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Elecsys β-Amyloid (1-42) CSF

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REF	Σ	SYSTEM
		MODULAR ANALYTICS E170
06986811 190	60	**cobas e** 601
		cobas e 602

English

System information

For MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number: 170

Please note

The measured β-amyloid (1-42) value in a given sample, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent. Values determined on samples by different assay methods cannot be used interchangeably.

Please note that due to the sticky properties of the β-amyloid protein, the Elecsys assay cutoff provided in this document is only valid if the below described pre-analytical handling procedure (see section "Specimen collection and preparation") is strictly followed.

All performance data were generated using frozen cerebrospinal fluid (CSF) material and therefore cannot be transferred to fresh CSF. A positive β-amyloid (1-42) result in CSF does not establish a diagnosis of Alzheimer's disease (AD) and should always be interpreted in conjunction with clinical information.

Intended use

Elecsys β-Amyloid (1-42) CSF is an in vitro diagnostic immunoassay intended for the quantitative determination of the β-amyloid (1-42) protein concentration in human CSF. The Elecsys β-Amyloid (1-42) CSF assay is intended to be used in adult subjects with cognitive impairment being evaluated for AD.

An Elecsys β-Amyloid (1-42) CSF assay result above the cutoff is consistent with a negative amyloid positron emission tomography (PET) scan.

Negative β-amyloid PET scans indicate sparse to no neuritic plaques and are inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD.

The Elecsys β-Amyloid (1-42) CSF assay is an adjunct to other clinical diagnostic evaluations.

Limitations of use

- A positive Elecsys β-Amyloid (1-42) CSF assay result does not establish a diagnosis of AD or other cognitive disorder.
- The safety and effectiveness of the Elecsys β-Amyloid (1-42) CSF assay have not been established for:
  Predicting development of dementia or other neurologic conditions.
  Monitoring responses to therapies.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Summary

The Elecsys β-Amyloid (1-42) CSF assay is designed to detect the β-amyloid (1-42) peptide, a small, 4 kDa protein of about 40 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein (APP). Cleavage of APP occurs via two events: cleavage by β-secretase within the extracellular domain and cleavage by γ-secretase in the transmembrane region. Due to its hydrophobic nature, the β-amyloid (1-42) peptide has the property to form aggregates and oligomers. Oligomers of higher order form fibrils that accumulate into β-amyloid plaques.[1]

Clinical relevance of β-amyloid (1-42)

β-Amyloid (1-42) peptide deposition in the brain as one of the two hallmarks of AD, besides neurofibrillary tangles, can be detected by several methods: (a) histopathological staining of β-amyloid (1-42) deposits in post mortem brain tissue; (b) use of radiolabeled tracers that bind to β-amyloid deposits in the brain and can then be detected in vivo using PET scan; (c) measuring the β-amyloid 42 level in CSF because lower titers in CSF are believed to reflect accumulation of this molecule in the brain.[2,3]

The use of AD biomarkers has been included in the new consensus research diagnostic criteria for AD, mild cognitive impairment (MCI), and preclinical AD, proposed by the National Institute on Aging (NIA) and the Alzheimer's Association. These new criteria take into account that AD dementia is part of a continuum of clinical and biological phenomena.[4,5] The new IWG-2 (International Working Group 2) criteria recommend the use of either CSF biomarker or PET imaging for evaluation of AD patients.[6] In Europe, the CHMP (Committee for Medicinal Products for Human use) published a number of positive opinions on the use of biomarkers in the context of AD for enrichment of clinical trials in pre-dementia and mild-to-moderate AD.[7,8]

Pathological changes in the β-amyloid metabolism are the earliest alterations during AD development known so far that can be utilized diagnostically. They are reflected by the decrease in the CSF concentrations of β-amyloid (1-42) as well as by the increase in the brain uptake of the specific tracers on the β-amyloid PET.[9] Current clinical diagnostic criteria for AD require a patient to have dementia before a diagnosis of AD can be made, and are largely based on the exclusion of other disorders. No clinical method is available for identifying prodromal AD in patients with MCI, as such individuals have only mild disturbances in episodic memory.[10]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, a biotinylated monoclonal β-amyloid (1-42)-specific antibody (21F12) and a monoclonal β-amyloid (1-42)-specific antibody (3D6) labeled with a ruthenium complex[a)] react to 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 or e-barcode.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack is labeled as Abeta42.

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

R1 Anti-β-amyloid (1-42)-Ab~biotin (gray cap), 1 bottle, 6.5 mL: monoclonal anti-β-amyloid (1-42) antibody 21F12 (mouse) 2.0 mg/L; phosphate buffer > 100 mmol/L, pH 7.2; preservative.

