Elecsys IGF-1

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REF		Σ	SYSTEM
07475896190	07475896500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 1060
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 555

Intended use

Immunoassay for the in vitro quantitative determination of insulin-like growth factor-1 (IGF-1) in human serum and plasma. The IGF-1 determination is intended to be used as an aid in the assessment of growth disorders in conjunction with other clinical and laboratory findings.

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

Summary

IGF-1, a 70 amino-acid polypeptide with a molecular mass of 7.5 kDa,[1] is ubiquitously expressed in every tissue but it is mainly synthesized and secreted by the liver (~75 % of circulating IGF-1) and regulated by growth hormone (GH).[2] Around 80 % of IGF-1 in the circulation is bound in a ternary complex with IGFBP-3 (Insulin-like growth factor binding-protein 3) and ALS (Acid-labile subunit). The half-life of IGF-1 in this complex is around one hour. Another 20 % of IGF-1 is bound to IGFBP-3 without ALS. Only 1 % of IGF-1 is not bound at all with a half-life of only a few minutes.[3]

IGF-1 (also known as somatomedin)[4] was the first established marker to screen for growth hormone deficiency (GHD).[5] GH is secreted in pulses peaking every 60-90 minutes and has a short half-life. Additionally, GH levels are affected by external factors (e.g. exercise, fasting). In contrast, IGF-1 levels are more robust and as a consequence, the determination of IGF-1 is widely used as a first step in diagnosis of both GH deficiency and excess.[6]

Short stature in children is mainly caused by conditions that affect the growth plates. In case no reason is found, the diagnosis is idiopathic short stature (ISS). GHD is one such condition that affects the growth plates. In this context, IGF-1 is one of several laboratory parameters recommended in guidelines to identify the cause of short stature in children.[7] In combination with other assessments an IGF-1 value around the mean-value of age or upper half of normal range of IGF-1 makes a GHD unlikely and no further testing would be required. Low IGF-1 concentrations (< 2 SD) would indicate a GHD with a high likelihood and should be confirmed with a GH-stimulation test. A GH-stimulation test would also be indicated with IGF-1 serum levels in the lower half of the normal range combined with clinical manifestations of GHD.[8]

GHD is also observed in adults. Interpretation of IGF-1 levels in the context of adults with GHD is different from short stature children. In adults a normal IGF-1 level does not exclude GHD. A very low IGF-1 level (< 2 SD) in patients with highly suspected GHD, or with long-lasting adult-onset, or multiple or total hypopituitarism may be considered as GHD without a GH-stimulation test.[9,10]

The determination of IGF-1 is also recommended for screening of growth disorders by GH-excess like acromegaly.[11]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Complexed antigen in the sample (10 µL) and diluted HCl react to cleave IGF-1 from IGFBP-3 and ALS.
- 2nd incubation: A biotinylated monoclonal IGF-1-specific antibody and a monoclonal IGF-1-specific antibody labeled with a ruthenium complex[a)] react to form a sandwich complex. 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 IGF-1.

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

R1 Diluted HCl (gray cap), 1 bottle, 10 mL: pH 1.5.

R2 Anti-IGF-1-Ab~biotin, anti-IGF-1-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL:
Biotinylated monoclonal anti-IGF-1 antibody (mouse) 0.6 µg/mL; monoclonal anti-IGF-1 antibody (mouse) labeled with ruthenium complex 1.5 µg/mL; phosphate buffer 100 mmol/L, pH 7.8; 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 mist or vapours.
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.
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, USA: 1-800-428-2336

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	28 days
on the analyzers	28 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-EDTA and K_3-EDTA plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 7 ng/mL + coefficient of correlation ≥ 0.95.

Stable for 24 hours at 15-25 °C, 48 hours at 2-8 °C, 28 days at -20 °C (± 5 °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 07475969190, CalSet IGF-1, for 4 x 1.0 mL
- REF 07476108190, PreciControl Growth, for 4 x 3.0 mL
- REF 05192943190, Diluent Universal 2, 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

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 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- 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
- 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.

cobas e 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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 WHO International Standard 02/254.

