Created June 2017.

Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

NAME

ARCHITECT B·R·A·H·M·S PCT

INTENDED USE

The ARCHITECT B·R·A·H·M·S PCT assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K_2EDTA) on the ARCHITECT iSystem.

Used in conjunction with other laboratory findings and clinical assessments, the ARCHITECT B·R·A·H·M·S PCT assay is intended for use as an:

- Aid in the risk assessment of critically ill patients on their first day of intensive care unit (ICU) admission for progression to severe sepsis and septic shock.
- 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, using a change in PCT level over time.
- Aid in decision making on antibiotic therapy for patients 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) – in an inpatient setting or an emergency department.
- Aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

WARNINGS AND PRECAUTIONS – TEST INTERPRETATION

- The ARCHITECT B·R·A·H·M·S PCT assay 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.
- **Decisions regarding antibiotic therapy should NOT be based solely on PCT 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 Sequential Organ Failure Assessment [SOFA] score) are also significant predictors of 28-day cumulative mortality risk.
- Certain patient characteristics, such as severity of renal failure or insufficiency, may influence PCT values and should be considered as potentially confounding clinical factors when interpreting PCT values.
- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.
- **Low PCT levels do not always indicate absence of bacterial infection.** Falsely low PCT levels in the presence of bacterial infection may occur during the early course of infections, in localized infections, and in subacute infectious endocarditis.
- **Increased PCT levels may not always be related to systemic bacterial infection.** There are a few situations where PCT levels may be elevated by non-bacterial causes. These include, but are not limited to, the following:
  - Neonates at < 48 hours of life (physiological elevation)[1, 2]
  - Severe illness such as polytrauma, burns, major surgery, and prolonged or cardiogenic shock
  - Treatment with OKT3 (muromonab-CD3) antibodies and other drugs stimulating the release of pro-inflammatory cytokines
  - Patients with invasive fungal infections
  - Patients with acute attacks of *Plasmodium falciparum* malaria[3]
  - Patients receiving peritoneal dialysis or hemodialysis treatment
  - Patients with biliary pancreatitis, chemical pneumonitis, or heat stroke
  - Patients with small cell lung cancer, severe liver cirrhosis and acute or chronic viral hepatitis,[4] or medullary C-cell carcinoma of the thyroid
- 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.
- ARCHITECT B·R·A·H·M·S PCT results should not be used interchangeably with other methods for PCT determinations for monitoring patients.

SUMMARY AND EXPLANATION OF THE TEST

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.

PCT is a 116 amino acid protein prohormone of calcitonin (CT). Under normal metabolic conditions, hormonally active CT is produced and secreted in the C-cells of the thyroid gland after specific intracellular proteolytic activity. In healthy individuals, the intact PCT is not secreted from the thyroid and levels in the blood are very low.[5]

Response to inflammatory stimuli, including bacterial infections, induces an increased expression of the CALC-I gene with production and secretion of intact PCT from all parenchymal tissues and differentiated cell types throughout the body.[6]

In healthy people, plasma PCT concentrations are found to be below 0.1 ng/mL.[7] Depending on the clinical background, a PCT concentration above 0.1 ng/mL can indicate clinically relevant bacterial infection, requiring antibiotic treatment.[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.[5] At a PCT concentration > 0.5 ng/mL, 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 de-escalation of antibiotic therapy).[13, 14]

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.

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT B·R·A·H·M·S PCT assay is a two-step immunoassay for the quantitative determination of PCT in human serum and plasma (lithium heparin and K_2EDTA) using CMIA technology with flexible assay protocols, referred to as Chemiflex.

1. Sample and anti-PCT coated paramagnetic microparticles are combined. The PCT present in the sample binds to the anti-PCT coated microparticles.
2. After washing, anti-PCT acridinium-labeled conjugate is added to create a reaction mixture.

3. Following another wash cycle, Pre-Trigger and Trigger Solutions are added to the reaction mixture.
4. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of PCT in the sample and the RLUs detected by the ARCHITECT iSystem optics.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Kit Contents

ARCHITECT B·R·A·H·M·S PCT 6P22

NOTE: Some kit sizes are not available in all countries or for use on all ARCHITECT iSystems. Please contact your local distributor.

REF	6P22-27	6P22-37
Σ	100	500
MICROPARTICLES	1 x 8.6 mL	1 x 27.0 mL
CONJUGATE	1 x 5.9 mL	1 x 26.3 mL

MICROPARTICLES Anti-PCT (rat, monoclonal) coated microparticles in Tris-based buffer with protein (bovine) stabilizer, rat IgG, and Triton X-405. Minimum concentration: 0.06% solids. Preservatives: ProClin 950 and sodium azide.

CONJUGATE Anti-PCT (mouse, monoclonal) acridinium-labeled conjugate in phosphate buffer with protein (bovine) stabilizer and Triton X-405. Minimum concentration: 270 ng/mL. Preservatives: ProClin 950 and sodium azide.

Other Reagents

PRE-TRIGGER SOLUTION ARCHITECT Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

TRIGGER SOLUTION ARCHITECT Trigger Solution containing 0.35 N sodium hydroxide.

WASH BUFFER ARCHITECT Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

Warnings and Precautions

- **IVD**
- For *In Vitro* Diagnostic Use
- **Rx ONLY**

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[15-18]

The following warnings and precautions apply to: **MICROPARTICLES**	
	
WARNING	Contains tris-based buffer, methylisothiazolone, and sodium azide.
H315	Causes skin irritation.
H317	May cause an allergic skin reaction.
H319	Causes serious eye irritation.
EUH032	Contact with acids liberates very toxic gas.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P264	Wash hands thoroughly after handling.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P333+P313	If skin irritation or rash occurs: Get medical advice / attention.
P337+P313	If eye irritation persists: Get medical advice / attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

The following warnings and precautions apply to: **CONJUGATE**	
	
WARNING	Contains methylisothiazolone and sodium azide.
H317	May cause an allergic skin reaction.
EUH032	Contact with acids liberates very toxic gas.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
P333+P313	If skin irritation or rash occurs: Get medical advice / attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

Safety Data Sheets are available at www.abbottdiagnostics.com or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Reagent Handling

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between kits.**
- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.