R2 Anti-β-amyloid (1-42)-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 6.5 mL: Monoclonal anti-β-amyloid antibody 3D6 (mouse) labeled with ruthenium complex 1.75 mg/L; phosphate buffer > 100 mmol/L, pH 7.2; 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).

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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.

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	8 weeks
on the analyzers	28 days

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Please follow the steps listed below for CSF sample collection and measurement.

The technical notes are an essential part of the instructions and must be read thoroughly before completing each step.

Steps	Technical notes
1. Lumbar Puncture (LP) using 22 gauge needle and drip method on patient.	Avoid the use of syringes or tubings. Perform LP before noon.
2. Discard first 1-2 mL.	None
3. Collect 12 mL of CSF in 15 mL tube Sarstedt 62.554.502.	Each sample should be checked for hemolysis. The CSF sample should not appear reddish. Use only 15 mL tubes from Sarstedt 62.554.502.
4. Centrifuge for 10 min at 2000 g at 4 °C.	Start centrifugation within 30 min after LP.
5. Transfer 0.5 mL aliquots from 15 mL collection tube into 0.5 mL Sarstedt tubes 72.730.005.	Use only 0.5 mL tubes from Sarstedt 72.730.005. Use a transfer pipet tip from Sarstedt. The pipette tips should be always saturated with β-amyloid by pipetting 3 times up and down before using a 1.25 mL Sarstedt pipette (70.1186.210).
6. Freeze aliquots (-60 °C or below).	The entire process of sample drawing to freezing of the aliquots should be done within 3 h. Store the samples at -60 °C at least for 3 days before measuring.
After freezing:	
7. Thaw CSF samples for 30 min at 20-25 °C in an upright position and subsequently for 20 min at 20-25 °C, using a roller mixer.	Directly use the sample vial for measuring on the analyzer. Do not transfer into new tubes. To prevent any evaporation, open the sample vials immediately before measurement.
8. Measuring on **cobas e** systems and MODULAR ANALYTICS E170: The 0.5 mL Sarstedt tube can only be run in combination with a Milian Carrier Tube.	

Stability of CSF samples (after freezing at -60 °C): Stable for 8 weeks at -20 °C ± 5 °C, 24 hours at 2-8 °C and 8 hours at 20-25 °C.[11,12,13]

Do not use hemolyzed CSF samples that are visibly colored red.

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.

Please always keep them capped if not in use.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 06986838190, CalSet β-Amyloid (1-42), for 4 x 1.0 mL
- REF 06986846190, PreciControl β-Amyloid (1-42), for 6 x 1.0 mL
- General laboratory equipment
- REF 62.554.502, Sarstedt, 15 mL, 120 x 17 mm, Polypropylene
- REF 72.730.005, Sarstedt, 0.5 mL Micro Tube Type A, Polypropylene
- REF 70.1186.210, Sarstedt, Transfer pipette 1.25 mL Biosphere Filter Tip, Polyethylene
- Centrifuge (at least 5000 g)
- REF 064200, Milian Carrier Tube (12 x 75 mm)
- Roller mixer

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 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, ISE Cleaning Solution/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 (except for the **cobas e** 602 analyzer).

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 by means of the candidate reference measurement procedure, traceable to NIST SRM2389a.[14]

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.

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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).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 4 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 β-Amyloid (1-42).

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.

Special care needs to be taken to ensure that the accuracy and precision of the testing stays within acceptable limits. Besides meeting the PreciControl β-Amyloid (1-42) target ranges provided, the user needs to ensure that the systematic bias with respect to the assigned target value is within ± 10 %, the intermediate precision CV is ≤ 10 % and the maximal total error is within ± 26.5 % (TE = |bias| + 1.65*CV). It is recommended to use quality control rule software.

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.

If necessary, repeat the measurement of the samples concerned.

Note: The controls are not barcode-labeled and therefore have to be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software.

Non-barcode labeled controls: Only one target value and range for each control level can be entered in the analyzer. The reagent lot-specific target values have to be re-entered each time a specific reagent lot with different control target values and ranges is used. Two reagent lots with different control target values and ranges cannot be used in parallel in the same run.

The exact lot-specific target values and ranges are printed on the enclosed (or electronically available) value sheet in the reagent kit or PreciControl kit.

Please make sure that the correct values are used.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in pg/mL.

Limitations - interference

The effect of the following substances and pharmaceuticals on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Criterion: Recovery within ± 48 pg/mL of initial value ≤ 480 pg/mL and within ± 10 % of initial value > 480 pg/mL.

