SIEMENS Healthineers

B-Type Natriuretic Peptide (BNP)

Current Revision and Date[a]	Rev. 06, 2022-08	
Product Name	Atellica IM B-Type Natriuretic Peptide (BNP)	REF 10995471 (100 tests) REF 10995472 (500 tests)
Abbreviated Product Name	Atellica IM BNP	
Test Name/ID	BNP	
Systems	Atellica IM Analyzer	
Materials Required but Not Provided	Atellica IM BNP CAL	REF 10995473
Optional Materials	Atellica IM BNP QC	REF 10995475
	Atellica IM BNP MCM	REF 10995474
Specimen Types	EDTA plasma	
Sample Volume	100 µL	
Measuring Interval	2.0–5000.0 pg/mL (0.58–1445.00 pmol/L)	

[a] A vertical bar in the page margin indicates technical content that differs from the previous version.

Intended Use

The Atellica® IM B-Type natriuretic peptide (BNP) assay is for *in vitro* diagnostic use in the quantitative determination of B-type natriuretic peptide in human plasma (EDTA) using the Atellica® IM Analyzer. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of the severity of heart failure. In patients with acute coronary syndromes (ACS), this test, in conjunction with other known risk factors, can also be used to predict survival as well as to predict the likelihood of future heart failure. This assay is not intended for use on any other system.

Summary and Explanation

Heart failure is an important clinical syndrome which compromises left ventricular systolic or diastolic function or a combination of both. Heart failure occurs when the heart is unable to pump blood at a rate sufficient for metabolic requirements. Its most common causes are coronary artery disease, hypertension, valvular heart diseases, and cardiomyopathies. Accurate and early diagnosis is important since effective therapeutic interventions (e.g., angiotensin converting enzyme inhibitors, beta-blockers) are available, which improve both morbidity and mortality. Based on clinical signs and symptoms, the severity of heart failure is classified into four classes of increasing disease progression according to the New York Heart Association classification (NYHA class I–IV).[1,2]

The natriuretic peptide system is a family of structurally similar but genetically distinct peptides, which include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) of myocardial cell origin and C-type natriuretic peptide (CNP) of endothelial cell origin. These peptides are characterized by a common 17 amino acid ring structure with a disulfide bond between 2 cysteine residues.[3-5] The cardiac natriuretic peptides are the naturally occurring antagonists of the renin-angiotensin-aldosterone system and of the sympathetic nervous system. They promote natriuresis and diuresis, act as vasodilators, and exert antimitogenic effects on cardiovascular tissues.[6] ANP and BNP are secreted by the heart in response to hemodynamic stress. Increased levels of BNP are produced mainly in response to left ventricular wall stretch and volume overload. ANP and BNP are expressed predominantly in the atria and ventricles, respectively, and are important in regulation of blood pressure, electrolyte and volume homeostasis.[6-10]

The cardiac natriuretic peptide system is activated to its highest degree in ventricular dysfunction and has an important role in maintaining the compensated state of asymptomatic heart failure and delaying disease progression. BNP is synthesized within the cardiomyocyte as a preprohormone (preproBNP) of 134 amino acids, from which a prehormone (proBNP) of 108 amino acids and a signal peptide of 26 amino acids is derived. The proBNP precursor protein is then cleaved into a physiologically active 32 amino acid C-terminal peptide (BNP 77–108; BNP) and a 76 amino acid N-terminal prohormone fragment (NT-proBNP 1–76). Studies indicate that the proBNP protein precursor is cleaved either within or on the surface of cardiomyocytes, and that both NT-proBNP (1–76) and physiologically active C-terminal BNP molecule (77–108) are released into the bloodstream.[11-13] The Atellica IM BNP assay measures only the physiologically active BNP molecule (77–108) and utilizes monoclonal antibodies specific to its C-terminal portion and ring structure.

Several studies indicate that BNP can be used for a wide range of clinical applications including diagnosis, monitoring, and prognosis.[3,4,11,12,14-16] The circulating levels of BNP increase with decreasing left ventricular function and increasing clinical severity of heart failure, according to the NYHA classification, which makes it an appropriate test for diagnosis and staging of heart failure.[17-27] Other studies have demonstrated that an increased level of circulating BNP correlates with higher incidence of cardiac events and mortality in patients with heart failure[28-31] and acute coronary syndromes,[32,33] and supports utilization of BNP as a marker for patient prognosis. The Thrombolysis in Myocardial Infarction 23 (ENTIRE-TIMI 23) substudy evaluated the prognostic performance of the ADVIA Centaur® BNP method assessed at the time of initial presentation in a well-characterized cohort of patients enrolled in the Enoxaparin and tenecteplase (TNK-tPA) with or without GPIIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation Myocardial Infarction (STEMI).[34] Plasma BNP was measured retrospectively in 438 STEMI patients who had an episode of ischemic discomfort of at least 30 minutes duration within the prior 6 hours. This study found that BNP levels > 80 pg/mL at presentation were associated with a substantially higher risk of death within the 30-day follow-up period. There are also indications that BNP can be used to provide an index to modulate treatment of patients with heart failure.[16,17,35,36]

It has been reported that patients with acute decompensated heart failure who are candidates for nesiritide (recombinant BNP) infusion should have a baseline BNP measurement taken prior to initiation of therapy. Measurements taken during infusion are reflective of the dose of nesiritide.[37] Because of the short half-life of BNP (20 minutes), measurements taken 2 hours after the cessation of treatment again reflect the level of endogenous BNP. It has also been reported that following infusion, endogenous BNP levels return to baseline by 1–2 hours and continue to drop at 6 hours to about 80% of preinfusion levels, suggesting a resetting of the neuro-hormonal axis and improvement in ventricular wall tension as a result of treatment.[38] The Atellica IM BNP assay is not approved for nesiritide monitoring.

