RESPONSE BIOMEDICAL

INSTRUCTIONS FOR USE

C1105-1.7

RAMP® NT-proBNP

FOR SALE IN THE USA ONLY

WARNING!

For *in vitro* diagnotic use only

Failure to follow RAMP® test procedures may result in invalid and/or erroneous results. Read the entire Instructions For Use prior to performing test.

INTENDED USE

The RAMP® NT-proBNP test is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in EDTA whole blood. Measurement of NT-proBNP aids in the diagnosis and assessment of severity in individuals suspected of having heart failure and may aid in the risk stratification of patients with heart failure.

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IVD

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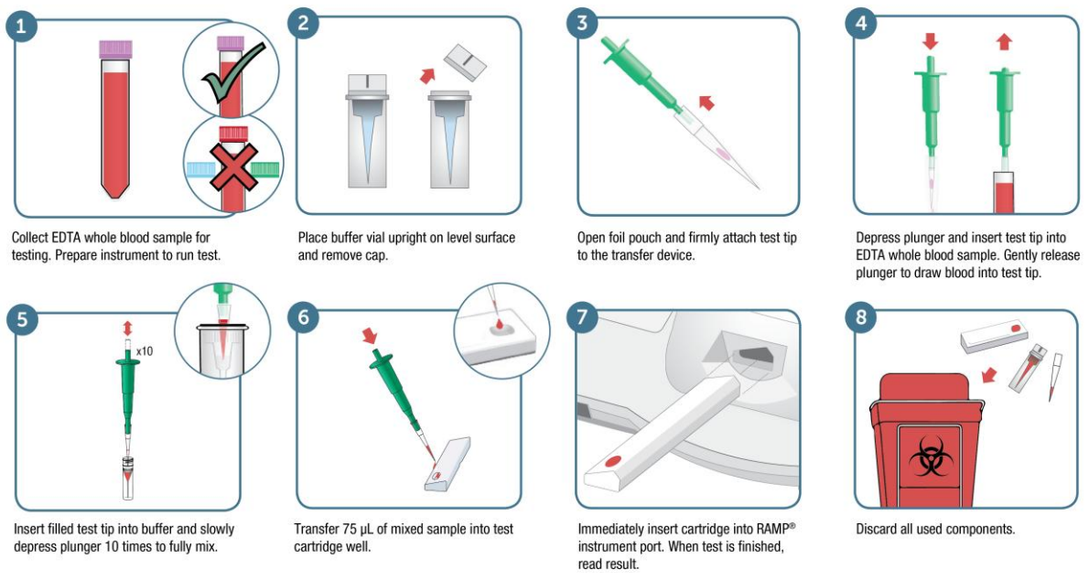
Running a test



SUMMARY AND EXPLANATION

Heart failure (HF) is a chronic, progressive disease in which the heart muscle weakens and its function becomes impaired, thus impeding the heart's ability to pump enough blood to support the body's metabolic demands. When cardiac muscle is stretched, such as with elevated ventricular filling pressure, the inactive prohormone B-type natriuretic peptide (proBNP) is released and rapidly cleaved into physiologically active BNP and the N-terminal fragment NT-proBNP [1]. Natriuretic peptides can be used for the diagnosis of clinical problems associated with left ventricular dysfunction [2]. The advent of testing for BNPs has improved the ability of physicians to make a qualified diagnosis of heart failure and to monitor the success of treatment [3]. Being able to test the levels of NT-proBNP in patient blood samples is very useful as these levels are indicative of the degree of HF, and when combined with clinical judgment they provide superior diagnostic performance than clinical judgment alone [4,5]. NT-proBNP has been used for risk stratification of patients with acute coronary syndrome and HF [6-8]. It has also been shown to aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for HF who have stable coronary artery disease [9-11].

Point-of-care (POC) or "near-patient" testing allows for diagnostic assays to be performed at the site of patient care delivery such as the emergency room (ER), chest pain evaluation center, or intensive care unit (ICU). Compared with centralized laboratory testing, POC testing provides for rapid clinical decision making by reducing the time spent ordering tests, collecting and transporting samples, as well as retrieving data.

