

proBNP II

N-terminal pro B-type natriuretic peptide

cobas®

REF		SYSTEM
04842464 190	100	Elecsys 2010 MODULAR ANALYTICS E170 cobas e 411 cobas e 601 cobas e 602

English

Intended use

Immunoassay for the in vitro quantitative determination of N-terminal pro B-type natriuretic peptide in human serum and plasma. This assay is indicated as an aid in the diagnosis of individuals suspected of having congestive heart failure and detection of mild forms of cardiac dysfunction.^{1, 2,3,4,5,6} The test also aids in the assessment of heart failure severity in patients diagnosed with congestive heart failure.⁷ This assay is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure, and it can also be used for monitoring the treatment in patients with left ventricular dysfunction.^{8,9}

The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Summary

Left ventricular dysfunction can occur as a part of coronary heart disease, arterial hypertension, valvular disease, and primary myocardial disease. If the left ventricular dysfunction remains untreated and is progressive, the potential for mortality is high, e.g. due to sudden cardiac death.

Chronic cardiac insufficiency is a clinical syndrome caused by impairment of the cardiac pumping function. Based on the symptoms, the severity of cardiac insufficiency is classified in stages (New York Heart Association classification [NYHA] I-IV). When patients are grouped according to their NYHA classification NT-proBNP levels increase with increasing class numbers and reflect the severity of cardiac impairment.⁷ The high sensitivity of NT-proBNP allows also the detection of mild forms of cardiac dysfunction in asymptomatic patients with structural heart disease.^{1,2,3,4} Clinical information and imaging procedures are used to diagnose left ventricular dysfunction.¹⁰

The significance of natriuretic peptides in the control of cardiovascular system function has been demonstrated. Studies reveal that natriuretic peptides can be used for diagnostic clinical problems associated with left ventricular dysfunction.¹¹ The following natriuretic peptides have been described: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).^{12,13}

ANP and BNP, as antagonists of the renin-angiotensin-aldosterone system, influence by means of their natriuretic and diuretic properties, the electrolyte and fluid balance in an organism.^{14,15} In subjects with left ventricular dysfunction, serum and plasma concentrations of BNP increase, as does the concentration of the putatively inactive amino-terminal fragment, NT-proBNP.

ProBNP, comprising 108 amino acids, is secreted mainly by the ventricle and, in this process, is cleaved into physiologically active BNP (77-108) and the N-terminal fragment NT-proBNP (1-76).¹³

Studies indicate that NT-proBNP can be used in diagnostic and prognostic applications.^{7,16,17} The concentration of NT-proBNP in serum or plasma correlates with the prognosis of the left ventricular dysfunction. Fisher, et al. found that congestive heart failure patients with NT-proBNP values above median had a one year mortality rate of 53 % compared to 11 % in patients below median.¹⁸ In the GUSTO IV study which involved more than 6800 patients it was shown that NT-proBNP was the strongest independent predictor of one year mortality in patients with acute coronary syndrome.¹⁹

The test is also useful in assigning symptoms to cardiac or non-cardiac causes, and helps to identify subjects with left ventricular dysfunction. The European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic Heart Failure recommend in their guidelines that natriuretic peptides including NT-proBNP "may be most useful clinically as a rule out test due to consistent and very high negative predictive values".¹⁰ When used with the recommended cutoff values, the Elecsys proBNP assay yields negative predictive values ranging from 97 % to 100 % depending on age and gender. Changes in NT-proBNP concentration can be used to evaluate the success of treatment in patients with left ventricular dysfunction. In addition NT-proBNP is suitable for use in assessing vascular

remodelling, and therefore contributes to the establishment of individualized rehabilitation procedures.^{20,21}

NT-proBNP also represents cardiac function and indicates increased risk in patients scheduled for potentially cardiotoxic drugs or interventions causing fluid retention or volume overload (e.g. COX-2 inhibitors, nonsteroidal anti-inflammatory drugs).^{22,23,24,25,26,27,28,29,30,31,32,33}

The Elecsys proBNP II assay contains two monoclonal antibodies which recognize epitopes located in the N-terminal part (1-76) of proBNP (1-108).

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (15 µL), a biotinylated monoclonal NT-proBNP-specific antibody, and a monoclonal NT-proBNP-specific antibody labeled with a ruthenium complex^{a)} form a sandwich complex.
- 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/ProCell M. 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.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The reagent rackpack is labeled as PRO-BNP II.

