ms_05390125190V5.0

hGH

cobas®

Human growth hormone

REF	Σ	SYSTEM
		Elecsys 2010
		MODULAR ANALYTICS E170
05390125 190	100	**cobas e** 411
		cobas e 601
		cobas e 602

For USA: Elecsys hGH Assay

English

Intended use

Immunoassay for the in vitro quantitative determination of human growth hormone (hGH; forms with molecular masses of 20 kDa and 22 kDa) in human serum and plasma.

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

Summary

Biochemical background of growth

Growth is stimulated and controlled by the anabolic and mitogenic activities of growth hormone (GH) and the insulin-like growth factors (IGFs).

Physiologically, hGH has general anabolic effects (i.e. increase of glucose uptake, protein synthesis, lipolysis) and its major function is to stimulate the elongation of bones in immature individuals by the following biochemical process:

1. Hypothalamus releases GHRH (Growth Hormone Releasing Hormone)
2. GHRH stimulates the pituitary to secrete hGH
3. hGH is transported through the bloodstream to the liver and other tissues
4. Liver and tissues respond to hGH by synthesizing IGF-1, an insulin-like growth factor
5. IGF-1 stimulates the cells at the growth centers of bones leading to linear growth

Molecular forms of growth hormone[1]

Human growth hormone (hGH) occurs in two different molecular forms with a molecular mass of 20 kDa and 22 kDa. More than 90 % of the circulating hGH is the 22 kDa isoform, composed of 191 amino acids. The 20 kDa isoform is co-secreted with the 22 kDa hGH, and is an alternatively spliced product of the pituitary hGH gene, lacking amino acid residues 32-46. It represents about 10 % of the total circulating hGH. The biological activity of both forms is thought to be comparable.

Synthesis and secretion of human growth hormone

Synthesis of hGH is controlled by hypothalamic and peripheral signals.[2] Typical promotors are growth hormone releasing hormone (GHRH), ghrelin,[3] sleep, physical exercise, insulin, low levels of blood sugar, increased androgen secretion during puberty and stimulation tests with arginine, clonidine or insulin.[4] The release of hGH is inhibited by somatostatin, glucose, glucocorticoids, fatty acids, L-dopa and beta-blockers and is further regulated by circulating concentrations of hGH and IGF-1 by a negative feedback mechanism.[1] hGH secretion is further under the influence of additional hormonal signals, sex steroids and thyroid hormone stimulation.[5,6]

Secretion patterns

In blood, growth hormone is bound to growth hormone binding protein (GHBP). GHBP serves as an intravascular hormone reservoir which attenuates the hGH oscillations that are caused by the pulsatile secretion of the anterior pituitary. Secretion occurs in several pulses or peaks each day[7] resulting in hGH plasma concentrations between 5 and 45 ng/mL,[8] lasting from 10 to 30 minutes before returning to basal levels usually less than 5 ng/mL.[9] Basal levels of hGH are highest in early childhood and decline with age, reaching a nadir at the sixth decade.[10] In aged men, the daily hGH secretion is 1/5 to 1/20 of that observed in young adults.[11] hGH output decreases twice as rapidly in men as in women so that hGH release remains higher in women than in men after the age of 50.[12,13] The age-dependent decline in hGH secretion is secondary to a decrease in GHRH and to an increase in somatostatin secretion.[14] The decline in the production of sex steroids, physical activity, and the presence of aberrant sleep patterns also may contribute to the decline in hGH levels during aging.[15] The changes in GH secretion that occur with aging are accompanied by a progressive loss of muscle mass and strength, a decline in physical performance, an increase in body fat, and a decrease in bone mineral density (BMD).[16,17,18,19]

Caution must be exercised in the clinical interpretation of growth hormone levels, because they vary throughout the day, between genders, are age-related and are influenced by many internal and external factors (exercise, stress, hypoglycemia, etc.).

