Rheumatoid Factor Plus Test System

A Microparticle-Based Immunoassay for Rheumatoid Factor (RF) IgM Antibodies

Product Number: A91101M

INTENDED USE

The Zeus Scientific, Inc. **AtheNA Multi-Lyte®** RF Plus Test System is intended for the qualitative and/or quantitative detection of RF IgM class antibody. The test system is intended to be used as an aid in the diagnosis of rheumatoid arthritis. This test is for *in vitro* diagnostic use.

SIGNIFICANCE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, usually progressive inflammatory disorder of the joints. RA is a highly variable disease that ranges from a mild illness of brief duration to a progressive, destructive polyarthritis associated with a systemic vasculitis (1). The disease has been recently estimated to occur in one to two percent of the general population (2), and is two times more likely to occur in women than in men (1).

Clinical features of the early disease include lymphadenopathy, anorexia, weakness, fatigue, and morning stiffness or generalized achiness (1,3). RA is associated with a number of attributes which are measurable within the laboratory setting (4). The most common laboratory findings associated with RA include rheumatoid factor (RF), antinuclear antibodies (ANA), immune complexes, and characteristic complement levels (3). Measurement of serum RF IgM plays an important role in the diagnosis of RA, and more recently has been implicated with disease prognosis (6).

RF belongs to a group of immunoglobulins typically defined as antibodies which react to the Fc portion of human (and some other species of) IgG molecules (1,4). RF is a polyclonal antibody, reacting with a wide range of determinants on the IgG molecule (4). RF are of three major immunoglobulin classes; IgM, IgG, and IgA; however, IgE RF have also been described (5). IgM and IgG RF are the most common (1), with IgM RF being present in 75% of patients diagnosed with RA (4). RF has also been associated with some bacterial and viral infections such as hepatitis and infectious mononucleosis and some chronic infections such as tuberculosis, parasitic disease, subacute bacterial endocarditis, and cancer (1). Also, elevated levels of RF may be seen in 15% of the population greater than 65 years of age (4).

PRINCIPLE OF THE AtheNA Multi-Lyte RF PLUS ASSAY

The Zeus Scientific, Inc. **AtheNA Multi-Lyte** RF Plus Test System is designed to detect rheumatoid factor IgM class antibodies in human sera. The test procedure involves two incubation steps:

1. Test sera (properly diluted) are incubated in a vessel containing a multiplexed mixture of the bead suspension. The multiplexed bead suspension contains a mixture of distinguishable sets of polystyrene microspheres; each set conjugated with a different antigen. If present in patient sera, RF IgM will bind to the immobilized antigen on one of the bead sets.
2. Phycoerythrin-conjugated goat anti-human IgM (μ-chain specific) (PE conjugate) is added to the vessel and the plate is incubated. The conjugate will react with RF IgM antibody immobilized on the solid phase in step 1. The bead suspension is then analyzed by the **AtheNA Multi-Lyte** instrument. The bead set(s) are sorted (identified) and the amount of reporter molecule (PE conjugate) is determined for each bead set. Using the *Intra-Well Calibration Technology*™, internal calibration bead sets are used to convert raw fluorescence into outcome (units).

KIT COMPONENTS

Reactive Reagents: (All reactive reagents contain sodium azide as a preservative at a concentration of 0.1% w/v).

1. Multiplexed bead suspension. Ready to use, 5.5 mL bottle. The suspension contains a distinguishable 5.6 micron polystyrene beads that are conjugated with affinity-purified human IgG. The bead mix also contains one bead set designed to detect non-specific antibodies in the patient sample (if present) and four separate bead sets used for assay calibration.
2. Phycoerythrin conjugated goat anti-human IgM (μ-chain specific). Ready to use, 15 mL amber bottle.
3. Human positive serum control. One, 0.2mL vial.
4. Human negative serum control. One, 0.2mL vial.
5. Sample diluent. One 50 mL bottle containing phosphate-buffered-saline. Ready to use. NOTE, the sample diluent will change color in the presence of serum.
6. Wash Buffer Concentrate: Wash Buffer Concentrate: Dilute 1 part concentrate + 9 parts deionized or distilled water. One bottle containing 10 X concentrate of phosphate buffered saline.

Non-Reactive Components:

1. One 96-well filtration plate.
2. Data Labels: One label is adhered to the inside lid of the kit box and a second label is inside the kit box.
3. Package Insert providing instructions for use.
4. Calibration CD. A compact disc that includes all lot-specific kit calibration values required for specimen analysis and assay quality control.

PRECAUTIONS

Safety Precautions:

1. The Zeus Scientific, Inc. **AtheNA Multi-Lyte** RF Plus Test System is for *in vitro* diagnostic use only. Normal precautions exercised in handling laboratory reagents should be followed. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing, gloves, and eye/face protection. Do not breathe vapor. Dispose of waste observing all local, state, and federal laws.
2. The **AtheNA Multi-Lyte** RF Plus Test System conjugated micro-spheres do not contain viable organisms. However, the reagent should be considered **POTENTIALLY BIOHAZARDOUS MATERIALS** and handled accordingly.
3. The controls are **POTENTIALLY BIOHAZARDOUS MATERIALS**. Source materials from which these products were derived were found negative for HIV-1 antigen, HbsAg. and for antibodies against HCV and HIV by approved test methods. However, since no test method can offer complete assurance that infectious agents are absent, these products should be handled at the Biosafety Level 2 as recommended for any potentially infectious human serum or blood specimen in the Centers for Disease Control/National Institutes of Health manual "Biosafety in Microbiological and Biomedical Laboratories": current edition; and OSHA's Standard for Bloodborne Pathogens (9).
4. The sample diluent, controls, bead suspension and conjugate contain sodium azide at a concentration of 0.1% (w/v). Sodium azide has been reported to form lead or copper azides in laboratory plumbing which may cause explosions on hammering. To prevent, rinse sink thoroughly with water after disposing of solution containing sodium azide.

