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Vitamin D3 (25-OH)

cobas®

25-Hydroxyvitamin D_3

03314847 190 **100 tests**

• Indicates analyzers on which the kit can be used

Elecsys 2010	MODULAR ANALYTICS E170	**cobas e** 411	**cobas e** 601
•	•	•	•

English

Intended use

Immunoassay for the in vitro quantitative determination of 25-hydroxyvitamin D_3 in human serum and plasma. The Elecsys Vitamin D_3 (25-OH) assay is used as an aid in the assessment of Vitamin D_3 sufficiency in adults.
The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Summary

Vitamin D is a fat-soluble steroid hormone precursor that is mainly produced in the skin by exposure to sunlight or it is supplied via dietary sources (mainly egg yolk, fish oil and plants). Vitamin D is biologically inert and must undergo two successive hydroxylations in the liver and kidney to become the biologically active 1,25 dihydroxyvitamin D.[1]
The two most important forms of vitamin D are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). In contrast to vitamin D_3, vitamin D_2 has to be taken up with food. In the human body vitamin D_3 and D_2 are bound to vitamin D-binding protein in plasma and transported to the liver where both are hydroxylated in position 25 forming 25-OH vitamin D. 25-OH vitamin D is the metabolite that should be measured in blood to determine the overall vitamin D status because it is the major storage form of vitamin D in the human body. This primary circulating form of vitamin D is biologically inactive with levels approximately 1000-fold greater than the circulating 1,25 $(OH)_2$ vitamin D. The half life of circulating 25-OH vitamin D is 2-3 weeks.
More than 95% of 25-OH vitamin D, measurable in serum, is 25-OH vitamin D_3 whereas 25-OH vitamin D_2 reaches measurable levels only in patients taking vitamin D_2 supplements.[2,3,4]
Vitamin D deficiency is a common cause of secondary hyperparathyroidism. Elevations of PTH levels, especially in elderly vitamin D deficient adults can result in osteomalacia, increased bone turnover, reduced bone mass and risk of bone fractures.
Low 25-OH vitamin D concentrations are also associated with lower bone mineral density. In conjunction with other clinical data, the results may be used as an aid in the assessment of bone metabolism.[5,6,7,8,9,10]
The Elecsys Vitamin D_3 (25-OH) assay employs a polyclonal antibody directed against vitamin D_3.

Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: Vitamin D_3 from 35 µL sample competes with the biotin labeled vitamin D bound in the preformed complex biotin-vitamin D/polyclonal vitamin D_3-specific antibody labeled with a ruthenium complex. The remaining amount of immunocomplex biotin-vitamin D/polyclonal vitamin D_3-specific antibody labeled with ruthenium is dependent upon the analyte concentration in the sample.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Reagents - working solutions

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Reaction buffer (gray cap), 1 bottle, 8 mL: Acetate buffer approx. 220 mmol/L, pH 3.9; albumin (human) 2 g/L; preservative.

R2 Anti-vitamin D_3-Ab~Ru(bpy)$_3^{2+}$; vitamin D derivate~biotin (black cap), 1 bottle, 9 mL: Polyclonal anti-vitamin D_3 antibody (sheep) labeled with ruthenium complex 1.5 mg/L; biotinylated vitamin D 0.15 mg/L; phosphate buffer 20 mmol/L, pH 6.5; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.
All human material should be considered potentially infectious.
The materials of human origin used were tested for HIV, HBV and HCV infection. The findings were negative.
The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.
However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be treated just as carefully as a patient specimen. In the event of exposure the directives of the responsible health authorities should be followed.[11,12]
Avoid the formation of foam with all reagents and sample types (specimens, calibrators, and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.
All information required for correct operation is read in via the respective reagent barcodes.

Storage and stability

Store at 2-8°C.
Store the Elecsys Vitamin D_3 (25-OH) reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.
Stability:

unopened at 2-8°C:	up to the stated expiration date
after opening at 2-8°C:	8 weeks
on Elecsys 2010 and **cobas e** 411:	1 week
on MODULAR ANALYTICS E170 and **cobas e** 601:	2 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.
Serum collected using standard sampling tubes or tubes containing separating gel.
Li-heparin and K_3-EDTA plasma.
Criterion: Method comparison serum versus plasma, slope 0.9-1.1 + intercept within <± 3 x analytical sensitivity (LDL) + coefficient of correlation > 0.95.
Serum: Stable for 8 hours at 18-25°C, 4 days at 2-8°C, 6 months at -20°C.
K_3-EDTA plasma: Stable for 8 hours at 18-25°C, 4 days at 2-8°C, 6 months at -20°C.
Li-heparin plasma: Stable for 8 hours at 18-25°C, 1 day at 2-8°C; do not freeze samples containing Li-heparin.
Stability of serum obtained with separating tubes: 24 hours at 2-8°C (note the data provided by the tube manufacturer).
The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Vitamin D3 (25-OH)

cobas®

25-Hydroxyvitamin D_3

Centrifuge samples containing precipitates before performing the assay. Do not use heat-inactivated samples. Do not use samples and controls stabilized with azide.
Ensure the patients' samples, calibrators, and controls are at ambient temperature (20-25°C) before measurement.
Because of possible evaporation effects, samples, calibrators, and controls on the analyzers should be measured within 2 hours.