Principles of the Procedure

The Atellica IM BNP assay is a fully automated 2-site sandwich immunoassay using direct chemiluminescent technology which uses constant amounts of 2 monoclonal antibodies. The first antibody, in the Lite Reagent, is an acridinium-ester-labeled mouse monoclonal anti-human BNP $F(ab')_2$ fragment specific to the ring structure of BNP. The second antibody, in the Solid Phase, is a biotinylated mouse monoclonal anti-human antibody specific to the C-terminal portion of BNP, which is coupled to streptavidin magnetic particles.

A direct relationship exists between the amount of BNP present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Reagents

Material Description	Storage	Stability[a]
Atellica IM BNP ReadyPack® primary reagent pack **Lite Reagent** 10.0 mL/reagent pack Mouse monoclonal anti-human BNP $F(ab')_2$ fragment antibody (~0.50 µg/mL) labeled with acridinium ester in buffer; bovine gamma globulin; mouse gamma globulin; preservatives **Solid Phase** 20.0 mL/reagent pack Mouse monoclonal anti-human BNP antibody (~6.0 µg/mL); bovine gamma globulin; mouse gamma globulin; preservatives	Unopened at 2–8°C Onboard	Until expiration date on product 42 days

[a] Refer to *Storage and Stability*.

Warnings and Precautions

For *in vitro* diagnostic use.

For Professional Use.

CAUTION

Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.

Safety data sheets (SDS) available on siemens-healthineers.com.

CAUTION

This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

Note For information about reagent preparation, refer to *Preparing the Reagents* in the *Procedure* section.

Storage and Stability

Store reagents in an upright position. Protect the product from heat and light sources. Unopened reagents are stable until the expiration date on the product when stored at 2–8°C.

Do not use products beyond the expiration date printed on the product labeling.

Onboard Stability

Reagents are stable onboard the system for 42 days. Discard reagents at the end of the onboard stability interval.

Do not use products beyond the expiration date printed on the product labeling.

Specimen Collection and Handling

EDTA plasma is the recommended sample type for this assay. Plastic blood collection tubes are recommended for sample collection, as BNP is unstable in glass containers. Use of glass tubes and transfer pipettes affects accurate quantitation of BNP.[39,40]

Collecting the Specimen

- Observe universal precautions when collecting specimens. Handle all specimens as if they are capable of transmitting disease.[41]
- Follow recommended procedures for collection of diagnostic blood specimens by venipuncture.[42]
- Follow the instructions provided with your specimen collection device for use and processing.[43]
- Allow blood specimens to clot completely before centrifugation.[44]
- Keep tubes capped at all times.[44]
- Collect blood samples in EDTA collection tubes and mix gently.
- For optimal recovery of BNP values, it is suggested that uncentrifuged whole blood samples be tested within 24 hours. The average percentage of BNP recovery in uncentrifuged whole blood after 24-hour storage at 2–8°C or room temperature was 96%.
- After centrifugation, store separated plasma samples at 2–8°C until testing.
- For optimal recovery of BNP values, it is suggested that plasma samples be tested within 24 hours. The average percentage of BNP recovery in EDTA plasma after 24-hour-storage at 2–8°C was 91%. It is recommended not to store EDTA-plasma at room temperature.

Storing the Specimen

- If plasma samples are not tested within 24 hours, store samples in plastic tubes and freeze at ≤ -20°C. Do not store in a frost-free freezer.
- Samples may undergo up to 4 freeze-thaw cycles without degradation. Samples are stable for up to 9 months when stored at ≤ -20°C.
- Mix samples thoroughly after thawing and store at 2–8°C until use. Samples should be tested within 8 hours after thawing.

The handling and storage information provided here is based on data or references maintained by the manufacturer. It is the responsibility of the individual laboratory to use all available references and/or its own studies when establishing alternate stability criteria to meet specific needs.

Transporting the Specimen

Package and label specimens for shipment in compliance with applicable federal and international regulations covering the transport of clinical specimens and etiological agents.

Preparing the Samples

This assay requires 100 µL of sample for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample. For information about determining the minimum required volume, refer to the online help.

Note Do not use specimens with apparent contamination.

Before placing samples on the system, ensure that samples are free of:

- Bubbles or foam.
- Fibrin or other particulate matter.

Note Remove particulates by centrifugation according to CLSI guidance and the collection device manufacturer's recommendations.[44]

Note For a complete list of appropriate sample containers, refer to the online help.

Procedure

Materials Provided

The following materials are provided:

REF	Contents	Number of Tests
10995471	1 ReadyPack primary reagent pack containing Atellica IM BNP Lite Reagent and Solid Phase Atellica IM BNP master curve and test definition MC TDEF	100
10995472	5 ReadyPack primary reagent packs containing Atellica IM BNP Lite Reagent and Solid Phase Atellica IM BNP master curve and test definition MC TDEF	500

Materials Required but Not Provided

The following materials are required to perform this assay, but are not provided:

REF	Description	
	Atellica IM Analyzer[a]	
10995473	Atellica IM BNP CAL (calibrator)	2 x 2.0 mL low calibrator CAL L 2 x 2.0 mL high calibrator CAL H Calibrator lot-specific value sheet CAL LOT VAL

[a] Additional system fluids are required to operate the system: Atellica IM Wash, Atellica IM Acid, Atellica IM Base, and Atellica IM Cleaner. For system fluid instructions for use, refer to the Document Library.

