thermoscientific

B·R·A·H·M·S PCT SENSITIVE KRYPTOR

TRACE IVD Σ 50

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 PCT (procalcitonin) in human serum and plasma

Article number: 825.050 (50 determinations)

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR® is an immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE®) technology to determine the concentration of PCT (procalcitonin) in human serum and EDTA or heparin plasma.

The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended to be performed on the B·R·A·H·M·S KRYPTOR® analyzer family.

Used in conjunction with other laboratory findings and clinical assessments, B·R·A·H·M·S PCT sensitive KRYPTOR® is intended for use as follows:

- to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
- to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission,
- to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD),
- to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

Warnings and Precautions – Test Interpretation

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

Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations.

PCT results should always be interpreted in the context of the clinical status of the patient and other laboratory results. Changes in PCT levels for the prediction of mortality, and overall mortality, are strongly dependent on many factors, including pre-existing patient risk factors and clinical course.

The need to continue ICU care at Day 4 and other covariates (e.g., age and SOFA score) are also significant predictors of 28-day cumulative mortality risk.

The safety and performance of PCT-guided therapy for individuals younger than age 18 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydophila pneumoniae and Mycoplasma pneumoniae.[1]

Severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values.[2]

Increased PCT levels may not always be related to systemic infection [2-5]. These conditions include, but are not limited to:

- Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns;
- Patients under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis;
- Patients diagnosed with active medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid;
- Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C);
- Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies or after resuscitation from cardiac arrest;
- Patients receiving peritoneal dialysis or hemodialysis treatment;
- Patients with biliary pancreatitis, chemical pneumonitis or heat stroke;
- Patients with invasive fungal infections (e.g. candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria; and
- Neonates during the first 2 days of life.

Summary and Explanation

Sepsis is a daily challenge in the hospital setting. Today various therapeutic strategies are known to improve survival in patients with sepsis. Early assessment is important for determination of the appropriate treatment.

Acute respiratory tract infections account for almost 10% of the worldwide burden of morbidity and mortality. As much as 75% of all antibiotic doses are prescribed for acute respiratory-tract infections, despite a mainly viral cause for these infections. This inappropriate use of antibiotics is believed to be a primary cause of the spread of antibiotic-resistant bacteria. Thus, reduction of the excess use of antibiotics is essential to combat the increase of antibiotic-resistant microorganisms.

PCT is the prohormone of the hormone calcitonin, but PCT and calcitonin are distinct proteins. Calcitonin is exclusively produced by C-cells of the thyroid gland in response to hormonal stimuli, whereas PCT can be produced by several cell types and many organs in response to pro-inflammatory stimuli, in particular by bacterial products.[6]

In healthy people, plasma PCT concentrations are found to be below 0.1 µg/L.[7] Depending on the clinical background, a PCT concentration above 0.1 µg/L can indicate clinically relevant bacterial infection, requiring antibiotic treatment. In addition, low PCT concentrations at predefined cutoffs can identify patients without clinically relevant bacterial infections; in these individuals antibiotic therapy can be safely discontinued.[8]

PCT levels rise rapidly (within 6 - 12 hours) after an infectious bacterial insult with systemic consequences. The magnitude of the increase in PCT concentration correlates with the severity of the bacterial infection.[2] At a PCT concentration > 0.5 µg/L, a patient should be considered at risk of developing severe sepsis or septic shock.[9,10] On the other hand, the relief of the septic infection is accompanied by a decrease in the PCT concentration which returns to normal with a half-life of 24 hours,[11,12] i.e. the continuous decline of PCT is indicative of effective source control measures and has been implicated in the safe discontinuation of antibiotic therapy.[13,14]

Several randomized controlled trials have demonstrated the use of PCT to guide initiation as well as discontinuation of antibiotic therapy in patients with acute respiratory tract infection significantly reduces antibiotic consumption.[8,13,15-18] This reduction of antibiotic consumption was clinically safe without an increase in mortality rates or treatment failure.[19] Safe reduction of antibiotic consumption through PCT guidance was confirmed in routine clinical practice where all consecutive adult patients who present to the emergency department with lower respiratory tract infections were enrolled without any exclusion.[20]

Similarly, randomized controlled trials demonstrated the ability of PCT to guide the discontinuation of antibiotic therapy in the case of sepsis.[14,21-24] The Stop Antibiotics on Procalcitonin guidance Study (SAPS) showed a reduction in the duration of antibiotic therapy for patients with suspected or confirmed infection from 7 days in the standard-of-care group to 5 days in the procalcitonin-guided group and a reduction of 5.4% in 28-day mortality from 25% to 19.6%.[24]

By evaluating PCT concentrations, the physician may use the findings to aid in the risk assessment of critically ill patients for progression to severe sepsis and septic shock. In addition, the change of PCT levels over time offers information about the risk of mortality after diagnosis of severe sepsis or septic shock.[25]

Shortly after multiple traumas, major surgery, severe burns, or birth (neonates), PCT levels can be elevated independently of an infectious process, but the return to baseline is usually rapid. Viral infections, bacterial colonization, localized infections, allergic disorders, autoimmune diseases, and transplant rejection do not usually induce a significant PCT response (values < 0.5 µg/L). Therefore, PCT is an important marker enabling specific differentiation between a bacterial infection and other causes of inflammatory reactions.[2]

Principle

The B·R·A·H·M·S PCT sensitive KRYPTOR® is a homogeneous sandwich immunoassay for detection of PCT in human serum or plasma. The measuring principle is based on Time-Resolved Amplified Cryptate Emission (TRACE®) technology, which measures the signal that is emitted from an immunocomplex with time delay.

Measuring Principle

The basis of the TRACE® technology is a non-radiative energy transfer from a donor [a cage-like structure with a europium ion in the center (cryptate)] to an acceptor (XL 665). The proximity of donor (cryptate) and acceptor (XL 665) in a formed immunocomplex and the spectral overlap between donor emission and acceptor absorption spectra on the one hand intensifies the fluorescent signal and on the other hand extends the life span of the acceptor signal, allowing for the measurement of temporally delayed fluorescence.

After the sample to be measured has been excited with a nitrogen laser at 337 nm, the donor (cryptate) emits a long-life fluorescent signal in the milli-second range at 620 nm, while the acceptor (XL 665) generates a short-life signal in the range of nano-seconds at 665 nm. When both components are bound in an immunocomplex, both the signal amplification and the prolonged life span of the acceptor signal occur at 665 nm, and the life span is in the microsecond range. This delayed acceptor signal is proportional to the concentration of the analyte to be measured.

The specific fluorescence which is proportional to the antigen concentration is obtained through a double selection: spectral (separation depending on wave-length) and temporal (time resolved measurement). This enables an exclusive measurement of the signal emitted by the immunological complex and the ratio between the two wave-lengths (665/620) allows a real-time correction of the variations in optic transmission from the medium. See Figures 1 and 2.

Figure 1

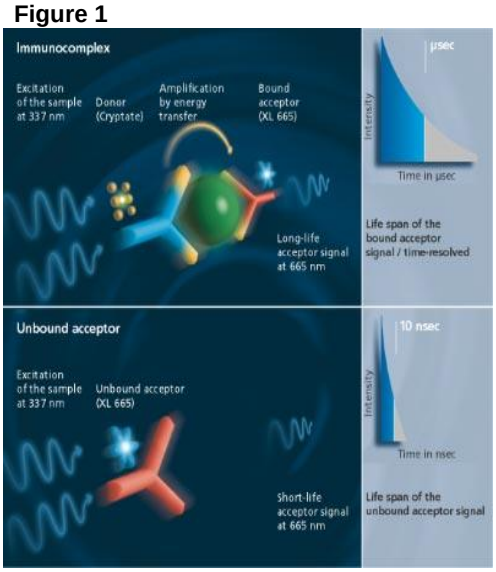
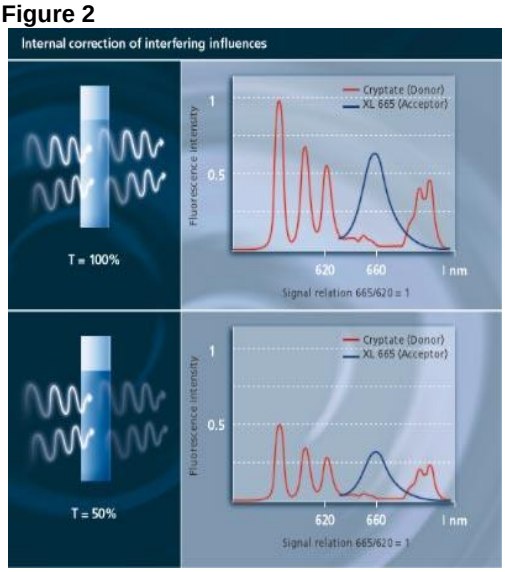


Figure 2



The B·R·A·H·M·S PCT sensitive 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 (> 50 µg/L) are detected in the first few seconds of incubation and may be diluted by the appropriate dilution factor, then re-assayed automatically.

