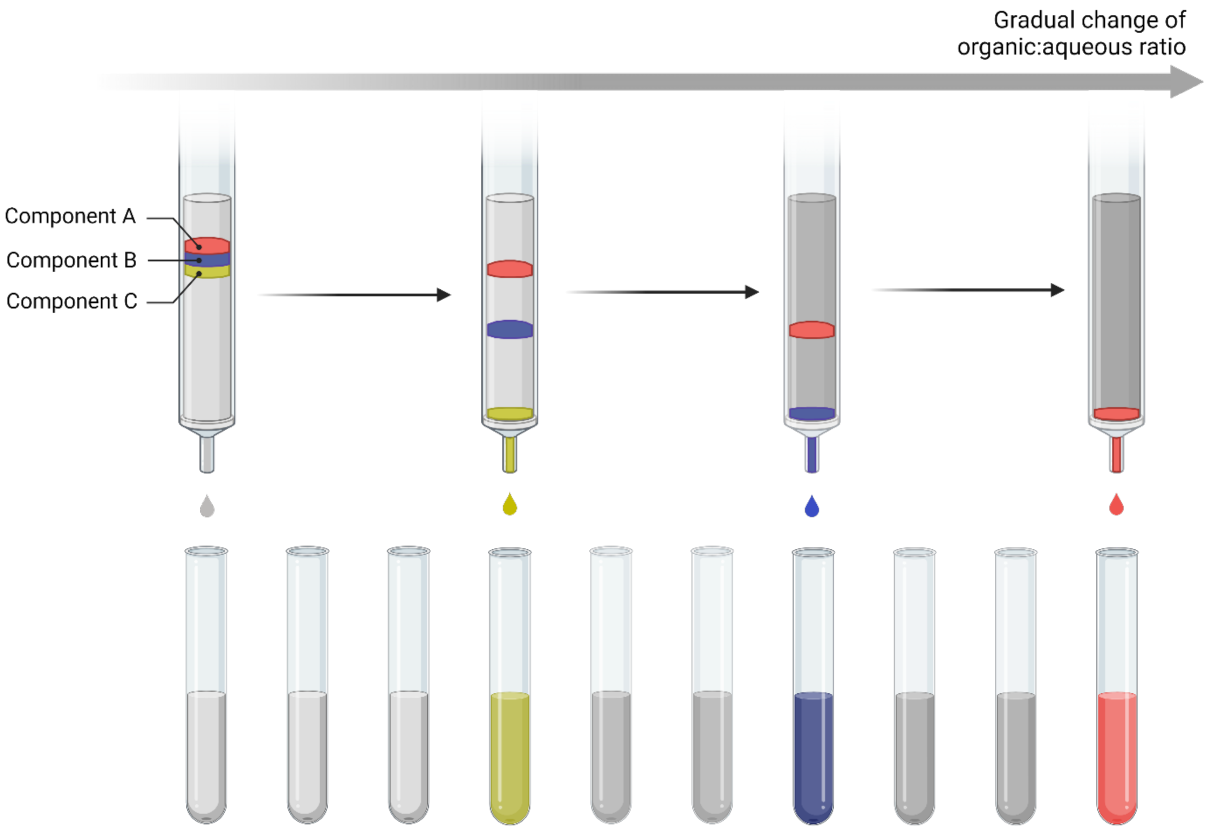


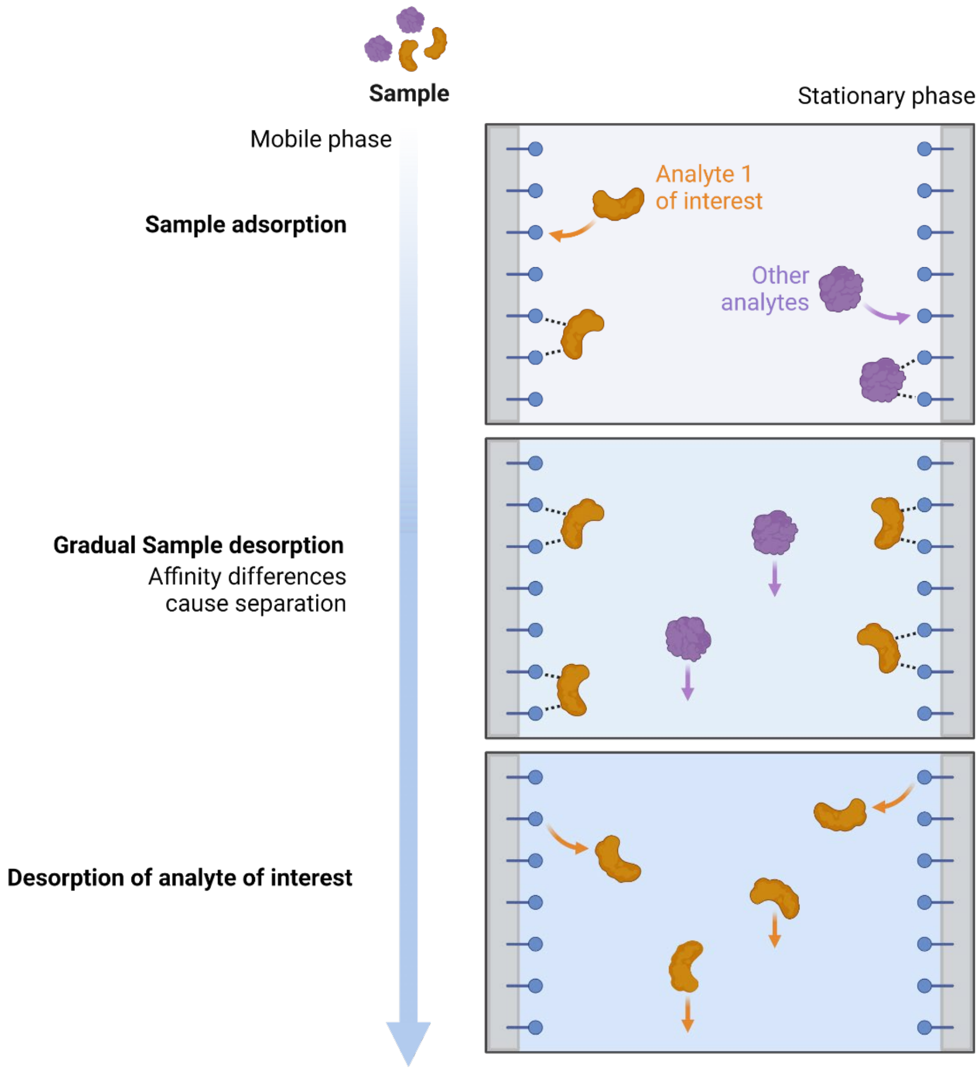
$25(OH)D_3$ PTAD $25(OH)D_3$-PTAD

Kattner, L. , Volmer, D. A. . Synthesis of Low Abundant Vitamin D Metabolites and Assaying Their Distribution in Human Serum by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) as a New Tool for Diagnosis and Risk Prediction of Vitamin DRelated Diseases. doi: 10.5772/64518

