



For in vitro diagnostic use, Rx only

Federal law restricts this device to sale by or on the order of a licensed Healthcare practitioner (applicable to USA classification only)

Immunofluorescent assay for the determination of Chromogranin A in human serum

Article number: 839050N (50 determinations)

Intended Use

B·R·A·H·M·S™ CgA II KRYPTOR™ is an automated immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE™) technology for quantitative determination of Chromogranin A concentration in human serum.

B·R·A·H·M·S™ CgA II KRYPTOR™ is to be used in conjunction with other clinical methods as an aid in monitoring of disease progression during the course of disease and treatment in patients with gastroentero-pancreatic neuroendocrine tumors (GEP-NETs, grade 1 and grade 2).

Warnings and Precautions

Test Interpretation:

B·R·A·H·M·S CgA II KRYPTOR should not be used for cancer screening or cancer diagnosis.

B·R·A·H·M·S CgA II KRYPTOR is not indicated to be used as a stand-alone monitoring assay and should be used in conjunction with clinical signs and symptoms and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

The results reported by the laboratory to the physician must include the identity of the Chromogranin A assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining Chromogranin A levels is changed, additional tests should be carried out to determine the baseline values.

High levels of Chromogranin A (CgA) could also be found in cases of benign diseases (such as gastro-intestinal disorders, kidney failure and cardiovascular disorders) and in cancers other than NETs (such as adenocarcinoma of the breast, lung, or colon) [1-6]. CgA values may rise during treatment with proton pump inhibitors [7].

Limitations

The effect of interfering substances has only been evaluated for those listed in the labeling. Interference by substances other than those described in the Interference section below could lead to erroneous results.

Accurate results are dependent on following the proper sample collection, storage, and handling procedures.

Summary and Explanation

CgA is an acidic, hydrophilic protein of 49 kDa present in chromaffin granules of the neuroendocrine cells and is a member of the granin family.

Neuroendocrine tumors (NETs) originate from neuroendocrine cells found in neuronal and endocrine tissues throughout the body. The most common sites of NETs are the lung, stomach, appendix, cecum, duodenum, pancreas, jejunum/ileum, colon and rectum [8]. NETs arising from the gastrointestinal tract are collectively known as gastroenteropancreatic neuroendocrine tumors [9].

Follow up and monitoring investigations of NETs are based on tumor markers together with other diagnostic measures and clinical signs [10, 11]. Besides its use as immunohistological marker, CgA has been well recognized as a general broad-spectrum serum marker in GEP-NETs [12-14].

Principle

The measurement principle of B·R·A·H·M·S KRYPTOR analyzers is based on TRACE technology, which measures a fluorescence signal that is emitted from an immunocomplex. The basis of the TRACE technology is a non-radiative energy transfer from a donor (cryptate) to an acceptor (Alexa Fluor™ 647).

Precise measuring of analyte concentration

The proximity of donor and acceptor when they are part of an immunocomplex and the spectral overlap between donor emission and acceptor absorption spectra, intensify the fluorescence signal of the donor and extend the life span of the acceptor signal, permitting the measurement of temporally delayed fluorescence.

Concretely, when the sample is excited with a nitrogen laser at 337 nm, the donor emits a long-lived fluorescence signal in the millisecond range at 620 nm, while the acceptor generates a short-lived signal in the nanosecond-range measured at 665 nm.

When the two components are bound in an immunocomplex, both the signal amplification and the prolongation of the life span of the acceptor signal occur at 665 nm, so that it can be measured over microseconds.