Materials provided
See "Reagents - working solutions" section for reagents.

Materials required (but not provided)
- Cat. No. 03314855, Vitamin D3 (25-OH) CalSet, for 4 x 1 mL
- Cat. No. 11972227, PreciControl Bone, for 2 x 2 mL each of PreciControl Bone 1, 2, and 3
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:
- Cat. No. 11662988, ProCell, 6 x 380 mL system buffer
- Cat. No. 11662970, CleanCell, 6 x 380 mL measuring cell cleaning solution
- Cat. No. 11930346, Elecsys SysWash, 1 x 500 mL washwater additive
- Cat. No. 11933159, Adapter for SysClean
- Cat. No. 11706802, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- Cat. No. 11706799, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170 and **cobas e** 601 analyzers:
- Cat. No. 04880340, ProCell M, 2 x 2 L system buffer
- Cat. No. 04880293, CleanCell M, 2 x 2 L measuring cell cleaning solution
- Cat. No. 12135027, CleanCell M, 1 x 2 L measuring cell cleaning solution (for USA)
- Cat. No. 03023141, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- Cat. No. 03005712, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- Cat. No. 12102137, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- Cat. No. 03023150, WasteLiner, waste bags
- Cat. No. 03027651, SysClean Adapter M

Accessories for all analyzers:
- Cat. No. 11298500, Elecsys SysClean, 5 x 100 mL system cleaning solution

Only available in the USA:
- Cat. No. 03314863, Elecsys Vitamin D_3 (25-OH) CalCheck, 3 concentration ranges

Assay
For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator manual for analyzer-specific assay instructions.
Resuspension of the microparticles takes place automatically before use.
Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.
MODULAR ANALYTICS E170, Elecsys 2010 and **cobas e** analyzers: Bring the cooled reagents to approx. 20°C and place on the reagent disk (20°C) of the analyzer. Avoid the formation of foam. The system **automatically** regulates the temperature of the reagents and the opening/closing of the bottles.

Calibration
Traceability: This method has been standardized against LC-MS-MS.[13]
Every Elecsys Vitamin D_3 (25-OH) reagent set has a barcoded label containing the specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer by the use of Elecsys Vitamin D_3 (25-OH) CalSet.
Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows:
MODULAR ANALYTICS E170, Elecsys 2010 and **cobas e** analyzers:
- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the specified limits

Quality control
For quality control, use Elecsys PreciControl Bone 1, 2, and 3.
Other suitable control material can be used in addition.
Controls for the various concentration ranges should be run as single determinations at least once every 24 hours when the test is in use, once per reagent kit, and after every calibration. The control intervals and limits should be adapted to each laboratory's individual requirements.
Values obtained should fall within the defined limits.
Each laboratory should establish corrective measures to be taken if values fall outside the limits.

Calculation
The analyzer automatically calculates the analyte concentration of each sample (either in ng/mL or nmol/L).

Conversion factors: nmol/L x 0.40 = ng/mL
ng/mL x 2.50 = nmol/L

Limitations - interference
The assay is unaffected by icterus (bilirubin < 205 µmol/L or < 12 mg/dL), hemolysis (Hb < 0.062 mmol/L or < 0.1 g/dL; samples showing visible signs of hemolysis may show interference. Falsely elevated results are obtained when using samples with hemoglobin (concentrations > 0.1 g/dL), lipemia (Intralipid < 400 mg/dL), and biotin (< 82 nmol/L or < 20 ng/mL).
Criterion: Mean recovery at limit of interference within ± 15% of initial value.
In patients receiving therapy with high biotin doses (i.e. > 5 mg/day), no sample should be taken until at least 8 hours after the last biotin administration.
No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.
In vitro tests were performed on 17 commonly used pharmaceuticals and 9 bone drugs. No interference with the assay was found.
The risk of interference from potential immunological interactions between test components and rare sera has been minimized by the inclusion of suitable additives.
In rare cases, interference due to extremely high titers of antibodies to streptavidin and ruthenium can occur.
For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Measuring range
4-100 ng/mL or 10-250 nmol/L (defined by the lower detection limit and the maximum of the master curve). Values below the detection limit are reported as < 4 ng/mL (< 10 nmol/L). Values above the measuring range are reported as > 100 ng/mL (> 250 nmol/L).