For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Reagent Storage

- Do not freeze.

When stored and handled as directed, reagents are stable until the expiration date.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened/ Opened	2-8°C	Until expiration date	May be used immediately after removal from 2-8°C storage. Store in upright position.
On board*	System temperature	25 days	Discard after 25 days. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.

* On board stability is tracked only when the reagent kit is on board the processing module. To update the on board stability timer, a reagent scan must be performed every time a reagent kit is unloaded.

Reagents may be stored on or off the ARCHITECT iSystem. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The ARCHITECT B·R·A·H·M·S PCT assay file must be installed on the ARCHITECT iSystem from an ARCHITECT iSystem Assay CD-ROM prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.

For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

Alternate Result Units

Edit assay parameter "Result concentration units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default result unit	Conversion factor	Alternate result unit
ng/mL	1	µg/L

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

Verified specimen types to be used with this assay:

Specimen Types	Collection Tubes
Serum	Serum Serum separator tubes (SST)
Plasma	Dipotassium EDTA (K_2EDTA) Lithium heparin

- Other specimen collection tube types have not been tested with this assay.
- **When monitoring patients, use the same specimen collection tube type throughout the evaluation.**
- Performance has not been established for the use of cadaveric specimens or the use of body fluids other than human serum/ plasma.
- The instrument does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.

Specimen Conditions

- Do not use specimens with the following conditions:
  - heat-inactivated
  - pooled
  - grossly hemolyzed
  - obvious microbial contamination
  - fungal growth
- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- For serum specimens, ensure that complete clot formation has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times. If the specimen is centrifuged before complete clot formation, the presence of fibrin may cause erroneous results. **The use of plasma is recommended for rapid turnaround of results.**
- To ensure consistency in results, recentrifuge specimens before testing if
  - they contain fibrin, red blood cells, or other particulate matter or
  - they were frozen and thawed.
- Recentrifugation of Fresh Specimens
  - Remove the serum or plasma from the clot, red blood cells, or separator gel and recentrifuge the serum or plasma at 100,000 g-minutes before testing.
  - Examples of acceptable time and force ranges that meet this criterion are listed in the table below. Centrifugation time using alternate Relative Centrifugal Force values (RCF) can be calculated using the following formula:

$$\text{Minimum Centrifugation time (minutes)} = \frac{\text{100,000 g-minutes}}{\text{RCF}}$$

Centrifugation Time (Minutes)	RCF (x g)	g-Minutes
10	10,000	100,000
20	5000	100,000
40	2500	100,000

- Preparation of Frozen Specimens
  - Thaw frozen specimens at room temperature (15-30°C). Frozen specimens must be completely thawed before mixing.
  - Mix thawed specimens thoroughly by low speed vortexing or by inverting 10 times. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous.
  - For specimens that were frozen and thawed, use of a refrigerated centrifuge (2-8°C) is recommended.
  - Examples of acceptable time and force ranges that meet this criterion are listed in the table below. Centrifugation time using alternate Relative Centrifugal Force values (RCF) can be calculated using the following formula:

$$\text{Minimum Centrifugation time (minutes)} = \frac{150{,}000 \text{ g-minutes}}{\text{RCF}}$$

Centrifugation Time (Minutes)	RCF (x g)	g-Minutes
30	5000-5500	150,000-165,000

- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- Inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

Specimen Storage

Specimen Type	Storage Temperature	Maximum Storage Time
Serum/Plasma	Room temperature	≤ 8 hours on the clot, red blood cells, or separator gel
		≤ 24 hours off the clot, red blood cells, or separator gel
	2-8°C	≤ 48 hours off the clot, red blood cells, or separator gel
	-10°C or colder	≤ 15 days off the clot, red blood cells, or separator gel

If stored beyond 8 hours, remove serum or plasma from the clot, red blood cells, or separator gel and store at 2-8°C or -10°C or colder.

EDTA-plasma and serum specimens stored frozen at -70°C or colder have demonstrated stability up to 18 months.[19]

Avoid more than 3 freeze/thaw cycles.

Testing of lithium heparin plasma specimens that were frozen and thawed up to 3 times resulted in a maximum mean % difference from fresh specimens of -11%. Testing of serum or plasma specimens from serum, SST, and dipotassium EDTA tubes that were frozen and thawed up to 3 times resulted in a maximum mean % difference from fresh specimens of -6%.

Specimen Shipping

- Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

6P22 ARCHITECT B·R·A·H·M·S PCT Reagent Kit

Materials Required but not Provided

- ARCHITECT B·R·A·H·M·S PCT Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com.
- 6P22-01 ARCHITECT B·R·A·H·M·S PCT Calibrators
- 6P22-10 ARCHITECT B·R·A·H·M·S PCT Controls or other control material
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Assay Procedure

- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Reagent Handling** section of this package insert.
- Load the reagent kit on the ARCHITECT iSystem.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- Minimum sample cup volume is calculated by the system and printed on the Orderlist report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

  Maximum number of replicates sampled from the same sample cup: 10
  - Priority:

    Sample volume for first test: 150 µL

    Sample volume for each additional test from same sample cup: 100 µL
  - ≤ 3 hours on board:

    Sample volume for first test: 150 µL

    Sample volume for each additional test from same sample cup: 100 µL
  - > 3 hours on board: Replace with a fresh sample (patient specimens, controls, and calibrators).
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare ARCHITECT B·R·A·H·M·S PCT Calibrators and Controls.
  - Refer to the ARCHITECT B·R·A·H·M·S PCT Calibrators package insert for preparation and usage of the ARCHITECT B·R·A·H·M·S PCT Calibrators. After thaw and use, store at -10°C or colder. Discard after 3 freeze/thaw cycles.
  - Refer to the ARCHITECT B·R·A·H·M·S PCT Controls package insert for preparation and usage of the ARCHITECT B·R·A·H·M·S PCT Controls. After thaw and use, store at 2-8°C for up to 30 days.
  - Mix calibrators and controls by gentle inversion before use.
  - Hold bottles **vertically** and dispense recommended volumes into each respective sample cup.
  - Recommended volumes:

    for each calibrator: 8 drops

    for each control: 6 drops
- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT System Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Specimen Dilution Procedures

Specimens with a PCT value exceeding 100 ng/mL (100 µg/L) are flagged with the code "> 100 ng/mL" ("> 100 µg/L") and may be diluted using the Automated Dilution Protocol.