Chromatography

High performance liquid chromatography (HPLC): separation of analytes



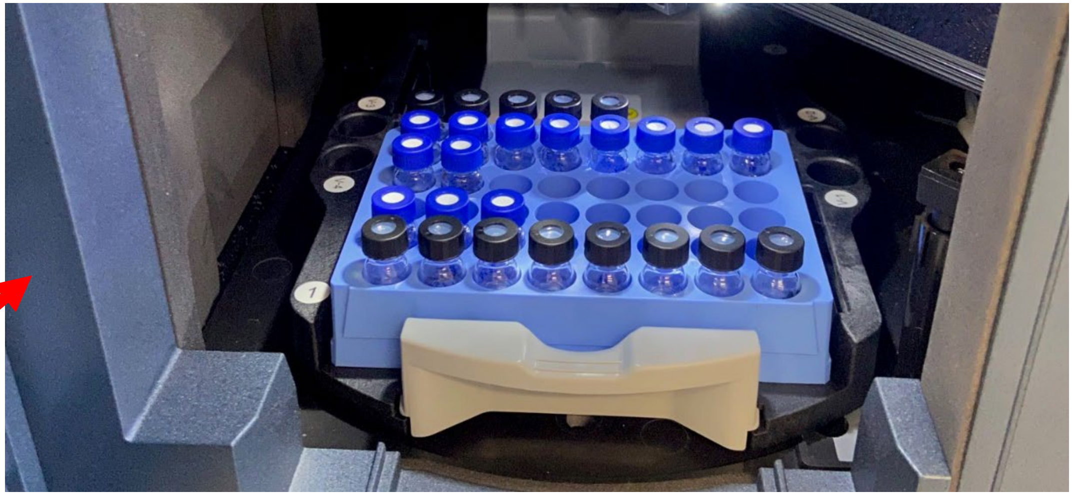


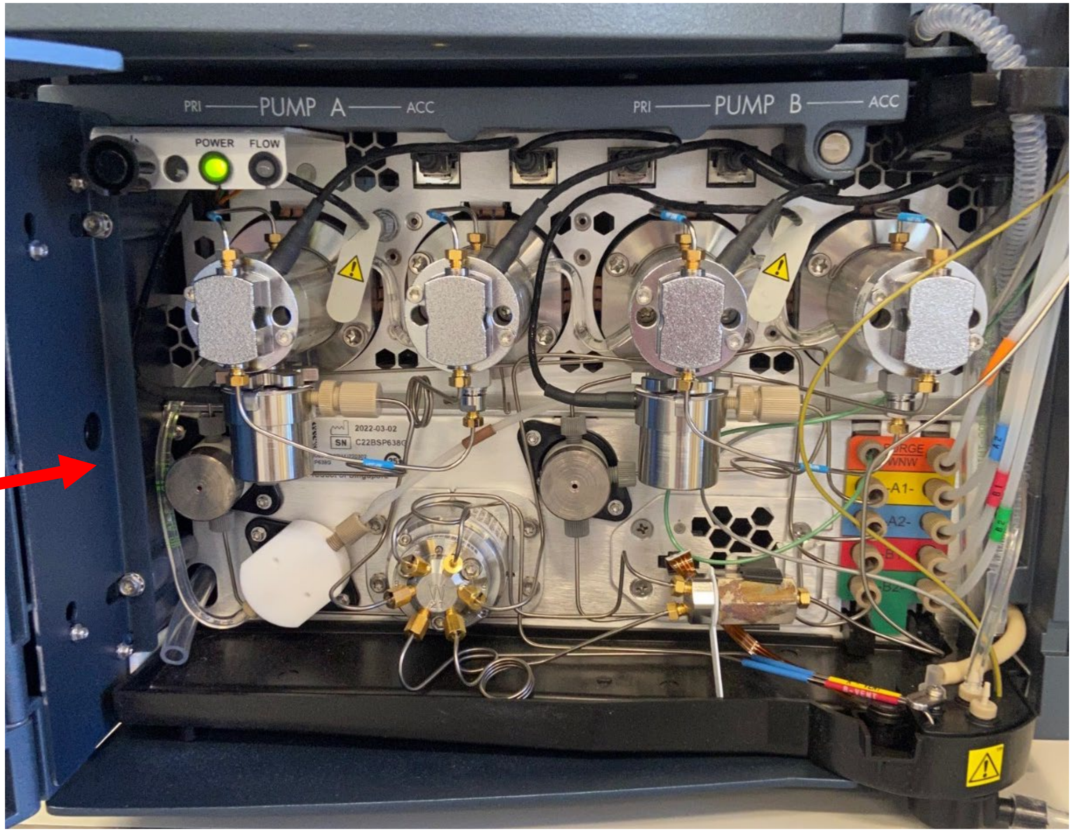
Separation based on: Size

Polarity

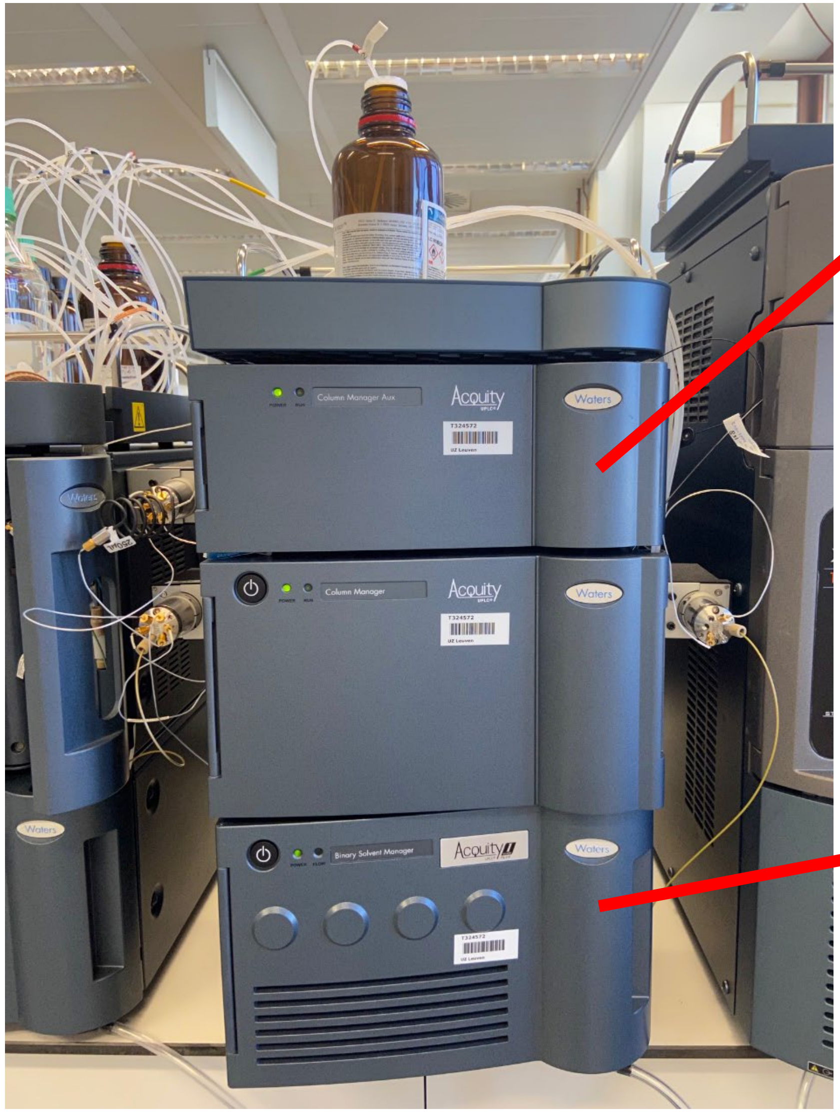
Charge

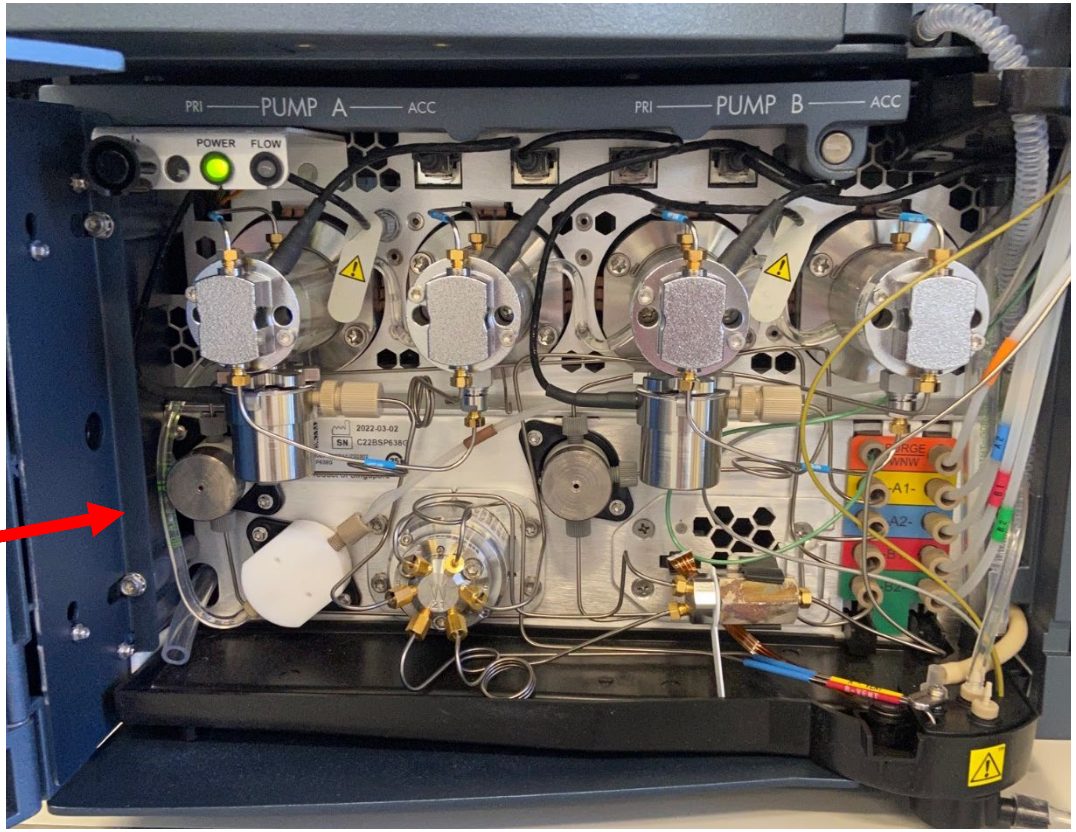
Chromatography





Chromatography



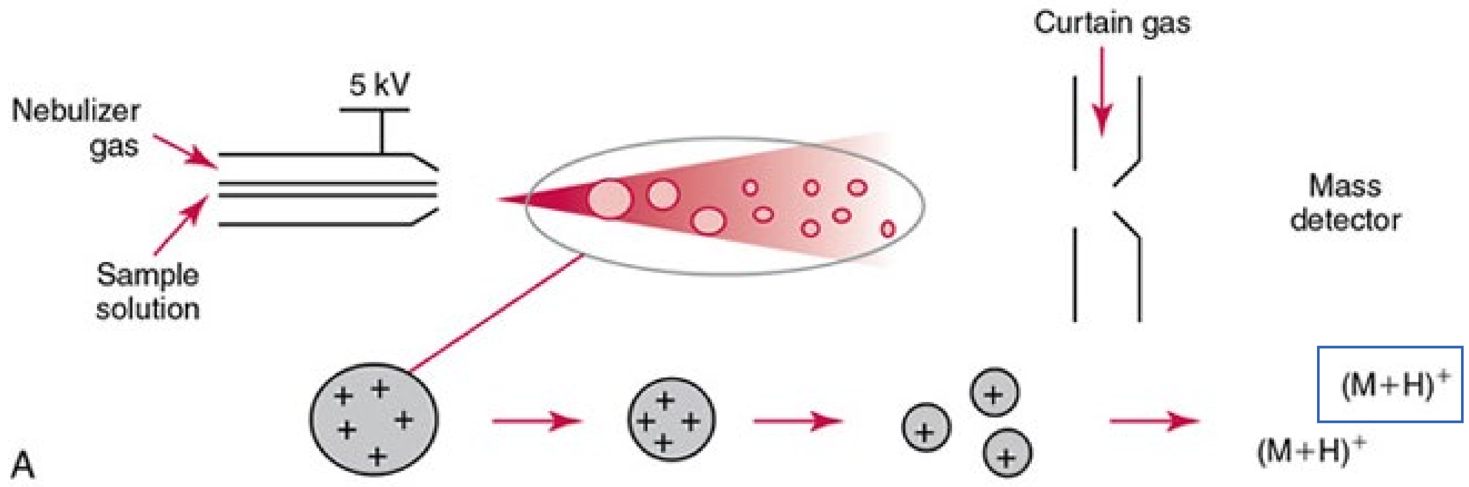


Mass spectrometry

Ionization

Many different options

Electron ionization (EI)
Chemical ionization (CI)