Optional Materials

The following materials may be used to perform this assay, but are not provided:

REF	Description	
10995475	Atellica IM BNP QC (quality control material)	3 x 2.0 mL quality control level 1 CONTROL 1 3 x 2.0 mL quality control level 2 CONTROL 2 3 x 2.0 mL quality control level 3 CONTROL 3 Quality control lot-specific value sheet CONTROL LOT VAL
10995474	Atellica IM BNP MCM (master curve material)	5 x 1.0 mL levels of master curve material MCM

Assay Procedure

The system automatically performs the following steps:

1. Dispenses 100 µL of sample into a cuvette.
2. Dispenses 100 µL of Lite Reagent, then incubates for 6 minutes at 37°C.
3. Dispenses 200 µL of Solid Phase, then incubates for 2 minutes at 37°C.
4. Separates, aspirates, then washes the cuvette with Atellica IM Wash.
5. Dispenses 300 µL each of Atellica IM Acid and Atellica IM Base to initiate the chemiluminescent reaction.
6. Reports results.

Preparing the Reagents

All reagents are liquid and ready to use. Before loading primary reagent packs onto the system, mix them by hand and visually inspect the bottom of the reagent pack to ensure that all particles are resuspended. For information about preparing the reagents for use, refer to the online help.

Preparing the System

Ensure that the system has sufficient reagent packs loaded in the reagent compartment. The system automatically mixes reagent packs to maintain homogeneous suspension of the reagents. For information about loading reagent packs, refer to the online help.

Master Curve Definition

Before initiating calibration on each new lot of reagent, load the assay master curve and test definition values by scanning the MC TDEF 2D barcodes. For loading instructions, refer to the online help.

Performing Calibration

For calibration of Atellica IM BNP assay, use the Atellica IM BNP CAL. Use the calibrators in accordance with the calibrator instructions for use.

Calibration Frequency

Perform a calibration if one or more of the following conditions exist:

- When changing lot numbers of primary reagent packs.
- At the end of the lot calibration interval, for a specified lot of calibrated reagent on the system.

- At the end of the pack calibration interval, for calibrated reagent packs on the system.
- When indicated by quality control results.
- After major maintenance or service, if indicated by quality control results.

At the end of the onboard stability interval, replace the reagent pack on the system with a new reagent pack. Recalibration is not required, unless the lot calibration interval is exceeded.

Stability Interval	Days
Lot Calibration	61
Pack Calibration	42
Reagent Onboard Stability	42

For information about lot calibration and pack calibration intervals, refer to the online help.

Follow government regulations or accreditation requirements for calibration frequency. Individual laboratory quality control programs and procedures may require more frequent calibration.

Performing Quality Control

For quality control of the Atellica IM BNP assay, use the Atellica IM BNP QC or an equivalent product at least once during each day that samples are analyzed.

For the assigned values, refer to the lot-specific value sheet CONTROL | LOT | VAL provided.

Additional quality control material can be used at the discretion of the laboratory. Use the quality control material in accordance with the quality control instructions for use.

In addition, perform quality control:

- Following a valid calibration
- With use of a new lot of reagent
- When troubleshooting test results that do not match clinical conditions or symptoms

Follow government regulations or accreditation requirements for quality control frequency. Individual laboratory quality control programs and procedures may require more frequent quality control testing.

Acceptable performance is achieved when the analyte values obtained are within the expected control interval for the system, as indicated by the manufacturer of the control material or within the interval determined by an internal laboratory quality control procedure.

Follow your laboratory's quality control procedures if the results obtained do not fall within the acceptable limits. For information about entering quality control definitions, refer to the system online help.

Taking Corrective Action

If the quality control results do not fall within the assigned values, do not report results. Perform corrective actions in accordance with established laboratory protocol. For suggested protocol, refer to the online help.

Results

Calculation of Results

The system determines the result using the calculation scheme described in the online help. The system reports assay results in pg/mL (common units) or pmol/L (SI units), depending on the units defined when setting up the assay.

Conversion formula: 1.0 pg/mL (common units) = 0.289 pmol/L (SI units)

For information about results outside the specified measuring interval, refer to *Measuring Interval*.

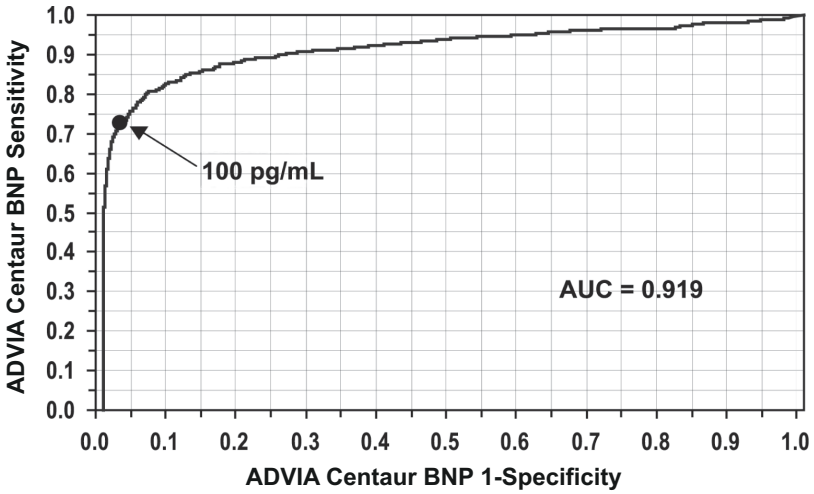
Interpretation of Results

The reagent formulations used on the Atellica IM Analyzer are the same as those used on the ADVIA Centaur system. The data shown below was generated using the ADVIA Centaur system.