The molecules of PCT present in the patient samples are sandwiched between the antibodies of the immunoassay. Thus, the intensity of the signal is proportional to the amount of PCT.

Instructions

Sample volume	50 µL
Incubation time	19 min
Results are given in	µg/L
Conversion factor	not applicable
Direct measuring range	0.02…50 µg/L
Measuring range with automatic dilution	0.02…5 000 µg/L
Sample type	serum, plasma (EDTA, heparin)
Kit stability on board	29 days
Calibrator	1 point
Calibration stability	15 days
Assay principle	sandwich

Reagents

The B·R·A·H·M·S PCT sensitive KRYPTOR® contains sufficient reagents for 50 determinations.

Materials Provided:

Reagent	Quantity for 50 determinations	Content
Cryptate Conjugate	1 bottle lyophilized	Cryptate conjugate, cryptate labeled, anti-PCT antibody (polyclonal, sheep), 3.2 mL after reconstitution with KRYPTOR® Solution 1 and KRYPTOR® Solution 2
XL665 Conjugate	1 bottle lyophilized	XL665 conjugate, XL665 labeled, anti-PCT antibody (monoclonal, mouse), 3.95 mL after reconstitution with KRYPTOR® Solution 1 and KRYPTOR® Solution 2
Diluent	1 bottle	Defibrinated human plasma, for diluting samples above 50 µg/L, ready for use

Additional Materials Required but Provided Separately:

- B·R·A·H·M·S PCT sensitive KRYPTOR® Calibrator

	Content
Calibrator	Lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 0.75 mL de-ionized water with conductivity of less than 50 µS/cm [range: 22.5 – 27.5 µg/L]

- B·R·A·H·M·S PCT sensitive KRYPTOR® Controls

	Content
Control 1	PCT control 1, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 0.2 – 0.4 µg/L]
Control 2	PCT control 2, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 8 – 12 µg/L]

- KRYPTOR® Consumables

	Content
KRYPTOR® Solution 1	ProClin® 150 Solution
KRYPTOR® Solution 2	Potassium fluoride solution
KRYPTOR® Solution 3	Active chlorine and sodium hydroxide solution
KRYPTOR® Solution 4	Sodium hydroxide solution
KRYPTOR® BUFFER	Phosphate Buffer Saline (PBS) buffer, not reconstituted, 5 liters after reconstitution

- Reaction plates KRYPTOR®
- Dilution plates KRYPTOR®

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.

Citrate plasma tubes should not be used as PCT concentrations are underestimated.

This reagent contains materials of human origin (e.g. human serum). 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.

The conjugates contain potassium fluoride, and are dangerous both in skin contact and ingestion. In case of contact with the eyes, immediately wash thoroughly and consult a specialist. If you feel ill, consult a doctor.

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.

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.

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 family (2 to 8°C).

Specimen Collection and Preparation

Specimens Recommended: Serum or plasma may be used. B·R·A·H·M·S recommends the use of only one matrix, i.e., use the same material (either serum or plasma [EDTA or heparin]) throughout the patient's clinical course. It is recommended that citrate plasma not be used, since concentrations were underestimated with citrate plasma.

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 50 µL. Place the sample in a tube suited for use on the B·R·A·H·M·S KRYPTOR® analyzer family (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 a total of 150µL of sample. If a dilution is requested either automatically or by the user, the volume of sample necessary will be an additional 25µL maximum.

Testing demonstrated that there is no difference between the use of glass and plastic collecting tube types and that filling volume has no impact on the result. In any case, the results of the B·R·A·H·M·S PCT sensitive 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.

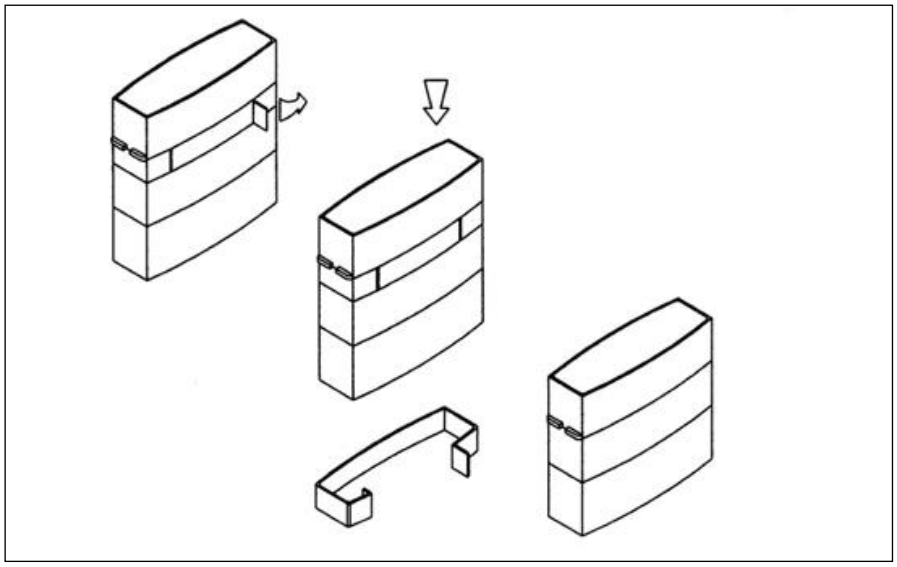
WARNING: Patient samples should be handled with care, as all materials of human origin are potentially hazardous. Specimen Handling and Storage: **Samples may be stored up to 5 days at 2 - 8°C. Samples may be frozen (-20 °C) and thawed four times.**

Procedure

The B·R·A·H·M·S PCT sensitive KRYPTOR® is to be used only with the B·R·A·H·M·S KRYPTOR® analyzer family. The operation and maintenance of the B·R·A·H·M·S KRYPTOR® analyzers are described in the User's Manual.

The B·R·A·H·M·S PCT sensitive KRYPTOR® procedure includes registering and/or loading the sample(s), reagent kit, calibrator and controls, as applicable. A sample volume of 50 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 19 minutes. The B·R·A·H·M·S PCT sensitive KRYPTOR® PCT results are given in µg/L.

To prepare a reagent unit, proceed as follows:



Sample Dilution: The B·R·A·H·M·S KRYPTOR® analyzer family makes periodic measurement of the signal emitted. If a sample presents a concentration higher than that of the direct reading zone (i.e., > 50 µg/L), it is detected in the first few seconds of incubation, diluted and re-assayed automatically. After measurement of the fluorescent signal, the program compares each result obtained with the stored standard curve.

Calibration using B·R·A·H·M·S PCT sensitive KRYPTOR® calibrator kit

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR® CAL is designed to readjust the standard curve memorized in the B·R·A·H·M·S KRYPTOR® analyzer family for the B·R·A·H·M·S PCT sensitive KRYPTOR®.

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

Each vial contains lyophilized recombinant PCT in defibrinated human plasma.

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

Preparation

Reconstitute a vial with de-ionized water (0.75 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 the calibrator/calibrators at room temperature or on the carousel for more than 4 hours.