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-NT-proBNP-Ab~biotin (gray cap), 1 bottle, 9 mL:
Biotinylated monoclonal anti-NT-proBNP antibody (mouse)
1.1 µg/mL; phosphate buffer 40 mmol/L, pH 5.8; preservative.
- R2 Anti-NT-proBNP-Ab~Ru(bpy)₃²⁺ (black cap), 1 bottle, 9 mL:
Monoclonal anti-NT-proBNP antibody (sheep) labeled with ruthenium complex 1.1 µg/mL; phosphate buffer 40 mmol/L, pH 5.8; 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.

Avoid foam formation in 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 from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

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Store the Elecsys 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	12 weeks
on the analyzers	8 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-, NH₄-heparin, K₂-EDTA and K₃-EDTA plasma.

Criterion: Recovery within 90-110 % of serum value or slope 0.9-1.1 + intercept within $\pm 2 \times$ analytical sensitivity (LDL) + coefficient of correlation > 0.95 .

Stable for 3 days at 20-25 °C, 6 days³⁴ at 2-8 °C, 24 months at -20 °C.

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.

Centrifuge samples containing precipitates before performing the assay.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- [REF] 04842472190, proBNP II CalSet, for 4 x 1 mL
- [REF] 04917049190, PreciControl Cardiac II, for 2 x 2 mL each of PreciControl Cardiac II 1 and 2
- [REF] 11732277122, Diluent Universal, 2 x 16 mL sample diluent or [REF] 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- [REF] 11662988122, ProCell, 6 x 380 mL system buffer
- [REF] 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- [REF] 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- [REF] 11933159001, Adapter for SysClean
- [REF] 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- [REF] 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- [REF] 04880340190, ProCell M, 2 x 2 L system buffer
- [REF] 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- [REF] 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- [REF] 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- [REF] 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- [REF] 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- [REF] 03023150001, WasteLiner, waste bags

- [REF] 03027651001, SysClean Adapter M

Accessories for all analyzers:

- [REF] 11298500316, Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to 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, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibration

Traceability: This method has been standardized against the proBNP assay ([REF] 03121640).

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant 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:

- after 12 weeks 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 defined limits

Quality control

For quality control, use PreciControl Cardiac II.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each 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 defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in pmol/L or pg/mL).

Conversion factors: pmol/L x 8.457 = pg/mL

pg/mL x 0.118 = pmol/L

Limitations - interference

The assay is unaffected by icterus (bilirubin $< 428 \mu\text{mol/L}$ or $< 25 \text{ mg/dL}$), hemolysis (Hb $< 0.621 \text{ mmol/L}$ or $< 1.0 \text{ g/dL}$), lipemia (Intralipid $< 17.1 \text{ mmol/L}$ or $< 1500 \text{ mg/dL}$) and biotin ($< 123 \text{ nmol/L}$ or $< 30 \text{ ng/mL}$).

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. $> 5 \text{ mg/day}$) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.

There is no high-dose hook effect at NT-proBNP concentrations up to 33400 pmol/L (300000 pg/mL).

In vitro tests were performed on 51 commonly used pharmaceuticals. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

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For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

5-35000 pg/mL or 0.6-4130 pmol/L (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 5 pg/mL (< 0.6 pmol/L). Values above the measuring range are reported as > 35000 pg/mL (> 4130 pmol/L) or up to 70000 pg/mL (8277 pmol/L) for 2-fold diluted samples.

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 5 pg/mL (0.6 pmol/L)

The lower 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, repeatability study, n = 21).

Dilution

Samples with NT-proBNP concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the MODULAR ANALYTICS E170, Elecsys 2010 or cobas e analyzers or manually). The concentration of the diluted sample must be > 1770 pmol/L or > 15000 pg/mL.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the MODULAR ANALYTICS E170, Elecsys 2010 and cobas e software automatically takes the dilution into account when calculating the sample concentration.

Dilutions of up to 1:10 may entail maximum deviations of 25 % from the theoretical value.

Clinical data

Interpretation of NT-proBNP values

With increasing age atherosclerosis and aging processes of the heart (e.g. fibrosis) result in cardiac dysfunction. Development of cardiac dysfunction is individually different and clinically asymptomatic in its early stages.^{35,36} NT-proBNP levels reflect cardiac function or dysfunction respectively. With increasing age elevated levels of NT-proBNP are more frequently found in apparently healthy individuals, thus reflecting the increasing frequency of cardiac dysfunction.