Matrix-assisted laser desorption (MALDI)
Electrospray ionization (ESI)



mass-to-charge ratio (m/z)

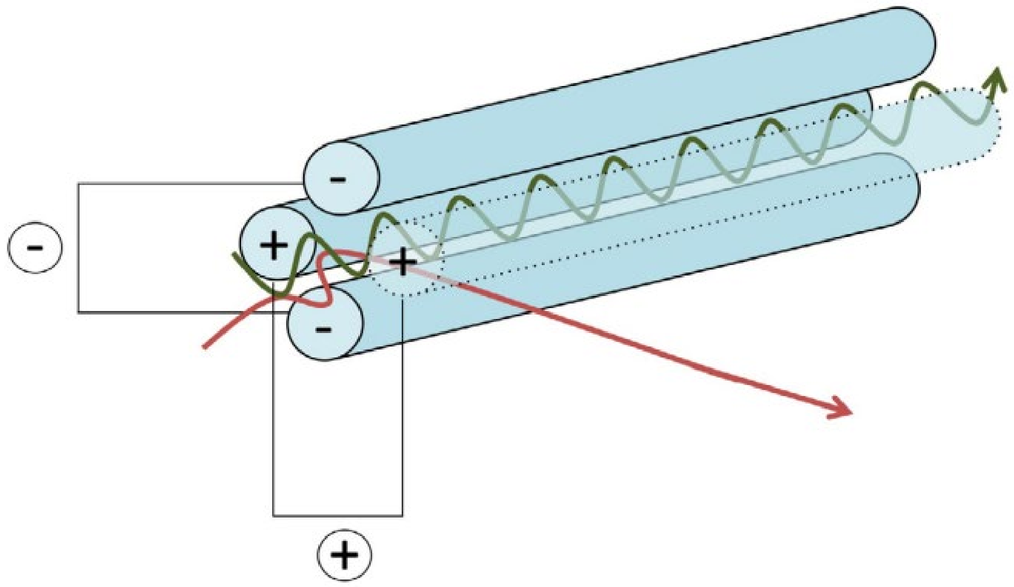
Small molecules: single charge
Peptides/proteins: multiple charges

Mass spectrometry

Ionization

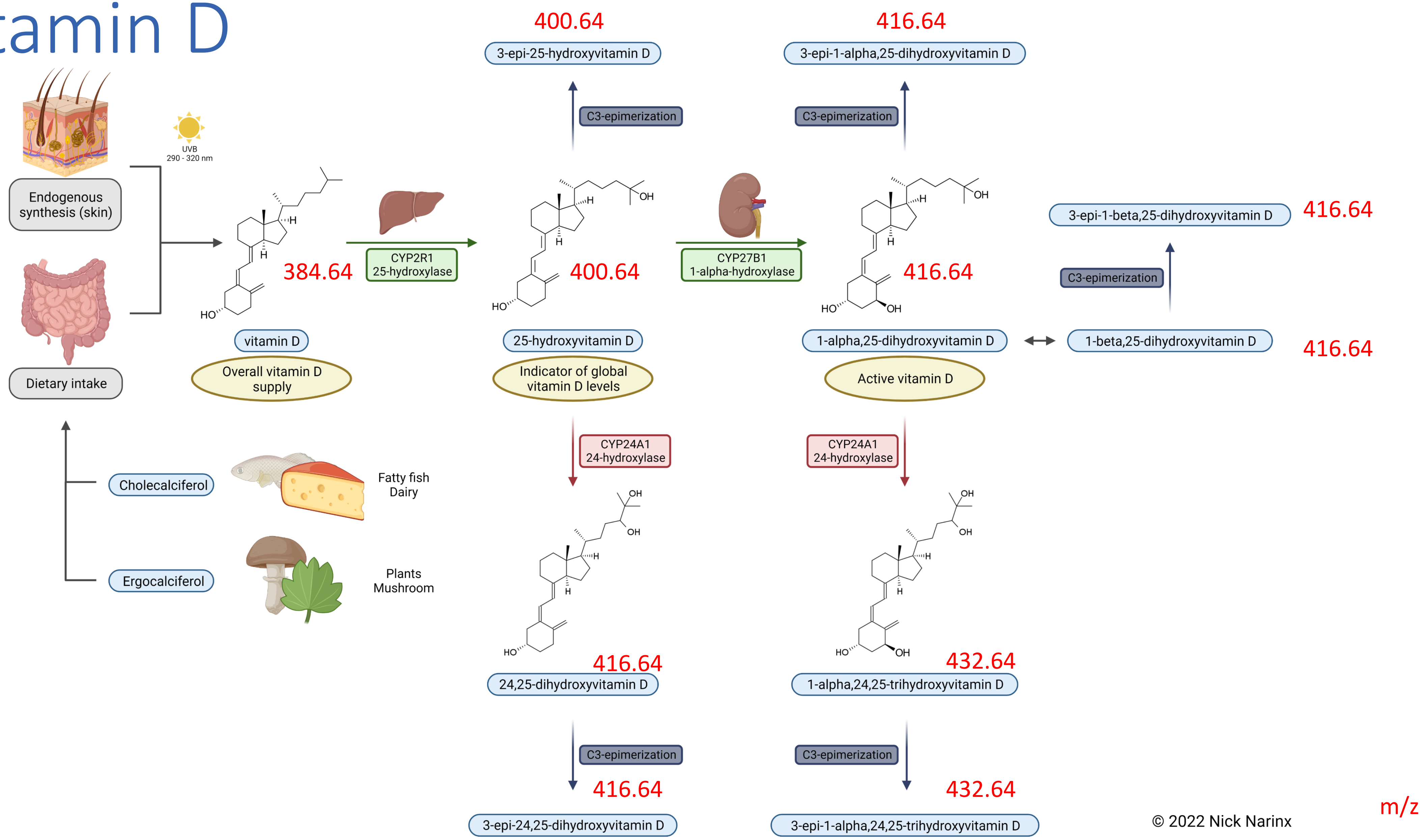
First quadrupole (Q1)

Selection →	Quantitative	Specific m/z
Screening →	Qualitative	Variable m/z



Molecule	m/z
Cholecalciferol (Vitamin D3)	384.64
Calcidiol (25-hydroxyvitamin D3)	400.64
Calcitriol (1,25-dihydroxyvitamin D3)	416.64