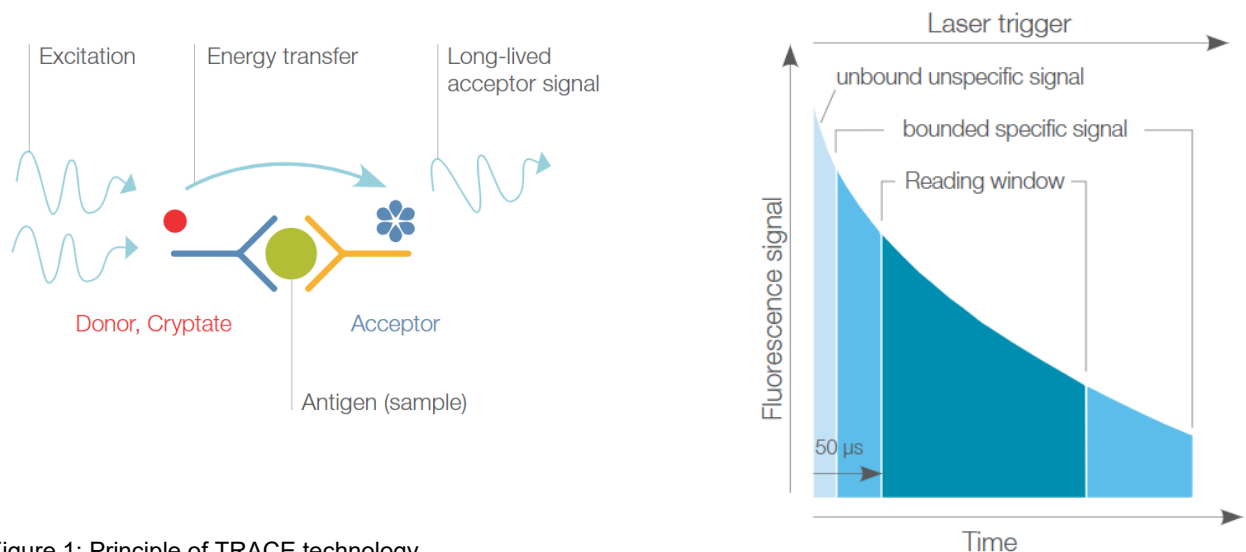


Figure 1: Principle of TRACE technology

Reliable prevention of interferences

Background fluorescence generated by non-specific signals, e.g., the signals from proteins emitting short-lived fluorescence, interferences or unbound acceptor are eliminated by temporal delay of the fluorescence measurement. The signal generated by the cryptate at 620 nm serves as an internal reference and is measured simultaneously with the long-lived acceptor signal at 665 nm which is the specific signal. Matrix absorption, e.g., from turbid sera, are automatically corrected by means of the internally calculated ratio of the intensities at these wavelengths.

Instructions

Sample volume.....	14 µL
Incubation time.....	29 min
Results are given in.....	ng/mL
Conversion factor.....	not applicable
Linear direct measuring range.....	20.0...3,000 ng/mL
Measuring range with automatic dilution.....	up to 1,000,000 ng/mL
Sample type.....	serum
Kit stability on board.....	29 days
Calibrator.....	1 point
Calibration stability.....	15 days
Assay principle.....	sandwich

Reagents

The B·R·A·H·M·S CgA II KRYPTOR assay contains sufficient reagents for 50 determinations.

Materials Provided:

Reagent	Quantity for 50 determinations	Content
Cryptate Conjugate	1 vial lyophilized	Anti-CgA monoclonal antibody conjugated with cryptate, buffer, bovine albumin, bovine immunoglobulins, murine immunoglobulins, trehalose, mannitol. Volume of 4.1 mL after automated reconstitution with B·R·A·H·M·S KRYPTOR compact Solution 1 and 2 within the instrument.
XL Conjugate	1 vial	Anti-CgA monoclonal antibody conjugated with Alexa Fluor™ 647, buffer, bovine albumin, bovine immunoglobulins, murine immunoglobulins, potassium fluoride.
Diluent	1 vial	Human serum, preservative, EDTA

Additional Materials Required but Provided Separately:

- B·R·A·H·M·S CgA II KRYPTOR Calibrator

	Content
Calibrator	Lyophilized recombinant CgA in horse serum, reconstitute with 0.65 mL de-ionized water with conductivity of less than 50 µS/cm [range: 990 - 1,210 ng/mL]

- B·R·A·H·M·S CgA II KRYPTOR QC Controls

	Content
Control 1	Lyophilized recombinant CgA in horse serum, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 64 - 96 ng/mL]
Control 2	Lyophilized recombinant CgA in horse serum, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 400 - 600 ng/mL]

- B·R·A·H·M·S KRYPTOR Analyzer Consumables

	Content
B·R·A·H·M·S KRYPTOR compact Solution 1	ProClin™ 150 solution
B·R·A·H·M·S KRYPTOR compact Solution 2	Potassium fluoride solution
B·R·A·H·M·S KRYPTOR compact Solution 3	Active chlorine and sodium hydroxide solution

	Content
B·R·A·H·M·S KRYPTOR compact Solution 4	Sodium hydroxide solution
KRYPTOR BUFFER	Phosphate Buffer Saline (PBS) buffer, not reconstituted, 5 liters after reconstitution
Reaction plates B·R·A·H·M·S KRYPTOR compact REACT (Reaction Plates)	60 reaction plates, containing 96 wells each. Additionally, 60 adhesive cover films are included.
Dilution plates B·R·A·H·M·S KRYPTOR compact DILCUP (Dilution plates)	30 dilution plates, containing 24 wells each. Additionally, 30 adhesive cover films are included.

Warnings and Precautions – Test Procedure:

For *in vitro* diagnostic use only.

Caution: US Federal Law restricts this device to sale by or on the order of a licensed practitioner.

For professional use only.

Plasma tubes should not be used.