Automated Dilution Protocol

The system performs a 1:10 dilution of the specimen and automatically calculates the concentration of the specimen before dilution and reports the result.

For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

Calibration

- Test Calibrators A-F in duplicate. The calibrators should be priority loaded.

  A single sample of each control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the ranges specified in the respective control package insert.
- Calibration Range: 0.00 - 100.00 ng/mL (0.00 - 100.00 µg/L).
- Once an ARCHITECT B·R·A·H·M·S PCT calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used.
  - Daily quality control results are outside of statistically-based quality control limits, as described in the Quality Control Procedure section of this package insert, used to monitor and control system performance.
    - If statistically-based quality control limits are not available then the calibration should not exceed a 30-day limit for recalibration frequency.

  The ARCHITECT B·R·A·H·M·S PCT assay may also need to be recalibrated after specified service procedures have been performed or maintenance to critical part or subsystems that might influence the performance of the assay.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

Quality Control Procedures

- The recommended control requirement for the ARCHITECT B·R·A·H·M·S PCT assay is that a single sample of each control level be tested:
  - Once every 24 hours each day of use
  - After performing calibration
  - After instrument service procedures or maintenance that may affect assay performance have been performed.

  If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures.
- Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.
- Each laboratory should establish control ranges to monitor the acceptable performance of the assay. If a control is out of its specified range, the associated sample results are invalid and the samples must be retested. Recalibration may be indicated.
- To establish statistically-based control limits, each laboratory should establish its own concentration target and ranges for new control lots at each control level. This can be accomplished by assaying a minimum of 20 replicates over several (3-5) days and using the reported results to establish the expected average (target) and variability about this average (ranges) for the laboratory. Sources of variation that should be included in this study in order to be representative of future system performance include:
  - Multiple stored calibrations
  - Multiple reagent lots
  - Multiple calibrator lots
  - Multiple processing modules
  - Data points collected at different times of the day
- These results should be applied to your laboratory's quality control practices. In addition, the laboratory must ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.
- Refer to Clinical and Laboratory Standards Institute (CLSI) Document C24-A3 or other published guidelines for general quality control recommendations.[20]

Quality Control Guidance

Refer to "Basic QC Practices" by James O Westgard, Ph.D. for guidance on laboratory quality control practices.[21]

Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B.

The ARCHITECT B·R·A·H·M·S PCT assay belongs to method group 1.

RESULTS

Calculation

The ARCHITECT B·R·A·H·M·S PCT assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.

For information on alternate result units, refer to the **INSTRUMENT PROCEDURE, Alternate Result Units** section of this package insert.

Interpretation of Results

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

   The ARCHITECT B·R·A·H·M·S PCT assay 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.

   Systemic inflammatory response syndrome (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.[22]

   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, 23]

   - **PCT > 2.0 ng/mL:** A PCT level above 2.0 ng/mL 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 ng/mL:** A PCT level below 0.5 ng/mL 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 ng/mL 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 ng/mL and 2.0 ng/mL 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 6–24 hours if any concentrations < 2.0 ng/mL 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**

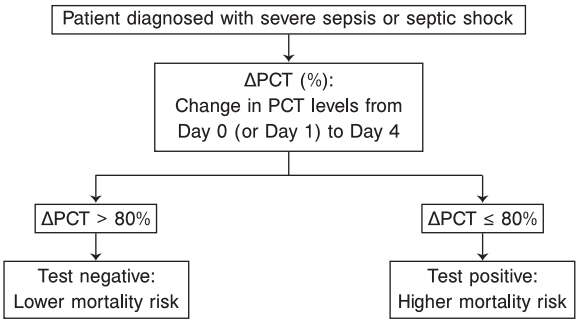
   In addition to the interpretative risk assessment criteria above, the change in PCT concentration over time provides prognostic information about the risk of mortality[24] within 28 days for patients diagnosed with severe sepsis or septic shock coming from the Emergency Department, ICU, other medical wards, or directly from outside the hospital. Mortality rates found in an observational prospective study of 858 patients diagnosed with severe sepsis or septic shock showing an overall mortality of 22%.[25]

   - A PCT level that declines ≤ 80% from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to 4 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 ng/mL or > 2.0 ng/mL) 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.[25]

Data support the use of PCT determinations from the day severe sepsis or septic shock is first diagnosed (Day 0) or day thereafter (Day 1) and the fourth day after diagnosis (Day 4) for the classification of patients into higher and lower risk for mortality within 28 days according to the workflow below:

$$\Delta PCT \text{ (Change in PCT)} = \frac{PCT_{Day\ 0\ (or\ Day\ 1)} - PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}} \times 100\%$$



ΔPCT ≤ 80%: A decrease in 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 in 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 (www.BRAHMS-PCT-Calculator.com) 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 4 days thereafter.

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,[26] based upon physician discretion taking into account patient's evolution and progress. 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 is > 80%.

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

$$\Delta PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

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, reevaluate and consider treatment failure or other causes.

4. **Decision making on antibiotic discontinuation for suspected or confirmed septic patients**[27]

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,[26] based upon physician discretion taking into account the patients' evolution and progress. 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 is > 80%.

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

$$\Delta PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

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, reevaluate and consider treatment failure or other causes.

