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# Evaluation of a Procalcitonin Assay on the Atellica IM Analyzer

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## Abstract

**Background:** Procalcitonin (PCT) is a 116-amino-acid peptide that shares a common structure with the prohormone of calcitonin. Under normal metabolic conditions, calcitonin prohormone is produced by the thyroid's C-cells, where it undergoes proteolysis to yield the hormone calcitonin. Calcitonin is then involved in calcium homeostasis.[1,2] Under normal conditions, plasma levels of the calcitonin prohormone have been shown to be below 0.1 ng/mL.[3,4,5] However, during episodes of severe bacterial infection and sepsis, the amount of blood-circulating PCT increases to levels generally above 2 ng/mL.[6] In response to proinflammatory stimuli, such as bacterial infection, operation, or trauma, PCT can be produced by nearly every tissue of the body.[7,8,9] Siemens Healthineers has developed a PCT assay for the Atellica® Immunoassay (IM) Analyzer with acceptable sensitivity, precision, and linearity to aid in the risk assessment of critically ill patients for progression to severe sepsis and septic shock on their first day of intensive-care unit (ICU) admission. The PCT assay is an 18-minute sandwich immunoassay with a range of 0.04 to 50.00 ng/mL. The assay is aligned to the B•R•A•H•M•S PCT sensitive KRYPTOR® assay.

**Method:** The precision and functional sensitivity of the Atellica IM BRAHMS PCT Assay was performed in accordance with recognized standards from Clinical Laboratory Standards Institute (CLSI) EP05-A3. The study was conducted using two levels of control material, a panel of five human serum precision samples, and a panel of five human serum functional sensitivity samples containing low levels of PCT analyte, tested twice a day for 20 days for a total of 80 replicates. For each analyte concentration level, the mean value with variance components (standard deviation and %CV) was determined. Linearity studies were conducted according to CLSI EP06-A using nine human serum samples equally spaced across the assay range in a known mathematical relationship. The mean dose value of each sample was used to determine the % deviation from the linear fit. A method comparison study was performed in accordance with CLSI EP09-A3 to B•R•A•H•M•S PCT sensitive KRYPTOR dose-assigned samples. A total of 522 samples were tested. Analysis was performed by Weighted Deming regression. Expected values were established according to CLSI Guideline EP28-A3c. In a population of 120 serum samples, 120 had PCT values <0.05 ng/mL.

**Results:** The data obtained with the Atellica IM BRAHMS PCT assay demonstrated correlation to the B•R•A•H•M•S PCT sensitive KRYPTOR assay, yielding a slope of 1.02 and regression coefficient of 0.98. A 20-day precision study yielded within-lab precision CVs between 11.7 and 2.6% for samples containing between ~0.06 and ~20.73 ng/mL of PCT analyte respectively. Functional sensitivity was ≤0.04 ng/mL. Linearity studies demonstrated that the Atellica IM BRAHMS PCT Assay is linear across the assay range. Expected values were established using serum samples from apparently healthy individuals. In a population of 120 subjects, the PCT values corresponding to the 99th percentile was <0.05 ng/mL.

**Conclusion:** The performance of the Atellica IM BRAHMS PCT Assay has been assessed, and the results show an accurate, sensitive, and precise method for the measurement of procalcitonin in human serum and plasma. The Atellica IM BRAHMS PCT Assay is in alignment with the B•R•A•H•M•S PCT sensitive KRYPTOR assay and may be a valuable tool in clinical laboratories for the accurate measurement of procalcitonin.