Compound	Concentration tested
Bilirubin	≤ 5.13 µmol/L or ≤ 0.3 mg/dL
Hemoglobin	≤ 0.0068 mmol/L or ≤ 11 mg/dL
Intralipid	≤ 3 mg/dL
Biotin	≤ 12.26 nmol/L or ≤ 3 ng/mL
Rheumatoid factors	≤ 14 IU/mL
IgG	≤ 0.02 g/dL
IgA	≤ 0.003 g/dL
IgM	≤ 0.002 g/dL
Albumin	≤ 0.17 g/dL

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

There is no high-dose hook effect at β-amyloid (1-42) concentrations up to 6000 pg/mL.

In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

Commonly used pharmaceuticals

Pharmaceutical	Concentration tested mg/L
Acetylcystein	150
Ampicillin-Na	1000
Ascorbic acid	300
Cyclosporine	5
Cefoxitin	250
Heparin	5000 U
Levodopa	20
Methyldopa	20
Metronidazole	200
Phenylbutazone	100
Doxycyclin	10
Acetylsalicylic acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophylline	100

In addition, the following special 15 drugs were tested. No interference with the assay was found.

Drug	Concentration tested mg/L
Atorvastatin	6
Clopidogrel	0.3
Digoxin	5
Donepezil	30
Escitalopram	15
Esomeprazole	170
Furosemide	90
Galantamine	250
Hydrochlorothiazide	120
Lisinopril	500
Memantine	250
Metformin	4000
Metoprolol	900
Rivastigmine	45
Simvastatin	3

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.

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

200-1700 pg/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as

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< 200 pg/mL. Values above the measuring range are reported as > 1700 pg/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 60 pg/mL

Limit of Detection = 120 pg/mL

Limit of Quantitation = 200 pg/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable relative error of 30 %.

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, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 601 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human CSF 1	395	8.32	2.1	8.32	2.1
Human CSF 2	718	22.0	3.1	26.4	3.7
Human CSF 3	743	26.4	3.6	30.1	4.0
Human CSF 4	897	16.5	1.8	21.4	2.4
Human CSF 5	1450	24.6	1.7	38.1	2.6
PC[b] β-Amyloid (1-42) 1	487	4.25	0.9	7.36	1.5
PC β-Amyloid (1-42) 2	885	8.82	1.0	13.3	1.5

b) PC = PreciControl

Analytical specificity

The test is highly specific for human β-amyloid (1-42). The following potential cross-reactivity was found.[15]

Cross-reactant	**Concentration tested pg/mL**	**Cross-reactivity %**
β-Amyloid (1-38)	10000	< 0.9
β-Amyloid (1-40)	10000	< 1.6

Clinical performance

Each laboratory should investigate the transferability of the expected values to its own patient population.

Concordance with PET visual read was assessed in a retrospective study (Roche study number RD002145) based on samples from the BioFINDER cohort.[16] The primary analysis population consisted of 277 mild cognitive symptoms (MCS) patients for whom banked CSF samples and PET scan results were available (PET tracer: [18F]-Flutemetamol). Of the 277 patients, 120 had subjective cognitive deficiency (SCD), 153 MCI and for 4 patients no assignment was available. The average age was 70 years (range 59-80 years), 42 %/ 58 % of patients were female/male and 45 %/ 54 % of patients were ApoE4 carriers/non-carriers. The amyloid PET scans were read by three independent trained readers and majority voting was used to call the image positive or negative, resulting in 110 (40 %) positive, and 167 (60 %) negative PET reads. As the BioFINDER study used a different pre-analytical handling procedure, an adjustment factor was determined in study RD002575. The resulting cutoff after adjustment was as follows:

- Elecsys β-Amyloid (1-42) CSF ≤ 1000 pg/mL - test result positive
- Elecsys β-Amyloid (1-42) CSF > 1000 pg/mL - test result negative

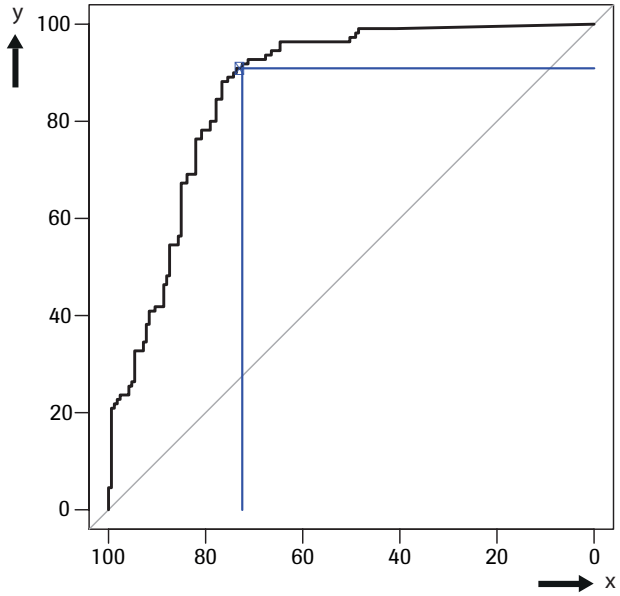
Based on the selected cutoff, agreement with the PET scan results was as follows:

Agreement rates (%)	
PPA[c]	90.9 (95 % CI[d]: 83.9-95.6)
NPA[e]	72.5 (95 % CI: 65.0-79.1)
Overall percentage agreement	79.8 (95 % CI: 74.6-84.4)

c) PPA = Positive percentage agreement (sensitivity)

d) CI = confidence interval

e) NPA = Negative percentage agreement (specificity)



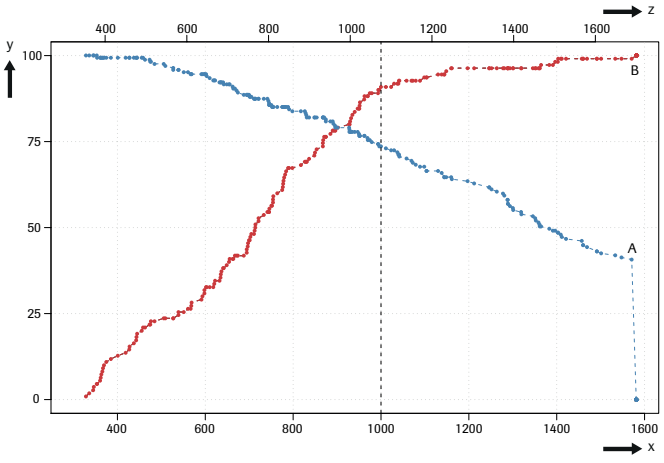
ROC curve

Cutoff (after adjustment) = 1000 pg/mL

x: NPA (specificity) (%)

y: PPA (sensitivity) (%)

AUC = 86.5 % (95 % CI: 82.3 %-90.7 %)



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PPA (sensitivity) and NPA (specificity) as a function of cutoff

x: β-AMYLOID (1-42) (pg/mL), ROCHE pre-analytical handling procedure

z: β-AMYLOID (1-42) (pg/mL), BioFINDER pre-analytical handling procedure

y: agreement (%)

A: NPA (specificity) (%)
B: PPA (sensitivity) (%)

References

1 Vandenberghe R, Adamczuk K, Dupont P, et al. Amyloid PET in clinical practice: Its place in the multidimensional space of Alzheimer's disease. Neuroimage Clinical 2013;2:497-511.

2 Blennow K, Zetterberg H, Anne M. Fluid Biomarkers in Alzheimer Disease. Cold Spring Harb Perspect 2012;2:a006221:1-23.

3 Bates KA, Verdile G, Li QX, et al. Clearance mechanisms of Alzheimer's amyloid-β peptide: implications for therapeutic design and diagnostic tests. Molecular Psychiatry 2009;14:469-486.

4 Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257-62.

5 Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease. Alzheimers & Dement 2011;7:270-279.

6 Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614-629.

7 EMA/CHMP/SAWP/893622/2011; Committee for Medicinal Products for Human Use (CHMP) ; 17 November 2011; Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau signature and/or PET-amyloid imaging (positive/ negative) as a biomarkers for enrichment, for use in regulatory clinical trials – in mild and moderate of Alzheimer's.

8 EMA/CHMP/539931/2014 2; Committee for Medicinal Products for Human Use (CHMP); 28 January 2016; Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias.

9 Lewczuk P, Mroczko B, Fagan A, et al. Biomarkers of Alzheimer's disease and mild cognitive impairment: a current perspective. Advances in Medical Sciences 2015;60:76-82.

10 Blennow K, Hampel H, Weiner M, et al. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat. Rev. Neurol. 2010;6:131-144.

11 Bjerke M, Portelius E, Minthon L, et al. Confounding Factors Influencing Amyloid Beta Concentration in Cerebrospinal Fluid. Int J Alzheimers Dis 2010;1-11.

12 Zimmermann R, Lelental N, Ganslandt O, et al. Preanalytical sample handling and sample stability testing for the neurochemical dementia diagnostics. J Alzheimers Dis 2011; 25:739-45.

13 Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnostics: A consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers and Dement 2012;8 65-73.

14 Leinenbach A. Pannee J, Dülffer T, et al. Mass spectrometry-based candidate reference measurement procedure for quantification of amyloid-β in cerebrospinal fluid. ClinChem 2014;987-994.

15 Bittner T, Zetterberg H, Teunissen CE, et al.Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement 2016;12:517-526.

16 http://biofinder.se/the_biofinder_study_group/

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see https://usdiagnostics.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE

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