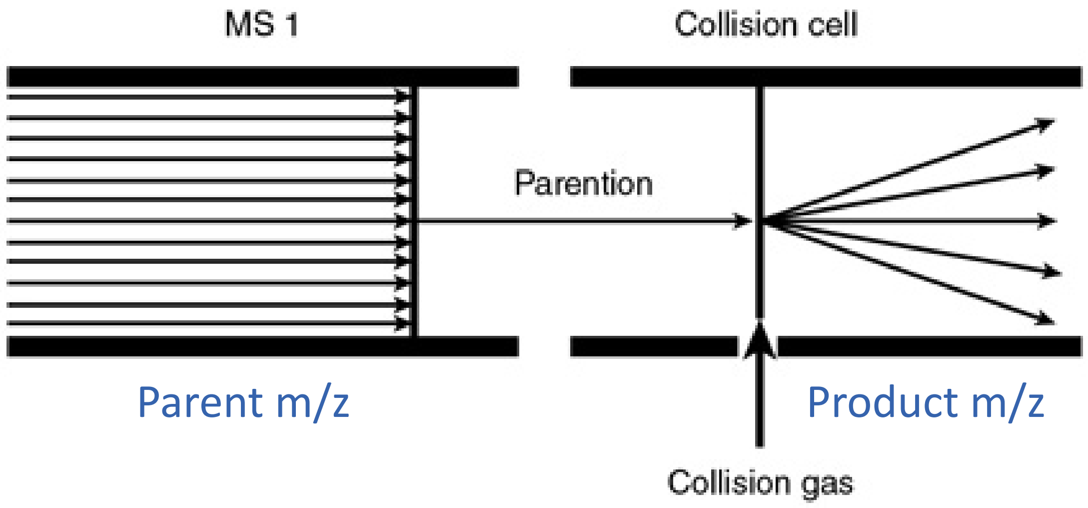
Vitamin D

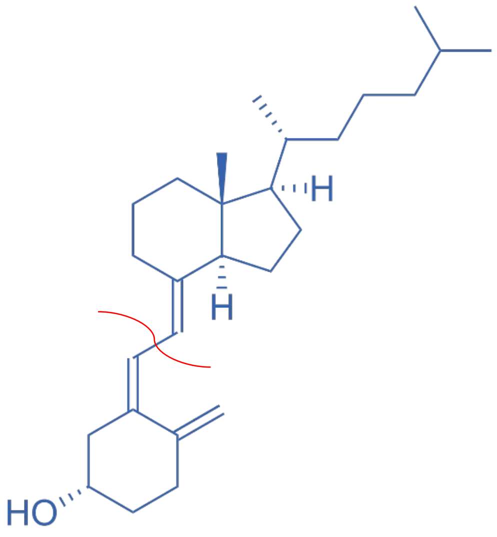


UVB
290 - 320 nm
Endogenous synthesis (skin)
Dietary intake
Cholecalciferol
Fatty fish
Dairy
Ergocalciferol
Plants
Mushroom
384.64
vitamin D
Overall vitamin D supply
CYP2R1
25-hydroxylase
400.64
25-hydroxyvitamin D
Indicator of global vitamin D levels
C3-epimerization
400.64
3-epi-25-hydroxyvitamin D
CYP27B1
1-alpha-hydroxylase
416.64
1-alpha,25-dihydroxyvitamin D
Active vitamin D
C3-epimerization
416.64
3-epi-1-alpha,25-dihydroxyvitamin D
1-beta,25-dihydroxyvitamin D
416.64
C3-epimerization
3-epi-1-beta,25-dihydroxyvitamin D
416.64
CYP24A1
24-hydroxylase
416.64
24,25-dihydroxyvitamin D
C3-epimerization
416.64
3-epi-24,25-dihydroxyvitamin D
CYP24A1
24-hydroxylase
432.64
1-alpha,24,25-trihydroxyvitamin D
C3-epimerization
432.64
3-epi-1-alpha,24,25-trihydroxyvitamin D
m/z

Mass spectrometry

Ionization
First quadrupole (Q1)
Second quadrupole (Q2) Collision cell ⟶ Fragmentation to product ions



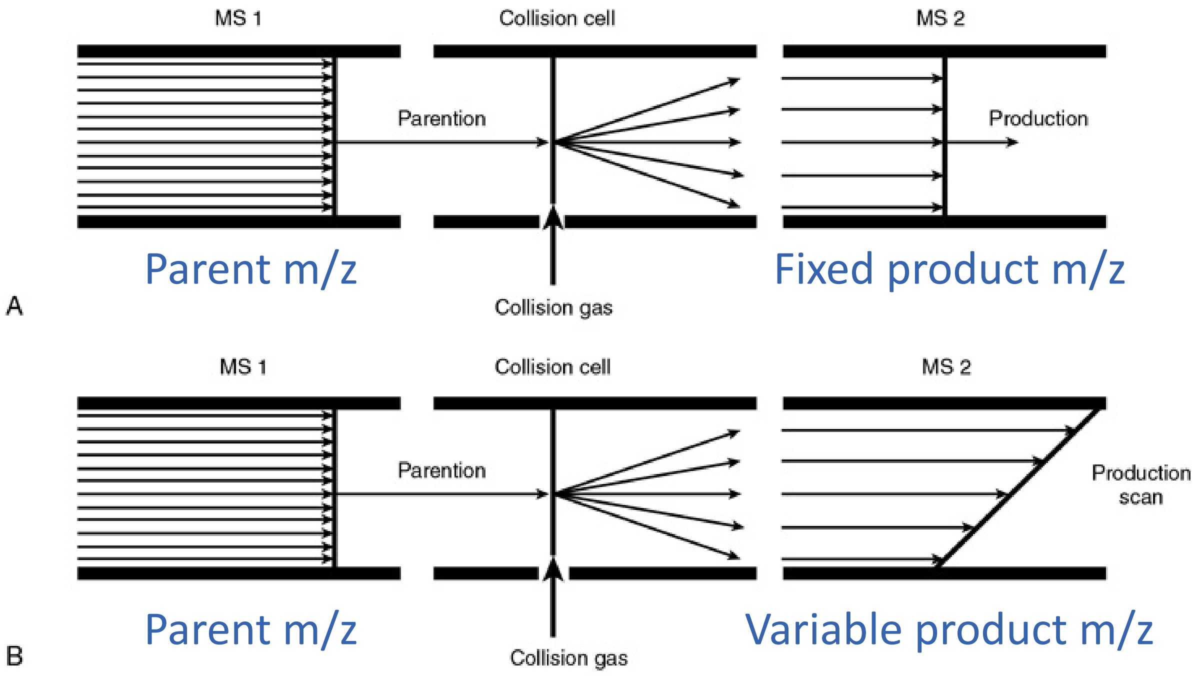


Mass spectrometry

Ionization
First quadrupole (Q1)
Second quadrupole (Q2)
Third quadrupole (Q3) Product selection

Product scan

Compound	MRM (m/z)
25OHD3	558.4 > 298.2 (161.2)
25OHD2	570.4 > 298.2 (280.2)