Recommendations for Laboratory Reports:

The Change in Procalcitonin Calculator is available at www.BRAHMS-PCT-Calculator.com. The Change in Procalcitonin Calculator can be used to determine ΔPCT results. It is suggested to report the numerical PCT values (individual or paired). For paired 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 ARCHITECT B·R·A·H·M·S PCT reagent package insert for a guided interpretation of the test results.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

Measuring Interval

Measuring interval is defined as the range of values in ng/mL (µg/L) which meets the limits of acceptable performance for both imprecision and bias for an undiluted sample.

The measuring interval of the ARCHITECT B·R·A·H·M·S PCT assay is 0.02 to 100.00 ng/mL (0.02 to 100.00 µg/L). When using the 1:10 automated dilution protocol, the assay can report values up to 1000.00 ng/mL (1000.00 µg/L).

LIMITATIONS OF THE PROCEDURE

- Potential interference has not been evaluated for substances other than those described in the **SPECIFIC PERFORMANCE CHARACTERISTICS**, **Interference** section.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as ARCHITECT B·R·A·H·M·S PCT that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.[28, 29]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed. Additional information may be required for diagnosis.[30]
- Rheumatoid factor (RF) in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[30]

EXPECTED VALUES

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

It is recommended that each laboratory determine its own reference range based upon its particular locale and population characteristics.

A study was performed based on guidance from CLSI Document C28-A3c.[31] Human plasma specimens from 446 apparently healthy individuals were evaluated in dipotassium EDTA tubes.

The observed overall PCT concentration (97.5th percentile) was 0.07 ng/mL (0.07 µg/L).

SPECIFIC PERFORMANCE CHARACTERISTICS

Data in the section **SPECIFIC PERFORMANCE CHARACTERISTICS** were generated using the ARCHITECT i2000SR System.

Assay results obtained in individual laboratories may vary from data presented.

Precision

A study was performed based on guidance from CLSI Document EP05-A3.[32] Testing was conducted using 2 lots of ARCHITECT B·R·A·H·M·S PCT Reagents, 2 lots of ARCHITECT B·R·A·H·M·S PCT Calibrators, and 1 lot of ARCHITECT B·R·A·H·M·S PCT Controls on 2 instruments. Three controls and 3 human plasma panels were assayed in a minimum of 2 replicates at 2 separate times per day on 20 different days.

Sample	Instrument / Reagent Lot	Calibrator Lot	n	Mean (ng/mL)	Within-Run SD	Within-Run %CV	Within-Laboratory (Total)[a] SD	Within-Laboratory (Total)[a] %CV
Low Control	1	1	80	0.19	0.0052	2.7	0.0054	2.8
		2	80	0.20	0.0053	2.7	0.0055	2.8
	2	1	80	0.20	0.0046	2.4	0.0049	2.5
		2	80	0.20	0.0045	2.3	0.0049	2.5
Medium Control	1	1	80	1.94	0.0437	2.2	0.0480	2.5
		2	80	1.97	0.0439	2.2	0.0482	2.5
	2	1	80	1.92	0.0320	1.7	0.0412	2.1
		2	80	1.94	0.0324	1.7	0.0418	2.2
High Control	1	1	80	68.60	1.8407	2.7	2.4899	3.6
		2	80	70.41	1.9577	2.8	2.6485	3.8
	2	1	80	67.33	1.6972	2.5	2.4172	3.6
		2	80	67.73	1.6146	2.4	2.3667	3.5
Panel A	1	1	80	0.06	0.0015	2.4	0.0016	2.5
		2	80	0.07	0.0016	2.4	0.0016	2.5
	2	1	80	0.06	0.0013	2.1	0.0016	2.5
		2	80	0.06	0.0013	2.1	0.0016	2.5
Panel B	1	1	80	1.33	0.0235	1.8	0.0286	2.1
		2	80	1.35	0.0237	1.8	0.0288	2.1
	2	1	80	1.31	0.0207	1.6	0.0279	2.1
		2	80	1.32	0.0209	1.6	0.0283	2.1
Panel C	1	1	80	13.24	0.2505	1.9	0.2943	2.2
		2	80	13.30	0.2516	1.9	0.2957	2.2
	2	1	80	12.62	0.1936	1.5	0.2917	2.3
		2	80	12.85	0.1979	1.5	0.2989	2.3

[a] Includes within-run, between-run, and between-day variability.

Total error was determined for clinical decision points and Limit of Quantitation (LoQ = 0.01 ng/mL) and is presented in the table below.

PCT Level (ng/mL)	Bias (%)	%CV	Total Error (%)
0.01	12.2	8.1	26.1
0.10	3.6	2.7	8.1
0.25	3.0	2.5	7.2
0.5	2.9	2.4	6.9
2.0	2.7	2.4	6.7

Linearity

A study was performed based on guidance from CLSI Document EP06-A.[33] The ARCHITECT B·R·A·H·M·S PCT assay demonstrated linearity from 0.02 to 100.00 ng/mL (0.02 to 100.00 µg/L).

Sensitivity

Limit of Blank, Limit of Detection, and Limit of Quantitation

A study was performed based on guidance from CLSI Document EP17-A2.[34] The highest observed Limit of Blank (LoB) value was 0.00 ng/mL, and the highest observed Limit of Detection (LoD) value was 0.00 ng/mL.

The Limit of Quantitation (LoQ) is the lowest concentration observed at ≤ 20% CV. The highest observed LoQ value was 0.01 ng/mL with the ARCHITECT B·R·A·H·M·S PCT assay.

Note: LoB, LoD, and LoQ values are rounded to 2 decimal places in alignment with the reported results for the assay.

Specificity

Cross-Reactivity

A study was performed based on guidance from CLSI Document EP07-A2.[35] The cross-reactants listed below were evaluated to determine whether PCT concentrations were affected when using the ARCHITECT B·R·A·H·M·S PCT assay. Samples containing the cross-reactant were prepared at 2 target PCT concentrations (0.5 and 2.0 ng/mL).