TEST PRINCIPLE

The RAMP® NT-proBNP test is a quantitative immunochromatographic test for the determination of NT-proBNP in EDTA whole blood. The EDTA whole blood is mixed with buffer and antibody-coated, labeled particles, and applied into the sample well of the test cartridge. The red blood cells are retained in the sample pad and the separated plasma migrates along the strip. Fluorescent-dyed particles coated with anti-NT-proBNP antibodies bind to NT-proBNP, if present in the sample. As the sample migrates along the strip, NT-proBNP bound particles are captured at the detection zone and excess fluorescent-dyed particles are captured at the control zone.

The RAMP® instrument then measures the amount of fluorescence emitted by the complexes bound at the detection zone and at the control zone. Using a ratio between the two fluorescence values, a quantitative reading is calculated. For further information on the use of the instrument, refer to the RAMP® Operator's Manual.

REAGENTS

- The RAMP® test kit contains all the reagents necessary for the quantification of NT-proBNP in EDTA whole blood.
- The sample buffer contains phosphate buffer, animal protein, surfactant, and ProClin® 300 / ProClin® 900 as preservatives.

WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use. The RAMP® NT-proBNP test must be operated in a laboratory setting when used with the RAMP® 200.
- For use by qualified personnel per local, state, or Federal regulations or accrediting agency requirements.
- Read the entire instructions for use (IFU) prior to use. Directions should be read and followed carefully, or invalid or erroneous results may occur.
- Do not interchange or mix components of different RAMP® tests, lots or components from other manufacturers.
- Do not use the kit or any kit component beyond the stated expiry date.
- Do not use any visibly damaged components.
- Do not insert a cartridge on which blood or any other fluid is spilled, into the instrument.
- Disposal of all waste materials should be in accordance with local guidelines.
- Exercise standard precautions required for handling all laboratory reagents and patient samples.
- The device contains material of animal origin and should be handled as a potential biohazard.
- The sample buffer provided contains ProClin®, a potential skin sensitizer. Avoid spilling or splashing reagents containing ProClin® on skin or clothing. In case of contact, thoroughly flush with water.

STORAGE AND STABILITY

Store at 2 to 8°C (35 to 46°F). Do not freeze.

Stability

Unopened at 2 to 8°C (35 to 46°F)	Up to the stated expiration date
When stored at 15 to 25°C (59 to 77°F)	14 days

SAMPLE COLLECTION & PREPARATION

- Use ONLY EDTA Whole Blood (Plastic K_2EDTA tubes are recommended). Other sample types and anticoagulants have not been evaluated.
- Avoid blood samples that show gross hemolysis as these may interfere with the test and cause erroneous results. If this occurs, another blood sample should be obtained and tested.
- Testing must be completed within 2 hours of phlebotomy. However, if this is not possible, the EDTA whole blood can be stored for up to 2 days at 2 to 8°C. If stored, allow blood samples to equilibrate to 18 to 25°C for at least 15 minutes prior to use.

MATERIALS PROVIDED

- 25 pouches, each containing 1 RAMP® test cartridge and 1 test tip
- 25 RAMP® buffer vials
- 1 transfer device for 75 µL
- 1 lot card
- 1 instructions for use (IFU)

MATERIALS REQUIRED (BUT NOT PROVIDED)

- REF: C1100 RAMP® Reader instrument; or
- REF: C2100 RAMP® 200 instrument control module, and
  REF: C3100 RAMP® 200 instrument test module
- REF: C2003 RAMP® Cardiac Controls (optional)
- Optional accessories such as RAMP® printer and/or barcode scanner
- Specimen collection tubes: EDTA (Venous Whole Blood)

Use only the listed RAMP® instruments with this test.

LOT CARD CALIBRATION

Each RAMP® test kit includes a lot card that is individually packaged in an anti-static pouch. The lot card provides information specific to the kit test cartridge lot, including lot number, expiration date, and standard curve information. For further details on loading lot-specific information, see the RAMP® instrument Operator's Manual. No additional calibration beyond insertion of the lot card is necessary. This operation is required only once per test kit lot.