Refer to the B·R·A·H·M·S KRYPTOR® analyzer family User's 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 each new B·R·A·H·M·S PCT sensitive KRYPTOR® lot, then repeated on a regular basis automatically managed by the B·R·A·H·M·S PCT sensitive 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 PCT sensitive KRYPTOR® on the B·R·A·H·M·S KRYPTOR® analyzer family. Rather, the standard curve is included with 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 PCT sensitive KRYPTOR® measures concentrations between 0.02 and 5000 µg/L. The Limit of Quantification is 0.075 µg/L (with bias ≤ 5%, % CV ≤ 15% and total error ≤ 30%).

Quality Control using B·R·A·H·M·S PCT sensitive KRYPTOR® QC kit

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR® QC is designed for quality control on board the B·R·A·H·M·S KRYPTOR® analyzer family for the B·R·A·H·M·S PCT sensitive KRYPTOR®.

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

Each vial contains lyophilized recombinant PCT in defibrinated human plasma. The two series of vials correspond to two levels of antigen concentration.

- B·R·A·H·M·S PCT sensitive KRYPTOR® - Control 1 (level 1): 0.2 – 0.4 µg/L
- B·R·A·H·M·S PCT sensitive KRYPTOR® - Control 2 (level 2): 8 – 12 µg/L

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 family 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 (2.0mL) 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.
- 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 and use immediately for measurement. A control tube will be processed like a sample tube.

After reconstitution, do not keep a vial more than four (4) hours at 18-25 °C or 24 hours at 2-8 °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® analyzer.

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® analyzer family User's 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® analyzer family 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 PCT sensitive KRYPTOR® PCT results are given in µg/L.

Linearity / High Dose Hook Effect

The B·R·A·H·M·S PCT sensitive KRYPTOR® is homogenous, and does not require separation or washing steps. It is thus possible to obtain data without interrupting the immunological reaction. High concentration samples (> 50 µg/L) 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 50 µg/L. 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 50 µg/L up to 5000 µg/L.

Interpretation of Results

1. Risk assessment for progression to severe sepsis and septic shock

The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

SIRS, Sepsis, Severe Sepsis, and Septic Shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine.[26]

PCT should always be interpreted in the clinical context of the patient. Therefore, clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patient.

Data support the following interpretative risk assessment criteria:[9,10]

PCT > 2 µg/L
A PCT level above 2.0 µg/L on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.

PCT < 0.5 µg/L
A PCT level below 0.5 µg/L on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

Note: PCT levels below 0.5 µg/L do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low.

Various non-infectious conditions are known to induce changes in PCT level, PCT levels between 0.5 µg/L and 2.0 µg/L should be interpreted in the context of the specific clinical background and condition(s) of the individual patient. It is recommended to retest PCT within 6-24hrs if any concentrations <2.0 µg/L are obtained.

2. Percent change in PCT level over time to aid in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock

In addition to the interpretative risk assessment criteria above, the change of PCT concentration over time provides prognostic information about the risk of mortality[25,27] within 28 days for patients diagnosed with severe sepsis or septic shock coming from the Emergency Department, Intensive Care Unit, other medical wards or directly from outside the hospital.

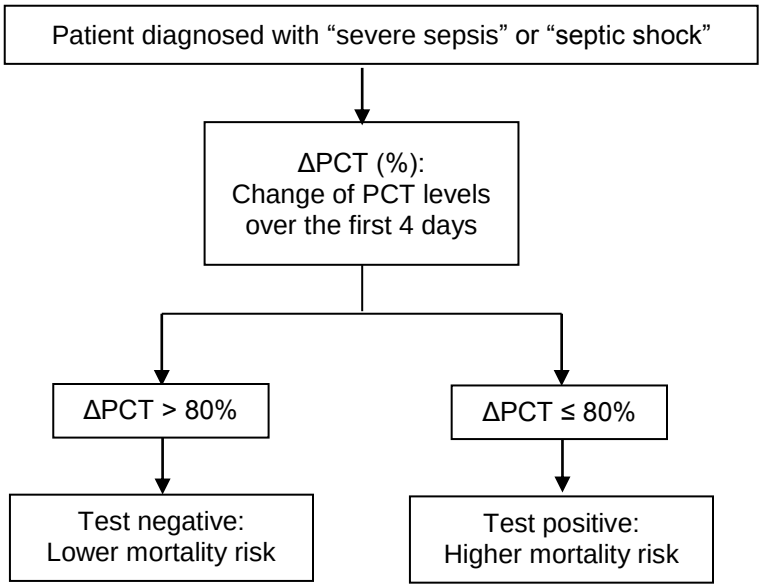
- A PCT level that declines ≤ 80% from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80%.
- The combination of the first PCT level (≤ 2.0 µg/L or > 2.0 µg/L) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk.
- The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

Data support the classification of patients into higher and lower risk for mortality within 28 days according to the workflow below:

$$\Delta PCT = \frac{PCT_{\text{Day0 (or Day1)}} - PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}} \times 100\%$$

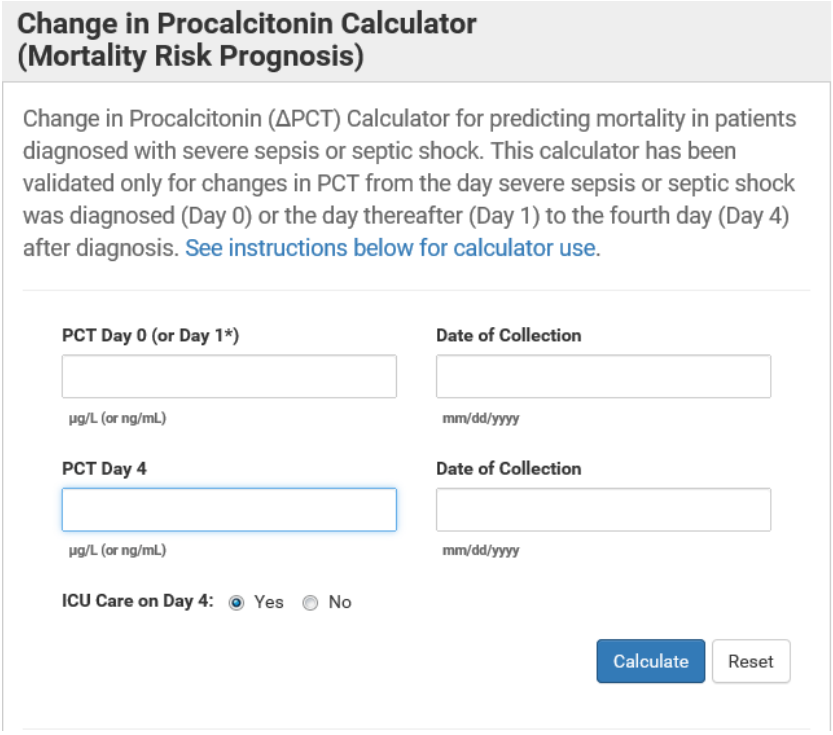
ΔPCT ≤ 80%
A decrease of PCT levels below or equal to 80% defines a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

ΔPCT > 80%
A decrease of PCT levels of more than 80% defines a negative ΔPCT result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.