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 8 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

Use PreciControl Growth or other suitable controls for routine quality control procedures.

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 ng/mL, µg/L or nmol/L).

Conversion factors:	ng/mL x 1 = µg/L
	ng/mL x 0.131 = nmol/L

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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	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.311 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 205 nmol/L or ≤ 50 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 3.3 g/dL
IgA	≤ 0.5 g/dL
IgM	≤ 1.0 g/dL
Albumin	≤ 7.0 g/dL

Criterion: Recovery within ± 4 ng/mL for IGF-1 concentrations ≤ 40 ng/mL or ± 10 % for concentrations > 40 ng/mL of initial value.

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 IGF-1 concentrations up to 20000 ng/mL.

Pharmaceutical substances

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

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

Special growth disorder drugs

Drug	Concentration tested mg/L
Somatotropin	3.0
Octreotide	1.5
Pegvisomant	80

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

7-1600 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 7 ng/mL. Values above the measuring range are reported as > 1600 ng/mL (or up to 16000 ng/mL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 3.5 ng/mL

Limit of Detection = 7 ng/mL

Limit of Quantitation = 15 ng/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 the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with IGF-1 concentrations above the measuring range can be diluted with Diluent Universal 2. The recommended dilution is 1:10 (either automatically by the analyzers or manually). The concentration of the diluted sample must be > 140 ng/mL.

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

Expected values were obtained in a clinical study (CIM RD002173) that enrolled over 3000 female and over 3500 male subjects, including over 1400 subjects ≤ 17 years old.

See "Distribution of expected values" section for details.

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, 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 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	12.7	1.24	9.8	1.56	12.2
Human serum 2	173	3.86	2.2	6.67	3.8
Human serum 3	705	13.4	1.9	27.9	4.0
Human serum 4	1594	49.6	3.1	98.4	6.2
PC[b)] Growth 1	50.2	1.27	2.5	2.01	4.0
PC Growth 2	358	8.26	2.3	14.0	3.9

b) PreciControl

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	14.5	0.298	2.0	0.518	3.6
Human serum 2	171	2.35	1.4	4.65	2.7
Human serum 3	693	11.4	1.6	17.5	2.5
Human serum 4	1519	52.6	3.5	70.2	4.6
PC Growth 1	50.0	0.508	1.0	1.42	2.8
PC Growth 2	350	5.45	1.6	10.3	2.9

Method comparison

A comparison of the Elecsys IGF-1 assay (y), with a commercially available IGF-1 assay (x), using clinical samples gave the following correlations (ng/mL):

Number of samples measured: 146

Passing/Bablok[12] Linear regression

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y = 1.13x - 14.0 y = 1.11x - 12.0

τ = 0.969 r = 0.995

The sample concentrations were between 24.4 ng/mL and 1147 ng/mL.

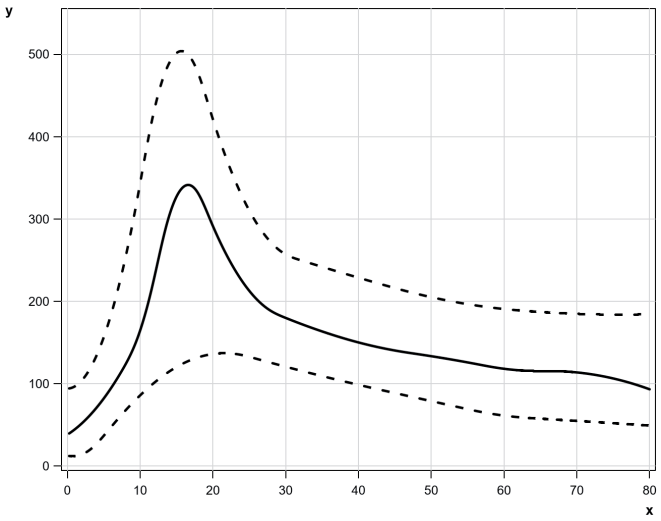
Analytical specificity

No significant cross-reactivity was found for the following substances:

Substances	Concentration tested
IGF-2	4000 ng/mL
IGFBP-3	20000 ng/mL
Insulin	1000 mIU/mL
Proinsulin	1000 nmol/L

Distribution of expected values

The graphic below depicts the distribution of the expected values for male subjects:



x-axis: age
y-axis: IGF-1 value in ng/mL
solid line: 50 % quantile
dashed line: 2.5 % and 97.5 % quantile

The table below is a representative read-out of the age-depended expected values based on the graphic depicted above. The values represent the indicated quantiles (2.5 %, 50 % and 97.5 %) for each age.

Male subjects				
Age (years)	**N**	**2.5 % (ng/mL)**	**50 % (ng/mL)**	**97.5 % (ng/mL)**
0.25	41	12.0	39.4	94.1
0.5	44	11.8	40.9	94.6
1	59	11.8	44.2	96.4
2	38	13.9	51.7	104
3	28	18.9	60.5	116
4	29	26.8	70.6	134
5	34	36.6	81.9	156
6	51	47.1	94.5	184
7	34	57.5	108	216
8	58	67.5	123	254
9	61	76.9	141	296
10	51	85.7	164	343
11	49	93.9	194	392

Male subjects				
Age (years)	**N**	**2.5 % (ng/mL)**	**50 % (ng/mL)**	**97.5 % (ng/mL)**
12	47	101	231	434
13	42	108	270	467
14	35	115	304	489
15	15	120	327	501
16	13	125	339	503
17	4	129	340	495
18	1	132	331	476
19	2	134	312	450
20	4	136	291	421
21	10	137	272	394
22	10	137	254	370
23	16	136	238	348
24	19	135	225	328
25	25	132	213	310
26	15	130	203	295
27	19	128	194	282
28	16	125	188	271
29	18	123	183	263
30	18	120	180	257
31	17	118	176	253
32	16	116	173	250
33	15	114	170	247
34	21	111	166	244
35	14	109	163	242
36	16	107	160	239
37	16	105	158	236
38	19	103	155	234
39	18	101	152	231
40	39	98.5	150	229
41	92	96.4	148	226
42	93	94.4	146	223
43	101	92.4	144	221
44	99	90.5	142	218
45	75	88.5	140	216
46	100	86.5	139	214
47	98	84.6	137	211
48	79	82.6	136	209
49	88	80.6	135	207
50	97	78.7	133	205
51	61	76.7	132	203
52	78	74.8	130	201
53	76	72.8	129	200
54	54	70.9	127	198
55	62	68.9	126	196
56	44	67.0	124	195
57	63	65.3	122	194

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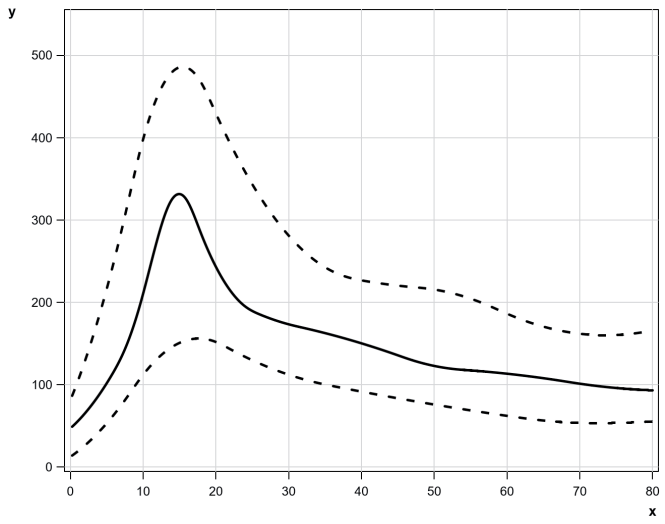
Male subjects				
Age (years)	**N**	**2.5 % (ng/mL)**	**50 % (ng/mL)**	**97.5 % (ng/mL)**
58	70	63.7	121	193
59	70	62.3	119	192
60	61	61.1	118	191
61	58	60.0	117	190
62	85	59.2	116	189
63	62	58.5	116	188
64	64	57.9	115	188
65	46	57.4	115	187
66	57	56.8	115	186
67	53	56.3	115	186
68	58	55.8	115	185
69	68	55.2	114	185
70	68	54.7	114	185
71	68	54.1	113	184
72	64	53.6	111	184
73	72	53.0	110	184
74	40	52.4	108	184
75	39	51.9	106	184
76	32	51.3	104	184
77	27	50.7	102	184
78	19	50.2	99.0	184
79	14	49.6	96.1	184
80	0	-	-	-