For each new lot, remove the lot card from its pouch and insert it into the lot card slot on the instrument. Once the lot card has been uploaded, return to its pouch and do not discard. Avoid touching the contacts at the end of the lot card.

PROCEDURE

Prior to sample preparation allow all components to come to room temperature for at least 15 minutes.

- Keep the test cartridge and test tip in the sealed foil pouch until ready for use. Once opened, test cartridges and test tips must be used or discarded within 60 minutes.
- The test cartridge, test tip, and buffer vial should be discarded after a single-use. Do not reuse.

1. Prepare RAMP® instrument for test cartridge. Refer to the RAMP® Operator's Manual for detailed instructions on Starting a Test.
2. Ensure that the EDTA whole blood sample is well mixed by gentle inversion.
3. Uncap the buffer vial and place upright on a clean, dry level surface, or in a holder.
4. Open a test pouch and remove the test cartridge and tip. Place the test cartridge on a clean, level surface. Firmly attach the test tip to the supplied transfer device.
5. Before inserting the test tip into the sample, fully depress the transfer device plunger.
6. Insert tip into sample and fully release plunger. The test tip should fill with 75 µL of blood.
7. Immediately transfer the filled test tip into the buffer vial close to, but not touching, the bottom.
8. Mix sample slowly by fully pressing and releasing the plunger 10 times; while keeping the tip submerged in the buffer for optimal mixing and to minimize air bubbles.
9. Once mixing is complete, draw 75 µL of sample into the test tip by releasing the plunger one final time and immediately dispense liquid into the sample well of the test cartridge. Small droplets may remain in the tip; this is expected.
10. Immediately insert the test cartridge fully into the instrument and press until firm resistance is felt.
11. The instrument will draw the cartridge in and test development will begin.
12. The instrument will analyze the cartridge and report the result in approximately 15 minutes.
13. Record the result, if required. For additional information on printing and/or uploading results, please refer to the Operator's Manual.
14. Remove the used test cartridge and discard all used test components according to local biohazard procedures. DO NOT reuse.

For additional information on the general operation and troubleshooting of the instrument, please refer to the RAMP® Operator's Manual.

QUALITY CONTROL

Refer to the RAMP® Operator's Manual for full details on quality control operation and troubleshooting.

SYSTEM QUALITY CONTROL

The RAMP® instrument has error checking and self-diagnostic functions (Internal Quality Control (IQC)) that assure system integrity. These include algorithms and measurements used to confirm acceptable operator technique, sample handling, and test performance. Frequency of IQC may be programmed at desired intervals.

Valid results are displayed only after all performance requirements have been met.

PROCEDURAL CONTROLS

- Each RAMP® test has built-in controls. Test cartridges have a control zone that is scanned as part of the test protocol to ensure proper sample flow.
- Control limits for each lot of test cartridges are established during the manufacturing process and are incorporated in the test-specific lot parameters. If a control result does not meet specifications, the sample result is not reported and a message is displayed.

LIQUID QUALITY CONTROL (LQC)

- It is recommended that quality control materials be run with the RAMP® test in conformance with Federal, state and local requirements for quality control testing.
- While the running of commercial control materials are recommended, it is not a requirement to use, or assure, performance of the RAMP® test unless specified by local regulations or institutional requirements.
- To run a LQC sample, follow the instructions under the "Procedure" section in this IFU. Treat the control as a whole blood sample.

TEST RUN MESSAGES

When the RAMP® instrument is unable to continue a specific task it will emit an audio alarm and display a message. Refer to the RAMP® Operator's Manual 'Troubleshooting Guide' section for a full description of all messages. If repeated tests give unexpected results, contact Response Biomedical Technical Support for assistance

LIMITATIONS

- For diagnostic purposes, the patient's medical history, clinical examination and other findings should always be assessed in conjunction with the RAMP® test results. A test result that is inconsistent with the clinical signs and symptoms should be interpreted with caution.
- Factors such as technical or procedural errors or the presence of substances in blood specimens other than those that have been evaluated (see Interference section of this IFU), may interfere with the RAMP® test and cause erroneous results.
- As with any immunoassay, patient specimens may contain heterophilic antibodies that may result in either falsely elevated or depressed results. Presence of these antibodies may be due to elevated levels of rheumatoid factor, treatment with mouse monoclonal antibodies for diagnostic or therapeutic purposes, or other undetermined factors. The RAMP® test has been formulated to reduce the effects of heterophilic antibodies, but complete elimination of heterophilic interference from all samples cannot be guaranteed.
- Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.