Use the Change in Procalcitonin Calculator to determine ΔPCT results from the absolute PCT concentrations of a patient obtained on the day severe sepsis or septic shock was first diagnosed (or 24 hours later) and four days thereafter **(see detailed instructions below).**

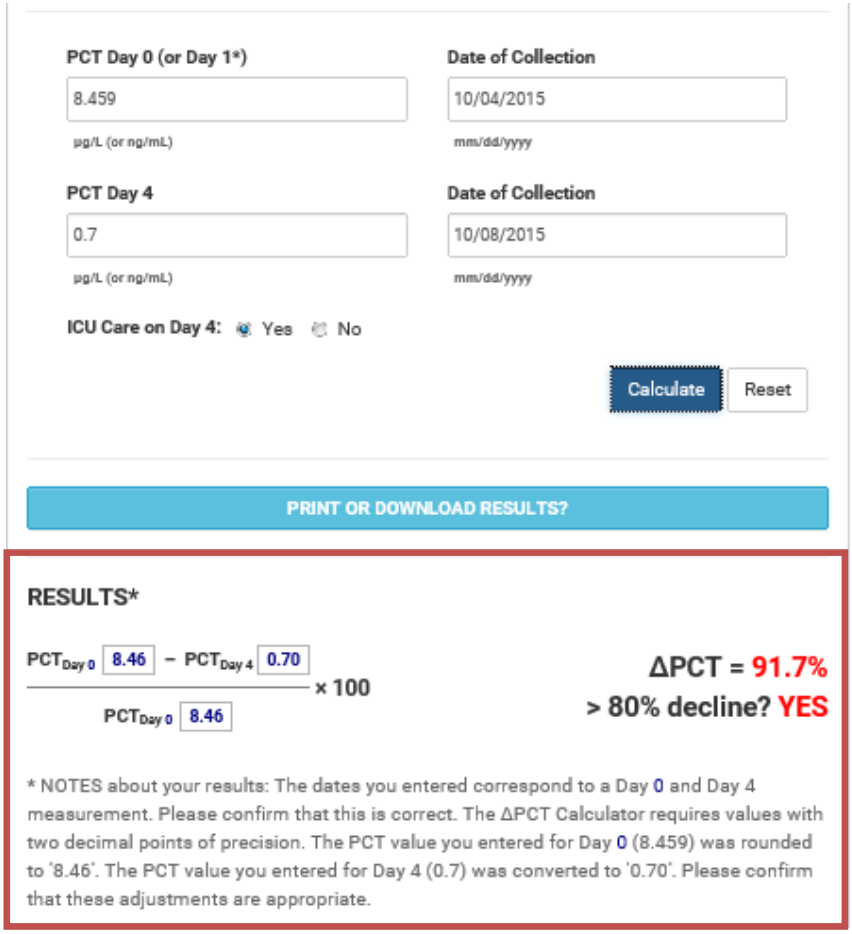
1) Start your internet browser (javascript must be enabled).
2) Go to www.BRAHMS-PCT-Calculator.com



3) Follow the on screen instructions
   a) Enter PCT values (in µg/L or ng/mL, which are equivalent), including all available digits
   b) * If no Day 0 value is available, enter Day 1 value in its place
   c) If more than one PCT value is available on Day 0 (or Day 1), enter the highest value
   d) If more than one PCT value is available on Day 4, enter the most recent value
   e) Select the dates of sample collection for the entered PCT values in the pop up calendar
   f) Indicate if patient received ICU Care on Day 4 (Yes or No)
   g) Click “Calculate” to view calculation results and mortality risk prognosis classification
   Note: Click on “Reset” between each calculation.

4) If incorrect information is entered, the following error messages will be displayed:
   a) If no value is entered, ‘Required field.’ will appear.
   b) If no numeric value is entered, ‘Values must be between 0.02 and 5000.’ will appear
   c) If date of collection is incorrect, ‘Range between Day 0 and Day 4 is too long.’ will appear

5) The change in PCT will be displayed in the **Results** section with the calculation formula being shown for user reference (example given below).
   a) Change in PCT (ΔPCT) will be displayed as percentage for declining PCT values.
   b) If PCT increases from Day 0 (or Day 1), the change in PCT result shows as ‘Day 4 PCT increases’.
   c) The decline in PCT > 80% is classified as “Yes” or “No”



The ‘NOTES about your results’ indicate the time points for the entered PCT values based on the dates you selected. If you entered PCT values with more than two decimal places you will be informed that the values have been rounded to two decimal places for the calculation. If you entered PCT values with less than two decimal places, you will be informed that the values have been adjusted to two decimal places for the calculation by addition of trailing zeros. Since the calculated ΔPCT is rounded to one decimal point of precision, you will be informed if a result shown as 80.0% is actually larger than 80%.

6) The ΔPCT classification is linked to the **Interpretation of Results** section and the appropriate test interpretation is highlighted (yellow background, boldface font) based on mortality rates found in an observational prospective study of 858 patients diagnosed with severe sepsis or septic shock showing an overall mortality of 22%. An example is given below.

INTERPRETATION OF RESULTS*

ΔPCT Day 0 – Day 4	28 day Mortality if Remaining in ICU at Day 4	28 day Mortality if Discharged from ICU by Day 4
≤ 80% decline	30.4% (23.8-37.0%) 27.2 if PCT ≤ 2.0 µg/L on Day 0 32.7% if PCT > 2.0 µg/L on Day 0	10.8% (6.4-15.1%) 7.7% if PCT ≤ 2.0 µg/L on Day 0 16.8% if PCT > 2.0 µg/L on Day 0
> 80% decline	**19.4% (10.6-28.2%)** **11.8% if PCT ≤ 2.0 µg/L on Day 0** **20.4% if PCT > 2.0 µg/L on Day 0**	5.8% (1.9-9.7%) 5.1% if PCT ≤ 2.0 µg/L on Day 0 5.9% if PCT > 2.0 µg/L on Day 0

7) You may choose to document the result output by selecting the “Print or Download Results” button. Please complete the additional information boxes that appear.

   a) Enter your name under “Calculator Operator Name (your name)”
   b) Enter the Patient Identifier for which you calculated the ‘Change in Procalcitonin Result’ under “Patient Identifier”

   Note: The calculator does not transmit these sensitive data from your computer. The durable record will be created on your local device itself.

   Select the “Print” or “Download” option and follow the prompts on the screen. The print option will generate a print job for your local printer. The “Download” option will generate a PDF with a unique file name (based on the timestamp of your calculation) that either opens in a new window or can be saved directly depending on your system settings.

8) A link to the PDF version of this package insert can be found at the bottom of the “Change in Procalcitonin” calculator.

9) The following computer browsers and platforms have been validated with the “Change in Procalcitonin” calculator:

Chrome 31.0; 36.0; 44.0; 45.0	Android Browser (on Android)
Safari 8.0	Safari (on iOS)
Microsoft Internet Explorer 7.0 -11.0	Microsoft Edge 12
Firefox 40	

3. Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Initiation:

PCT Result	<0.10 ng/mL	0.10-0.25 ng/mL	0.26-0.50 ng/mL	>0.50 ng/mL
Interpretation	Antibiotic therapy strongly discouraged.	Antibiotic therapy discouraged	Antibiotic therapy encouraged.	Antibiotic therapy strongly encouraged.
Follow-up	Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6-24 hours.		In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days, based upon physician discretion taking into account patient's evolution and progress.[28] Antibiotic therapy may be adjusted using the discontinuation table below:	

Discontinuation:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80%.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \text{ X } 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

If clinical picture has not improved and PCT remains high, re-evaluate and consider treatment failure or other causes.

4. Decision making on antibiotic discontinuation for suspected or confirmed septic patients

In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days, based upon physician discretion taking into account the patients' evolution and progress.[28] Antibiotic therapy may be adjusted using the discontinuation table below:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80%.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \text{ X } 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as failure to control a local infection, or ongoing physiologic instability.

If clinical picture has not improved, and PCT remains high, re-evaluate and consider treatment failure or other causes.

Suggestions for Laboratory Reports

It is suggested to report the absolute PCT values (single or serial). For serial PCT values the report should also indicate if the ΔPCT(%) was ≤ 80% or > 80%. The laboratory report should include a reference or a link to the B·R·A·H·M·S PCT sensitive KRYPTOR® package insert for a guided interpretation of the test results.

Reference Range

In non-infected subjects, PCT concentrations are usually <0.1 µg/L. In a population of 132 self-reported healthy individuals, 128 tested <0.1 µl/L and the top end 95th percentile was calculated at 0.0895 µg/L.

Performance Characteristics

1. Risk assessment for progression to severe sepsis and septic shock

The clinical data were obtained from a total of 179 patients in two independent, controlled prospective studies performed in ICUs of academic hospital settings using B·R·A·H·M·S PCT LIA.[9,10] The data from these two studies were pooled and the cut-offs 0.5 µg/L and 2.0 µg/L were evaluated. In 44 patients with a PCT level < 0.5 µg/L, no patient had severe sepsis or septic shock. In 77 patients with severe sepsis or septic shock, only one (1) had a PCT level ≤ 2.0 µg/L.

PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock
Cut Off 0.5 µg/L

PCT Result	No infection or SIRS/Sepsis	Severe Sepsis/ Septic Shock	Totals
PCT < 0.5	44	0	44
PCT > 0.5	58	77	135
Totals	102	77	179

PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock
Cut Off 2.0 µg/L

PCT Result	No infection or SIRS/Sepsis	Severe Sepsis/ Septic Shock	Totals
PCT < 2.0	79	1	80
PCT > 2.0	23	76	99
Totals	102	77	179

2. Percent change in PCT level over time to aid in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock

The B·R·A·H·M·S PCT sensitive KRYPTOR® was evaluated for the prediction of cumulative 28-day all-cause mortality in a study of 858 adult patients diagnosed with severe sepsis or septic shock recruited across 13 investigational sites in the US. The analysis population (598 subjects) comprised 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) versus septic shock (49%). Infections were mainly community acquired (91%).[25]

The binary test result (ΔPCT >80% or ≤80%) was significantly associated with 28-day cumulative mortality (vital status on day 28) (Two-sided Fisher's Exact Test p-value = 0.002). Adjusted for ICU vs. non-ICU patient subgroups (based on hospital location at day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel Test p-value = 0.020). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on day 4 and/or the selection of Day 0 vs. Day 1 as the baseline measurement day for the ΔPCT calculation are as follows:

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive					
ΔPCT Interval	**Day 4 Patient Location**	**28 Day Mortality Risk**		**Prognostic Accuracy***	
		ΔPCT > 80% (95% CI)	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 0 until Day 4	**ICU**	**19.4%** (10.6-28.2%)	**30.4%** (23.8-37.0%)	**78.9%** (69.5-88.4%)	**32.6%** (26.0-39.3%)
	non-ICU	**5.8%** (1.9-9.7%)	**10.8%** (6.4-15.1%)	**72.3%** (56.0-88.7%)	**42.8%** (37.0-48.6%)
Day 1 until Day 4	**ICU**	**21.6%** (13.0-30.3%)	**29.9%** (23.2-36.7%)	**73.6%** (63.3-83.9%)	**35.7%** (28.9-42.5%)
	non-ICU	**6.9%** (2.5-11.2%)	**9.9%** (5.8-14.0%)	**68.9%** (52.0-85.8%)	**40.1%** (34.3-45.9%)

*Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

Additional stratification of patients based on absolute initial PCT levels (> or ≤ 2.0 µg/L) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on Day 4. Mortality risk and prognostic performance are given for the following subgroups in the tables below:

1. Patients with PCT > 2.0 µg/L at Day 0 (or Day 1) receiving ICU care on Day 4
2. Patients with PCT ≤ 2.0 µg/L at Day 0 (or Day 1) receiving ICU care on Day 4
3. Patients with PCT > 2.0 µg/L at Day 0 (or Day 1) without ICU care on Day 4
4. Patients with PCT ≤ 2.0 µg/L at Day 0 (or Day 1) without ICU care on Day 4

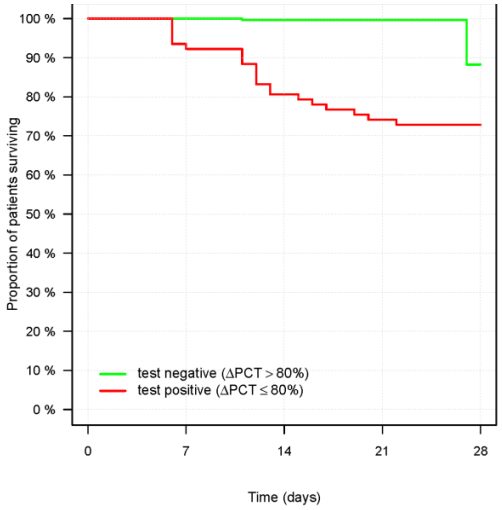
28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute PCT Value on *Day 0*: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive						
ΔPCT Interval	**Day 4 Patient Location**	**PCT at Day 0**	**28 Day Mortality Risk**		**Prognostic Accuracy***	
			ΔPCT > 80% (95% CI)	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 0 until Day 4	**ICU**	≤ 2.0 µg/L	**11.8%** (0.0-33.4%)	**27.2%** (17.2-37.1%)	**95.3%** (86.4-100.0%)	**12.1%** (3.9-20.3%)
		> 2.0 µg/L	**20.4%** (10.9-29.9%)	**32.7%** (23.9-41.5%)	**71.7%** (59.2-84.3%)	**42.8%** (34.3-51.4%)
	non ICU	≤ 2.0 µg/L	**5.1%** (0.0-15.0%)	**7.7%** (3.1-12.3%)	**90.9%** (73.9-100.0%)	**13.5%** (7.4-19.5%)
		> 2.0 µg/L	**5.9%** (1.7-10.2%)	**16.8%** (7.7-25.9%)	**61.0%** (38.4-83.6%)	**67.2%** (59.6-74.7%)

*Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

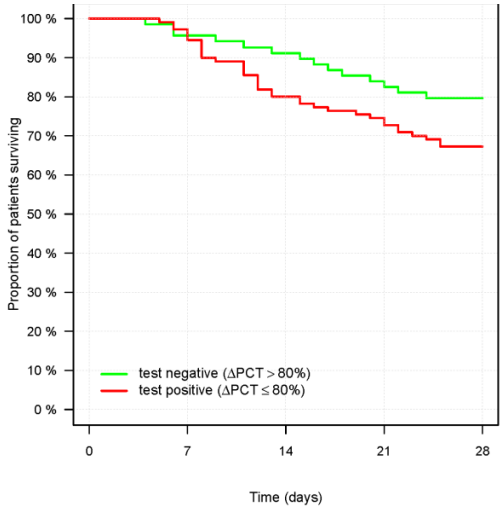
28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute PCT Value on *Day 1*: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive						
ΔPCT Interval	**Day 4 Patient Location**	**PCT at Day 1**	**28 Day Mortality Risk**		**Prognostic Accuracy***	
			ΔPCT > 80% (95% CI)	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 1 until Day 4	**ICU**	≤ 2.0 µg/L	**20.9%** (0.0-57.5%)	**24.3%** (14.5-34.1%)	**94.4%** (83.8-100.0%)	**6.8%** (0.0-13.6%)
		> 2.0 µg/L	**21.7%** (12.8-30.6%)	**34.0%** (24.8-43.1%)	**66.1%** (53.3-79.0%)	**48.7%** (40.2-57.3%)
	non ICU	≤ 2.0 µg/L	**0.0%** (0.0-23.2%)	**6.8%** (2.5-11.1%)	**100.0%** (66.4-100.0%)	**10.3%** (4.8-15.7%)
		> 2.0 µg/L	**7.7%** (2.9-12.6%)	**15.8%** (7.1-24.4%)	**54.9%** (33.1-76.7%)	**64.7%** (57.0-72.5%)

*Prognostic accuracy refers to how accurate the ΔPCT (≤ 80% vs. > 80%) can predict mortality risk.