To mass detector

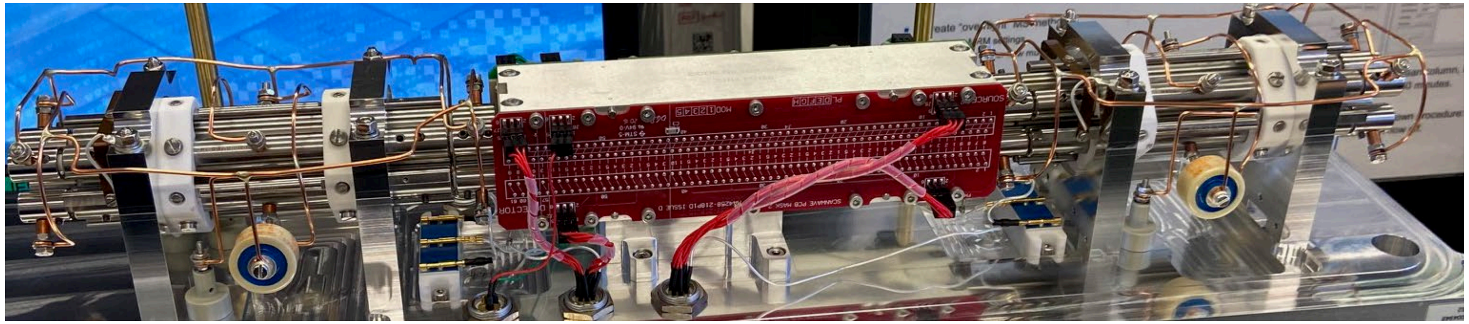
To mass detector

Vitamin D MRM on MS

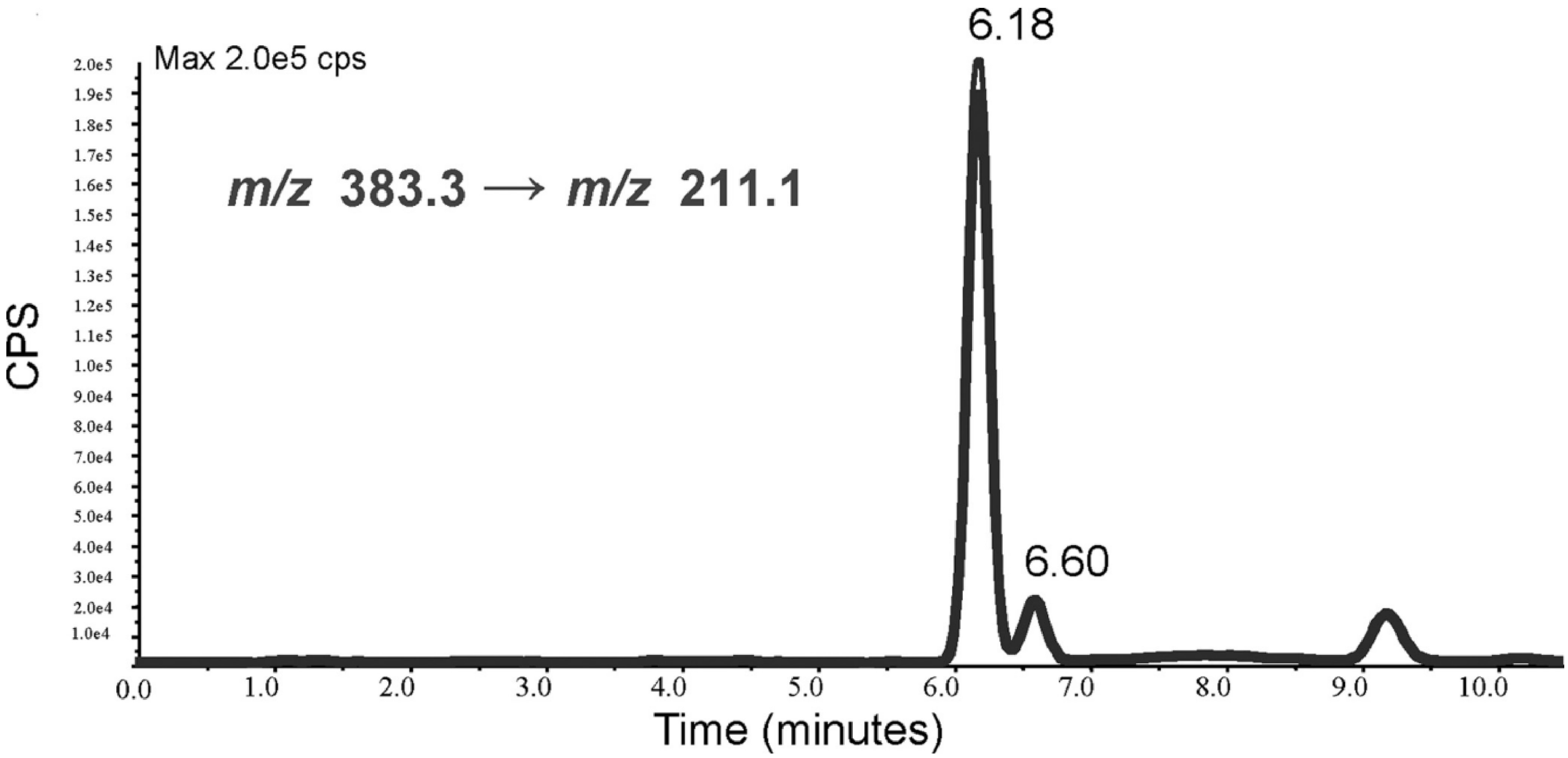
MRM transitions, collision energies and cone voltages of vitamin D metabolites.

Compound	Abbrev.	MRM transitions	Collision energy (eV)	Cone voltage (V)
25-Hydroxyvitamin D3	25OHD3	383.2 > 91.0 383.2 > 107.0	52 32	28 28
3-Epi-25-hydroxyvitamin D3	3-Epi25OHD3	383.2 > 95.4 383.2 > 107.0	36 32	26 26
1α,25-Dihydroxyvitamin D3	1α,25$(OH)_2$D3	399.2 > 105.1 399.2 > 151.1	46 24	22 22
23R,25-Dihydroxyvitamin D3	23R,25$(OH)_2$D3	417.4 > 325.3 417.4 > 343.3	12 10	12 12
24R,25-Dihydroxyvitamin D3	24R,25$(OH)_2$D3	417.4 > 121.1 417.4 > 381.4	14 10	14 14
25-Hydroxyvitamin D2	25OHD2	395.3 > 91.0 395.3 > 119.0	54 22	26 26
24-Hydroxyvitamin D2	24OHD2	395.3 > 340.9 395.3 > 119.0	36 26	66 30
3-Epi-25hydroxyvitaminD2	3-Epi-25OHD2	395.3 > 91.0 395.3 > 119.0	50 26	26 26
1α,25-DihydroxyvitaminD2	1α,25$(OH)_2$D2	411.3 > 133.0 411.3 > 151.0	30 22	26 26
1α,24-DihydroxyvitaminD2	1α,24$(OH)_2$D2	411.3 > 133.0 411.3 > 151.0	30 20	26 26
Ergocalciferol	Vitamin D2	397.4 > 69.0 397.4 > 107.1	22 28	16 16
Cholecalciferol	Vitamin D3	385.4 > 107.0 385.4 > 259.3	30 16	20 20
7α-Hydroxy-4-cholesten-3-one	7αC4	401.4 > 97.0 401.4 > 117.1	26 24	34 32
1α,25-DihydroxyvitaminD3-d3	1α,25$(OH)_2$D3-d3	402.4 > 138.0 402.4 > 154.1	18 20	22 22
3-Epi-hydroxyvitamin-d3	3-Epi-25OHD3-d3	404.4 > 107.2 404.4 > 109.4 404.4 > 368.4	40 22 12	40 22 12
25 Hydroxyvitamin D3	25OHD3 d3	386.4 > 95.1 386.4 > 109.3	26 24	26 26
Ergocalciferol-d3	Vitamin D2-d3	400.3 > 109.8 400.3 > 69.02 400.3 > 83.02	24 30 22	16 16 16