The graphic below depicts the distribution of the expected values for female subjects:



x-axis: age
y-axis: IGF-1 value in ng/mL
solid line: 50 % quantile
dashed line: 2.5 % and 97.5 % quantile

The table below is a representative read-out of the age-depended expected values based on the graphic depicted above. The values represent the indicated quantiles (2.5 %, 50 % and 97.5 %) for each age

Female subjects				
Age (years)	**N**	**2.5 % (ng/mL)**	**50 % (ng/mL)**	**97.5 % (ng/mL)**
0.25	28	13.8	48.8	86.4
0.5	35	15.4	50.9	92.0
1	37	18.7	55.3	104
2	34	26.1	65.0	128
3	48	34.2	76.0	155
4	42	43.2	88.2	185
5	50	53.0	102	216
6	49	63.6	116	250
7	37	75.0	133	286
8	47	87.3	154	324
9	39	99.9	180	363
10	42	112	210	398
11	50	123	244	427
12	54	132	278	451
13	38	140	306	468
14	38	146	325	480
15	21	151	331	485
16	11	154	324	485
17	14	156	305	479
18	5	156	283	466
19	3	155	261	449
20	13	152	243	429
21	7	148	227	410
22	7	143	214	392
23	15	138	203	375
24	16	134	195	359
25	15	130	189	343
26	18	126	185	329
27	13	122	182	315
28	13	118	179	303
29	14	115	176	292
30	10	112	173	281
31	12	109	171	271
32	10	107	169	263
33	7	104	167	255
34	10	102	165	248
35	11	100	163	242
36	9	98.3	160	238
37	14	96.5	158	234
38	15	94.8	155	231
39	6	93.1	153	228
40	51	91.4	150	227
41	74	89.8	147	225

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Female subjects				
Age (years)	N	2.5 % (ng/mL)	50 % (ng/mL)	97.5 % (ng/mL)
42	88	88.1	145	224
43	79	86.5	142	222
44	71	84.9	139	221
45	72	83.3	136	220
46	53	81.8	132	219
47	70	80.2	130	218
48	69	78.7	127	218
49	94	77.2	125	217
50	59	75.7	123	215
51	47	74.3	121	214
52	52	72.8	120	212
53	48	71.4	119	210
54	44	70.0	118	207
55	68	68.6	117	204
56	46	67.3	117	201
57	55	65.9	116	198
58	51	64.6	115	194
59	36	63.3	114	190
60	59	62.0	113	186
61	60	60.7	112	182
62	55	59.5	111	179
63	57	58.3	110	176
64	47	57.3	109	173
65	40	56.3	108	170
66	50	55.5	106	168
67	41	54.8	105	166
68	71	54.2	104	164
69	45	53.8	102	163
70	48	53.5	101	162
71	59	53.3	99.8	161
72	47	53.2	98.7	160
73	44	53.2	97.6	160
74	33	53.3	96.7	160
75	24	53.5	95.8	160
76	24	53.7	95.1	161
77	20	54.0	94.4	162
78	25	54.3	93.9	163
79	10	54.7	93.4	164
80	3	55.1	93.0	166

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets 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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.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 for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

Elecsys IGF-1

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For USA: Rx only

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