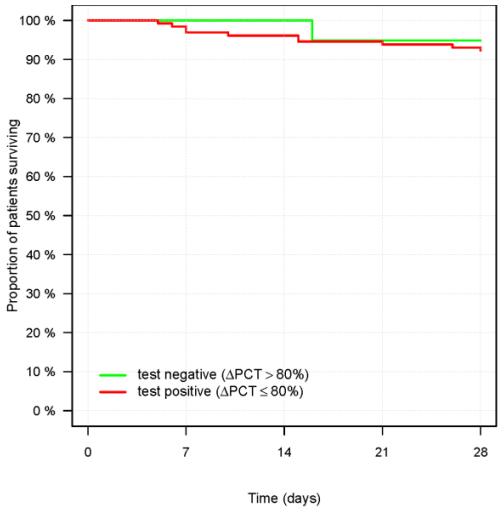
Survival until Day 28 for Patients with PCT ≤ 2.0 µg/L at Day 0 receiving ICU Care on Day 4 (n=86)



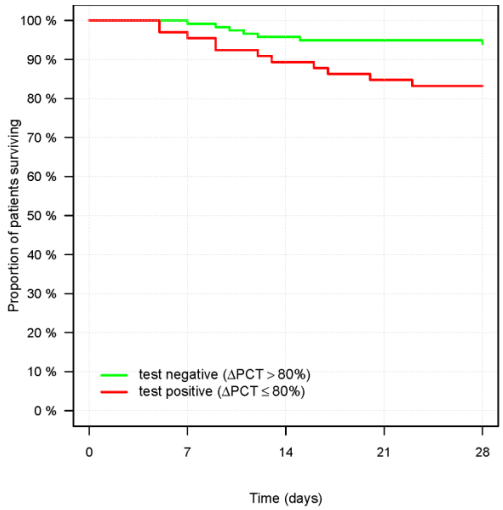
Survival until Day 28 for Patients with PCT > 2.0 µg/L at Day 0 receiving ICU Care on Day 4 (n=179)



Survival until Day 28 for Patients with PCT ≤ 2.0 µg/L at Day 0 without ICU Care on Day 4 (n=149)



Survival until Day 28 for Patients with PCT > 2.0 µg/L at Day 0 without ICU Care on Day 4 (n=184)



Time-to-event analysis illustrated by the Kaplan-Meier curves above shows that patients in the ICU or with an initial PCT value > 2.0 µg/L had a lower survival probability (higher cumulative mortality risk) from study Day 4 until the end of follow-up time (28 days) when the ΔPCT test result was positive compared to when the ΔPCT result was negative(patient subgroups according to hospital location on Day 4 and initial PCT level).

A generally lower mortality rate was observed in the non-ICU subgroup. **The mortality ratios for ΔPCT positive vs. ΔPCT negative patient subgroups were:**

1.6 for Patients with PCT > 2.0 µg/L at Day 0 receiving ICU care on Day 4

2.3 for Patients with PCT ≤ 2.0 µg/L at Day 0 receiving ICU care on Day 4

2.8 for Patients with PCT > 2.0 µg/L at Day 0 without ICU care on Day 4

1.5 for Patients with PCT ≤ 2.0 µg/L at Day 0 without ICU care on Day 4

Based on relative mortality ratios a decrease by more than 80% from Day 0 (or Day 1) to Day 4 constitutes a lower risk for mortality within 28 days compared to smaller declines in each subgroup. **For the prediction of absolute mortality risks ICU disposition at Day 4 and initial PCT concentrations should be considered**:

a) An initial PCT level ≤ 2.0 µg/L on Day 0 followed by a PCT decline of more than 80% until Day 4 indicates an almost 2-fold lower cumulative 28-day mortality risk (11.8%) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT level > 2.0 µg/L (20.4%). Regardless of the initial PCT level, patients in the ICU on Day 4 that do not decline by more than 80% in PCT plasma concentration from Day 0 to Day 4 have an even higher mortality risk of 27.2 – 32.7%.

b) An initial PCT level > 2.0 µg/L that does not decline by more than 80% until Day 4 signals that such patients remain at high mortality risk (16.8%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 5.1 to 7.7 % for patients discharged from the ICU by Day 4.

Performance of ΔPCT from Day 0 to Day 4 (≤80% vs. >80%) as a prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis with a hazard ratio of **2.02** (95% CI:1.27-3.23; p-value = 0.0031). That is the relative risk of cumulative 28-day mortality is about **2-fold higher** if an individual tests positive for ΔPCT (≤ 80%) than if an individual tests negative (>80%).

As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the study population.

Predictors	Comparison	Hazard Ratio	95% CI	p-Value
ΔPCT (Day 0 to Day 4)	**≤80% vs. >80%**	**2.02**	**1.27 - 3.23**	**0.0031**
ΔPCT (Day 1 to Day 4)	≤80% vs. >80%	1.59	1.03 – 2.47	0.0385
APACHE on Day 1	difference of 5 units	1.36	1.22 - 1.53	< 0.001
Max SOFA of Day 0-Day 4	difference of 3 units	1.73	1.50 - 2.00	< 0.001
Antibiotic Adequacy	no vs. yes	1.59	1.00 - 2.53	0.051
Sepsis Severity	septic shock vs. severe sepsis	1.19	0.80 - 1.76	0.39
ICU Care on Day 4	yes vs. no	3.45	2.24 - 5.31	< 0.001
Biological Infection Type	gram positive vs. gram negative	0.83	0.48 - 1.45	0.52
Biological Infection Type	fungal vs. gram negative	2.44	0.87 - 6.84	0.090
Clinical Infection Type	nosocomial vs. community aquired	0.76	0.35 - 1.64	0.48
Positive Blood Culture	yes vs. no	1.05	0.69 - 1.58	0.83
PCT on Day 0	>2 µg/L vs. ≤ 2 µg/L	1.36	0.90 - 2.07	0.14
Age	difference of 5 years	1.16	1.08 - 1.24	< 0.001
Gender	male vs. female	0.95	0.64 - 1.40	0.78

ΔPCT from Day 0 (or Day 1) to Day 4 remains a prognostic parameter for the risk of cumulative 28-day mortality in patients diagnosed with severe sepsis or septic shock even when the hazard ratio is adjusted for other mortality predictors in Cox multiple regression models. The relative mortality risk estimates for ΔPCT and selected predictors are given below with 95% confidence intervals. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the two binary results.

Model		**Hazard Ratio (95% Confidence Interval)**				
		Binary Predictors		**Continuous Predictors (HR per 1 SD)**		
ΔPCT Interval	**Score + Covariates***	**ΔPCT (≤80% vs. >80%)**	Day 4 Patient Location (ICU vs. no ICU)	APACHE (1 SD = 8.13)	max SOFA (1SD = 3.98)	Age (1SD = 16.18)
Day 0 until Day 4	APACHE	**1.80** (1.05-3.08)	2.61 (1.63-4.19)	1.24 (0.99-1.56)	---	1.57 (1.25-1.96)
	max SOFA	**1.56** (0.92-2.66)	1.69 (1.03-2.78)	---	1.96 (1.52-2.53)	1.67 (1.34-2.08)
Day 1 until Day 4	APACHE	1.53 (0.93-2.51)	2.66 (1.66-4.26)	1.29 (1.03-1.61)	---	1.57 (1.25-1.96)
	max SOFA	1.41 (0.86-2.31)	1.73 (1.06-2.84)	---	2.00 (1.56-2.57)	1.67 (1.34-2.08)

*The models also included the following predictors (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT on Day 0, Gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules.[29]

The change of PCT over time can also be described by the ratio of PCT values from Day 4 and Day 0 (or Day 1):

$$PCT_{ratio} = \frac{PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}}$$

A decline of ΔPCT = 80% translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decline is below 80% which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, **the relative mortality risk** for such patients **is higher the larger the PCT ratio**. The following table lists the hazard ratios for an increase by the factor 2 in PCT ratio, i.e. the relative increase in mortality risk for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio. For comparison selected predictors are indicated with corresponding equivalents in standard deviation (0.53 SD for Day0 until Day 4 and 0.72 SD for Day1 until Day 4). For the patient location at Day 4, the risk estimate compares the hazards for patients with vs. without ICU care on Day 4.