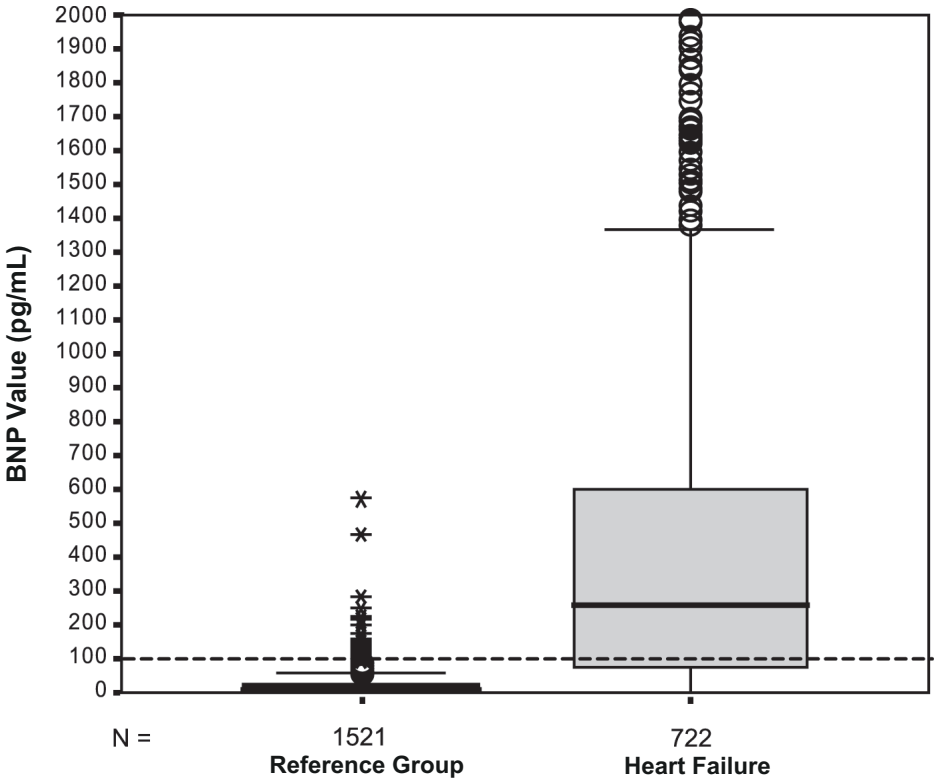
The receiver operating characteristic (ROC) curve compares clinical sensitivity and specificity at various decision thresholds. The ROC analysis is presented in the following figure. The area under the curve (AUC) is 0.919 with a 95% confidence interval (CI) of 0.904–0.934.

ROC Curve

Reference Group (n = 1521) vs. Heart Failure Population (n = 722)



A box and whisker plot for the clinical study population is also presented below, with a horizontal dashed line representing the suggested decision threshold of 100 pg/mL.



Results of this assay should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Limitations

The following information pertains to limitations of the assay:

- This test has been evaluated with plasma using EDTA as the anticoagulant. Serum, sodium citrate, lithium heparin, and sodium fluoride sample tubes have also been tested and are not recommended.
- Atellica IM BNP test results should not be used interchangeably with other manufacturers' BNP assays, nor should Atellica IM BNP test results be used interchangeably with NT-proBNP assay results.
- Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay is designed to minimize interference from heterophilic antibodies.[45,46]

Expected Values

The reagent formulations used on the Atellica IM Analyzer are the same as those used on the ADVIA Centaur system. Expected values were established using the ADVIA Centaur system and confirmed by assay comparison. Refer to *Assay Comparison*.

BNP concentrations in the Reference Group are shown in the tables below. The decision threshold for diagnosing heart failure was determined based on the BNP level at the 95th percentile of the Reference Group. The most appropriate decision threshold for determining heart failure apparent from these distributions is 100 pg/mL. This BNP value translates into a general specificity of the test of > 97%.

The decision threshold for predicting survival and future heart failure in patients with acute coronary syndromes is 80 pg/mL.

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference interval for the diagnostic evaluation of patient results.[47] Consider these values as guidance only.

Reference Group

To establish the expected results, the circulating BNP concentration was determined from 1521 individuals without heart failure (736 men and 785 women). This population included apparently healthy individuals and individuals with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. The descriptive statistics for BNP concentrations in the population without heart failure are shown in the following tables. These values are representative of the results obtained from clinical studies. Published research indicates that BNP levels increase with age in the general population, with the highest values seen in individuals > 75 years of age.[48] In this subgroup of patients, age should be taken into consideration for accurate interpretation of test results.

Reference Group: All

	Age Group					
	All	**< 45 years**	**45–54 years**	**55–64 years**	**65–74 years**	**75+ years**
Mean, pg/mL	23.2	11.9	15.6	19.5	28.3	60.3
SD, pg/mL	32.5	12.9	15.9	22.6	25.4	73.0
Median, pg/mL	14.4	8.6	10.4	13.8	22.1	43.7
95th Percentile, pg/mL	70.8	33.3	46.7	53.2	72.3	176
% < 100 pg/mL	97.4	99.7	99.7	98.8	97.0	85.5
Minimum, pg/mL	< 2	< 2	< 2	< 2	< 2	< 2
Maximum, pg/mL	576	128	119	286	164	576
Number of samples	1521	317	291	403	365	145

Reference Group: Males

	Age Group					
	All	**< 45 years**	**45–54 years**	**55–64 years**	**65–74 years**	**75+ years**
Mean, pg/mL	17.9	9.1	11.2	14.5	25.8	41.9
SD, pg/mL	22.9	9.4	11.8	13.9	25.1	48.8
Median, pg/mL	11.3	5.9	7.6	11.9	17.8	26.1
95th Percentile, pg/mL	54.3	29.4	32.8	38.8	67.6	121
% < 100 pg/mL	98.6	100	100	99.5	96.8	94.6
Minimum, pg/mL	< 2	< 2	< 2	< 2	< 2	< 2
Maximum, pg/mL	250	56.6	88.9	132	151	250
Number of samples	736	129	140	223	188	56

Reference Group: Females

	Age Group					
	All	**< 45 years**	**45–54 years**	**55–64 years**	**65–74 years**	**75+ years**
Mean, pg/mL	28.1	13.8	19.8	25.6	31.0	71.9
SD, pg/mL	38.8	14.6	18.0	29.0	25.5	82.9
Median, pg/mL	18.5	10.4	14.8	19.4	25.7	54.3
95th Percentile, pg/mL	86.1	35.9	56.7	75.5	72.9	167
% < 100 pg/mL	96.3	99.5	99.3	97.8	97.1	79.8
Minimum, pg/mL	< 2	< 2	< 2	< 2	< 2	< 2
Maximum, pg/mL	576	128	119	286	164	576
Number of samples	785	188	151	180	177	89

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Patients with Heart Failure

To establish the expected results in individuals with heart failure, plasma samples were obtained from 722 patients diagnosed with heart failure (264 women and 458 men). The descriptive statistics for BNP concentrations in patients with heart failure are presented in the following tables. These values are representative of the results obtained from clinical studies. In addition, laboratories should be aware of their respective institution's current practice for the evaluation of heart failure.