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## Introduction

Severe sepsis and septic shock are among the leading causes of death in critically ill patients in the ICU. Despite great efforts to understand the underlying pathophysiology and improve therapeutic concepts, the mortality rate of sepsis remains high at 30–50%, with up to 80% mortality from septic shock. In the U.S., about 750,000 patients per year suffer from sepsis, causing an estimated 215,000 deaths per year, or over 500 per day. As the general population ages and technology supports and prolongs longevity, the frequency of sepsis is expected to increase at a rate of approximately 1.5% per year.[10,11] Early diagnosis and treatment of sepsis is associated with better patient outcomes.[12,13]

PCT consists of 116 amino acids and is the prohormone of calcitonin. When facing proinflammatory stimuli, particularly stemming from bacterial insult, several cell types and organs have been shown to accelerate PCT production.[1,2] In contrast, shortly after traumas that do not involve a bacterial insult (such as major surgery, severe burns, neonates at birth, viral infections, allergic disorders, autoimmune diseases, or rejection of organ transplant), PCT levels have been shown to rise temporarily to values <0.5 ng/mL, followed by a rapid return to baseline levels. Taken together, PCT has been established as an important blood marker capable of differentiating between a bacterial infection and other causes of proinflammatory stimuli.[12,13]

Used in conjunction with other laboratory findings and clinical assessments, the Atellica IM BRAHMS PCT Assay has been designed 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.

### Test Principle

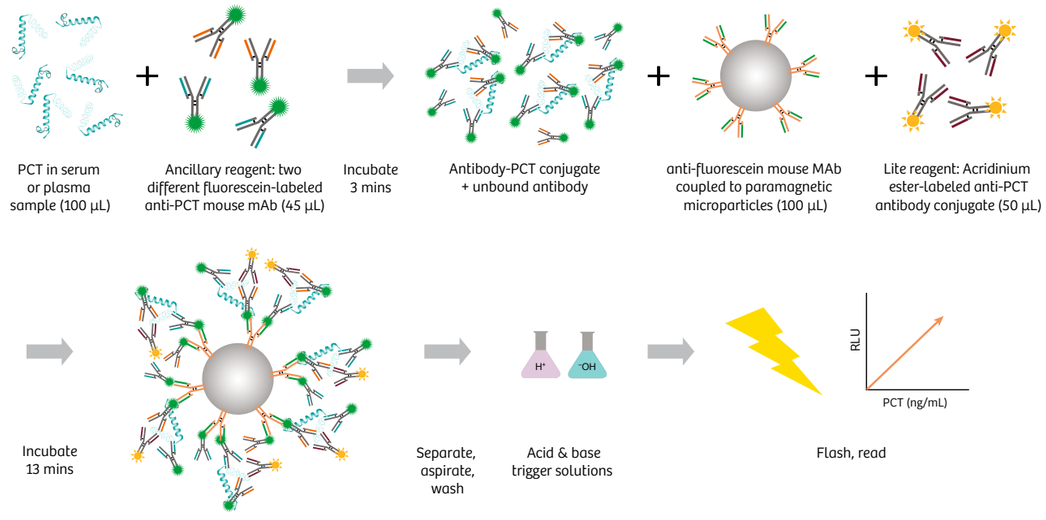


**Figure 1.** Atellica IM BRAHMS PCT Assay format





The Atellica IM BRAHMS PCT Assay is a two-site sandwich immunoassay that employs direct chemiluminescent technology and uses three mouse monoclonal antibodies specific for PCT. The first antibody, in the Lite Reagent, is a mouse monoclonal anti-PCT antibody labeled with the acridinium ester. The second and third antibodies, in the Ancillary Reagent, are mouse monoclonal anti-PCT antibodies labeled with fluorescein. The immunocomplex formed with PCT is captured with mouse monoclonal anti-fluorescein antibodies coupled to paramagnetic particles in the solid phase. A direct relationship exists between the amount of PCT present in the patient sample and the amount of relative light units (RLUs) detected by the system. Time to first result is 18 minutes.

## Materials and Methods

The assay was evaluated on the Siemens Healthineers Atellica IM Analyzer for repeatability and within-laboratory precision, method comparison, linearity, limit of detection (LoD), limit of quantitation (LoQ), calibration interval, onboard stability (OBS), hook effect, and endogenous interferences.

## Results

### Analytical performance

The overall analytical performance of the Atellica IM BRAHMS PCT Assay was very good. The assay has a range of 0.04–50.0 ng/mL. The LoB, LoD, and LoQ are <0.03 ng/mL, <0.04 ng/mL, and ≤0.06 ng/mL respectively, with no observed hook effect at 2000 ng/mL. The calibration interval is 35 days, and onboard stability is 60 days.