This reagent contains materials of human origin (e.g. human plasma). These materials have been screened for HBsAg, HIV I/II antibodies, and HCV antibodies; all tests were negative. However, the reagent and patient samples should be handled with care, as all materials of human origin are potentially hazardous.

Because glass vials are included in the kit, we explicitly point out that there will be a breakage hazard, and consequently a risk of injury.

Carefully follow the manufacturer's instructions. Improper handling of the reagents may falsify the test results.

Do not use reagents after the expiration date indicated on the label.

Do not mix reagents or disposables from different lots.

B·R·A·H·M·S Customer Service will gladly send the reagent-specific Safety Data Sheets upon request.

Tel.: 800.232.3342

Fax: 540.869.8126

E-Mail: techservice.mgc@thermofisher.com

The reagents as well as waste originated by the test must be disposed of in accordance with the specifications of local authorities.

Stability and Storage Conditions

Store all reagents at 2 to 8°C in their original shipping containers until directly prior to use. Observe the expiry dates specified on the main container and the vial labels. Do not use any reagents that have exceeded the expiration date printed on the label.

The reagent unit is stable 29 days after reconstitution when stored on board the B·R·A·H·M·S KRYPTOR analyzer (2-8°C).

Specimen Collection and Preparation

Specimens Recommended: Only serum must be used.

Specimen Collection: Clinical and Laboratory Standards Institute (CLSI) guidelines must be followed for collecting, transporting, and processing patient samples. The sample volume needed for each test is 14 µL. Place the sample in a tube suited for use on the B·R·A·H·M·S KRYPTOR analyzer (between 11 mm and 17 mm in diameter and 60 mm and 110 mm in height). The sample volume must be sufficient to ensure proper pipetting. The sample tube must contain a dead volume, which will vary depending on the diameter of the sample tube. A 13 mm diameter tube will require an additional 150 µL of sample.

The results of the B·R·A·H·M·S CgA II KRYPTOR should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

WARNING: Patient samples should be handled with care, as all materials of human origin are potentially hazardous.

Specimen Handling and Storage: Samples may be stored at room temperature and at 2-8 °C for up to 48h.

If the assay will not be completed within 48 hours or for shipment of samples, samples shall be aliquoted and stored frozen at -20°C or lower. A frozen sample can be stored for up to 3 months at -20°C.

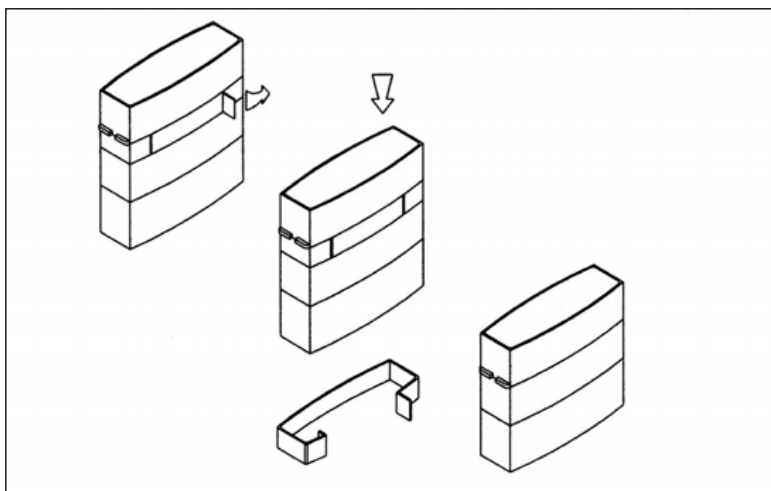
The analyte is stable up to 4 freeze-thaw cycles.

Procedure

The B·R·A·H·M·S CgA II KRYPTOR assay is to be used only with B·R·A·H·M·S KRYPTOR analyzers. The operation and maintenance of B·R·A·H·M·S KRYPTOR analyzers are described in the User Manuals.

The B·R·A·H·M·S CgA II KRYPTOR assay procedure includes registering and/or loading the sample(s), reagent kit, calibrator and controls, as applicable. A sample volume of 14 µL is needed for each test. Initially, a worklist for the day is created. Then the test is started. The sample probe of the analyzer pipettes and dispenses the conjugates from the reagent kit and the sample into the wells. The probe is heated to incubate the reagent-sample mixture, so it is at reaction temperature (37°C) prior to dispensing and mixing in the reaction well. After measurement of the fluorescent signal, the data obtained from the software is compared to the memorized standard curve. Incubation lasts 29 minutes. The B·R·A·H·M·S CgA II KRYPTOR assay results are given in ng/mL.