TEST CUT-OFF AND EXPECTED VALUES

The test cut-offs validated for the RAMP® NT-proBNP test are 125 ng/L for ≤ 75 years of age and 450 ng/L for > 75 years of age. Each laboratory should investigate the transferability of the expected values to its own patient population and, if necessary, determine its own reference ranges.

PERFORMANCE CHARACTERISTICS

MEASUREMENT RANGE

27 to 22,000 ng/L

NT-proBNP levels in excess of 22,000 ng/L are reported as greater than (>) 22,000 ng/L, values less than 27 ng/L should be reported as (<) 27 ng/L.

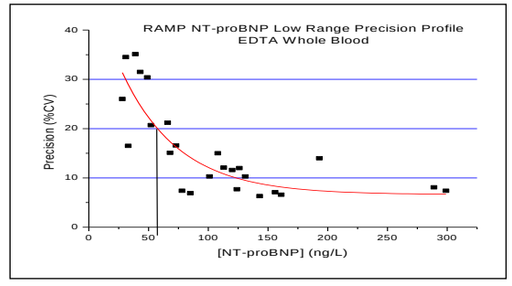
HOOK EFFECT

No high dose hook effect was observed for the RAMP® NT-proBNP test up to the highest level tested (350,000 ng/mL NT-proBNP).

DETECTION LIMIT

Following CLSI EP-17A the limit of blank (LoB) was calculated as the 95th percentile from 40 replicates of a blank sample run using the RAMP® NT-proBNP test and was determined to be 27 ng/L. The limit of detection (LoD) was determined to be 34 ng/L, The limit of quantitation (LoQ) is defined as the NT-proBNP level at which the test method displays a 20% coefficient of variation (% CV). As shown below, the 20% LoQ for the RAMP® NT-proBNP test was determined from whole blood analyses to be 57 ng/L.

NT-proBNP Low Range Precision Profile, EDTA Whole Blood



PRECISION

The within-run and between-run precision of the RAMP® NT-proBNP test were determined by one operator assaying duplicates of 3 concentrations of control material twice each day over a 10-day period. The mean, standard deviation and % CV were calculated for each reported concentration of NT-proBNP. The results of this precision analysis are detailed in the following table:

	NT-proBNP Standards Mean Concentration [ng/L]		
	140	449	1675
Within-run [%]	9.4	6.4	5.5
Total [%]	10.3	9.8	8.9

EDTA anticoagulated whole blood samples spanning the reportable range of the RAMP® NT-proBNP test were analyzed. Ten replicate measurements were carried out by a single operator in 1 day. The results of 11 samples from this precision analysis are shown below.

EDTA Whole Blood Samples

Mean NT-proBNP [ng/L]	CV [%]
52	20.7
73	16.6
113	12.1
131	10.3
161	6.6
299	7.4
2306	4.5
4051	4.4
5889	4.3
8445	5.4
19504	3.0

Precision in the hands of the end-user was evaluated at each clinical site (n=4). Each operator performed 3 replicates of a plasma-based control product. The results are presented for each operator and across operators below.

Operator	1	2	3	4	5	6	Combined
Level 1 CV [%]	9.3	9.5	15.5	8.8	11.8	-	11.0
Level 2 CV [%]	3.4	6.7	4.4	0.4	12.4	2.5	5.0

LINEARITY

A high NT-proBNP antigen concentration was prepared in normal donor EDTA whole blood and determined to contain 21,921 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted 6 times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with a correlation coefficient r value of 1.00, a slope of 1.06 and an intercept of -1.4 ng/L. The recovery of NT-proBNP antigen at the 6 dilutions ranged from 101 to 120% with an average of 108%.