Cross-Reactant	Cross-Reactant Concentration	% Cross-Reactivity 0.5 ng/mL PCT	% Cross-Reactivity 2.0 ng/mL PCT
Human Calcitonin	2 ng/mL	0.7%	0.5%
Human Katacalcin	10 ng/mL	0.8%	0.9%
Human α-CGRP	10 µg/mL	0.1%	1.0%
Human β-CGRP	10 µg/mL	0.4%	1.1%

Interference

Potentially Interfering Drugs

A study was performed based on guidance from CLSI Document EP07-A2.[35] The potentially interfering drugs evaluated with the ARCHITECT B·R·A·H·M·S PCT assay were found not to affect the test performance at concentrations reasonably and consistently found in clinical situations. The drugs evaluated are presented in the table below.

Potentially Interfering Drug	Maximum Concentration Tested	No Interference Observed Up To
Drugs commonly used in treatment of septic patients:		
Cefotaxime Sodium Salt	89 mg/dL	89 mg/dL
Dobutamine Hydrochloride	11.3 µg/mL	11.3 µg/mL
Dopamine Hydrochloride	13 mg/dL	13 mg/dL
Furosemide	2 mg/dL	2 mg/dL
Heparin Sodium Salt	7969 U/L	7969 U/L
Imipenem Monohydrate	1.18 mg/mL	1.18 mg/mL
Norepinephrine Bitartrate Salt	2 µg/mL	2 µg/mL
Vancomycin Hydrochloride	2.6 mg/mL	2.6 mg/mL
Other drugs:		
Acetaminophen	19.95 mg/dL	19.95 mg/dL
Acetylsalicylic Acid	65.32 mg/dL	65.32 mg/dL
Alcohol (Ethanol)	405.63 mg/dL	405.63 mg/dL
Azithromycin	1.17 mg/dL	1.17 mg/dL
Caffeine	6.03 mg/dL	6.03 mg/dL
Celecoxib	23.98 mg/dL	23.98 mg/dL
Cetirizine HCl	0.36 mg/dL	0.36 mg/dL
Dextromethorphan	0.14 mg/dL	0.14 mg/dL
Doxycycline	50.57 mg/L	50.57 mg/L
Epinephrine	1.79 mg/dL	1.79 mg/dL
Fentanyl	10.35 mg/L	10.35 mg/L
Ibuprofen	49.72 mg/dL	49.72 mg/dL
Levofloxacin	1.75 mg/dL	1.75 mg/dL
Loratadine	0.03 mg/dL	0.03 mg/dL
Nicotine	0.10 mg/dL	0.10 mg/dL
Oxymetazoline HCl	0.01 mg/dL	0.01 mg/dL
Phenylephrine	0.02 mg/dL	0.02 mg/dL
Prednisolone	8.34 µmol/L	8.34 µmol/L
Salmeterol	60.28 ng/mL	60.28 ng/mL
Tiotropium	21.74 ng/mL	21.74 ng/mL

Potentially Interfering Substances

A study was performed based on guidance from CLSI Document EP07-A2.[35] Potentially interfering substances were evaluated to determine whether PCT concentrations were affected when using the ARCHITECT B·R·A·H·M·S PCT assay. Samples containing bilirubin, hemoglobin, total protein, and triglycerides were prepared at approximately 0 ng/mL, 0.3 ng/mL, and > 10 ng/mL PCT, and samples containing HAMA and RF were prepared at approximately 0 ng/mL, 1 ng/mL, and > 10 ng/mL PCT. The samples were assayed, and the PCT concentrations of the spiked samples were compared to the reference samples. The observed differences for the zero level sample and the 0.3 ng/mL sample ranged from 0.00 to 0.05 ng/mL. The substances evaluated are presented in the following table.

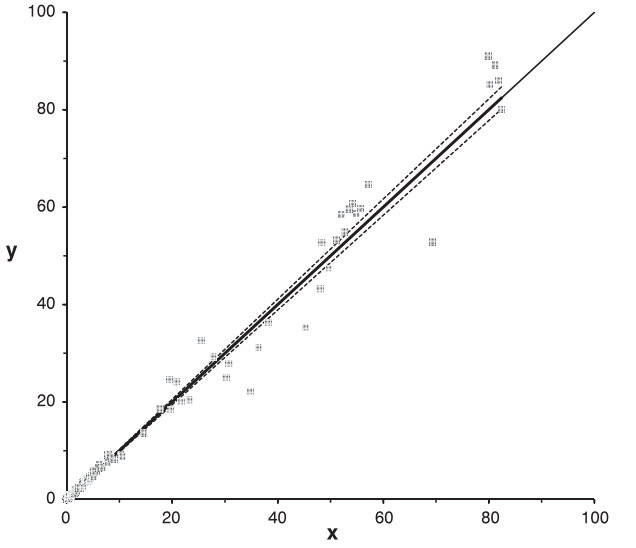
Interferent	Maximum Concentration Tested	No Interference Observed Up To
Conjugated Bilirubin	42 mg/dL	42 mg/dL
Unconjugated Bilirubin	22 mg/dL	22 mg/dL
Hemoglobin	599 mg/dL	599 mg/dL
Total Protein	12 g/dL	12 g/dL
Triglycerides	3409 mg/dL	3409 mg/dL
Human Anti-Mouse Antibodies	7982.5 ng/mL	3602.6 ng/mL
Rheumatoid Factor	1969.62 IU/mL	1969.62 IU/mL

The effect of interfering substances has only been evaluated for those listed in this package insert.

Method Comparison

A correlation study using human plasma specimens (n = 142) was performed based on guidance from CLSI Document EP09-A3.[36] The specimens were tested with the ARCHITECT B·R·A·H·M·S PCT assay and compared to values obtained with the B·R·A·H·M·S PCT sensitive KRYPTOR assay. The results were evaluated using a weighted Deming regression method.[37] The data are summarized in the following table and graph.