Dilution
Samples with 25-OH vitamin D_3 concentrations above the measuring range can be diluted manually using a suitable human serum with a low analyte concentration. The recommended dilution is 1:2. The concentration of the diluted sample must be > 51 ng/mL (> 128 nmol/L). After manual dilution, multiply the results by the dilution factor 2. The endogenous analyte concentration of the human serum used for dilution has to be taken into account.

Expected values
Health based reference values (to be used as a guideline):
Currently there is no standard definition of the optimal vitamin D status. Many specialists consider the commonly used population based reference values too low. Health based reference values are recommended to replace population based reference values.[14]
There is a consensus opinion that the minimal vitamin D_3 (25-OH) level for bone health is between 20-32 ng/mL (50-80 nmol/L).[18]
A more recent consensus of experts leads to the conclusion that for general health a desirable concentration of vitamin D_3 (25-OH) is ≥ 30 ng/mL (≥ 75 nmol/L).[15]

Population based reference values (for information only):
In addition to the above given consensus of experts, the values shown below were performed on samples from an apparently healthy German population during summertime, using the Elecsys Vitamin D_3 (25-OH) assay.
Out of 500 apparently healthy volunteers, 358 (178 men, 180 women) sera were selected for calculation. The sera were collected between May and August in the northern part of Germany. The age range was between 20 and 70 years. The health status was assessed by measurement of

04896645001V1

Vitamin D3 (25-OH)

25-Hydroxyvitamin D_3

a standard clinical chemistry and hematology profile, a brief medical examination, and a medical questionnaire. Pregnant or lactating women were excluded. The reference population was selected according to normal clinical chemistry parameters, normal hematology results, no vitamin intake, normal PTH (15-65 pg/mL) and normal calcium (2.09-2.54 mmol/L (12-60 years), 2.19-2.54 mmol/L (> 60 years)) values.

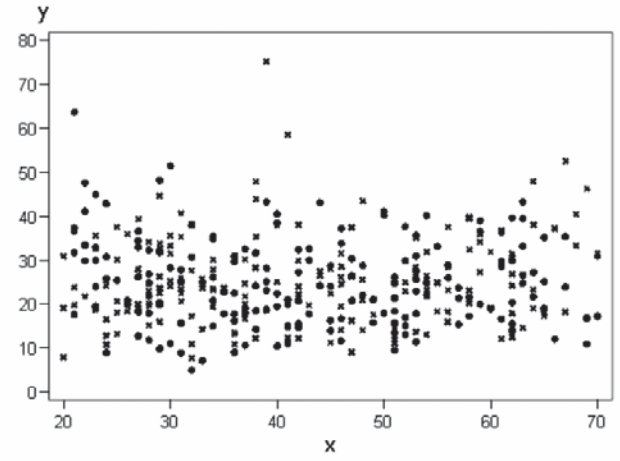
N	PTH	25-OH vitamin D_3			
		Median		5th-95th percentile	
	pg/mL	ng/mL	nmol/L	ng/mL	nmol/L
358	15-65	24.1	60.2	11.1-42.9	27.7-107

The subgrouping of the above cohort according to PTH level nicely show the inverse relationship between the concentrations of PTH and 25-OH vitamin D_3.

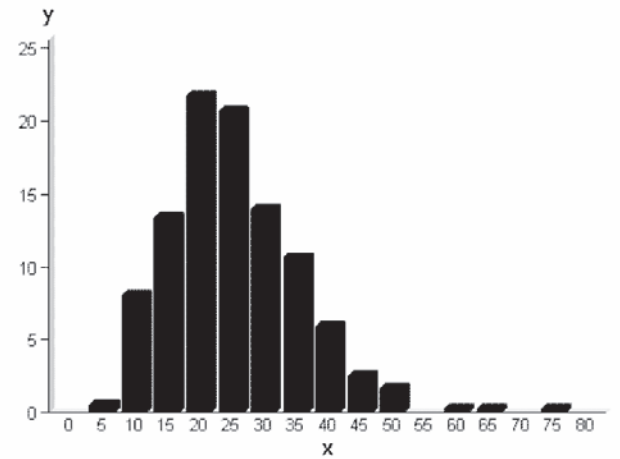
N	PTH	Median (25-OH vitamin D_3)	
	pg/mL	ng/mL	nmol/L
72	< 30	26.9	67.3
183	30-45	24.8	62.0
103	> 45-65	20.2	50.5