To prepare a reagent unit, proceed as follows:



Calibration Using B·R·A·H·M·S CgA II KRYPTOR Calibrator Kit

Intended Use

The B·R·A·H·M·S CgA II KRYPTOR CAL calibrators, when used in conjunction with the B·R·A·H·M·S CgA II KRYPTOR assay and B·R·A·H·M·S CgA II KRYPTOR QC controls, are intended for calibration of the B·R·A·H·M·S CgA II KRYPTOR assay.

The B·R·A·H·M·S CgA II KRYPTOR calibrator kit contains 6 vials and a bar code card.

Each vial contains lyophilized recombinant CgA in horse serum.

A bar code card is provided with the vials and contains information related to the calibrator lot including its concentration.

Preparation

Reconstitute a vial with de-ionized water (0.65 mL) as indicated on the vial label. Use de-ionized water with conductivity of less than 50 µS/cm.

Mix gently after reconstitution.

Do not leave calibrators at room temperature or on the carousel for more than 5 hours.

Refer to the B·R·A·H·M·S KRYPTOR analyzers User Manuals. The calibrator bar code card must be read for each new lot of calibrator. Calibration must be carried out before the first use of new B·R·A·H·M·S CgA II KRYPTOR lot, then repeated on a regular basis automatically managed by the B·R·A·H·M·S CgA II KRYPTOR in order to readjust the standard curve.

The previous curve, as well as the curve obtained from a calibration, may be viewed on the analyzer screen.

A standard curve does not need to be established for B·R·A·H·M·S CgA II KRYPTOR on the B·R·A·H·M·S KRYPTOR analyzer. Rather, the standard curve is included within the bar code information from the calibration card and is stored in the analyzer. The calibrations are performed using a disposable calibrator vial in order to readjust the standard curve. The previous curve, as well as the curve obtained from a calibration, may be viewed on the analyzer screen.

The B·R·A·H·M·S CgA II KRYPTOR measures concentrations between 20 and 3,000 ng/mL.

Samples up to 1,000,000 ng/mL will be diluted automatically.

Quality Control Using B·R·A·H·M·S CgA II KRYPTOR QC Kit

Intended Use

The B·R·A·H·M·S CgA II KRYPTOR QC controls, when used in conjunction with the B·R·A·H·M·S CgA II KRYPTOR assay and B·R·A·H·M·S CgA II KRYPTOR CAL calibrators, are intended for quality control of the B·R·A·H·M·S CgA II KRYPTOR assay.

The B·R·A·H·M·S CgA II KRYPTOR QC kit contains 2 series of 3 vials, a bar code card, bar code stick-on labels and the concentration ranges by level.

Each vial contains lyophilized recombinant CgA in horse serum. The 2 series of vials correspond to 2 levels of antigen concentration:

- B·R·A·H·M·S CgA II KRYPTOR - Control 1 (level 1): 64 – 96 ng/mL
- B·R·A·H·M·S CgA II KRYPTOR - Control 2 (level 2): 400 – 600 ng/mL

The bar code card contains information related to the control batch (i.e., the target concentrations, the standard deviations, and the concentration acceptance ranges). The information is visible on the B·R·A·H·M·S KRYPTOR analyzer monitor screen in the quality control section.

Preparation

To ensure good reproducibility of the controls, follow the procedure below.

- Reconstitute a vial with de-ionized water (2 mL) as indicated on the vial label. Use de-ionized water with conductivity of less than 50 µS/cm.
- Allow 15 minutes for the complete dissolution of the lyophilisate.
- Homogenize the control sample using a vortex mixer.
- Transfer aliquots into sample tubes.
- Use one sample tube for immediate measurements. Freeze the other tubes immediately at < -16°C and store up to one month.
- After thawing an aliquot, mix using a vortex mixer and use immediately for measurement. A control tube will be processed like a sample tube.

After reconstitution, do not keep a vial more than 2 hours at 18 to 25°C or 24 hours at 2 to 8°C. Once thawed, a control aliquot must not be refrozen.

The bar code stick-on labels are used for identifying the controls when used on the B·R·A·H·M·S KRYPTOR analyzers. The control kit bar code card must be entered for each new lot of control. Refer to the B·R·A·H·M·S KRYPTOR analyzers User Manuals. A control should be carried out after each calibration.

Good laboratory practices imply that control samples be used regularly to ensure the quality of the results obtained. These samples must be processed exactly the same way as the patient samples, and it is recommended that their results be analyzed using appropriate statistical methods.

If selected, the B·R·A·H·M·S KRYPTOR analyzers can automatically check the quality of control results at intervals, by statistical analysis on Levey Jennings graphs. National quality assurance guidelines for quantitative tests in the medical laboratory (current version) must be complied with. For instance, test accuracy and precision can be monitored by means of laboratory in-house and/or commercially available control materials. If unacceptable control values are obtained, proceed as outlined in standard laboratory diagnostic procedures to determine the cause and implement corrective measures.