**Table 1**. Analytical performance

| Performance Attribute | Value |
|---|---|
| Assay range | 0.04–50.0 ng/mL |
| LoB | <0.03 ng/mL |
| LoD | <0.04 ng/mL |
| LoQ | ≤0.06 ng/mL |
| Hook effect | Not observed at ≥2000 ng/mL |
| Calibration interval | 35 days |
| Onboard stability | 60 days |

### Precision

Precision was determined in accordance with CLSI document EP05-A3. Five samples and two controls were evaluated on an Atellica IM Analyzer in duplicate, in two runs per day for 20 days. The assay was designed to have within-laboratory precision of ≤25% CV for samples from 0.05–0.10 ng/mL, and ≤15% CV for samples >0.10 ng/mL.

**Table 2.** Precision

| | | | Repeatability | | Within-Laboratory Precision | |
|---|---|---|---|---|---|---|
| **Sample Type** | **N[a]** | **Mean (ng/mL)** | **SD[b] (ng/mL)** | **CV[c] (%)** | **SD (ng/mL)** | **CV (%)** |
| Serum A | 80 | 0.06 | 0.01 | 10.0 | 0.01 | 11.7 |
| Serum B | 80 | 0.30 | 0.01 | 1.9 | 0.01 | 2.7 |
| Serum C | 80 | 0.81 | 0.02 | 2.1 | 0.03 | 3.4 |
| Serum D | 80 | 1.64 | 0.03 | 1.6 | 0.04 | 2.6 |
| Serum E | 80 | 20.73 | 0.36 | 1.7 | 0.59 | 2.9 |
| Control 1 | 80 | 0.24 | 0.01 | 3.3 | 0.01 | 4.7 |
| Control 2 | 80 | 7.76 | 0.11 | 1.4 | 0.54 | 7.0 |

a Number of samples tested
b Standard deviation
c Coefficient of variation

### Linearity

Linearity of the Atellica IM BRAHMS PCT Assay was performed using a normal human serum sample spiked with recombinant PCT to create a high PCT sample pool. The low-pool sample is a normal human serum sample. The mean dose value of three replicates per sample was used in the data analysis. The assay was shown to be linear across the analytical measuring range.

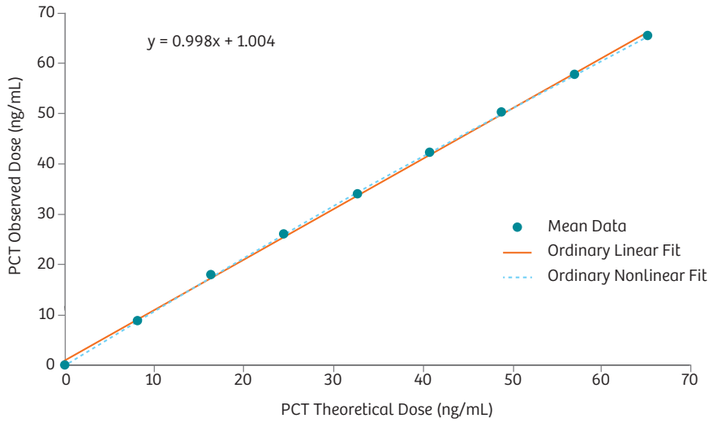


**Figure 2.** Linearity

### Interference

Less than 10% endogenous interference was observed for all tested interferents.