Growth hormone excess

Growth hormone excess is typically associated with gigantism and acromegaly. Gigantism is an abnormal high linear growth due to excessive action of hGH and IGF-1 while the epiphyseal growth plates are open during childhood resulting in tall stature. Acromegaly is the same disorder of hGH and IGF-1 excess when it occurs after the growth plate cartilage fuses in adulthood. It is frequently caused by hGH-secreting somatotrope adenomas of the anterior pituitary gland.[20] The clinical manifestations of acromegaly range from subtle signs, such as acral overgrowth and coarsening of facial features, to significant metabolic, cardiovascular, and respiratory manifestations, leading to an increase in morbidity and mortality.[21,22]

Growth hormone deficiency (GHD)

GHD in children results in retardation of longitudinal growth compared to bone age whereas severe GHD in adults is associated with reduced muscle strength and bone mass, insulin sensitivity, abdominal adipositas and increased cardiovascular risk factors (i.e. abnormal lipid profile, atherosclerosis).[23,24,25,26,27,28] With progressing GHD adults show renal, skeletal and intestinal cell insensitivity to parathyroid hormone (PTH) leading to a mild state of PTH resistance and increased serum PTH levels.[29] Consistent with a decrease in end-organ sensitivity, the calcemic response to PTH is delayed.[30]

Stimulation or suppression tests in the diagnosis of growth hormone disorders

The diagnosis of human growth hormone (hGH) deficiency or excess is based on clinical-auxological criteria and NMR imaging of the pituitary gland.[31] It is confirmed by a determination of hGH concentration in serum via stimulation or suppression tests (i.e. a combination of arginine and hGH releasing hormone (GHRH), clonidine or insulin).[32]

For a correct assessment basal hGH levels and levels after stimulation or suppression should be measured. Cutoff levels for the diagnosis of hGH deficiency vary depending on the type of stimulation test and are influenced by the body mass index (BMI).[33] Guidance on cutoff levels should be taken from literature.[31,34,35]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 40 µL of sample, a biotinylated monoclonal hGH-specific antibody and a polyclonal hGH-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 ($Ru(bpy)_3^{2+}$)

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Reagents - working solutions

The reagent rackpack is labeled as HGH.

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

R1 Anti-hGH-Ab~biotin (gray cap), 1 bottle, 8 mL:
Biotinylated monoclonal anti-hGH antibody (mouse) 1.1 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-hGH-Ab~Ru(bpy)$_3^{2+}$ (black cap), 1 bottle, 8 mL:
Polyclonal anti-hGH antibody (sheep) labeled with ruthenium complex 2.4 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.

For USA: For prescription use only.

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	84 days
on the analyzers	56 days

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, K_2- and K_3-EDTA plasma.

Criterion: Method comparison serum versus plasma, slope 0.9-1.1 + intercept within < ± 0.04 ng/mL + coefficient of correlation > 0.90.

Serum and plasma: Stable for 8 hours at 15-25 °C, 1 day at 2-8 °C, 28 days at -20 °C. Freeze only once!

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 05390133190, hGH CalSet, for 4 x 1 mL
- REF 05192943190, Diluent Universal 2, 2 x 36 mL sample diluent or REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent or REF 05341787190, PreciControl Multimarker, for 2 x 2 mL each of PreciControl Multimarker 1 and 2
- REF 05341787160, PreciControl Multimarker, for 2 x 2 mL each of PreciControl Multimarker 1 and 2 (for USA)
- 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, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution
- REF 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution (for USA)

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 IRP (International Reference Preparation), NIBSC (National Institute for Biological Standards and Control) code 98/574.

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 Multimarker.

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 ng/mL, pg/mL or mIU/L).

Conversion factors:
ng/mL x 1000 = pg/mL
pg/mL x 0.001 = ng/mL
ng/mL x 3.0 = mIU/L
mIU/L x 0.333 = ng/mL

Limitations - interference

Do not use samples that show visible signs of hemolysis.

The assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.310 mmol/L or < 0.500 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 123 nmol/L or < 30 ng/mL).

Criterion: Recovery within ± 12 % of initial value for samples > 0.7 ng/mL or ± 0.08 ng/mL for samples ≤ 0.7 ng/mL.

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.

No interference was observed from rheumatoid factors up to a concentration of 600 IU/mL.

There is no high-dose hook effect at hGH concentrations up to 2000 ng/mL.