Note: Control material should be tested in accordance with guidelines or requirements of local, state, and/or federal regulations or accrediting organizations.

Result Output

After measurement of the fluorescent signal, the data obtained from the software is compared to the memorized standard curve. The B·R·A·H·M·S CgA II KRYPTOR assay results are given in ng/mL.

Reference Range

This study was performed on the B·R·A·H·M·S KRYPTOR compact PLUS analyzer. Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

A reference range was established based on serum samples from 206 self-declared healthy individuals from both sexes and from different age-groups. The 95th percentile has been found at 187.0 ng/mL. The median was found at 61.8 ng/mL.

Note: It is recommended that each laboratory establishes reference ranges based on representative patient collectives and/or test the validity of the manufacturer's commercial test kit data.

Interpretation of Results

CgA values need to be evaluated in combination with clinical symptoms and/or other laboratory parameters. The change of CgA concentration over time provides diagnostic information whether a tumor progression has occurred.

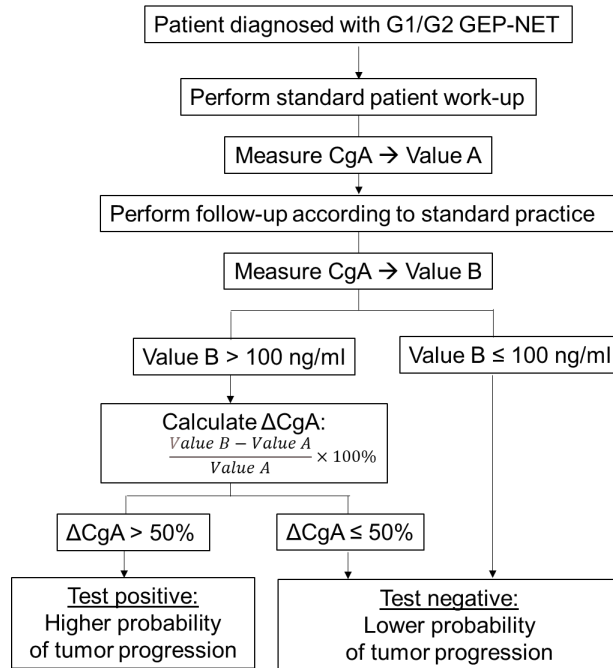
$$\Delta CgA = \frac{CgA \text{ concentration of current visit} - CgA \text{ concentration of previous visit}}{CgA \text{ concentration of previous visit}} \times 100\%$$

- $\Delta CgA > 50\%$ and $CgA > 100 \text{ ng/ml}$:

An increase of CgA serum concentrations of more than 50% to a value of greater than 100 ng/ml between consecutive monitoring visits defines a positive test result representing a higher probability that a tumor progression has occurred.

- $\Delta CgA \leq 50\%$ or $CgA \leq 100 \text{ ng/ml}$:

A change of CgA serum concentrations of equal or less than 50% increase between monitoring visits or to a value of 100 ng/ml or less defines a negative test result representing a lower probability that a tumor progression has occurred.



Clinical Performance Characteristics

A prospective, multi-center, observational study with 153 evaluable neuroendocrine tumor patients was performed to validate the performance of B·R·A·H·M·S CgA II KRYPTOR assay in monitoring grade 1 and grade 2 GEP-NET progressive or non-progressive disease within 32 months. Course of disease was assessed by standard imaging (CT/MRI scans) and tumors were classified by RECIST 1.1 criteria for progression (progressive disease) vs. no progression (complete response, partial response, or stable disease).

Change of CgA was calculated from measurements at consecutive routine monitoring visits within a typical interval of 3 to 6 months and was considered test-positive if serum CgA concentration increased by more than 50% to an absolute value greater than 100 ng/mL. A positive CgA-change test was shown to be significantly associated with tumor progression ($p < 0.001$) and the following diagnostic performance measures for tumor progression were obtained (estimate and 95% confidence interval):

		Tumor Progression		Total
		Progression	No Progression	
Binary CgA increase*	Positive	33	24	57
	Negative	63	339	402
Total		96	363	459

*Cut-off 50% CgA increase and CgA > 100 ng/mL

Performance Measurement	Value	Lower CI*	Upper CI*
Sensitivity	34.4% (33/96)	23.2%	45.5%
Specificity	93.4% (339/363)	90.2%	96.0%
PPV	57.9% (33/57)	40.5%	73.6%
NPV	84.3% (339/402)	79.3%	89.1%
PLR	5.20	2.90	9.66
NLR	0.70	0.58	0.83
Prevalence	20.9% (96/459)		

*CI = 95% Confidence interval; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio

It can be concluded that the B·R·A·H·M·S CgA II KRYPTOR achieves the clinical performance required for the intended use of B·R·A·H·M·S CgA II KRYPTOR and provides benefit for patients diagnosed with GEP-NETs of grade 1 or 2.