Heart Failure Population: All

	NYHA Functional Class				
	All	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**
Mean, pg/mL	505	178	270	525	1134
SD, pg/mL	711	347	402	576	1141
Median, pg/mL	262	64.3	130	355	843
5th percentile, pg/mL	10.8	1.6	5.4	21.1	109
95th percentile, pg/mL	1873	772	999	1696	3157
% ≥ 100 pg/mL	72.6	43.1	58.7	82.0	95.8
Minimum, pg/mL	< 2	< 2	< 2	< 2	4.0
Maximum, pg/mL	6989	2310	3107	4052	6989
Number of samples	722	72	242	289	119

Heart Failure Population: Males

	NYHA Functional Class				
	All	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**
Mean, pg/mL	518	121	308	542	1214
SD, pg/mL	726	135	475	588	1200
Median, pg/mL	245	77.7	135	339	950
5th percentile, pg/mL	10.7	3.9	4.4	23.2	71.5
95th percentile, pg/mL	1946	400	1280	1852	3157
% ≥ 100 pg/mL	72.9	44.7	61.3	81.4	93.9
Minimum, pg/mL	< 2	< 2	< 2	< 2	33.7
Maximum, pg/mL	6989	552	3107	3503	6989
Number of samples	458	47	150	194	66

Heart Failure Population: Females

	NYHA Functional Class				
	All	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**
Mean, pg/mL	482	285	207	492	1034
SD, pg/mL	687	551	228	556	1068
Median, pg/mL	291	62.5	117	355	779
5th percentile, pg/mL	11.0	0	9.5	15.9	115
95th percentile, pg/mL	1575	1447	552	1518	2970
% ≥ 100 pg/mL	72.0	40.0	54.3	83.2	98.1
Minimum, pg/mL	< 2	< 2	< 2	4.8	4.0
Maximum, pg/mL	5845	2310	1231	4052	5845
Number of samples	264	25	92	94	53

These results show that there is a relationship between the severity of the clinical signs and symptoms of heart failure and the median BNP concentrations of each NYHA functional class. The proportional increase in BNP concentration is greater than 2-fold as heart failure severity increases from Class I to II, II to III, and III to IV. Siemens' BNP test results should not be used interchangeably with other manufacturers' BNP assays, nor should Siemens' BNP test results be used interchangeably with NT-proBNP assay results.

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Performance Characteristics

The reagent formulations used on the Atellica IM Analyzer are the same as those used on the ADVIA Centaur system. Some performance characteristics for the Atellica IM assay were established using the ADVIA Centaur system.

Measuring Interval

The Atellica IM BNP assay provides results from 2.0–5000.0 pg/mL (0.58–1445.00 pmol/L). The lower end of the measuring interval is defined by the design requirement for the analytical sensitivity. Report results below the measuring interval as < 2.0 pg/mL (0.58 pmol/L).

Specificity

Cross-reactivity was determined in accordance with CLSI Document EP7-A2[49] by spiking each of the following compounds into a plasma sample with known BNP concentration.

$$\% \text{ cross-reactivity} = \frac{(\text{concentration of spiked sample - concentration of unspiked sample})}{(\text{concentration of compound added})} \times 100$$

Compound	Concentration Added	Percent Cross-Reactivity
Alpha-ANP (1-28)	1000 pg/mL	ND[a]
NT-proBNP (1-21)	1000 pg/mL	ND
NT-proBNP (1-46)	1000 pg/mL	ND
NT-proBNP (1-76)	1000 pg/mL	ND
NT-proBNP (22-46)	1000 pg/mL	ND
NT-proBNP (47-76)	1000 pg/mL	ND
CNP (7-28)	1000 pg/mL	ND
DNP	1000 pg/mL	ND
VNP	1000 pg/mL	ND
Adrenomedullin	1000 pg/mL	ND
Aldosterone	1000 ng/mL	ND
Angiotensin I	600 pg/mL	ND
Angiotensin II	600 pg/mL	ND
Angiotensin III	1000 pg/mL	ND
Arg-Vasopressin	1000 pg/mL	ND
Renin	50 ng/mL	ND
Urodilatin	1000 pg/mL	ND

[a] Not detectable.

Results were established using the ADVIA Centaur system.

Detection Capability

Detection capability was determined in accordance with CLSI Document EP17-A2.[50] The assay is designed to have an analytical sensitivity < 2.0 pg/mL (0.58 pmol/L), functional sensitivity < 4.0 pg/mL (1.16 pmol/L), a limit of blank (LoB) < 2.0 pg/mL (0.58 pmol/L) and limit of detection (LoD) < 4.0 pg/mL (1.16 pmol/L).

Representative detection capability data are shown below. Assay results obtained at individual laboratories may vary from the data presented.

Analytical sensitivity is defined as the concentration of BNP that corresponds to the RLUs that are 2 standard deviations more than the mean RLUs of 20 replicate determinations of the BNP zero standard. This response is an estimate of the minimum detectable concentration with 95% confidence. The analytical sensitivity for the Atellica IM BNP assay is 1.4 pg/mL (0.40 pmol/L).