Age group (years)	20-29	30-39	40-49	50-59	60-70	Total
Female	42	39	34	38	27	180
Male	42	44	34	33	25	178
Total	84	83	68	71	52	358

Distribution of 25-OH vitamin D_3 in an apparently healthy population (n = 358):



x: Age (years); • = female, x = male
y: Elecsys Vitamin D_3 (25-OH) assay, (ng/mL)



x: Elecsys Vitamin D_3 (25-OH) assay, (ng/mL)
y: Frequency (%)

Please note: These values should only be used as a guideline. It should be taken into consideration that differences in vitamin D_3 levels may exist with respect to gender, age, season, geographical latitude and ethnic groups.[16,17]
Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Population based reference ranges should not be taken as clinical cutoff to recommend or dissuade from vitamin D supplementation. Guidance for supplementation should be taken from recent literature.[14,15,18]

Specific performance data
Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision
Reproducibility was determined using Elecsys reagents, pooled human sera, and controls in a modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute; formerly NCCLS): 6 times daily for 10 days (n = 60); within-run precision on MODULAR ANALYTICS E170 analyzer, n = 21. The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers

Sample	Mean		**Within-run precision** SD		CV	**Total precision** SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%	ng/mL	nmol/L	%
HS[a] 1	25.2	63.0	1.45	3.63	5.7	2.48	6.20	9.9
HS 2	39.9	99.9	2.26	5.65	5.7	2.91	7.28	7.3
HS 3	65.6	164	3.53	8.83	5.4	4.50	11.3	6.9
PC[b] Bone1	22.7	56.8	1.09	2.73	4.8	1.96	4.90	8.6
PC Bone2	44.9	112	1.79	4.48	4.0	3.47	8.68	7.7
PC Bone3	74.2	185	3.02	7.55	4.1	4.88	12.2	6.6

a) HS = human serum
b) PC = PreciControl

MODULAR ANALYTICS E170 and **cobas e** 601 analyzers

Sample	**Within-run precision** Mean		SD		CV	**Total precision** Mean		SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%	ng/mL	nmol/L	ng/mL	nmol/L	%
HS 1	18.7	46.8	0.91	2.28	4.9	19.4	48.6	1.51	3.78	7.8
HS 2	27.5	68.8	1.17	2.93	4.2	29.5	73.8	1.69	4.23	5.7
HS 3	71.6	179	2.51	6.28	3.5	70.8	177	3.00	7.50	4.2
PC Bone1	24.3	60.8	1.39	3.48	5.7	24.6	61.5	1.21	3.03	4.9
PC Bone2	39.6	99.0	1.10	2.75	2.8	38.1	95.2	1.56	3.90	4.1
PC Bone3	68.0	170	1.61	4.03	2.4	67.6	169	2.47	6.18	3.7

Analytical sensitivity (lower detection limit)
4 ng/mL (10 nmol/L)
The detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (master calibrator, standard 1 + 2 SD, within-run precision, n = 21).

Method comparison
1. A comparison of the Elecsys Vitamin D_3 (25-OH) assay (y) using samples measured with LC-MS-MS (x) gave the following correlations (ng/mL or nmol/L):
Number of samples measured: 771

Passing/Bablok[19]	y = 1.008x + 0.045
Pearson	r = 0.902

The sample concentrations were between approx. 4 ng/mL (10 nmol/L) and 96 ng/mL (240 nmol/L).

Vitamin D3 (25-OH)

cobas®

25-Hydroxyvitamin D_3

2. A comparison of the Elecsys Vitamin D_3 (25-OH) assay (y) with a commercially available automated 25-OH vitamin D assay (x) using clinical samples gave the following correlations (ng/mL or nmol/L):
Number of samples measured: 291

Passing/Bablok[19]	y = 1.272x - 0.045
Pearson	r = 0.912

The sample concentrations were between approx. 4 ng/mL (10 nmol/L) and 96 ng/mL (240 nmol/L).

Analytical specificity
The following cross-reactivities were found, tested with 25-OH vitamin D_3 concentrations of 30 ng/mL and 80 ng/mL:

	Concentration tested ng/mL	Cross-reactivity %
25-OH vitamin D_2	1000	< 10
24,25-$(OH)_2$ vitamin D_3	1000	< 20
1,25-$(OH)_2$ vitamin D_3[c]	not applicable	up to 100
Cholecalciferol (vitamin D_3)	5000	< 1
Ergocalciferol (vitamin D_2)	5000	< 1

c) Circulating 1,25 $(OH)_2$ vitamin D_3 levels in serum are approximately 1000-fold lower than the circulating 25-OH vitamin D_3.

No cross-reactivity was found with PTH fragments 1-84, 1-34 and 7-84.

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