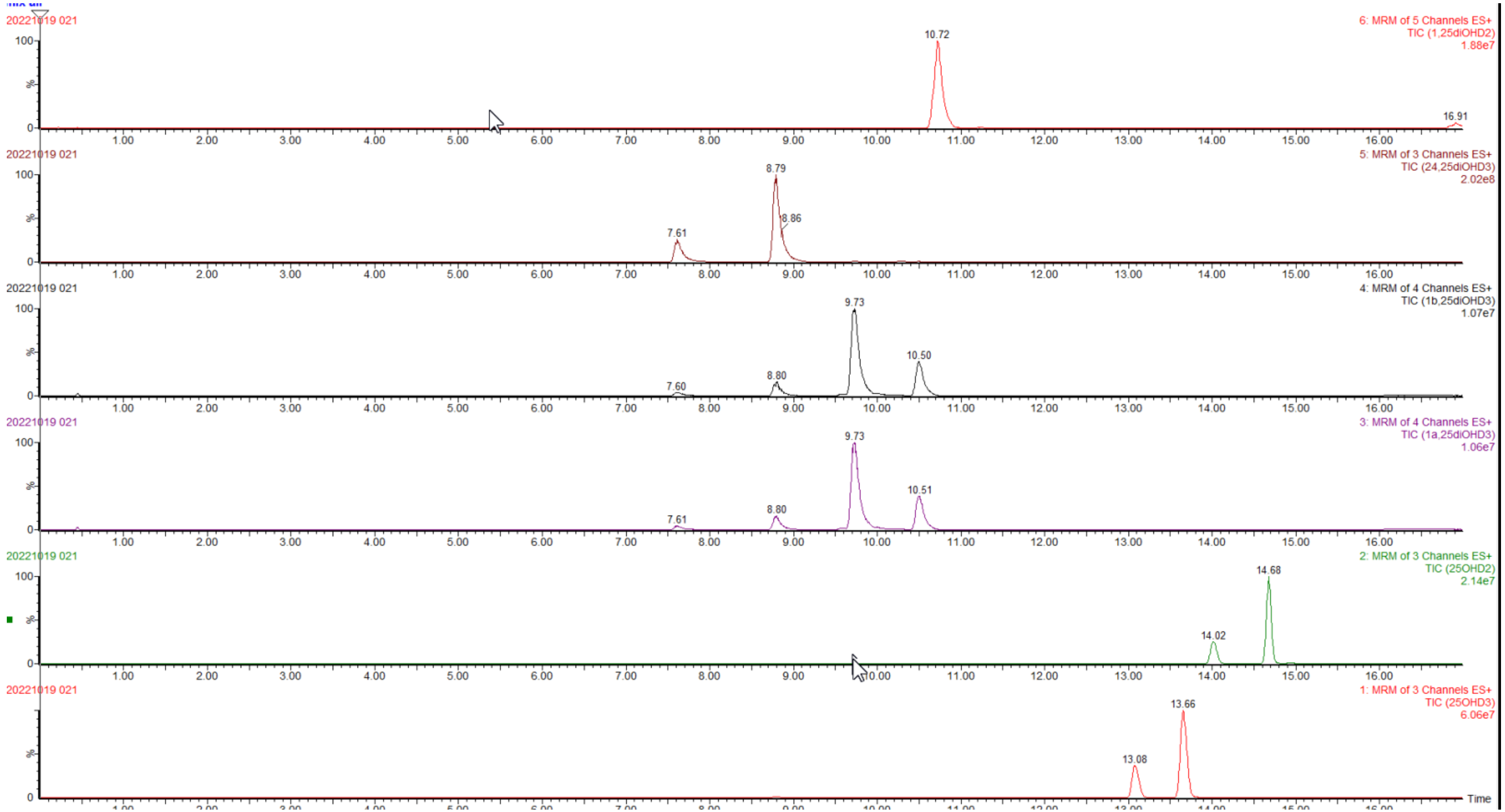
Mass spectrometry



Mass spectrometry data analysis



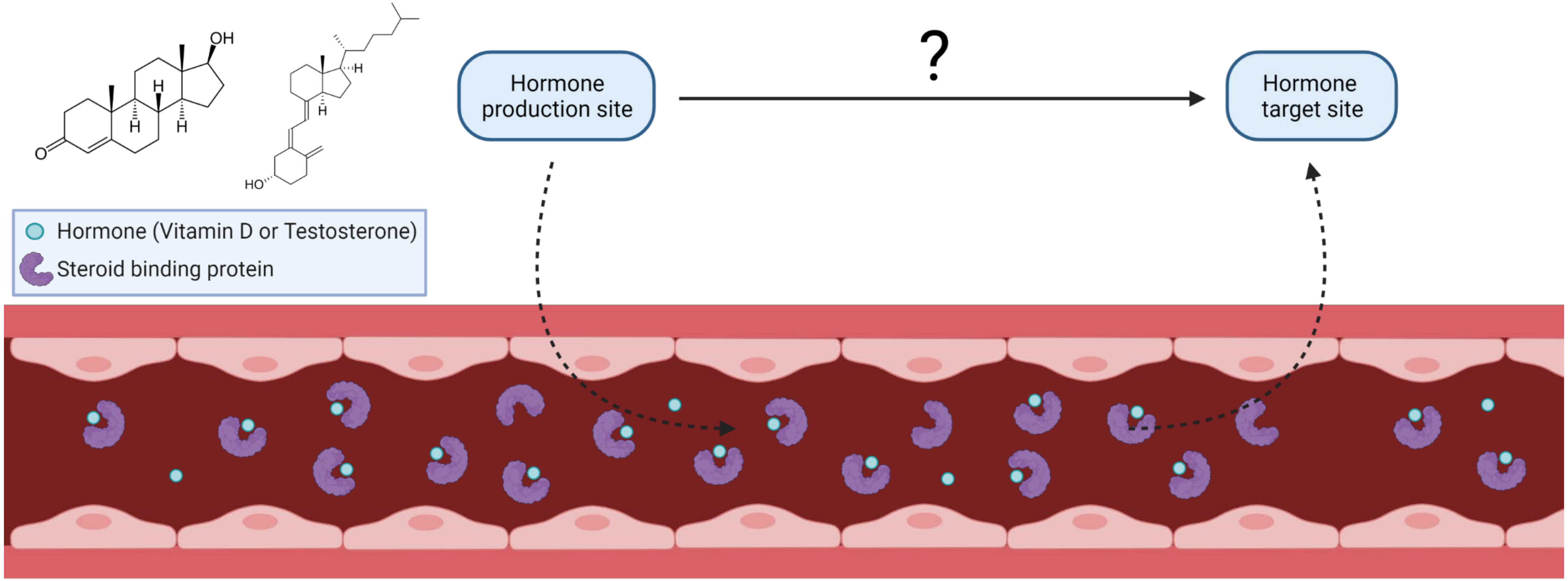
Mass spectrometry data analysis



Total and free hormones

Free hormone hypothesis

Steroid binding proteins



Steroid binding proteins

Specific carriers

Vitamin D binding protein (DBP)

GC/DBP
chr4q11-13

> 120 genetic variants
GC1s, GC1f and GC2

52-58 kDa glycoprotein
Binds all vitamin D-metabolites

Sex hormone-binding globulin (SHBG)

SHBG
chr17p12-13

Genetic variability through SNPs

90-100 kDa homodimeric glycoprotein
Binds all androgens,
except DHEA-sulfate and androstenedione