The LoB corresponds to the highest measurement result that is likely to be observed for a blank sample. The LoB of the Atellica IM BNP assay is 1.1 pg/mL (0.32 pmol/L).

The LoD corresponds to the lowest concentration of BNP that can be detected with a probability of 95%. The LoD for the Atellica IM BNP assay is 2.4 pg/mL (0.69 pmol/L), and was determined using 420 determinations, with 350 blank and 70 low-level replicates, and an LoB of 1.1 pg/mL (0.32 pmol/L).

Functional sensitivity corresponds to the lowest amount of analyte in a sample at which the within-laboratory CV is ≤ 20%. The functional sensitivity of the Atellica IM BNP assay is < 1.5 pg/mL (0.43 pmol/L), and was determined using multiple patient samples in the interval 0.1–11 pg/mL (0.03–3.18 pmol/L). All samples were assayed in duplicate in each of 2 runs per day using 1 reagent lot, over a period of 20 days.

Clinical Sensitivity and Specificity

The clinical sensitivity and specificity were determined using a decision threshold of 100 pg/mL (29 pmol/L) for various age groups within each gender are presented in the following tables.

Clinical Sensitivity and Specificity vs. Age and Gender

Males

	Age Group				
	< 45 years	**45–54 years**	**55–64 years**	**65–74 years**	**75+ years**
% Sensitivity	58.7% (37/63)	49.2% (31/63)	69.9% (86/123)	83.7% (87/104)	88.6% (93/105)
95% Confidence Interval	40.4–71.0	36.4–62.1	61.0–77.9	75.1–90.2	80.9–93.9
% Specificity	100% (129/129)	100% (140/140)	99.5% (222/223)	96.8% (182/188)	94.6% (53/56)
95% Confidence Interval	97.2–100	97.4–100	97.6–100	93.2–98.8	85.1–98.9

Females

	Age Group				
	< 45 years	**45–54 years**	**55–64 years**	**65–74 years**	**75+ years**
% Sensitivity	45.5% (10/22)	56.3% (18/32)	60.4% (29/48)	68.9% (31/45)	87.2% (102/117)
95% Confidence Interval	24.4–67.8	37.7–73.7	45.3–74.2	53.4–81.8	79.7–92.6
% Specificity	99.5% (187/188)	99.3% (150/151)	97.8% (176/180)	97.2% (172/177)	79.8% (71/89)
95% Confidence Interval	97.1–100	96.4–100	94.4–99.4	93.5–99.0	69.9–87.6

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Prognostic Utility in Patients with Acute Coronary Syndromes

Two independent retrospective studies have demonstrated the prognostic utility of BNP in patients with ACS.

In the first study, BNP was assayed on 438 patients with myocardial infarction (MI) from the ENTIRE-TIMI 23 multi-national trial.[51] The baseline BNP level was significantly higher in patients who died within 30 days (n = 15, 89 pg/mL; 25th–75th, 40–192 pg/mL) compared to survivors (n = 423, 15 pg/mL; 25th–75th, 8.8–32 pg/mL, $p < 0.0001$). BNP levels > 80 pg/mL were associated with a substantially higher risk of death through 30 days of follow-up (17.4% vs. 1.8%, $p < 0.0001$). The odds ratio for death within 30 days for patients with BNP levels > 80 pg/mL was 11.5. The odds ratio for death within 30 days for patients with BNP levels > 80 pg/mL, adjusted for age, history of hypertension, and prior angina, was 8.3 with a 95% confidence interval of 2.7–25.8. Patients with elevated BNP levels also had an increased risk of composite end points for death and heart failure combined (23.9% vs. 5.1%, $p < 0.0001$). The odds ratio for death or heart failure within 30 days for patients with BNP levels > 80 pg/mL was 5.8. The odds ratio for death or heart failure within 30 days for patients with BNP levels > 80 pg/mL, adjusted for age, history of heart failure, history of hypertension, and prior angina, was 3.6 with a 95% confidence interval of 1.5–8.8. Elevated levels of BNP at initial presentation are associated with an increased risk of mortality in patients with MI.[34]

Another study was performed on 2525 patients with acute coronary syndromes. Patients with a BNP level of > 80 pg/mL were significantly more likely to die, have a new recurrent infarction, or have new or progressive heart failure than those with a level of ≤ 80 pg/mL. After adjustment for other independent predictors of the long-term risk of death, a BNP level of > 80 pg/mL remained significantly associated with an increased 10-month mortality rate ($p = 0.04$).[32]

Analytical Comparison and Clinical Agreement

A paired comparison was performed at 2 clinical trial sites to assess the relationship of the ADVIA Centaur BNP assay to the predicate device. A total of 167 patients with heart failure (HF; clinical diagnoses of Class I–IV) and 20 individuals without heart failure (non-HF) were compared for both analytical and clinical agreement at a decision threshold of 100 pg/mL.

Analytical Comparison of the ADVIA Centaur vs. Predicate Device

		Predicate Device		
		≥ 100 pg/mL	**< 100 pg/mL**	**Total**
ADVIA Centaur	≥ 100 pg/mL	145	4	149
	< 100 pg/mL	6	32	38
	Total	151	36	187

	Estimate	**95% Confidence Interval**
% Analytical Agreement	94.7% (177/187)	90.4%–97.4%

Clinical Agreement of the ADVIA Centaur BNP

		Clinical Status		
		HF	**Non-HF**	**Total**
ADVIA Centaur	≥ 100 pg/mL	146	3	149
	< 100 pg/mL	21	17	38
	Total	167	20	187

	Estimate	**95% Confidence Interval**
% Clinical Agreement	87.2% (163/187)	81.5%–91.6%
% Sensitivity	87.4% (146/167)	81.4%–92.0%
% Specificity	85.0% (17/20)	62.1%–96.8%

Clinical Agreement of the Predicate Device

		Clinical Status		
		HF	**Non-HF**	**Total**
Predicate Device	≥ 100 pg/mL	146	5	151
	< 100 pg/mL	21	15	36
	Total	167	20	187

	Estimate	**95% Confidence Interval**
% Clinical Agreement	86.1% (161/187)	80.3%–90.7%
% Sensitivity	87.4% (146/167)	81.4%–92.0%
% Specificity	75.0% (15/20)	50.9%–91.3%

Assay results obtained at individual laboratories may vary from the data presented.