Concentration Range (ng/mL)				
ARCHITECT B·R·A·H·M·S PCT	B·R·A·H·M·S PCT Sensitive KRYPTOR	Correlation Coefficient (r)	Slope	Intercept
0.01 - 91.03	0.03 - 82.39	0.99	1.00	-0.02



x B·R·A·H·M·S PCT sensitive KRYPTOR (ng/mL)

y ARCHITECT B·R·A·H·M·S PCT (ng/mL)

—— Weighted Deming fit (y = -0.02 + 1.00x)

------ 95% Confidence Interval (CI)

Qualitative agreement between the ARCHITECT B·R·A·H·M·S PCT and B·R·A·H·M·S PCT sensitive KRYPTOR assays were compared at clinical decision points (0.5 ng/mL and 2.0 ng/mL).

	KRYPTOR			
ARCHITECT	≤ 0.5 ng/mL	0.5 ng/mL to 2.0 ng/mL	> 2.0 ng/mL	Total
≤ 0.5 ng/mL	48	4	0	52
0.5 ng/mL to 2.0 ng/mL	1	24	0	25
> 2.0 ng/mL	0	0	65	65
Total	49	28	65	142

In addition, the following concordance data between the ARCHITECT B·R·A·H·M·S PCT and B·R·A·H·M·S PCT sensitive KRYPTOR assays were obtained from the clinical performance study (n = 2331) at clinical decision points.

Clinical Decision Point (ng/mL)	Positive Agreement % (95% CI)	Negative Agreement % (95% CI)	Total Agreement (%)	Cohen's Kappa
0.10	96.1 (95.2-96.9)	95.2 (88.3-98.7)	96.1	0.619
0.25	96.8 (95.9-97.5)	95.2 (92.4-97.2)	96.5	0.871
0.50	96.9 (96.0-97.7)	96.8 (95.0-98.1)	96.9	0.920
2.00	96.9 (95.7-97.8)	98.4 (97.4-99.0)	97.6	0.951

Clinical Performance

The ARCHITECT B·R·A·H·M·S PCT assay was evaluated for the prediction of cumulative 28-day all-cause mortality using retrospective samples from a study of 858 adult patients diagnosed with severe sepsis or septic shock recruited across 13 investigational sites in the United States.[25] The analysis population (598 subjects) included 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) vs septic shock (49%). Infections were mainly community acquired (91%). Testing was performed at 2 external and one internal site using the ARCHITECT i2000SR.

The binary test result (ΔPCT > 80% or ≤ 80%) was significantly associated with 28-day cumulative mortality (i.e., vital status on Day 28). The 2-sided Fisher's exact test p-value was 0.001. Adjusted for ICU vs non-ICU patient subgroups (based on patient location at Day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel test p-value = 0.017). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on Day 4 and the selection of Day 0 vs Day 1 as the baseline measurement day for the ΔPCT calculation:

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive

		Mortality (%)		Prognostic Accuracy (%)[a]	
ΔPCT Interval	Day 4 Patient Location	ΔPCT > 80% (95% CI)	ΔPCT ≤ 80% (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Day 0 to Day 4	ICU	20.7 (12.4-29.0)	30.6 (23.7-37.5)	73.4 (63.2-83.7)	38.0 (31.0-45.0)
	Non-ICU	5.7 (2.1-9.4)	11.4 (6.7-16.2)	68.8 (51.8-85.7)	49.1 (43.1-55.1)
Day 1 to Day 4	ICU	20.2 (12.1-28.3)	31.2 (24.2-38.3)	72.6 (62.0-83.1)	40.4 (33.3-47.5)
	Non-ICU	5.3 (1.7-8.9)	11.6 (6.9-16.3)	71.9 (55.3-88.5)	47.6 (41.5-53.7)

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

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

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

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	Initial PCT Concentration (Day 0 or Day 1)	Mortality (%)		Prognostic Accuracy (%)[a]	
			ΔPCT > 80% (95% CI)	ΔPCT ≤ 80% (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Day 0 to Day 4	ICU	≤ 2.0 ng/mL	7.3 (0.0-21.1)	24.7 (14.5-34.9)	94.1 (82.8-100.0)	20.7 (10.6-30.8)
		> 2.0 ng/mL	23.2 (13.8-32.6)	34.5 (25.4-43.7)	66.5 (53.9-79.2)	46.8 (38.0-55.6)
	Non-ICU	≤ 2.0 ng/mL	3.3 (0.0-9.8)	8.6 (3.5-13.7)	90.9 (73.9-100.0)	21.6 (14.0-29.1)
		> 2.0 ng/mL	6.3 (2.1-10.5)	17.0 (7.2-26.7)	55.2 (32.1-78.3)	71.1 (63.7-78.6)
Day 1 to Day 4	ICU	≤ 2.0 ng/mL	12.4 (0.0-32.3)	25.7 (15.1-36.2)	91.7 (77.7-100.0)	17.9 (8.0-27.7)
		> 2.0 ng/mL	21.3 (12.5-30.1)	35.0 (25.6-44.5)	65.7 (52.8-78.7)	50.9 (42.2-59.7)
	Non-ICU	≤ 2.0 ng/mL	0.0 (0.0-12.3)[b]	8.5 (3.5-13.5)	100.0 (69.2-100.0)[b]	19.8 (12.5-27.1)
		> 2.0 ng/mL	6.5 (2.1-10.9)	18.2 (7.9-28.5)	56.1 (33.1-79.0)	71.4 (63.7-79.1)

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

[b] Normality approximation of within-imputation variance not valid, therefore the estimate corresponds to within-imputation variation based on exact confidence intervals.[38]

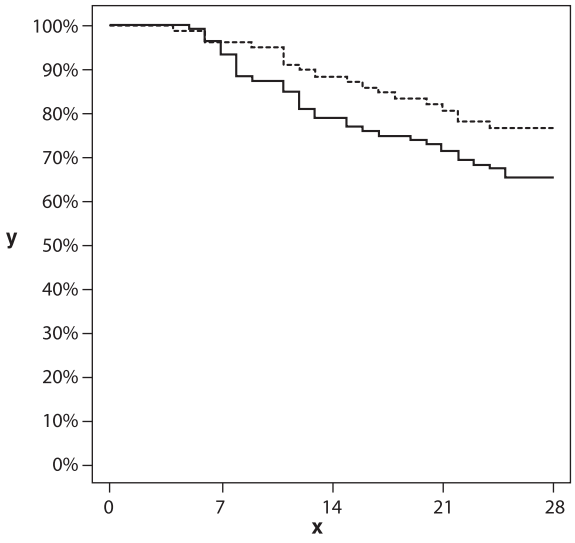
The relative mortality ratios for ΔPCT positive (≤ 80%) vs ΔPCT negative (> 80%) patient subgroups were:

- 1.49 for patients with PCT > 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 3.38 for patients with PCT ≤ 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 2.70 for patients with PCT > 2.0 ng/mL at Day 0 without ICU care on Day 4
- 2.61 for patients with PCT ≤ 2.0 ng/mL at Day 0 without ICU care on Day 4

Based on relative mortality ratios, a decrease in PCT concentration by ≤ 80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to > 80% decreases in each subgroup.

Time-to-event analyses, illustrated by the Kaplan-Meier curves below, demonstrate that patients had a lower survival probability (higher cumulative mortality risk) from Day 4 until the end of follow-up time (Day 28) when the ΔPCT test result was positive compared to when the ΔPCT result was negative in all patient subgroups according to patient location on Day 4 and initial PCT concentration.

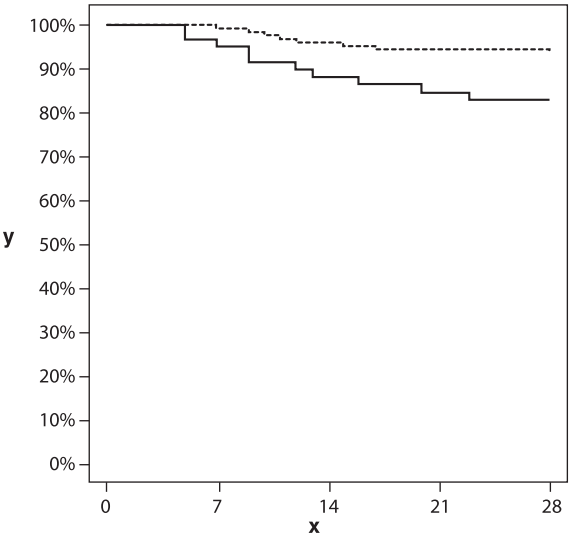
Survival until Day 28, PCT > 2.0 ng/mL at Day 0, ICU Day 4 (n=182)



x Time (days) ------ ΔPCT=negative, n=78, deaths=18

y Proportion of patients surviving —— ΔPCT=positive, n=104, deaths=36

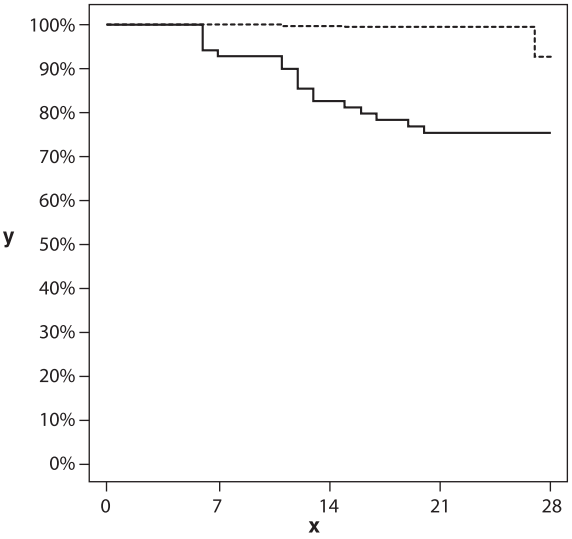
Survival until Day 28, PCT > 2.0 ng/mL at Day 0, non-ICU Day 4 (n=187)



x Time (days) ------ ΔPCT=negative, n=128, deaths=8

y Proportion of patients surviving —— ΔPCT=positive, n=59, deaths=10

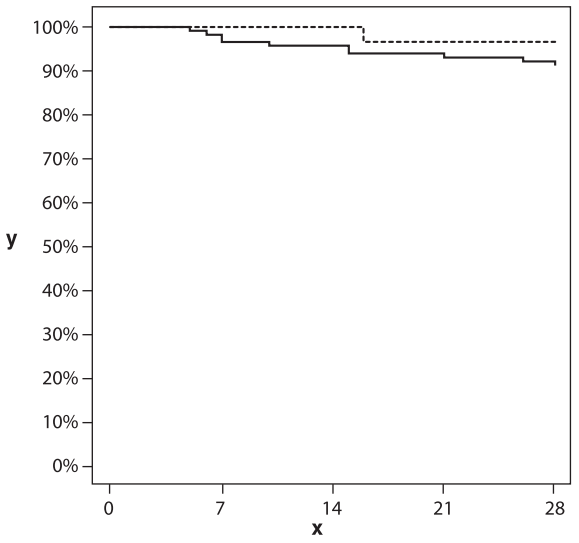
Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, ICU Day 4 (n=84)



x Time (days) ------ ΔPCT=negative, n=14, deaths=1

y Proportion of patients surviving —— ΔPCT=positive, n=69, deaths=17

Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, non-ICU Day 4 (n=147)



For the prediction of absolute mortality risks, patient location on Day 4 and initial PCT concentration should be considered:

- An initial PCT concentration ≤ 2.0 ng/mL on Day 0 followed by a PCT concentration decrease of more than 80% by Day 4 indicates approximately a one-third lower cumulative 28-day mortality risk (7.3%) 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 concentration > 2.0 ng/mL (23.2%). Regardless of the initial PCT concentration, patients in the ICU on Day 4 that do not have a PCT concentration decrease of more than 80% in PCT plasma concentration from Day 0 to Day 4 have even higher mortality risks of 24.7% and 34.5%.
- An initial PCT concentration > 2.0 ng/mL that does not decrease by more than 80% by Day 4 signals that such patients remain at high mortality risk (17.0%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 3.3% to 8.6% for patients discharged from the ICU by Day 4.