**Table 3.** Endogenous interference testing summary

| Endogenous Interference | Concentration Tested | % Interference |
|---|---|---|
| Bilirubin (conjugated) | 40 mg/dL | <10% |
| Bilirubin (unconjugated) | 40 mg/dL | <10% |
| Hemoglobin | 500 mg/dL | <10% |
| Triglycerides | 1000 mg/dL | <10% |
| Fluorescein | 0.1 µg/mL | <10% |
| Biotin | 3500 ng/mL | <10% |
| Total protein | 12 g/dL | <10% |





### Method comparison

The method comparison study was designed to evaluate the agreement of the Atellica IM BRAHMS PCT Assay to that of the predicate device (B•R•A•H•M•S PCT sensitive KRYPTOR assay). A total of 522 native human serum samples with assigned B•R•A•H•M•S PCT sensitive KRYPTOR dose values (0.06–49.20 ng/mL) were tested on four Atellica IM Analyzers using four PCT reagent lots. The samples were tested over 7 nonconsecutive days using within-run calibration. Slope was calculated by Weighted Deming regression.

**Table 4.** Method comparison between Atellica IM BRAHMS PCT and B•R•A•H•M•S PCT sensitive KRYPTOR assays

| Attribute | Atellica IM BRAHMS PCT vs B•R•A•H•M•S PCT sensitive KRYPTOR |
|---|---|
| n | 522 |
| Minimum* | 0.06 ng/mL |
| Maximum* | 49.20 ng/mL |
| Slope | 1.02 |
| Intercept | -0.02 |
| r | 0.98 |

*The minimum and maximum dose values are based on results from the predicate device

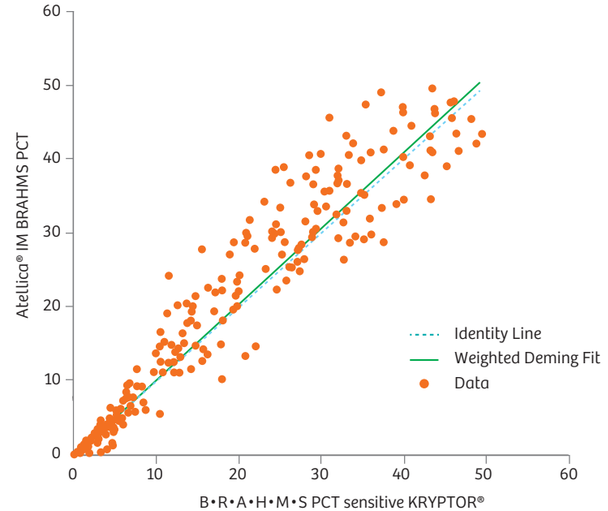


**Figure 3**. Method comparison: Atellica IM BRAHMS PCT Assay vs. B•R•A•H•M•S PCT sensitive KRYPTOR assay

### Concordance

A total of 623 native human serum samples with assigned B•R•A•H•M•S PCT sensitive KRYPTOR dose values, tested on four Atellica IM Analyzers using four PCT reagent lots, were analyzed for concordance at 0.1, 0.25, 0.5, and 2.0 ng/mL. From the total n = 623 samples tested, the percent agreement between the Atellica IM BRAHMS PCT assay and the predicate B•R•A•H•M•S PCT sensitive KRYPTOR assay at the cutoffs were determined.

**Table 5**. Concordance analysis: PCT Results at the 0.10 ng/mL cutoff

| | | B•R•A•H•M•S PCT sensitive KRYPTOR | | |
|---|---|---|---|---|
| | | **>0.10 ng/mL** | **≤0.10 ng/mL** | **Total** |
| Atellica IM BRAHMS PCT | >0.10 ng/mL | 539 | 4 | 543 |
| | ≤0.10 ng/mL | 4 | 76 | 80 |
| | **Total** | **543** | **80** | **623** |

Positive % Agreement = 99.3%; 95% Confidence Interval: 98.1%-99.7%
Negative % Agreement = 95.0%; 95% Confidence Interval: 87.8%-98.0%
Overall % Agreement = 98.7%; 95% Confidence Interval: 97.5%-99.4%

**Table 6.** Concordance analysis: PCT Results at the 0.25 ng/mL cutoff

| | | B•R•A•H•M•S PCT sensitive KRYPTOR | | |
|---|---|---|---|---|
| | | >0.25 ng/mL | ≤0.25 ng/mL | Total |
| Atellica IM BRAHMS PCT | >0.25 ng/mL | 488 | 7 | 495 |
| | ≤0.25 ng/mL | 5 | 123 | 128 |
| | **Total** | **493** | **130** | **623** |