Detection Capability

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined following CLSI guideline EP17-A2 using 3 lots of reagents and multiple instruments.

The LoB is the 95th percentile from 60 determinations of 4 analyte-free samples.

The LoD is determined based on the LoB and the standard deviation of 4 low level samples from 60 determinations of low analyte samples. The LoD is the lowest amount of CgA in a sample that can be detected with 95% probability.

The LoQ is calculated with guidance from CLSI EP17-A2, appendix D1 and CLSI EP05-A3, and is the lowest analyte concentration that can be reproducibly measured with an intermediate within-lab precision coefficient of variation (CV) of $\leq 20\%$.

The maximum LoB, LoD, and LoQ observed are indicated below:

LoB = 11.3 ng/mL

LoD = 14.0 ng/mL

LoQ = 20.0 ng/mL

Precision

Precision (repeatability, within-laboratory, reproducibility and lot-to-lot precision) was determined following CLSI guideline EP05-A3.

Repeatability and Within-Laboratory CVs were calculated from the measurement of samples over 20 days, with 2 runs per day in 2 replicates :

Sample	Mean Value (ng/mL)	Repeatability CV	Within-Laboratory CV
1.1	23.0	5.2%	10.0%
1.2	26.0	5.1%	9.9%
1.3	34.6	3.7%	8.8%
1.4	56.3	2.8%	8.4%
1.5	86.3	1.7%	8.3%
1.6	132	1.3%	7.1%
1.7	228	1.7%	6.9%
1.8	463	1.1%	4.4%
1.9	744	1.6%	2.8%
1.10	1,177	1.1%	4.0%
1.11	1,825	1.3%	4.7%
1.12	2,687	1.6%	7.4%

Lot-to-lot CVs were calculated from the measurement of samples over 5 days, with 5 replicates per day using 3 reagent lots and 1 instrument:

Sample	Mean Value (ng/mL)	Lot-to-Lot	
		SD	CV
39LOT_01	26,3	0.3	1.2%
39LOT_02	48,9	0.0	0.0%
39LOT_03	96,8	0.1	0.1%
39LOT_04	513	8.3	1.6%
39LOT_05	757	14.0	1.9%

39LOT_06	963	23.6	2.4%
39LOT_07	1,441	39.1	2.7%
39LOT_08	2,030	88.9	4.4%
39LOT_09	2,540	19.2	0.8%
39LOT_10	2,895	0.0	0.0%

For reproducibility, samples have been measured on 5 days, with 2 runs per day in 3 replicates using 1 reagent lot at 3 different sites (different instruments):

Sample	Mean Value (ng/mL)	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
2.1	25.7	1.66	6.5%	0.0	0.0%	0.55	2.2%	1.50	5.8%	2.30	9.0%
2.2	53.6	1.93	3.6%	1.53	2.8%	2.94	5.5%	0.00	0.0%	3.83	7.1%
2.3	104	2.07	2.0%	1.51	1.5%	2.04	2.0%	2.88	2.8%	4.37	4.2%
2.4	515	9.52	1.8%	5.87	1.1%	9.55	1.9%	12.6	2.5%	19.4	3.8%
2.5	1,089	16.7	1.5%	23.9	2.2%	41.0	3.8%	38.9	3.6%	63.6	5.8%
2.6	1,723	29.2	1.7%	63.4	3.7%	61.8	3.6%	0.0	0.0%	93.2	5.4%
2.7	2,923	62.3	2.1%	66.8	2.3%	64.5	2.2%	178	6.1%	210	7.2%
2.8	92,561	2,669	2.9%	2,993	3.2%	1,584	1.7%	2,803	3.0%	5,143	5.6%

Linearity / High Dose Hook Effect

B·R·A·H·M·S CgA II KRYPTOR is a homogenous immunoassay and does not require separation or washing steps. It is thus possible to obtain data without interrupting the immunological reaction. High concentration samples (> 3,000 ng/mL) are detected in the first few seconds of incubation and may be diluted by the appropriate dilution factor, then re-assayed automatically.

- In other words, potential Hook Effect is detected by kinetics analysis of the samples by B·R·A·H·M·S KRYPTOR analyzer family. Measurement is stopped for samples greater than 3,000 ng/mL. If automatic dilution is activated, then the B·R·A·H·M·S KRYPTOR analyzer automatically dilutes the sample at an appropriate dilution. If automatic dilution is not activated, then the B·R·A·H·M·S KRYPTOR analyzer family adds the dilution of the sample to the worklist and the user has to validate the worklist to launch the dilution of the sample. This process allows for sample measurements greater than 3,000 ng/mL up to 1,000,000 ng/mL.