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 1.99 (95% CI of 1.28–3.09, p-value = 0.0021). 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%	1.99	1.28-3.09	0.002
ΔPCT (Day 1 to Day 4)	≤ 80% vs > 80%	2.03	1.30-3.18	0.002
APACHE[a]	Difference of 5 Units	1.36	1.22-1.53	< 0.001
Maximum SOFA	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	0.386
Biological Infection Type	Gram Positive vs Gram Negative	0.83	0.48-1.45	0.522
	Other vs Gram Negative	0.99	0.63-1.54	0.960
	Fungal vs Gram Negative	2.44	0.87-6.84	0.090
Clinical Infection Type	Nosocomial vs Community	0.76	0.35-1.64	0.481
Positive Blood Culture	Yes vs No	1.05	0.69-1.58	0.834
PCT on Day 0	> 2 ng/mL vs ≤ 2 ng/mL	1.59	1.04-2.45	0.034
Age	Difference of 5 Years	1.16	1.08-1.24	< 0.001
Gender	Male vs Female	0.95	0.64-1.40	0.782
ICU Care on Day 4	Yes vs No	3.45	2.24-5.31	< 0.001

[a] Acute Physiology and Chronic Health Evaluation

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 presented below with 95% confidence intervals. For continuous predictors, the hazard ratio was calculated for one SD change in the predictor. For binary predictors, the risk estimate compares the hazards for the 2 binary results.

Model		Hazard Ratio (HR) (95% CI)				
		Binary Predictors		Continuous Predictors (HR per 1 SD)		
ΔPCT Interval	Score + Covariates[a]	ΔPCT (≤ 80% vs > 80%)	Day 4 Patient Location (ICU vs Non-ICU)	APACHE (1 SD = 8.13)	Maximum SOFA (1 SD = 3.98)	Age (1 SD = 16.18)
Day 0 to Day 4	APACHE	1.89 (1.14-3.14)	2.59 (1.61-4.15)	1.22 (0.98-1.53)	N/A	1.60 (1.28-2.00)
	Maximum SOFA	1.55 (0.94-2.57)	1.70 (1.03-2.80)	N/A	1.93 (1.49-2.49)	1.69 (1.35-2.11)
Day 1 to Day 4	APACHE	1.96 (1.20-3.22)	2.61 (1.63-4.18)	1.26 (1.01-1.58)	N/A	1.56 (1.24-1.95)
	Maximum SOFA	1.74 (1.06-2.86)	1.72 (1.05-2.83)	N/A	1.94 (1.51-2.50)	1.65 (1.32-2.06)

[a] 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 concentration on Day 0, and gender.

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

$$PCT_{ratio} = \frac{PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}}$$

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 decrease is less than 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 Day 0 until Day 4 and 0.72 SD for Day 1 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% CI)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
ΔPCT Interval	Score + Covariates[a]	PCT Ratio (2-Fold Increase)	APACHE (SD Equivalent)[b]	Maximum SOFA (SD Equivalent)[b]	Age (SD Equivalent)[b]	Day 4 Patient Location ICU vs Non-ICU
Day 0 to Day 4	APACHE	1.28 (1.14-1.44)	1.07 (0.95-1.21)	N/A	1.29 (1.15-1.45)	2.50 (1.55-4.02)
	Maximum SOFA	1.21 (1.07-1.36)	N/A	1.36 (1.19-1.55)	1.32 (1.18-1.48)	1.69 (1.02-2.78)
Day 1 to Day 4	APACHE	1.35 (1.17-1.57)	1.18 (1.01-1.38)	N/A	1.38 (1.18-1.61)	2.54 (1.58-4.06)
	Maximum SOFA	1.29 (1.10-1.50)	N/A	1.55 (1.31-1.84)	1.44 (1.23-1.67)	1.74 (1.06-2.86)

[a] 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 concentration on Day 0, and gender.

[b] A unit change of ΔPCT on log-2-scale corresponded to 0.52 SD of ΔPCT from Day 0 until Day 4 (0.69 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SD (i.e., 0.52 or 0.69, respectively).

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 presented below:

		All Patients			
Variable	Class	(n = 598)	Dead (n)	Alive (n)	Mortality (%)
Gender	Female	264	46	218	17.4%
	Male	334	55	279	16.5%
Age (Years)	≤ 30	39	1	38	2.6%
	> 30 to 45	45	4	41	8.9%
	> 45 to 55	74	8	66	10.8%
	> 55 to 65	149	26	123	17.4%
	> 65 to 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 (ng/mL)	< 0.5	127	19	108	15.0%
	0.5 to 2.0	96	10	86	10.4%
	> 2.0	360	72	288	20.0%
	Missing	15	0	15	0.0%

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Key to Symbols

	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
CONJUGATE	Conjugate
CONTAINS: AZIDE	Contains Sodium Azide. Contact with acids liberates very toxic gas.
CONTROL NO.	Control Number
DISTRIBUTED IN THE USA BY	Distributed in the USA by
INFORMATION FOR USA ONLY	Information needed for United States of America only
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
MICROPARTICLES	Microparticles
PRE-TRIGGER SOLUTION	Pre-Trigger Solution
PRODUCED FOR ABBOTT BY	Produced for Abbott by
PRODUCT OF USA	Product of USA
REACTION VESSELS	Reaction Vessels
REAGENT LOT	Reagent Lot
REF	List Number
REPLACEMENT CAPS	Replacement Caps
Rx ONLY	For use by or on the order of a physician only (applicable to USA classification only).
SAMPLE CUPS	Sample Cups
SEPTUM	Septum
SN	Serial number
TRIGGER SOLUTION	Trigger Solution
WARNING: EYE IRRITANT	Warning: Causes serious eye irritation.
WARNING: SENSITIZER	Warning: May cause an allergic reaction.
WARNING: SKIN IRRITANT	Warning: Causes skin irritation.
WASH BUFFER	Wash Buffer

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