A low NT-proBNP antigen concentration was prepared in normal donor EDTA whole blood and determined to contain 264 ng/L NT-proBNP by assaying the sample in duplicate. The sample was serially diluted 4 times. Regression analysis using the method of Passing-Bablok of actual versus expected NT-proBNP concentration resulted with a correlation coefficient r value of 1.00, a slope of 1.06 and an intercept of -2.0 ng/L. The recovery of NT-proBNP antigen at the 4 dilutions ranged from 85 to 110% with an average of 100%.

INTERFERENCE

Hemoglobin, triglycerides, bilirubin, cholesterol, and heparin at levels of high physiological concentrations were tested for possible interference. No interference was observed when tested at the concentrations up to, and including those shown in the following table:

Compound	Concentration
Hemoglobin	2 g/dL
Triglycerides	4 g/dL
Bilirubin	35 mg/dL
Cholesterol	500 mg/dL
Heparin	104 IU/mL

Potentially interfering substances were evaluated by spiking different concentrations of potential interferents into normal donor EDTA whole blood with NT-proBNP added to provide levels of 125 and 450 ng/L. Different blood samples were used for each potential interferent with an average difference of less than 10% from the un-spiked samples observed in each case. The therapeutic compounds tested (at concentrations up to, and including those indicated) are listed in the following table:

Pharmaceutical Compounds

Compound	Concentration	Compound	Concentration
Acetaminophen	20 mg/dL	Furosemide	6 mg/dL
Acetylsalicylic acid	100 mg/dL	Hydralazine	20 µg/mL
Allopurinol	4 mg/dL	Hydrochlorothia-zide	20 µg/mL
Amiodarone	20 µg/mL	Indomethacin	40 µg/mL
Amiodipine Besylate	4 µg/mL	Insulin	120 µU/mL
Ampicillin sodium salt	100 mg/dL	Isosorbide Dinitrate	15 mg/dL
Ascorbic acid	30 mg/dL	Lisinopril	4 mg/dL
Atenolol	1 mg/dL	Methyldopa	2.5 mg/dL
Caffeine	10 mg/dL	Metoprolol Tartrate	2 mg/dL
Captopril	15 mg/dL	Nicotine	2 mg/dL
Carvedilol	5 mg/dL	Nifedipine	6 mg/dL
Chloramphenicol	25 mg/dL	Nitroglycerin	19.2 mg/dL
Clopidogrel Hydrogensulfate	7.5 mg/dL	Oxytetracycline	100 µg/mL
Cyclosporin A	0.5 mg/dL	Probenecid	600 µg/mL
Diclofenac	60 µg/mL	Propranolol	0.2 mg/dL
Digitoxin	0.03 mg/dL	Quinidine	20 µg/mL
Digoxin	0.05 mg/dL	Simvastatin	4 mg/dL
Diltiazem	120 µg/mL	Theophylline	100 mg/dL
Phenytoin	10 mg/dL	Trimethoprim	60 µg/mL
Dipyridamole	30 µg/mL	Verapamil	16 mg/dL
Enalapril Maleate	4 mg/dL	Warfarin	20 µg/mL
Erythromycin	20 mg/dL		

ANALYTICAL SPECIFICITY

Human anti-mouse antibodies (HAMA) and Rheumatoid Factor (RF) appear to have minimal cross-reactivity with RAMP® NT-proBNP. Possible cross-reactivity of other substances was evaluated by spiking different concentrations of the potential cross-reactants into normal donor EDTA whole blood, which had NT-proBNP added. No cross-reactivity was observed with the RAMP® NT-proBNP test up to the maximum levels tested for the compounds listed in the following table:

Compound	Concentration
ANP_{28}	3.1µg/mL
BNP_{32}	3.5 µg/mL
CNP_{22}	2.2 µg/mL
$preproANP_{26-55}$	3.5 µg/mL
$preproANP_{56-92}$	1 ng/mL
$preproANP_{104-123}$	1 ng/mL
Aldosterone	0.6 ng/mL
Angiotensin I	0.6 ng/mL
Angiotensin II	0.6 ng/mL
Angiotensin III	1 ng/mL
Endothelin	20 ng/L
Arg-Vasopressin	1 ng/mL
Renin	50 ng/mL
Andrenomedullin	1 ng/mL
Urodilatin	3.5 µg/mL

