Elecsys free βhCG

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REF		Σ	SYSTEM
			cobas e 411
08860297190	08860297500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 690
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 033

Please note

The measured free βhCG value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the free βhCG assay method used. Free βhCG values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations. If there is a change in the free βhCG assay procedure used while monitoring therapy, then the free βhCG values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods.

Intended use

Immunoassay for the in vitro quantitative determination of free βhCG (free β-subunit of human chorionic gonadotropin) in human serum. This assay is intended for the use as one component in combination with other parameters to evaluate the risk of trisomy 21 (Down syndrome) during the first trimester of pregnancy. Further testing is required for diagnosis of chromosomal aberrations.

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

Summary

Human chorionic gonadotropin (hCG) is a glycoprotein hormone (~37 kDa) composed of 2 noncovalently linked subunits – the α- and β-chain (~15 and 22 kDa respectively). The protein is produced by trophoblast tissue; it serves to maintain the corpus luteum during the early weeks of pregnancy and it stimulates progesterone production.[1,2,3,4]

Naturally, hCG appears only in blood and urine of pregnant women. The concentration of hCG rises exponentially in the first trimester of pregnancy to peak around 9th week of gestation.[5] Subsequently, the hormone level decreases between gestational weeks ~10-16 to approximately one-fifth of peak concentration and remains at this level until term. In non-pregnant women, hCG can be produced by trophoblastic and non-trophoblastic tumors and germ cell tumors with trophoblastic components.[2,3,4,5,6]

The serum of pregnant women mainly contains intact hCG. However, minor fraction of α- and β-subunits circulate in an unbound form. The proportion of free βhCG averages ~1 % compared to intact hCG. As a result of the protein degradation process, additional hCG variants can be detected in blood and urine (e.g. nicked hCG, nicked βhCG, β core fragment). However, only the intact hormone is biologically active.[3,7]

Free βhCG in combination with serum pregnancy-associated plasma protein A (PAPP-A) and the sonographic determination of nuchal translucency (NT) identifies women at an increased risk of carrying a fetus affected with Down syndrome during the first trimester (week 8-14) of pregnancy.[8,9,10] Using this marker combination, detection rates of up to 70 % (serum markers only) and 90 % (combined with NT) have been described at a false positive rate of 5 %.[11,12,13]

When the sonographic examination also includes the presence of the nasal bone, the detection rate was found to reach 97 %.[14]

Based on the maternal age, the risk for having a Down syndrome pregnancy can be calculated using a specific algorithm.[9,15,16]

Based on the risk assessment thus obtained, Non-Invasive Prenatal Testing (NIPT) based on circulating cell-free fetal DNA may be indicated.[17,18,19,20] Women found to have increased risk of aneuploidy with 1st trimester screening should be offered genetic counselling and the option of Chorionic Villus Sampling (CVS) or amniocentesis.[21]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample, biotinylated monoclonal βhCG-specific antibodies, and a monoclonal free βhCG-specific antibody 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 F-BHCG.

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

R1 Anti-βhCG-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-βhCG antibody (mouse) 3.5 mg/L; phosphate buffer 40 mmol/L, pH 6.8; preservative.

R2 Anti-free βhCG-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL: Monoclonal anti-free βhCG antibody (mouse) labeled with ruthenium complex 1.6 mg/L; phosphate buffer 40 mmol/L, pH 7.0; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.

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P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

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.

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	4 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.

Do not use plasma.

Stable for 25 hours at 15-25 °C, 8 days at 2-8 °C, 12 months at -20 °C (± 5 °C). The samples may be frozen 3 times.

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 heat-inactivated samples.

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 04854080200, free βhCG CalSet, for 4 x 1.0 mL
- REF 04899881200, PreciControl Maternal Care, for 6 x 2.0 mL
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- 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, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

For risk calculation of trisomy 21:

- REF 08860173190, Elecsys PAPP-A, 100 tests
- REF 04854101200, PAPP-A CalSet, for 4 x 1.0 mL
- A suitable software, e.g. REF 05126193, SsdwLab (V5.0 or later)

Additional materials for **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, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials 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.

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 International Reference Preparation of Chorionic Gonadotrophin β subunit from the National Institute for Biological Standards and Control (NIBSC), code 75/551.

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).

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

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 Maternal Care.

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.

If necessary, repeat the measurement of the samples concerned.

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

Calculation

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

Conversion factors: IU/L x 1 = mIU/mL
IU/L x 1 = ng/mL
mIU/mL x 1 = ng/mL

Limitations - interference

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

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 428 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1000 IU/mL
IgG	≤ 7.0 g/dL

Criterion: For concentrations ≤ 10 IU/L the deviation is ≤ 1.0 IU/L. For concentrations > 10 IU/L the deviation is ≤ 10 %.

There is no high-dose hook effect at free βhCG concentrations up to 800 IU/L.

Pharmaceutical substances

In vitro tests were performed on 18 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.

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

0.1-190 IU/L (defined by the Limit of Blank and the maximum of the master curve). Values below the Limit of Blank are reported as < 0.1 IU/L. Values above the measuring range are reported as > 190 IU/L (or up to 1900 IU/L for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.1 IU/L

Limit of Detection = 0.3 IU/L

Limit of Quantitation = 0.5 IU/L

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 the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with free βhCG concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:10 (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 15 IU/L.

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

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values and clinical performance

The following results were obtained with the Elecsys free βhCG assay:

1. Reference range study using a panel of samples from 251 healthy non-pregnant female donors (Roche study No. R04P026)

All results were below the lower detection limit of < 0.1 IU/L.