Model		**Hazard Ratio (95% Confidence Interval)**				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				**Binary Predictor**
ΔPCT Interval	**Score + Covariates***	**PCT ratio (2-fold increase)**	APACHE (SD equivalent)	max SOFA (SD equivalent)	Age (SD equivalent)	Day 4 Patient Location (ICU vs. no ICU)
Day 0 until Day 4	APACHE	**1.24** (1.10-1.40)	1.08 (0.96-1.23)	---	1.29 (1.14-1.46)	2.57 (1.60-4.13)
	max SOFA	**1.18** (1.05-1.33)	---	1.39 (1.21-1.59)	1.33 (1.18-1.49)	1.69 (1.03-2.79)
Day 1 until Day 4	APACHE	1.30 (1.11-1.52)	1.20 (1.03-1.41)	---	1.38 (1.18-1.62)	2.54 (1.58-4.07)
	max SOFA	1.25 (1.06-1.46)	---	1.62 (1.35-1.93)	1.45 (1.24-1.70)	1.73 (1.05-2.83)

*The models also included the following predictors (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT on Day 0, Gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules.[29]

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients (χ^2 p-value = 0.84). Demographics with outcome information are shown below:

Variable	class	all patients (N=598)	dead	alive	% dead
Gender	**female**	264	46	218	17.4%
	male	334	55	279	16.5%
Age, years (categorized)	**≤ 30**	39	1	38	2.6%
	> 30, ≤ 45	45	4	41	8.9%
	> 45, ≤ 55	74	8	66	10.8%
	> 55, ≤ 65	149	26	123	17.4%
	> 65, ≤ 75	125	21	104	16.8%
	> 75	166	41	125	24.7%
Ethnicity	**African-American**	202	32	170	15.8%
	Asian	7	0	7	0.0%
	Caucasian	362	64	298	17.7%
	Hispanic	23	5	18	21.7%
	Other	4	0	4	0.0%
PCT on Day 0, µg/L	**< 0.5**	117	16	101	13.7%
	≥ 0.5, ≤ 2.0	363	68	295	18.7%
	> 2.0	118	17	101	14.4%

3. Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Two systematic literature reviews were performed to produce both study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results (FDA public docket FDA-2016-N-2880). The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate. The endpoints evaluated were: proportion of subjects initiating antibiotics, duration of antibiotic therapy, exposure to antibiotics, length of hospital stay, mortality, and complications (patient level only).

The study-level meta-analysis encompassed 11 randomized control trials (RCTs) [6,13,15-18,30-34] which were published between 2004-2016, and included 4090 patients.
The patient-level meta-analysis encompassed 13 RCTs [6,13-18,21-23, 30, 31,35] which were published between 2004-2011, and included 3142 patients as listed below.

Publication	N patients	PCT device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive KRYPTOR®
Briel, 2008	300	B·R·A·H·M·S PCT sensitive KRYPTOR®
Burkhardt, 2010	550	B·R·A·H·M·S PCT sensitive KRYPTOR®
Christ-Crain, 2004	243	B·R·A·H·M·S PCT sensitive KRYPTOR®
Christ-Crain, 2006	302	B·R·A·H·M·S PCT sensitive KRYPTOR®
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Kristoffersen, 2009	223	B·R·A·H·M·S PCT sensitive KRYPTOR®
Long, 2011	172	B·R·A·H·M·S PCT sensitive KRYPTOR®
Long, 2009	127	B·R·A·H·M·S PCT LIA®
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive KRYPTOR®
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA®
Schuetz, 2009	1381	B·R·A·H·M·S PCT sensitive KRYPTOR®
Stolz, 2007	226	B·R·A·H·M·S PCT sensitive KRYPTOR®

These meta-analyses concluded that PCT guided antibiotic therapy resulted in:

- 19.2% reduction in relative antibiotic initiation for all patients
- 38% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for inpatients
- 51% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for patients who presented to the Emergency Department and other associated clinics, but were not admitted
- 2.9 day reduction in antibiotic duration [1.25 day reduction in study-level]
- 3.6 day reduction in total antibiotic exposure [2.79 day reduction in study-level]
- No negative effects in regards to mortality, complications, or length of stay

Overview of the patient-level meta-analysis:

Parameter	Standard Care Therapy		PCT Guided Therapy	
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)
Initiation of antibiotics	1606	1420 (88.4%)	1536	1096 (71,4%)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)
Total exposure of antibiotics	1606	9 (8, 12)	1536	5 (0, 8)
30 day mortality	1606	119 (7.4%)	1536	103 (6.7%)
Complications	1606	339 (21.1%)	1536	276 (18.0%)
Hospital length of stay	1583	6 (0, 13)	1508	7 (0, 12)

4. Decision making on antibiotic discontinuation for suspected or confirmed septic patients

Two systematic literature reviews were performed along with study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results. The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate (see tables below). The endpoints evaluated were: duration of antibiotic therapy (study level only), exposure to antibiotics (patient level only), length of ICU stay, length of hospital stay (patient level only), and mortality.

The study-level meta-analysis encompassed 10 RCTs [14,21-24,36-40] which were published between 2008-2016, and included 3489 patients. (See FDA public docket FDA-2016-N-2880).

The above patient-level meta-analysis encompassed 5 RCTs [14,21,22,37,41] which were published between 2008-2010, and included 598 patients as listed below.

Publication	N patients*	PCT device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive KRYPTOR®
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive KRYPTOR®
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA®
Stolz, 2009	101	B·R·A·H·M·S PCT sensitive KRYPTOR®

*Patients that did not classify as sepsis were removed prior to analysis (185 for PCT group and 164 for control group), leaving 598 patients

Using this subset of meta-analyses it was concluded that PCT guided antibiotic therapy resulted in:

- 1.5 day reduction in antibiotic duration
- 3.2 day reduction in total antibiotic exposure
- 23% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy)
- No negative effects in regards to mortality, hospital length of stay, or ICU length of stay.

Overview of the patient-level meta-analysis:

Parameter	Standard Care Therapy		PCT Guided Therapy	
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)
Total exposure of antibiotics	311	12 (8, 18)	287	8 (5, 15)
30 day mortality	311	74 (23.8%)	287	57 (19.9%)
Hospital length of stay	288	23 (13, 38)	259	21 (11, 37)
ICU length of stay	311	12 (6, 22)	287	12 (6, 23)

Method Comparison to VIDAS® B·R·A·H·M·S PCT:

A comparison study is published by Schuetz et al. based on 203 samples from the ProRESP trials which included consecutive patients with clinically suspected COPD, acute bronchitis and CAP.[42] The overall agreement between B·R·A·H·M·S PCT sensitive KRYPTOR® and VIDAS® B·R·A·H·M·S PCT ranged from 86.7% (95% CI: 81.2 - 91.0%) to 99.0% (95% CI: 96.4 - 99.9%) across the relevant medical decision points.

		VIDAS® B·R·A·H·M·S PCT					
		≤0.1 µg/L	>0.1 and ≤0.25 µg/L	>0.25 and <0.50 µg/L	≥0.50 and <2.00 µg/L	≥2.00 µg/L	TOTAL
B·R·A·H·M·S PCT sensitive KRYPTOR®	≤0.1 µg/L	99	12	0	0	0	111
	>0.1 and ≤0.25 µg/L	15	19	2	0	0	36
	>0.25 and <0.50 µg/L	0	3	8	2	0	13
	≥0.50 and <2.00 µg/L	0	0	0	19	5	24
	≥2.00 µg/L	0	0	0	0	19	19
	TOTAL	114	34	10	21	24	203

Limit of Quantification (LOQ)

The LOQ is the lowest amount of PCT in a sample that can be quantitatively determined with stated acceptable precision and trueness.

The LOQ was determined following CLSI Guideline EP17-A. Samples at different targets (from 0.06 µg/L to 0.075 µg/L) were prepared with master calibrators for which actual concentrations were determined independently. These samples were run in 5 runs, with 10 replicates per run, thus a total of 50 replicates per sample. For the 5 runs, 3 different B·R·A·H·M·S KRYPTOR® analyzers and 2 different batches of reagents were used. For each sample, the total standard deviation (SDs) was calculated as well as the difference between the mean of all replicates and the reference value of the sample (bias) and imprecision with 95% probability (2x SDs).

Results for replicates and SD_s, imprecision and bias calculation are shown below:

Replicates	Run 1	Run 2	Run 3	Run 4	Run 5
1	0.0868	0.0809	0.0623	0.0687	0.0726
2	0.0611	0.0761	0.0708	0.0644	0.0861
3	0.0841	0.0754	0.0622	0.0663	0.0780
4	0.0525	0.1016	0.0759	0.0887	0.0588
5	0.0774	0.0751	0.0735	0.0901	0.0782
6	0.0578	0.0790	0.0569	0.0619	0.0686
7	0.0735	0.0682	0.0779	0.0658	0.0765
8	0.0872	0.0767	0.0855	0.0798	0.0807
9	0.0895	0.0755	0.0871	0.0715	0.0819
10	0.0604	0.0810	0.0753	0.0693	0.0785

Average value (µg/L):	0.0747 µg/L
Target (µg/L):	0.0750 µg/L
Bias (µg/L):	-0.0003 µg/L
SDs (µg/L):	0.0102 µg/L
Imprecision (µg/L):	0.0204 µg/L
Total Error (µg/L):	0.0207 µg/L
Total Error/Target:	**27.6% (< 30%)**

The LOQ determined as the lowest reported concentration level with bias ≤ 5%, % CV ≤ 15% and total error ≤ 30% was determined at 0.075 µg/L.