In vitro tests were performed on 18 commonly used pharmaceuticals. No interference with the assay was found. No interference was found for L-Thyroxin.

The assay is affected by pegvisomant (a highly selective GH receptor antagonist) and is therefore not suitable for patients under pegvisomant treatment. There is no interference with Octreotide (somatostatin analogue) or Cabergoline (dopamine agonist).

The assay is not suitable for the determination of hGH in samples from pregnant women. This is due to a cross-reactivity to placental hGH. Placental hGH is a variant of pituitary hGH[36] and its serum levels increase during the course of pregnancy.

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

0.030-50.0 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below 0.030 ng/mL are reported as < 0.030 ng/mL. Values above the measuring range are reported as > 50.0 ng/mL.

Lower limits of measurement

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

Limit of Blank = 0.020 ng/mL

Limit of Detection = 0.030 ng/mL

Limit of Quantitation = 0.050 ng/mL

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

The Limit of Quantitation was determined using the result of functional sensitivity testing.

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

Dilution

Samples with hGH concentrations above the measuring range can be diluted automatically with Diluent Universal 2. Manual dilution can be performed with Diluent Universal 2 or Diluent Universal. The recommended dilution is 1:2. The concentration of the diluted sample must be > 25 ng/mL.

After manual dilution, multiply the result by the dilution factor 2.

Expected values

Basal levels of hGH do not have a diagnostic relevance and stimulation tests are needed (see above) to assess a growth hormone disorder. Therefore the following values from healthy subjects are for information only and should not be used for diagnostic purposes.

Percentiles	Girls (n = 43) 0-10 years, median: 5 years	Boys (n = 86) 0-10 years, median: 5 years
	hGH (ng/mL)	
5	0.120	0.094
50	0.689	0.814
95	7.79	6.29

Percentiles	Girls (n = 38) 11-17 years, median: 15 years	Boys (n = 33) 11-17 years, median: 15 years
	hGH (ng/mL)	
5	0.123	0.077
50	0.432	0.322
95	8.05	10.8

Percentiles	Women (n = 150) 21-77 years, median: 50 years	Men (n = 149) 20-79 years, median: 50 years
	hGH (ng/mL)	
5	0.126	< 0.030
50	0.944	0.119
95	9.88	2.47

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

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 (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84). The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
HS[b] 1	0.163	0.003	1.9	0.005	3.0
HS 2	8.23	0.165	2.0	0.244	3.0
HS 3	35.1	0.535	1.5	0.800	2.3
PC MM[c]1	0.698	0.011	1.5	0.020	2.8
PC MM2	7.91	0.099	1.3	0.211	2.7

b) HS = human serum

c) PreciControl Multimarker

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
HS 1	0.176	0.004	2.3	0.005	3.0
HS 2	8.63	0.192	2.2	0.260	3.0
HS 3	35.5	0.877	2.5	1.19	3.4
PC MM1	0.710	0.013	1.8	0.019	2.8
PC MM2	7.93	0.133	1.7	0.213	2.7

Method comparison

A comparison of the Elecsys hGH assay (y) with a commercial hGH test (x) using clinical samples gave the following correlations (ng/mL):

Number of samples measured: 209

Passing/Bablok[37]	Linear regression
y = 1.063x + 0.029	y = 0.890x + 0.174
τ = 0.911	r = 0.998

The sample concentrations were between 0.05 ng/mL and 35.4 ng/mL.

Analytical specificity

The following cross-reactivities were found, tested with hGH concentrations of 1 ng/mL and 10 ng/mL:

	Concentration tested	Cross-reactivity (%)
TSH	100 µIU/mL	≤ 0.672
FSH	200 µIU/mL	≤ 1.30
LH	200 mIU/mL	≤ 1.32
hCG	10000 mIU/mL	≤ 0.025
Prolactin	470 ng/mL	≤ 0.544
hPL	40 ng/mL	≤ 0.728
IGF-1	900 ng/mL	≤ 0.161
hGH isoform 20 kDa (WHO: 80-505)	100 ng/mL	≥ 75.4

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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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

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

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www.roche.com

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Roche Diagnostics, Indianapolis, IN
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