Linearity was determined following CLSI guideline EP06-A 2nd Edition guidance.

Analytical Measuring Interval (AMI)

The assay is linear from 20.0 ng/mL (LoQ) up to 3,000 ng/mL. The extended measuring range extends from 3,000 ng/mL up to 1,000,000 ng/mL.

Interfering Substances

Interference was assessed in accordance with CLSI guideline EP07-A3. The substances evaluated with the B·R·A·H·M·S CgA II KRYPTOR were found not to affect the test performance (bias ≤ 10%) at concentrations reasonably and consistently found in clinical situations. The substances included the following:

Endogenous factors:

Interfering substance	Interference
Albumin	No interference up to 50 g/L
Bilirubin (unconjugated)	No interference up to 500 mg/L
HAMAs	No interference up to 300 µg/L
Hemoglobin	No interference up to 10 g/L
Rheumatoid factors	No interference up to 1,000 kIU/L
Triglycerides	No interference up to 5 g/L

Concomitant medications and nutritional supplements:

Interfering substance	Interference
Acetaminophen	No interference up to 238.3 mg/L
Alprazolam	No interference up to 6.0 mg/L
Amlodipine	No interference up to 100.2 µg/L
Aspirin	No interference up to 546.6 mg/L
Biotin	No interference up to 3,510 ng/mL
Fish Oil	No interference up to 2.4 g/L
Hydrocodon	No interference up to 200.3 µg/L
Hydrochlorothiazide	No interference up to 6.0 mg/L
Ibuprofen	No interference up to 499.6 mg/L
Lisinopril	No interference up to 300.4 µg/L
Lorazepam	No interference up to 998.3 µg/L
Metoprolol	No interference up to 5.0 mg/L
Multivitamin: Vitamin A Vitamin C Vitamin D Vitamin E Thiamin (B1) Riboflavin (B2) Niacin Vitamin B6 Vitamin B12	No interference up to: 16.7 kIU/L 1,000 mg/L 5.33 kIU/L 100.0 IU/L 200 mg/L 250 mg/L 170 mg/L 170 mg/L 3,333 µg/L
Oxycodon	No interference up to 500.9 µg/L
Pancrelipase	No interference up to 480 KU/L

Therapeutics:

Interfering substance	Interference
Bevacizumab	No interference up to 720 mg/L
Capecitabine	No interference up to 2.85 g/L
Carboplatin	No interference up to 1 g/L
Cisplatin	No interference up to 2 g/L
Etoposide	No interference up to 114 mg/L
Everolimus	No interference up to 6 mg/L
Fluorouracil	No interference up to 684 mg/L
Interferon (IFN-α-2b)	No interference up to 3,000 kU/L
Lanreotide	No interference up to 72 mg/L
Octreotide	No interference up to 12 mg/L
Oxaliplatin	No interference up to 96.9 mg/L
Sunitinib	No interference up to 22.5 mg/L
Temozolomide	No interference up to 228 mg/L
Temsirolimus	No interference up to 15 mg/L

Cross reactants:

Cross reactant	Amino acids	Maximum concentration tested (nmol/L)	Cross reactivity
Parastatin (porcine)	347 to 365	100	0.08 %
Pancreastatin (human)	250 to 301	182	2.1 %
Vasostatin I (human)	17 to 76	9	6.7 %
Vasostatin II (human)	19 to 131	5	21.6 %
Vasostatin II Cterm (human)	97 to 131	15	1.8 %
Catestatin (human)	352 to 372	452	0.15 %
Chromostatin (bovin)	124 to 143	10	11.0 %
Chromogranin A protein fragment (human)	260 to 454	217	0.19 %

Cross reactant	Amino acids	Maximum concentration tested (nmol/L)	Cross reactivity
Chromogranin B (Secretogranin 1) (human)	21 to 677	72	1.3 %
Chromogranin C (Secretogranin 2) (human)	1 to 617	148	0.72 %
WE14 (human)	315 to 329	606	0.18 %