Positive % Agreement = 99.0%; 95% Confidence Interval: 97.7%-99.6%
Negative % Agreement = 94.6%; 95% Confidence Interval: 89.3%-97.4%
Overall % Agreement = 98.1%; 95% Confidence Interval: 96.7%-98.9%

**Table 7.** Concordance analysis: PCT Results at the 0.50 ng/mL cutoff

| | | B•R•A•H•M•S PCT sensitive KRYPTOR | | |
|---|---|---|---|---|
| | | >0.50 ng/mL | ≤0.50 ng/mL | Total |
| Atellica IM BRAHMS PCT | >0.50 ng/mL | 414 | 5 | 419 |
| | ≤0.50 ng/mL | 14 | 190 | 204 |
| | **Total** | **428** | **195** | **623** |

Positive % Agreement = 96.7%; 95% Confidence Interval: 94.6%-98.0%
Negative % Agreement = 97.4%; 95% Confidence Interval: 94.1%-98.8%
Overall % Agreement = 97.0%; 95% Confidence Interval: 95.3%-98.0%

**Table 8.** Concordance analysis: PCT Results at the 2.0 ng/mL cutoff

| | | B•R•A•H•M•S PCT sensitive KRYPTOR | | |
|---|---|---|---|---|
| | | >2.00 ng/mL | ≤2.00 ng/mL | Total |
| Atellica IM BRAHMS PCT | >2.00 ng/mL | 279 | 8 | 287 |
| | ≤2.00 ng/mL | 8 | 328 | 336 |
| | **Total** | **287** | **336** | **623** |

Positive % Agreement = 97.2%; 95% Confidence Interval: 94.6%-98.6%
Negative % Agreement = 97.6%; 95% Confidence Interval: 95.4%-98.8%
Overall % Agreement = 97.4%; 95% Confidence Interval: 95.9%-98.4%





## Conclusion

The performance of the Atellica IM BRAHMS PCT Assay has been assessed, and the results show an accurate, sensitive, and precise method for the measurement of procalcitonin in human serum and plasma. The Atellica IM BRAHMS PCT Assay is in alignment with the B•R•A•H•M•S PCT sensitive KRYPTOR assay with good concordance at 0.1, 0.25, 0.50, and 2.0 ng/mL and may be a valuable tool in clinical laboratories for the accurate measurement of procalcitonin.

**References:**


1. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 341 (8844):515-518.
2. Christ-Crain M, Muller B. Procalcitonin in bacterial infections: hype, hope, more or less? Swiss Med Wkly. 2005; 135(31-32):451-460.
3. Snider RH, Nylen ES, Becker KL. Procalcitonin and ist component peptides in systemic inflammation: immunochemical characterization. J Investig Med. 1997; 45(9):552-560.
4. BRAHMS PCT sensitive KRYPTOR assay instruction manual (version 2.0us).
5. Morgenthaler NG, Struck J, et al. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. Clin Lab. 2002; 48(5-6):263-270.
6. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med. 2001; 164(3):396-402.
7. Meisner M, et al. Postoperative plasma concentrations of procalcitonin after different types of surgery. Intensive Care Med. 1998; 24(3):664-672.
8. Chiesa C, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clinl Infect Dis. 1998; 26(3):664-672
9. Reith HB, et al. Procalcitonin in early detection of postoperative complications. Dig Surg. 1998; 15(3):260-265.
10. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29(7):1303-10.
11. Dellinger RP, Levy MM, Rhodes A. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013; 41(2):580-637.
12. Christ-Crain M, Jaccard-Stolz D, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded intervention trial. Lancet. 2004; 363(9409):600-7.
13. Yu DT, Black E, Sands KE, et al.: Academic Medical Center Consortium Sepsis Project Working Group. Severe sepsis: variation in resource and therapeutic modality use among academic centers. Crit Care. 2003; 7(3):R24-R34.