NT-proBNP values need to be interpreted in conjunction with the medical history, clinical findings and other information (e.g. imaging, laboratory findings, accompanying disorders, treatment effects).³⁵

Cutoff values

A number of studies support a decision threshold for NT-proBNP of 125 pg/mL. NT-proBNP values < 125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of heart failure e.g. dyspnea.^{37,38} NT-proBNP values > 125 pg/mL may indicate cardiac dysfunction and are associated with an increased risk of cardiac complications (myocardial infarction, heart failure, death).

Recommended cutoffs in patients with diagnosed stable chronic heart failure

Patients with stable heart failure (n = 721) were compared to the reference group (n = 2264).

ROC plot analysis at the cutoff value of 125 pg/mL showed a sensitivity of 88 %, a specificity of 92 %, a negative predictive value (NPV), and a positive predictive value (PPV) of 96.7 % and 80.6 %, respectively.

Expected values

NT-proBNP concentrations in the reference group are shown in the following tables. The most appropriate decision threshold apparent from these distributions is 125 pg/mL.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Reference group

The circulating NT-proBNP concentration was determined in samples from 1981 blood donors aged between 18 and 65 as well as 283 elderly patients aged between 50 and 90, both populations without known cardiac risks, symptoms or medical history.

The descriptive statistics for NT-proBNP concentrations (pg/mL) in the reference group are shown in the following table:

All						
Age (years)	N	Mean	SD	Median	95 th percentile	97.5 th percentile
18-44	1323	35.6	30.2	20.4	97.3	115
45-54	408	49.3	63.3	30.7	121	172
55-64	398	72.6	84.4	47.3	198	263
65-74	102	107	85.9	85.1	285	349
≥ 75	33	211	152	174	526	738
Total	2264	50.3	62.4	27.9	149	196

Males						
Age (years)	N	Mean	SD	Median	95 th percentile	97.5 th percentile
18-44	815	27.7	25.5	20.0	62.9	85.8
45-54	278	39.0	63.6	21.6	83.9	121
55-64	259	57.2	74.5	37.7	161	210
65-74	61	105	87.9	83.9	241	376
≥ 75	13	163	116	151	486	486
Total	1426	39.8	55.3	20.0	113	169

Females						
Age (years)	N	Mean	SD	Median	95 th percentile	97.5 th percentile
18-44	508	48.2	32.8	37.1	116	130
45-54	130	71.5	56.7	55.4	169	249
55-64	139	101	94.0	79.6	247	287
65-74	41	109	83.8	85.2	285	301
≥ 75	20	243	167	191	738	738
Total	838	68.2	69.3	47.8	177	254

In the pediatric population aged between 1 and 18 the following NT-proBNP values were obtained using the Elecsys proBNP II assay:³⁹

Age (years)	N	NT-proBNP (ng/L)	
		75 th percentile	97.5 th percentile
1-3	13	231	320
4-6	21	113	190
7-9	32	94	145
10	11	73	112
11	69	93	317
12	21	95	186
13	23	114	370
14	18	68	363
15	24	74	217
16	24	85	206
17	24	71	135
18	12	53	115

Correlation of NT-proBNP with NYHA classification in patients diagnosed with CHF

NT-proBNP values (pg/mL) for patients with restricted left ventricular ejection fraction (majority under therapy).

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NYHA functional class				
	NYHA I	NYHA II	NYHA III	NYHA IV
N	182	250	234	35
Mean	1016	1666	3029	3465
SD	1951	2035	4600	4453
Median	342	951	1571	1707
5 th percentile	33.0	103	126	148
95 th percentile	3410	6567	10449	12188
% > 125 pg/mL	78.6	94.0	95.3	97.1

Patients presenting acute dyspnea - ICON (International Collaborative of NT-proBNP) study⁴⁰

NT-proBNP concentrations were determined in samples from 1256 patients presenting with acute shortness of breath to emergency departments at four hospitals. This population included patients with a prior history of hypertension, coronary artery disease, myocardial infarction, heart failure, or pulmonary disease. 720 subjects were found to be suffering from acute exacerbation of heart failure, while the remainder were determined to present dyspnea due to other causes. The descriptive statistics for NT-proBNP concentrations (pg/mL) for both groups are shown in the following table:

ICON Population	Acute dyspnea without acute heart failure			Acute dyspnea with acute heart failure		
	< 50	50-75	> 75	< 50	50-75	> 75
Age (years)	< 50	50-75	> 75	< 50	50-75	> 75
Mean	163	500	1209	7947	7964	10519
SD	484	1239	2703	9093	12892	15961
Median	42	121	327	5044	3512	5495
5 th percentile	5	10	24	393	416	658
25 th percentile	16	44	139	2257	1608	2154
95 th percentile	104	402	910	9825	9262	11900
97.5 th percentile	778	2101	7916	36201	29089	35183
Min.	1	1	2	196	38	17
Max.	4386	10467	15725	43177	117390	117390
N	150	281	105	33	251	436

Result interpretation in patients presenting acute dyspnea

By using the optimal cutoffs established by the ICON study group and shown in the table below, physicians can increase the specificity and accuracy for diagnosing heart failure in patients presenting acute dyspnea in the emergent setting.

Category	Optimal cut-point pg/mL	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Rule in cut-point						
< 50 years (n = 184)	450	97	93	79	99	94
50-75 years (n = 537)	900	90	82	83	88	85
> 75 years (n = 535)	1800	85	73	92	55	83
Rule out cut-point						
All patients	300	99	60	77	98	83

Specific performance data

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

Precision

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

Elecsys 2010 and cobas e 411 analyzers					
Sample	Repeatability				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	44.0	5.19	1.84	0.22	4.2
Human serum 2	126	14.9	3.06	0.36	2.4
Human serum 3	2410	284	31.7	3.74	1.3
Human serum 4	33606	3966	922	109	2.7
PC CARDII ^{b)} 1	82.0	9.68	2.11	0.25	2.58
PC CARDII2	2318	274	27.3	3.22	1.18

b) PC CARDII = PreciControl Cardiac II

Elecsys 2010 and cobas e 411 analyzers					
Sample	Intermediate precision				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	44.0	5.19	2.02	0.24	4.6
Human serum 2	126	14.9	3.23	0.38	2.6
Human serum 3	2410	284	44.2	5.22	1.8
Human serum 4	33606	3966	1288	152	3.8
PC CARDII1	82.0	9.68	2.27	0.27	2.8
PC CARDII2	2318	274	36.6	4.32	1.6

MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers

Sample	Repeatability				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	64	7.55	1.21	0.14	1.9
Human serum 2	124	14.6	1.82	0.22	1.5
Human serum 3	14142	1669	182	21.5	1.3
PC CARDII1	77.0	9.09	1.41	0.17	1.8
PC CARDII2	2105	248	24.8	2.92	1.2

MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers

Sample	Intermediate precision				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	46	5.43	1.44	0.17	3.1
Human serum 2	125	14.75	3.43	0.40	2.7
Human serum 3	32930	3885	546	64.4	1.7
PC CARDII1	77.0	9.09	2.12	0.25	2.7
PC CARDII2	2170	256	59.4	7.01	2.7

Method comparison

A comparison of the Elecsys proBNP II assay (y) with the Elecsys proBNP assay (x) using clinical samples gave the following correlations (pg/mL):

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Number of samples measured: 2133

Passing/Bablok⁴¹

Linear regression

$y = 0.977x + 1.89$

$y = 0.999x - 13.36$

$r = 0.946$

$r = 0.996$

The sample concentrations were between approximately 5 and 30022 pg/mL (approximately 0.6 and 3543 pmol/L).

Analytical specificity

The Elecsys proBNP II assay does not show any significant cross reactions with the following substances, tested with NT-proBNP concentrations of approximately 230 pg/mL and 2300 pg/mL (max. tested concentration):

Adrenomedullin (1.0 ng/mL), aldosterone (0.6 ng/mL), angiotensin I (0.6 ng/mL), angiotensin II (0.6 ng/mL), angiotensin III (1.0 ng/mL), ANP₂₈ (3.1 µg/mL), Arg-vasopressin (1.0 ng/mL), BNP₃₂ (3.5 µg/mL), CNP₂₂ (2.2 µg/mL), endothelin (20 pg/mL) NT-proANP₁₋₃₀ (preproANP₂₆₋₅₅) (3.5 µg/mL), NT-proANP₃₁₋₆₇ (preproANP₅₆₋₉₂) (1.0 ng/mL), NT-proANP₇₉₋₉₈ (preproANP₁₀₄₋₁₂₃) (1.0 ng/mL), renin (50 ng/mL), urodilatin (3.5 µg/mL).

Functional sensitivity

50 pg/mL (5.9 pmol/L)

The functional sensitivity is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of 20 %.

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proBNP II

N-terminal pro B-type natriuretic peptide



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