CLINICAL EVALUATIONS

METHOD COMPARISON

699 subjects were enrolled in the clinical evaluation. The presenting population included 46% (323) with hypertension, 30% (208) who presented with shortness of breath, 22% (152) with diabetes, 14% (99) with pulmonary disorders, 12% (84) with coronary disease, 8% (56) with atrial fibrillation, 4% (31) with renal failure, 19% (133) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.). EDTA and heparin whole blood samples were obtained for each of these subjects. An aliquot of EDTA whole blood was used for the RAMP® NT-proBNP test and heparinized plasma was prepared for the Roche Elecsys proBNP assay. From these analyses it was determined that 580 samples contained between 34 ng/L (RAMP® LoD) and 22,000 ng/L NT-proBNP. Of these, 274 were diagnosed with heart failure (HF) based on individual hospital criteria (164 males and 110 females) and 306 were non-HF reference group subjects (124 males and 182 females). Regression analysis data of RAMP® NT-proBNP versus Elecsys NT-proBNP using the method of Passing-Bablok is presented in the table below.

Comparative Method	Slope	Intercept [ng/L]	Correlation Coefficient [r]
Roche Elecsys	0.97	19.39	0.98
95% CI[a]	0.95 to 1.00	14.20 to 24.67	0.97 to 0.98

a) Confidence Interval

CLINICAL SENSITIVITY & SPECIFICITY

Clinical sensitivity and specificity were calculated using data collected from 858 subjects. Of these, 299 were diagnosed with HF using local hospital criteria, 189 individuals without HF but with potentially confounding co-morbidity (diabetes, renal insufficiency, hypertension or chronic obstructive pulmonary disease) and 370 reference individuals. This reference group includes an additional 159 subjects added from an additional clinical site without concomitant testing in the Elecsys system. Of these, 55% (87) were male and 8% (12) were more than 75 years old. None of these subjects had reported co-morbidities. These subjects were healthy individuals with no clinical indications for natriuretic peptide testing. The use of the cut-offs of 125 ng/L for ≤ 75 years of age and 450 ng/L for > 75 years of age was evaluated across all subjects stratifying by the presence or absence of co-morbidities (diabetes, renal insufficiency, hypertension or chronic obstructive pulmonary disease). Sensitivity and specificity are shown in the following table:

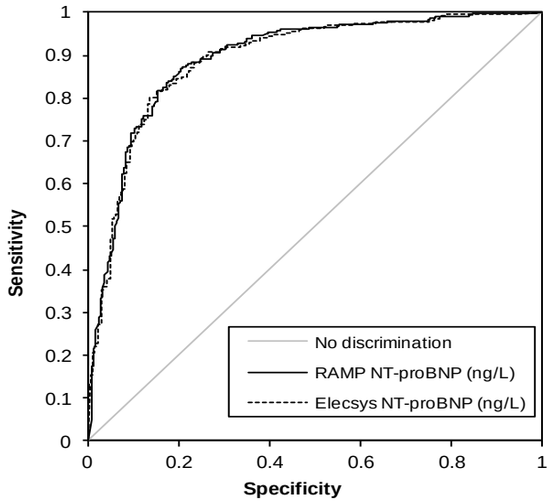
Age Stratified Sensitivity & Specificity: 125/450 ng/L for Ages ≤75 and >75

HF Subjects		
Age (years)	≤ 75	> 75
n	217	82
Sensitivity	0.89	0.99
95% CI	(0.84 to 0.93)	(0.92 to 1.0)
Non-HF, no co-morbidity[b]		
Age (years)	≤ 75	> 75
n	340	30
Specificity	0.85	0.72
95% CI	(0.80 to 0.88)	(0.53 to 0.87)
Non-HF, with co-morbidity		
Age (years)	≤ 75	> 75
n	124	65
Specificity	0.43	0.48
95% CI	(0.43 to 0.52)	0.35 to 0.60)

b) includes additional159 healthy subjects

RECEIVER OPERATOR CHARACTERISTIC (ROC)

The ROC analyses for both the RAMP® NT-proBNP and Roche Elecsys proBNP tests for the clinical trial population are shown below. The additional 159 patients without results from the Elecsys system were excluded from this comparison. The area under the curve (AUC) for both the RAMP® NT-proBNP test and Elecsys proBNP test is 0.87.