2. Performance evaluation study of the Elecsys free βhCG assay and the Elecsys PAPP-A assay in first trimester trisomy 21 risk assessment (Roche study No. B05P020 and Roche study No. CIM 000950)[22]

Measurements with the Elecsys free βhCG assay and the Elecsys PAPP-A assay were conducted in 6 clinical centers in Belgium, Switzerland, Denmark, England and Germany. For the first trimester 4746 free βhCG values were available (gestational weeks 8+0 to 13+6). Median values were estimated for each day of the respective gestational age by regression of the calculated medians per day (for details refer to the software SsdwLab). The table below shows the number of single values available for each week and the median predicted by the regression function for the middle day of the respective week (week n+3). Gestational age was calculated from ultrasound crown-to-rump length (CRL) according to Robinson.[23]

Gestational week	8+0 to 8+6	9+0 to 9+6	10+0 to 10+6	11+0 to 11+6	12+0 to 12+6	13+0 to 13+6
Number of samples	178	302	465	805	1557	1439
Median value at the middle of the week (IU/L)	70.7	75.5	57.3	42.8	34.5	29.5

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

For prenatal testing it is recommended that the median values be re-evaluated periodically.

Clinical performance data

In total, 2629 samples from clinical routine with known outcome were examined. 107 out of the 2629 samples were from pregnancies with confirmed Down syndrome. All samples were measured in parallel with FMF (Fetal Medicine Foundation) certified PAPP-A and free βhCG tests. Risk calculation was performed using the software SsdwLab version 5.0. This software makes use of an algorithm described by Palomaki et al.[24] by means of the mathematical calculations for Gaussian multivariate distribution as already published.[25] Risk analysis is based on maternal age, nuchal translucency as well as on the results of the biochemical parameters, corrected by different factors such as maternal weight, smoking and ethnic background of the pregnant woman.

Individual risk calculation

The calculation of a woman's individual risk of carrying a single fetus affected by trisomy 21 was assessed without consideration of nuchal translucency (NT) data to demonstrate the performance of the biochemical methods. Maternal weight and smoking behavior were taken into account as correction factors. Concordance of risk analysis compared to a competitor method was examined using the cutoff value established in the participating laboratory.[26,27]

It is the responsibility of the user to choose the cutoff which will apply for further procedures.

Concordance analysis data

A. Concordance analysis in unaffected pregnancies (n = 2522)

Cutoff 5 % FPR*	Risk > cutoff (Roche**)	Risk < cutoff (Roche**)
Risk > cutoff (competitor***)	109 (4.32 %)	18 (0.71 %)

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Cutoff 5 % FPR*	Risk > cutoff (Roche**)	Risk < cutoff (Roche**)
Risk < cutoff (competitor***)	17 (0.67 %)	2378 (94.3 %)

In 2522 unaffected samples the Roche methods correctly classified 2396 samples (specificity: 95.0 %) in comparison to 2395 (specificity: 95.0 %) correctly classified by the competitor methods.

B. Detection rate in confirmed trisomy 21 pregnancies (n = 107)

Cutoff 5 % FPR*	Risk > cutoff (Roche**)	Risk < cutoff (Roche**)
Risk > cutoff (competitor***)	86 (80.4 %)	0
Risk < cutoff (competitor***)	4 (3.74 %)	17 (15.9 %)

In 107 affected samples the Roche methods showed a detection rate of 84.1 % (90/107) in comparison to 80.4 % (86/107) obtained with the competitor methods.

* FPR = False positive rate

** Combination of results from the Elecsys free βhCG assay and the Elecsys PAPP-A assay

*** Combination of results from the competitor's free βhCG and PAPP-A methods

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 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 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Human serum 1	0.517	0.012	2.3	0.019	3.7
Human serum 2	9.09	0.182	2.0	0.422	4.6
Human serum 3	9.29	0.230	2.5	0.467	5.0
Human serum 4	89.7	2.05	2.3	3.95	4.4
Human serum 5	181	3.45	1.9	8.96	5.0
PC[b)] Maternal Care 1	15.2	0.280	1.8	0.587	3.9
PC Maternal Care 2	52.6	0.929	1.8	2.21	4.2
PC Maternal Care 3	106	2.41	2.3	4.40	4.2

b) PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Human serum 1	0.484	0.014	3.0	0.024	4.9
Human serum 2	8.23	0.234	2.8	0.339	4.1
Human serum 3	8.41	0.218	2.6	0.380	4.5
Human serum 4	81.8	1.84	2.2	2.96	3.6
Human serum 5	174	4.50	2.6	7.79	4.5
PC Maternal Care 1	13.8	0.345	2.5	0.540	3.9
PC Maternal Care 2	47.2	1.07	2.3	1.97	4.2
PC Maternal Care 3	95.9	1.96	2.0	4.04	4.2

Method comparison

A comparison of the Elecsys free βhCG assay, REF 04854071200 (y) with a commercially available free βhCG assay (x) using human sera gave the following correlations:

Number of samples measured: 3373

Passing/Bablok[28]	Linear regression
y = 0.944x - 2.74	y = 0.994x - 4.84
τ = 0.902	r = 0.976

The sample concentrations were between 4.96 and 187 IU/L.

Analytical specificity

Cross-reactivity against intact hCG < 0.05 %. No cross-reactivity against hCGα chain and TSH detectable.

References

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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.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.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 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
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