Aspecific carrier

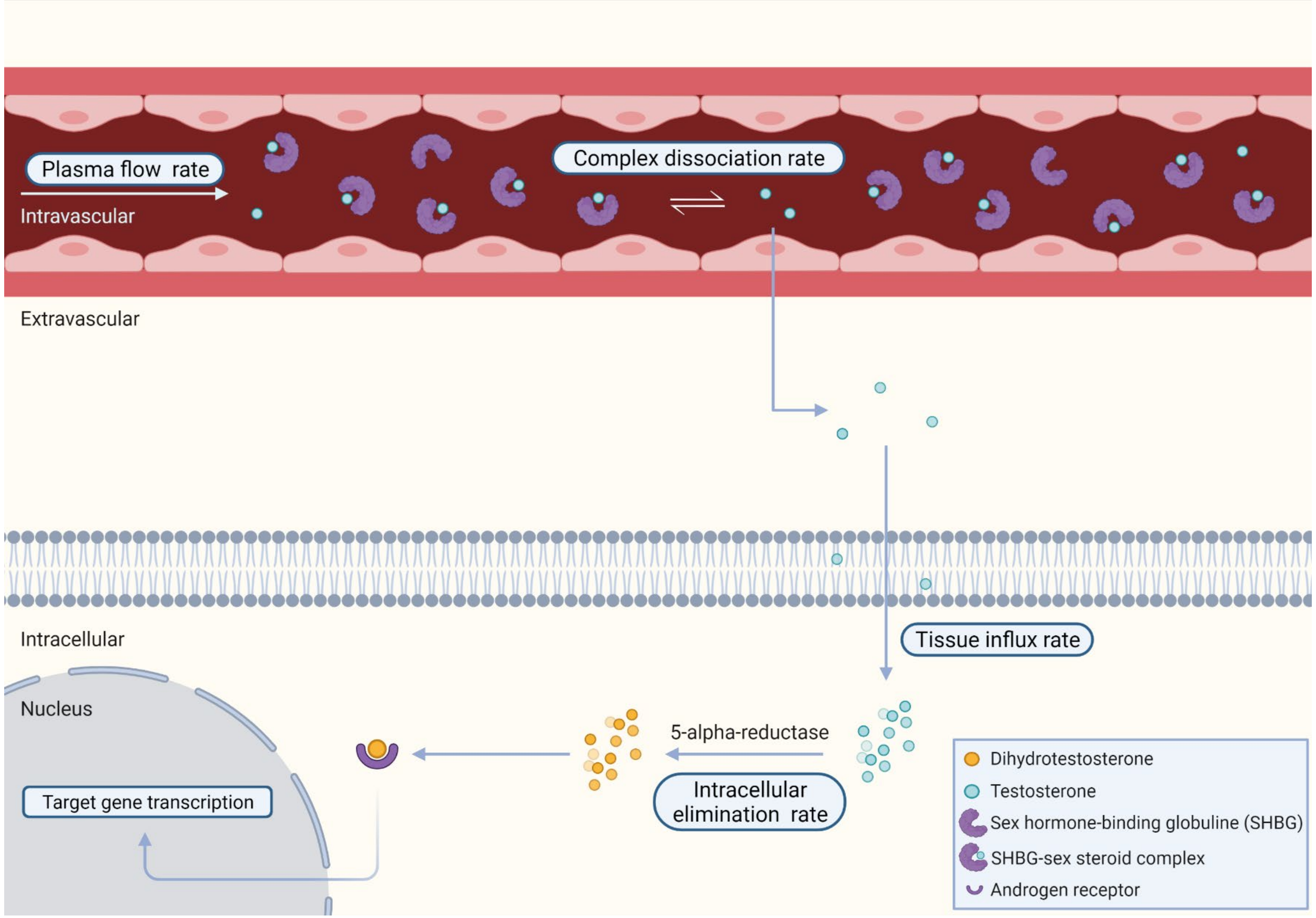
Albumin

ALB
chr4q13.3

66.5 kDa glycoprotein

Transport (fatty acids, drugs…)
Homeostasis (calcium ions…)
Oncotic pressure

Free hormone hypothesis



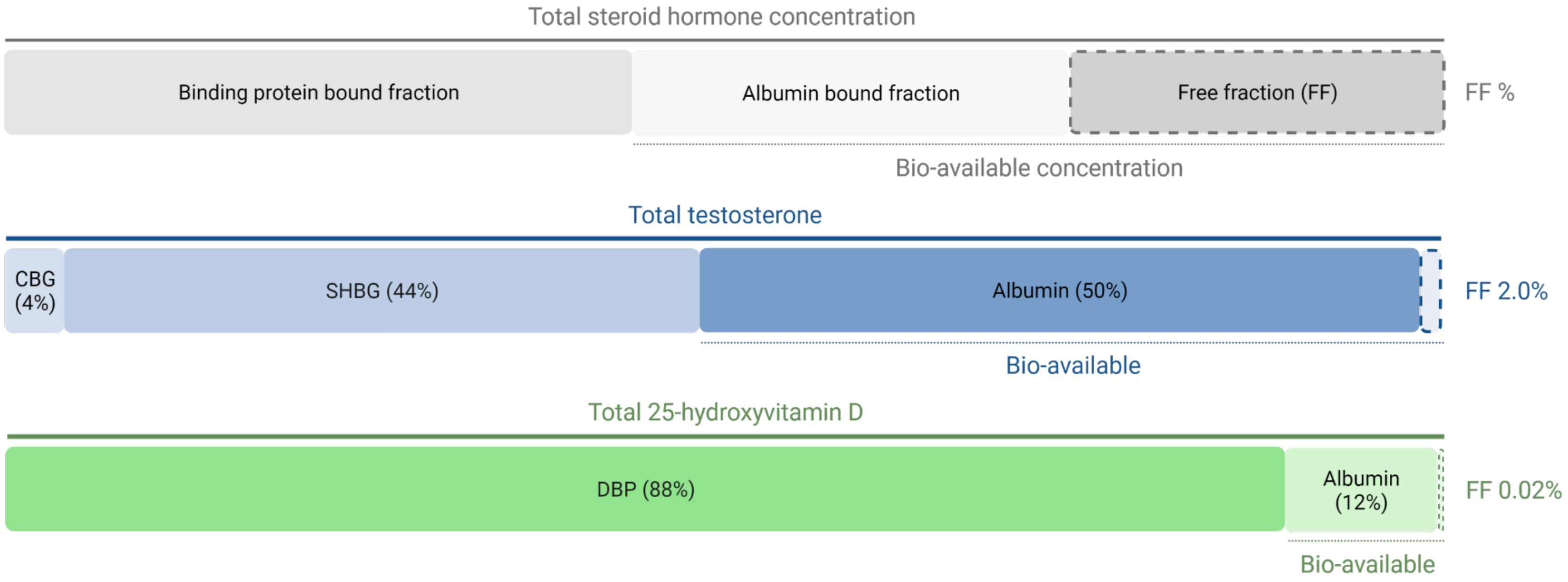
Intracellular hormone concentrations (=biological activity) depend on the concentration of free rather than protein-bound hormone in plasma

Only free hormones can cross the cellular membrane.
(= free hormone transport hypothesis)

Narinx, N., et al. (2022). doi:10.1007/s00018-022-04562-1

Steroid protein binding milieu

Characteristics of binding proteins and fractions per hormone							
	Specific carrier			Aspecific carrier			
Hormone	Binding Protein	Binding affinity (in $M^{-1} s^{-1}$)	Bound fraction (in %)	Binding Protein	Binding affinity (in $M^{-1} s^{-1}$)	Bound fraction (in %)	Free fraction (%)
Testosterone	SHBG	2.0×10^9	44.0	Albumin	4.0×10^4	50.0	2.0
				CBG	5.3×10^6	4.0	
Estradiol	SHBG	7.0×10^8	20.0	Albumin	6.0×10^4	78.0	2.0
25(OH)D	DBP	$7.0\text{-}9.0 \times 10^8$	88.0	Albumin	6.0×10^5	12.0	0.02 - 0.04
$1,25(OH)_2D$	DBP	4.0×10^7	85.0	Albumin	5.4×10^4	15.0	0.3 - 0.4



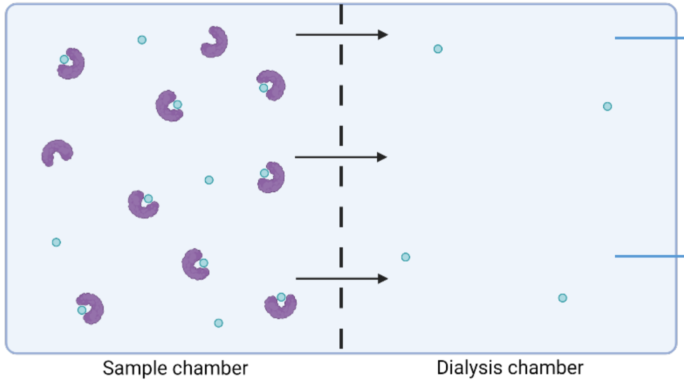
Narinx, N., et al. (2022). doi:10.1007/s00018-022-04562-1

Diagnostic use of free hormones

Assessment of free vitamin D

1. Measurement

Equilibrium Dialysis (ED)



or

Indirect ED

Radio immunosorbent Assay (RIA)

Direct ED

LC-MS/MS

Ultrafiltration (UF)

Direct ELISA - DIAsource

Diagnostic use of free hormones

Assessment of free vitamin D

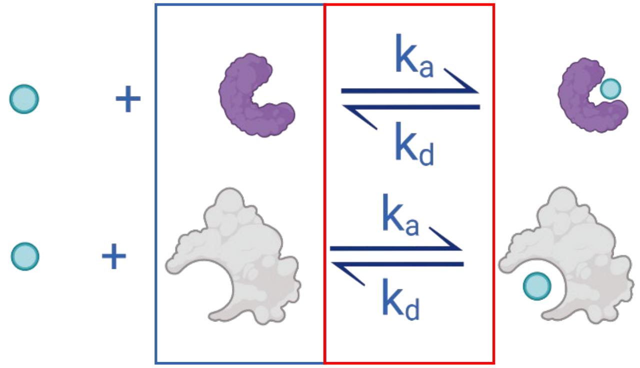
2. Calculation

Total vitamin D concentration

Carrier concentration

DBP

Albumin



Binding affinity

$$free\ vitamin\ D\ metabolite = \frac{total\ vitamin\ D\ metabolite}{1+(Ka_{alb}*albumin)+(Ka_{DBP}*DBP)}$$

Bikle, DD. et al. (2019). doi: 10.3389/fendo.2019.00317.

Methodologic limitations and issues

Why don't we measure free vitamin D directly?

CON's	PRO's
Technically difficult	Gold standard
Labor intensive	Independent of carrier fluctuation
Expensive	
Not routinely available	
No reference range	

What about calculation of free vitamin D?

CON's	PRO's
Formula not generally applicable	Cheap & Convenient
Alteration of DBP binding milieu	Clinically useful
DBP Polymorphisms	Correlated with clinical endpoints
Dependent on quality of total vitamin D and DBP assays	

Valorization of a patient's vitamin D status in clinical settings where DBP levels are altered, such as CKD, obesity and liver problems, has been deemed more appropriate when using free serum 25(OH)D as compared to total serum 25(OH)D.

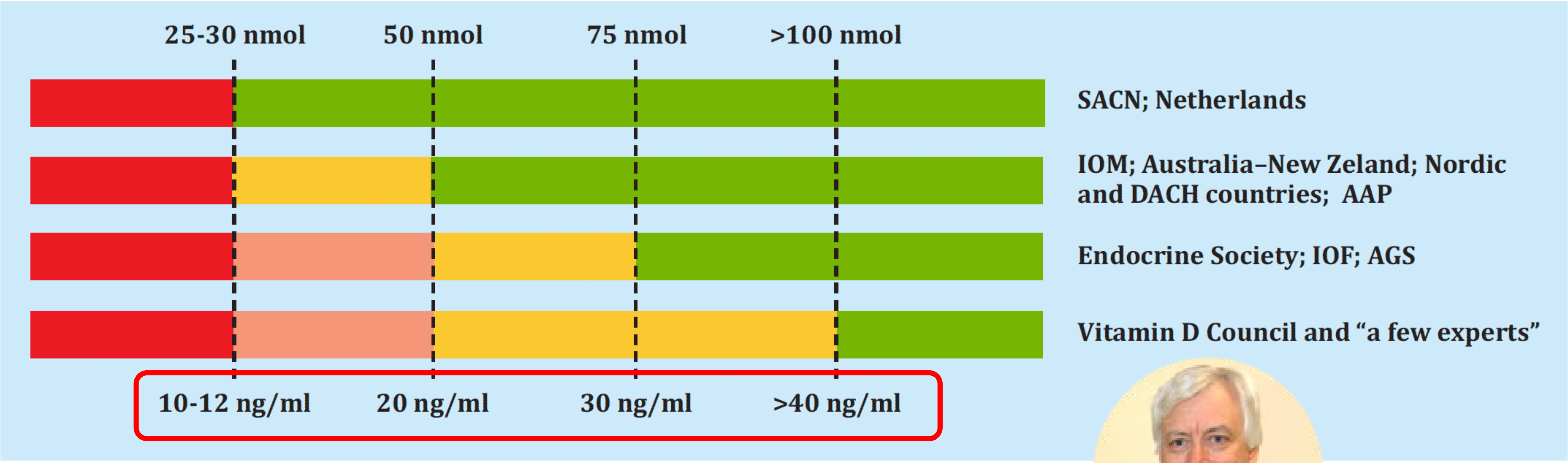
DD Bikle et al., J Clin Invest **78** (3), 748 (1986).
MS Johnsen et al., Scand J Clin Lab Invest **74** (3), 177 (2014).
O Tsuprykov et al., J Steroid Biochem Mol Biol **190**, 29 (2019).
C Yu et al., Circ Res **123** (8), 996 (2018).