HF POPULATION BY NYHA CLASSIFICATION

The 299 subjects diagnosed with heart failure were evaluated using the RAMP® NT-proBNP test. The descriptive statistics for NT-proBNP concentrations are presented according to NYHA Functional Classification in the table below.

NYHA Class	I	II	III	IV
All				
n	58	91	84	66
Mean	1686	2831	5737	8308
SD	3161	4356	5939	7090
Median	832	1479	3608	6628
95th Percentile	5560	8104	20177	>22000
Male				
n	32	56	55	40
Mean	1737	2870	5799	8855
SD	3924	4641	6182	7612
Median	724	1318	3623	5772
95th Percentile	4722	10742	21068	>22000
Female				
n	26	35	29	26
Mean	1624	2771	5618	7466
SD	1918	3921	5551	6251
Median	907	1622	3598	6937
95th Percentile	5438	7306	16727	21839

NON-HF AND HF GROUP DESCRIPTIVE STATISTICS

The overall incidence of disease in the presenting population (n=858) included 38% (323) subjects with hypertension, 24% (208) who presented with shortness of breath, 18% (152) with diabetes, 12% (99) with pulmonary disorders, 10% (84) with coronary disease, 7% (56) with atrial fibrillation, 4% (31) with renal failure, 34% (292) were healthy, and the remainder had diagnoses not believed to be cardiac related (hepatitis, HIV, cancer, etc.).

The circulating NT-proBNP concentration was determined in 858 individuals with and without HF. The HF subjects included those with prior established heart failure that were not acutely destabilized at the time of enrollment (and thus similar to those who might be tested in the outpatient setting). Subjects (n=17) for whom the measured NT-proBNP level was greater than 22,000 ng/L are excluded. The descriptive statistics for the Non-HF (with and without co-morbidities) and the HF groups are presented in the following tables:

Non-HF Subjects – RAMP® Results [ng/L]

	No Co-morbidity			With Co-morbidity		All Subjects
Age (years)	≤75	>75	All Ages	≤75	>75	All Ages
n	340	30	370	124	65	559
Mean	133	450	159	871	1013	349
SD	671	811	688	3445	1525	996
Median	25	88	28	186	512	66
95th Percentile	216	2447	451	2463	3986	1544
% < 125 ng/L	84	-	-	44	-	-
% < 450 ng/L	-	74	-	-	48	-

HF Subjects – RAMP® Results [ng/L]

	With Co-morbidity		
Age (years)	≤75	>75	All
n	203	80	283
Mean	3133	4970	3652
SD	3755	5186	4280
Median	1735	3301	2040
95th Percentile	11373	19005	12800
% > 125 ng/L	89	-	-
% > 450 ng/L	-	100	-

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GLOSSARY OF SYMBOLS

EC REP Authorized Representative in European Community	LOT Batch Code	Catalogue Number
Caution	CE Mark	Consult Instructions for Use
Contains Sufficient for <n>Tests	Do Not Reuse	IVD In vitro Diagnostic Medical Device

Harmful, Irritant	Manufacturer	Rx Only Prescription Use Only
Temperature Limit	Use-by Date	

PRODUCT SUPPORT / ASSISTANCE

If you have any questions regarding the use of this product please contact Response Biomedical Corp. Technical Support:

- Within US or Canada (+1.866.525.7267)
- Outside US or Canada (+1.604.219.6119)
- By email at techsupport@responsebio.com

MANUFACTURER

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16530 Ventura Blvd., Suite 512
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Toll Free: 800-676-5565
info@jantdx.com
jantdx.com

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