Bibliography

1. Bottoni P, De Michele T and Scatena R, 2015, Adv Exp Med Biol 867: 317-323.
2. Giovanella L, Marelli M, Ceriani L, et al., 2001, Int J Biol Markers 16(4): 268-272.
3. Gkolfinopoulos S, Tsapakidis K, Papadimitriou K, et al., 2017, World J Methodol 7(1): 9-15.
4. Singh S and Law C, 2012, Expert Rev Gastroenterol Hepatol 6(3): 313-334.
5. Trape J, Filella X, Alsina-Donadeu M, et al., 2011, Clin Chem Lab Med 49(10): 1605-1620.
6. Tropea F, Baldari S, Restifo G, et al., 2006, Clin Drug Investig 26(12): 715-722.
7. Modlin IM et al., 2010; Ann Surg Oncol 17(9):2427–2443
8. Yao JC, Hassan M, Phan A et al., 2008; J. Clin. Oncol. 26(18) 3063–3072
9. Lawrence B, Gustafsson BI, Kidd M et al., 2011; Endocrinol.Metab. Clin. North Am. 40(1), 111–134, viii
10. Arnold R et al., 2009; Neuroendocrinology, vol. 90, no. 2, pp. 227-33
11. Ardill JE and O'Dorisio TM, 2010; Endocrinol Metab Clin North Am, vol. 39, no. 4, pp. 777-90
12. Deftos LJ, 1991; Endocr Rev, vol. 12, no. 2, pp. 181-7
13. Schurmann G, Raeth U, Wiedenmann B et al., 1992; World J Surg, vol. 16, no. 4, pp. 697-701; discussion 701-2
14. Tomassetti P et al., 2001; Eur J Gastroenterol Hepatol, vol. 13, no. 1, pp. 55-8

Revision History

Date: [2023-09-27]

(This version supersedes all earlier instruction manuals.)

Date of Revision	Version	Description of Changes
2023-09-19	Version 1.0	Initial release
2023-09-27	Version 1.1	Update of sample stability at 2 to 8°C and -20°C in section 'Specimen Collection and Preparation'



Manufactured by:
B·R·A·H·M·S GmbH
Neuendorfstrasse 25
16761 Hennigsdorf
GERMANY

Customer Service and Orders:
Fisher Scientific Company L.L.C
8365 Valley Pike
Middletown
Virginia 22645
USA

Tel.: 800.232.3342
Fax: 540.869.8126
E-Mail: techservice.mgc@thermofisher.com
www.thermoscientific.com/brahms

© 2023 Thermo Fisher Scientific Inc. All rights reserved. All trademarks are the property of Thermo Fisher Scientific and its subsidiaries unless otherwise specified.

B·R·A·H·M·S is a registered trademark of B·R·A·H·M·S GmbH.



























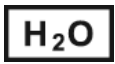







TRACE and KRYPTOR are trademarks of Cisbio Bioassays, licensed for use by B·R·A·H·M·S GmbH, a part of Thermo Fisher Scientific.









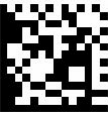
Other product names in this document are used for identification purposes; they may be trademarks and/or registered trademarks of their respective companies.

The manufacture and/or use of this product is covered by one or more of the following patents: www.brahms.de/patents

Symbols

Symbols used in Instruction for Use and Product Labelling of B·R·A·H·M·S KRYPTOR products.

Symbol	Usage	Symbol	Usage	Symbol	Usage
	Manufacturer		CE-Conformity Marking According to Regulation 2017/746/EC on In Vitro Diagnostic Medical Devices, Annex II with Reg.Number of Notified Body		Contains sufficient for (Number of) tests, e.g. 50
	Use by		Temperature Limitation	REF	Article Number/ Catalogue Number
	Green Dot according to German Law		Buffer		Bags Contained
	Consult Instructions for Use	 ifu.brahms.de	e-labeling Website Address		Batch Code
	Lyophilized, Freeze Dried	Intended Use	Reference to the intended use of the Medical Device		In Vitro Diagnostic Medical Device
	Contents		Calibrator		Control
	Bags		Plates Contained		Plates
	Vials Contained		Vials		Vial
	B·R·A·H·M·S KRYPTOR compact SOLUTION 1		B·R·A·H·M·S KRYPTOR compact SOLUTION 2		B·R·A·H·M·S KRYPTOR compact SOLUTION 3
	B·R·A·H·M·S KRYPTOR compact SOLUTION 4		Use Given Volume of Distilled Water (conductivity of less than 50 µS/cm is recommended) for Reconstitution, e.g. 0.75 mL		Reconstitute
	Biohazard		Wear Protective Gloves		Wear Safety Glasses
	Wash Hands		General Regulatory Sign		General Prohibitive Sign

Symbol	Usage	Symbol	Usage	Symbol	Usage
	Do not Smoke		Do not Eat and Drink		GHS07 Harmful
	GHS05 Corrosive	TRACE	Symbol related to TRACE Technology		Waste
	Do not Reuse		Caution, Consult Accompanying Documents		Accidental Release Measures
Rx only	Federal law restricts this device to sale by or on the order of a licensed Healthcare practitioner (applicable to USA classification only)		QR Code that Provides UDI Information		