Age-Matched Analysis

An age-matched analysis of the clinical data was performed with the following common age distribution in the groups of individuals with and without heart failure.

Individuals < 45 years old comprise 9% of the total number of observations, individuals 45–54 years old comprise 11% of the total, individuals 55–64 years old comprise 22% of the total, individuals 65–74 years old comprise 26% of the total, and individuals ≥ 75 years old comprise 32% of the total. This age distribution reflects the prevalence of heart failure within the age groups, according to data published by the American Heart Association in the *2000 Heart and Stroke Statistical Update*, and also reflects the age structure of the United States population, according to data published by the National Center for Health Statistics in *Health, United States, 2000*. The resulting area under the ROC curve is 0.906 with a 95% confidence interval of 0.886–0.927. The AUC is not significantly different from the AUC described previously (0.919).

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Precision

Precision was determined in accordance with CLSI Document EP05-A3.[52] Samples were assayed on an Atellica IM Analyzer in duplicate in 2 runs per day for 20 days. The assay was designed to have within-laboratory precision of ≤ 0.9 SD for samples < 10.0 pg/mL (2.89 pmol/L), ≤ 9% CV for samples from 10.0–49.0 pg/mL (2.89–14.2 pmol/L), and ≤ 7% CV for samples from 50.0–5000.0 pg/mL (14.45–144.50 pmol/L). The following results were obtained:

		Mean		Repeatability			Within-Laboratory Precision		
				SD[b]		CV[c]	SD		CV
Sample Type	N[a]	(pg/mL)	(pmol/L)	(pg/mL)	(pmol/L)	(%)	(pg/mL)	(pmol/L)	(%)
EDTA Plasma A	80	9.2	2.7	0.30	0.09	3.7	0.40	0.12	4.5
EDTA Plasma B	80	12.2	3.5	0.30	0.09	2.6	0.40	0.12	3.5
EDTA Plasma C	80	36.2	10.5	0.70	0.20	1.9	1.10	0.32	3.2
EDTA Plasma D	80	654.6	189.2	12.00	3.47	1.8	18.30	5.29	2.8
EDTA Plasma E	80	1523.7	440.3	19.50	5.64	1.3	34.50	9.97	2.3
EDTA Plasma F	80	4325.2	1250.0	64.20	18.55	1.5	107.60	31.10	2.5
Control 1	80	95.7	27.7	1.50	0.43	1.6	2.30	0.66	2.4
Control 2	80	392.3	113.4	4.90	1.42	1.3	7.90	2.28	2.0
Control 3	80	1485.9	429.4	18.50	5.35	1.2	29.40	8.50	2.0

[a] Number of samples tested.
[b] Standard deviation.
[c] Coefficient of variation.

Assay results obtained at individual laboratories may vary from the data presented.

Assay Comparison

The Atellica IM BNP assay is designed to have a correlation coefficient of ≥ 0.95 and a slope of 1.0 ± 0.20 compared to the ADVIA Centaur BNP assay. Assay comparison was determined using the Weighted Deming regression model in accordance with CLSI Document EP09-A3.[53] The following results were obtained:

Specimen	Comparative Assay (x)	Regression Equation	Sample Interval	N[a]	r[b]
EDTA Plasma	ADVIA Centaur BNP	y = 0.965x - 0.3 pg/mL (y = 0.965x - 0.091 pmol/L)	2.6–4962.8 pg/mL (0.75–1434.25 pmol/L)	177	0.997

[a] Number of samples tested.
[b] Correlation coefficient.

Agreement of the assays may vary depending on the study design, comparative assay, and sample population used. Assay results obtained at individual laboratories may vary from the data presented.

Interferences

Interference testing was performed in accordance with CLSI Document EP7-A2.[49]

The following drugs were added to a human plasma-based sample at 2 times the maximum therapeutic dosage and evaluated for potential interference. The results demonstrated a ≤ 10% interference from each drug at the following concentrations.

Drug	Drug Concentration	Drug	Drug Concentration
Acetaminophen	12 µg/mL	Indomethacin	16 µg/mL
Acetylsalicylic acid	200 µg/mL	Isosorbide dinitrate	4 µg/mL
Allopurinol	240 µg/mL	Lisinopril	16 µg/mL
Amiodarone	20 µg/mL	Lovastatin	16 µg/mL
Ampicillin	200 µg/mL	L-thyroxine	46 pg/mL
Ascorbic acid	24 µg/mL	Methyldopa	100 µg/mL
Amlodipine besylate	4 µg/mL	Milrinone lactate	2.4 µg/mL
Atenolol	40 µg/mL	Nicotine	1.6 µg/mL
Atorvastatin	32 µg/mL	Nicotinic acid	40 µg/mL
Caffeine	30 µg/mL	Nitrofurantoin	40 µg/mL
Captopril	40 µg/mL	Nitroglycerin	0.16 µg/mL
Chloramphenicol	50 µg/mL	Oxazepam	12 µg/mL
Clopidogrel Bisulfate	30 µg/mL	Oxytetracycline	100 µg/mL
Creatinine	110 µg/mL	Phenobarbital	40 µg/mL
Cyclosporine	40 µg/mL	Phenytoin	40 µg/mL
Diclofenac	60 µg/mL	Probenecid	200 µg/mL
Digitoxin	60 ng/mL	Procainamide	20 µg/mL
Digoxin	4 ng/mL	Propranolol	64 µg/mL
Diltiazem	120 µg/mL	Quinidine	20 µg/mL
Dipyridamole	30 µg/mL	Simvastatin	32 µg/mL
Dopamine HCl	116 pg/mL	Spironolactone	40 µg/mL
Enalapril Maleate	16 µg/mL	Sulfamethoxazole	320 µg/mL
Erythromycin	100 µg/mL	Theophylline	40 µg/mL
Furosemide	16 µg/mL	Trimethoprim	64 µg/mL
Heparin	8 U/mL	Verapamil	96 µg/mL
Hydralazine	20 µg/mL	Warfarin	4 µg/mL
Hydrochlorothiazide	20 µg/mL		