Precision

Total Error (TE) was determined for the lower end of the measuring range:

- TE ≤ 20% at 0.25 µg/L (with a bias ≤ 5% and a precision CV ≤ 10%)
- TE ≤ 30% at 0.10 µg/L (with a bias ≤ 5% and a precision CV ≤ 15%)

Target Value (µg/L)	%CV	%BIAS	%TE
0.05	23.48	3.46	42.20
0.10	10.33	2.07	19.11
0.23	5.04	1.85	10.17
0.27	6.71	0.76	11.83
0.53	4.16	1.19	8.06

Interfering Substances

Based on CLSI testing, the substances evaluated with the B·R·A·H·M·S PCT sensitive KRYPTOR® were found not to affect the test performance at concentrations reasonably and consistently found in clinical situations. The substances included the following

Interfering Substances	Maximum concentration tested	Interference
Hæmoglobin	500 mg/dL	No interference up to 500 mg/dL
Triglycerides	22.5 mg/mL	No interference up to 22.5 mg/mL
Unconjugated Bilirubin	40 mg/dL	No interference up to 20 mg/dL
Albumin	1 g/dL	No interference up to 1 g/dL
Human calcitonin	3.9 ng/mL	No interference up to 3.9 ng/mL
Human katacalcin	25.6 ng/mL	No interference up to 25.6 ng/mL
α-CGRP	30 ng/mL	No interference up to 30 ng/mL
β-CGRP	30 ng/mL	No interference up to 30 ng/mL
Salmon calcitonin	13.2 µg/mL	No interference up to 13.2 µg/mL
Eel calcitonin	7.5 µg/mL	No interference up to 7.5µg/mL
Imipenem	1.18 mg/mL	No interference up to 1.18 mg/mL

Cefotaxim	90 mg/dL	No interference up to 90 mg/dL
Vancomycin	3 mg/mL	No interference up to 2.6 mg/mL
Dopamine	13 mg/dL	No interference up to 13 mg/dL
Noradrenaline	2 µg/mL	No interference up to 2 µg/mL
Dobutamine	11.2 µg/mL	No interference up to 11.2 µg/mL
Heparin	8000 IU/L	No interference up to 8000 IU/L
Furosemide	2 mg/dL	No interference up to 2 mg/dL
Beclomethasone dipropionate	1 µg/mL	No interference up to 1 µg/mL
Budesonide	0.72 µg/mL	No interference up to 0.72 µg/mL
Flunisonide	2.4 µg/mL	No interference up to 2.4 µg/mL
Fluticasone	0.3 µg/mL	No interference up to 0.3 µg/mL
Triamcinolone	2.4 µg/mL	No interference up to 2.4 µg/mL
Methylsprednisolone	72 µg/mL	No interference up to 72 µg/mL
Prednisolone	8.31 µmol/L	No interference up to 8.31 µmol/L
Prednisone	0.84 µmol/L	No interference up to 0.84 µmol/L
Nedocromil	8.4 µg/mL	No interference up to 8.4 µg/mL
Albuterol	1.67 µmol/L	No interference up to 1.67 µmol/L
Salmeterol	60 ng/mL	No interference up to 60 ng/mL
Theophylline	222 µmol/L	No interference up to 222 µmol/L
Montelukast	6 µg/mL	No interference up to 6 µg/mL
Epinephrine	1.8 µg/mL	No interference up to 1.8 µg/mL
Terbutaline	0.9µg/mL	No interference up to 0.9µg/mL
Ipratropium bromide	0.9 µg/mL	No interference up to 0.9 µg/mL
Formoterol	28.8 ng/mL	No interference up to 28.8 ng/mL
Tiotropium	21.6 ng/mL	No interference up to 21.6 ng/mL
Cromolyn	24 µg/mL	No interference up to 24 µg/mL
Acetaminophen	20 mg/dL	No interference up to 20 mg/dL
Acetylsalicylic acid	65.2 mg/dL	No interference up to 65.2 mg/dL
Alcohol	400 mg/dL	No interference up to 400 mg/dL
Azithromycin	1.15 mg/dL	No interference up to 1.15 mg/dL
Cetirizine HCl	0.36 mg/dL	No interference up to 0.36 mg/dL
Dextramethorphan	0.14 mg/dL	No interference up to 0.14 mg/dL
Ibuprofen	50 mg/dL	No interference up to 50 mg/dL
Levofloxacin	1.75 mg/dL	No interference up to 1.75 mg/dL
Loratadine	0.03 mg/dL	No interference up to 0.03 mg/dL
Nicotine	0.1 mg/dL	No interference up to 0.1 mg/dL
Oxymetazoline HCl	0.009 mg/dL	No interference up to 0.009 mg/dL
Phenylephrine	0.018 mg/dL	No interference up to 0.018 mg/dL

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Revision History

Date: [2018-16-03]
(This version supersedes all earlier instruction manuals.)

Date of Revision	Version	Description of Changes
[2018-16-03]	Version19.0	***Page 15 and 16:*** Section 2, under all three tables, correction of typing error, Correct is: ΔPCT (≤ 80% vs. > 80%)

CE

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Symbols

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

Symbol	Usage	Symbol	Usage	Symbol	Usage
	Manufacturer	CE	CE Conformity Marking According to Directive 98/79/EC on In Vitro Diagnostic Medical Devices		Contains sufficient for (Number of) tests, e.g. 50
	Use by		Temperature Limitation	REF	Article Number/ Catalogue Number
	Green Dot according to German Law	BUF	Buffer	SOLN 1	B·R·A·H·M·S KRYPTOR® SOLUTION 1/ B·R·A·H·M·S KRYPTOR® compact SOLUTION 1
	Consult Instructions for use	LOT	Batch code	SOLN 2	B·R·A·H·M·S KRYPTOR® SOLUTION 2/ B·R·A·H·M·S KRYPTOR® compact SOLUTION 2
LYOPH	Lyophilized, freeze dried	**Intended Use**	Reference to the intended use of the Medical Device	IVD	In Vitro Diagnostic Medical Device
CONT	Contents	CAL	Calibrator	CONTROL	Control
SOLN 3	B·R·A·H·M·S KRYPTOR® SOLUTION 3/ B·R·A·H·M·S KRYPTOR® compact SOLUTION 3	SOLN 4	B·R·A·H·M·S KRYPTOR® SOLUTION 4/ B·R·A·H·M·S KRYPTOR® compact SOLUTION 4	CONT BAGS	Bags contained
BAGS	Bags	CONT PLATES	Plates contained	PLATES	Plates
CONT VIALS	Vials contained	VIALS	Vials	VIAL	Vial

Symbol	Usage	Symbol	Usage	Symbol	Usage
H_2O	Use given Volume of destilled Water (conductivity of less than 50 µS/cm is recommended) for Reconstitution, e.g. 0.75 mL	RCNS	Reconstitute	®	Registered Trade Mark
	See Accompanying Compact Disk		Biohazard		Wear Protective Gloves
	Wear Safety Glasses		Wash hands		General Regulatory Sign
	General Prohibitive Sign		Do not Smoke		Do not Eat and Drink
	GHS07 Exclamation Mark		GHS05 Corrosion	TRACE	Trade Mark for TRACE®-technology
CE 0483	CE-Conformity Marking According to Directive 98/79/EC on In Vitro Diagnostic Medical Devices, Annex II with Reg.Number of Notified Body		Do not Reuse		Caution, consult accompanying documents
	Accidental Release Measures		Waste		For IVD Performance Evaluation only
Rx only	Federal law restricts this device to sale by or on the order of a licensed Healthcare practitioner (applicable to USA classification only)		Barcode that provides UDI information according to FDA regulations		