→ Clinical use of free vitamin D is hampered!

NO CONSENSUS

“400 – 600 - 800 IU/day”

Figure 4. Definitions of vitamin D deficiency and sufficiency for bone health



“3000 IU/day”

Indications 25vit D testing (adults)

- Osteoporosis and osteomalacia
- Hyperparathyroidism
- Malabsorption (IBD, CF, coelic disease, bariatric surgery)
- Deeply pigmented skin or lacking sun exposure
- Chronic renal failure
- Obesity

PS: routine screening is NOT recommended

Indications 25vit D testing (children)

- Rickets
- Infants of mother with vitamin D deficiency
- Exclusively breastfed babies

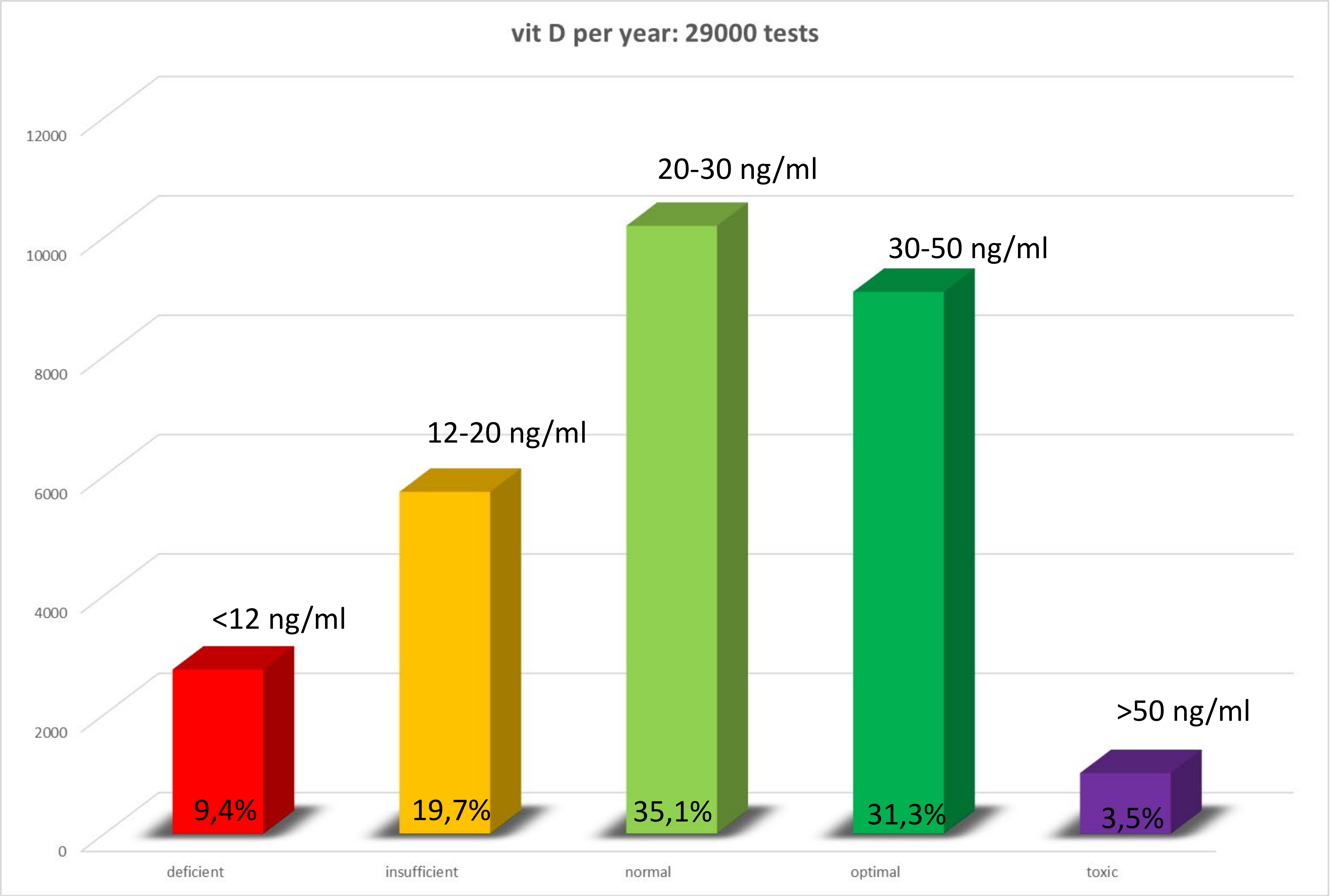
Indications for 1,25 vit D testing

- Chronic kidney disease
- Hyper- or hypocalcemia

- Hypercalcemia in granulomatous disease (sarcoidois, tuberculosis…)
- 1 alpha hydroxylase deficiency, hypophosfatemia
- Vitamin D receptor defect

- NOT for vitamin D reserve

Vit D: Leuven



<2 ng/ml = 0,1% n=30

> 100 ng/ml = 0,03% n=10

Vit D: terugbetaling RIZIV

559333-559344 Doseren van 1,25-dihydroxyvitamine D na chromatografie B 1400

Diagnoseregel 98

De verstrekkingen 1,25 vit D en FGF-23 mogen enkel worden aangerekend wanneer zij worden voorgeschreven:

1. geneesheer-specialist in de inwendige pathologie

2. in geval van gestoorde calcemie of fosforemie

3. maximum éénmaal per jaar

Wel of niet testen

- Gezonde **asymptomatische volwassenen** moeten **niet** gescreend worden op 25(OH)Vit D.
- Geïnstitutionaliseerde **bejaarden**, bejaarden met een hoog valrisico en alle 75+ moeten **geen** 25(OH)D gehaltebepaling krijgen. Zij krijgen best standaard een vitamine D- en calcium supplement toegediend.
- Patiënten die gekend zijn met een **osteoporose** (gedaalde BMD/fracturen) moeten een oppuntstelling krijgen met een dosering van 25(OH)D
- Bij de aanwezigheid van ziekten of factoren die het **risico op vitamine D deficiëntie** verhogen, kan het gerechtvaardigd zijn om éénmalig te doseren
- Patiënten met gekende **malabsorptie** (bariatrische chirurgie, chronisch inflammatoir darmlijden, coeliakie, mucoviscidose), chronische **nierinsufficiëntie** vanaf stadium IIIb1 met inbegrip van dialyse en transplantatiepatiënten en **hyperparathyreoïdie**

Motivering voor beperking 25(OH)D

De laatste vijf jaar werd een verdubbeling vastgesteld van het aantal aangevraagde 25- hydroxyvitamine D analyses waarvan 75% wordt aangevraagd door huisartsen en dit vooral bij patiënten tussen de 50 en de 82 jaar met een piek op 68 jaar. 25% van de patiënten wordt meer dan één maal per jaar getest.

Nochtans zijn er belangrijke beperkingen en hiaten in de huidige kennis omtrent het nut van vitamine D- en calcium-doseringen.

In tegenstelling tot vele andere biochemische parameters zijn de referentiewaarden voor vitamine D geen normaalwaarden voor de gemiddelde bevolking, maar streefwaarden die aangeven welke spiegel allicht voldoende is.

559311-559322 Doseren van 25-hydroxyvitamine D B 400

Diagnoseregel 155

Van de verstrekkingen 434490-434501 en 559311-559322 (25 vit D) mag er één verstrekking één maal per kalenderjaar aan de ZIV aangerekend worden

tenzij bij chronische *nierinsufficiëntie vanaf stadium IIIb*, bij nierdialyse, na niertransplantatie of bij *gedocumenteerde malabsorptie* (chronisch inflammatoir darmlijden, coeliakie, na bariatrische chirurgie, mucoviscidose) waar de verstrekkingen 3 maal per kalenderjaar aangerekend mogen worden

UZ Leuven

Per maand moeten we 130 facturaties van de 2500 blokkeren (100 ambulanten en 30 gehospitaliseerden) omdat er in de loop van het jaar reeds een 25-hydroxy vitamine D gevraagd werd.

Dit komt overeen met **5% van ons totaal aantal 25-hydroxyvitamine D bepalingen** (die dus niet aangerekend mogen worden).

Dit aantal weigeringen zal nog verder zakken als we de aanvrager laten beslissen of de patiënt DRIE bepalingen per jaar mag krijgen (wegens malabsorptie, zwaar nierlijden, hyper- of hypoparathyroïdie, fosfaatdiabetes of IV behandeling met bisfosfonaten).

Dit leidt tot de voorzichtige conclusie dat er relatief rationeel met de analyse wordt omgesprongen binnen ons ziekenhuis.