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Hemolysis, Icterus, Lipemia (HIL), and Other Interferences

Specimens that are . . .	Demonstrate ≤ 5% change in results up to . . .
icteric	25 mg/dL of unconjugated bilirubin
lipemic	800 mg/dL of triglycerides 1000 mg/dL of cholesterol
uremic	200 mg/dL of urea 2.5 mg/dL of creatinine

Specimens that are . . .	Demonstrate ≤ 7% change in results up to . . .
icteric	25 mg/dL of conjugated bilirubin
proteinemic	5.3 g/dL of human IgG

Specimens that are or that contain . . .	Demonstrate ≤ 10% change in results up to . . .
hemolyzed	100 mg/dL of hemoglobin
biotin	38 ng/mL of biotin

Analyte Concentration (pg/mL)	Biotin Test Level (ng/mL)							
	27	55	110	219	439	878	1755	3510
	% Bias							
50	-6%	-11%	-12%	-10%	-11%	-12%	-11%	-12%
450	-7%	-2%	-9%	-6%	-6%	-5%	-8%	-11%
1800	-3%	-4%	-5%	-6%	-5%	-5%	-8%	-8%

Specimens that contain biotin at a concentration of 38 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples.

The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin, and nail health may contain 5–100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively.[54] Subjects who take up to 300 mg of biotin per day may have plasma biotin levels as high as 1160 ng/mL.[55]

Results were established using the ADVIA Centaur system, except for biotin which were established using an Atellica IM Analyzer. Assay results obtained at individual laboratories may vary from the data presented.

High-Dose Hook Effect

Patient samples with high BNP concentrations can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, patient samples with BNP concentrations as high as 100,000 pg/mL (28,900 pmol/L) will report > 5000.0 pg/mL (1445.00 pmol/L). Results were established using the Atellica IM Analyzer.

Standardization

The Atellica IM BNP assay is traceable to an internal standard manufactured using synthetic human BNP (amino acid 77–108). Assigned values for calibrators and controls are traceable to this standardization.

Technical Assistance

For customer support, contact your local technical support provider or distributor.

siemens-healthineers.com

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Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Symbol Title	Source	Symbol	Symbol Title	Source
	Manufacturer	5.1.1[a]	EC REP	Authorized representative in the European Community	5.1.2[a]
	Use-by date	5.1.4[a]	CH REP	Authorized representative in Switzerland	Proprietary
REF	Catalog number	5.1.6[a]	LOT	Batch code	5.1.5[a]
	Consult Instructions for Use	5.4.3[a]	Σ	Contains sufficient for <n> tests	5.5.5[a]
< .../eifu >	Internet URL address to access the electronic instructions for use	Proprietary	Rev. XX	Version of Instructions for Use	Proprietary
IVD	*In vitro* diagnostic medical device	5.5.1[a]	Rev. REVISION	Revision	Proprietary
RxOnly	Prescription device (US only)	FDA[b]	UDI	Unique Device Identifier	5.7.10[c]
CE XXXX	CE Marking with Notified Body	EU IVDR[d]	CE	CE Marking	EU IVDR[d]
	Temperature limit	5.3.7[a]		Keep away from sunlight	5.3.2[a]
	Upper limit of temperature	5.3.6[a]		Lower limit of temperature	5.3.5[a]

Symbol	Symbol Title	Source	Symbol	Symbol Title	Source
	Do not re-use	5.4.2[a]		Do not freeze	Proprietary
	Recycle	1135[e]		This way up	0623[e]
	Biological risks	5.4.1[a]		Caution	5.4.4[a]
UNITS C	Common Units	Proprietary	UNITS SI	International System of Units	Proprietary
YYYY-MM-DD	Date format (year-month-day)	N/A	YYYY-MM	Date format (year-month)	N/A
	Document face up[f]	1952[e]		Handheld barcode scanner	Proprietary
	Target	Proprietary		Mixing of substances	5657[g]
CHECKSUM	Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.	Proprietary		Interval	Proprietary
MATERIAL ID	Unique material identification number	Proprietary	MATERIAL	Material	Proprietary
CONTROL TYPE	Type of control	Proprietary	CONTROL NAME	Name of control	Proprietary
CONTROL LOT VAL	Quality control lot value	Proprietary	CAL LOT VAL	Calibrator lot value	Proprietary

[a] International Standard Organization (ISO). ISO 15223-1 Medical Devices- Symbols to be used with medical device labels, labelling and information to be supplied.
[b] Federal Register. Vol. 81, No 115. Wednesday, June 15, 2016. Rules and Regulations: 38911.
[c] ISO 15223-1:2020-04
[d] IVDR REGULATION (EU) 2017/746
[e] International Standard Organization (ISO). ISO 7000 Graphical symbols for use on equipment.
[f] Indicates Assay-eNote
[g] International Electrotechnical Commission (IEC). IEC 60417-1 Graphical symbols for use on equipment – Part 1: Overview and Application

Legal Information

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