Procedural Precautions:

1. For *in vitro* diagnostic use only.
2. Dilution or adulteration of these reagents may generate erroneous results.
3. Reagents from other sources or manufacturers should not be used.
4. The bead suspension and conjugate are light sensitive reagents. Both have been packaged in light protective containers. Normal exposures experienced during the course of performing the assay will not affect assay performance. Do not expose these reagents to strong sources of visible light unnecessarily.
5. To optimize read times the bead suspension must be thoroughly mixed just prior to use. The most effective means to resuspend the beads is to first vortex the bead suspension for approximately 30 seconds and then sonicate for approximately 30 seconds in a small bath sonicator.
6. Never pipette by mouth. Avoid contact of reagents and patient specimens with skin and mucous membranes.
7. Avoid microbial contamination of reagents. Incorrect results may occur.
8. Cross contamination of reagents and/or samples could cause erroneous results
9. Strict adherence to the specified time and temperature of incubations is essential for accurate results. **All reagents must be allowed to reach room temperature (20-25°C) before starting the assay.** Return unused reagents to refrigerated temperature immediately after use.
10. Avoid splashing or generation of aerosols.
11. Treat the waste solution with 10% household bleach (0.5% sodium hypochlorite). Avoid exposure of reagents to bleach fumes.
12. Do not expose any of the reactive reagents to bleach-containing solutions or to any strong odors from bleach-containing solutions. Trace amounts of bleach (sodium hypochlorite) may destroy the biological activity of many of the reactive reagents within this kit.

STORAGE CONDITIONS

1. Store the unopened kit at 2-8°C.
2. Multiplex bead suspension: Store at 2-8°C. Remove only the required amount of solution to analyze the specimens to be tested and return the unused portion to storage at 2-8°C.
3. Phycoerythrin conjugated goat anti-human antibody: Store at 2-8°C.
4. Human controls: Store at 2-8°C.
5. Sample Diluent: Store at 2-8°C.
6. Wash Buffer Concentrate (10X). Store between 2-25°C. Diluted Wash Buffer (1X) is stable at room temperature (20-25°C) for up to 7 days or for 30 days at 2-8°C.

SPECIMEN COLLECTION

It is recommended that specimen collection be carried out in accordance with NCCLS document M29: Protection of Laboratory Workers from Infectious Disease. No known test method can offer complete assurance that human blood samples will not transmit infection. Therefore, all blood derivatives should be considered potentially infectious.

Only freshly drawn and properly refrigerated sera obtained by approved aseptic venipuncture procedures should be used in this assay (7, 8). No anticoagulants or preservatives should be added. Avoid using hemolyzed, icteric, lipemic, or bacterially contaminated sera.

Store sample at room temperature for no longer than 8 hours. If testing is not performed within 8 hours, sera may be stored at 2-8°C for no longer than 48 hours. If delay in testing is anticipated, store test sera at -20°C or lower. Avoid multiple freeze/thaw cycles which may cause loss of antibody activity and give erroneous results

ASSAY PROCEDURE

Materials required but not provided:

1. Pipettes capable of accurately delivering 10 to 200µL
2. Multichannel pipette capable of accurately delivering (50-200µL)
3. Reagent reservoirs for multichannel pipettes
4. Serological pipettes
5. Disposable pipette tips
6. Laboratory timer to monitor incubation steps
7. Plate shaker capable of shaking at approximately 800 RPM

Set-up of the Assay:

Remove the individual components from storage and briefly allow them to warm to room temperature (20-25°C). Determine the total number of controls and samples to be tested. It is necessary to include the Negative Control and the Positive Control with each run.

The Negative Control should be tested in well A1. The Positive Control should be tested in well B1. Each control and sample requires one microwell for processing.

Note 1. To optimize read times the bead suspension must be thoroughly mixed just prior to use. The most effective means to resuspend the beads is to first vortex the bead suspension for approximately 30 seconds and then sonicate for approximately 30 seconds in a small bath sonicator..

Note 2. For proper performance, it is important that the contents of the assay are thoroughly mixed. Suitable means of mixing include mixing the plate on a plate shaker for approximately 30 seconds at approximately 800 RPM or to set a pipettor to roughly ½ of the volume in the plate and repeatedly aspirate and expel (pump up and down) the contents of the well for a minimum of 5 cycles.

Serum Incubation

1. Prepare a 1:21 dilution of the Negative Control, the Positive Control and each of patient sera. (***Example****: Combine 10µL of serum with 200µL of Sample Diluent*). The sample diluent will undergo a color change confirming that the specimen has been combined with the diluent. For proper performance, it is important that the sample dilutions are thoroughly mixed. Mix according to **Note 2** above.
2. After determining the total number of wells to process, use a multichannel or a repeating pipette to dispense 50 µL of the bead suspension into each of the wells of the filtration plate.
3. Transfer 10µL of each diluted sample (1:21) and control from the dilution plate to the filtration plate. For proper performance, it is important that the sample dilution and bead suspension are thoroughly mixed. Mix according to **Note 2** above.
4. Incubate the plate at room temperature (20-25°C) for 30 +/- 10 minutes.
5. After the incubation, rinse the beads by vacuum filtration:
    a. Place the filtration plate on the vacuum manifold and remove the solution, leaving the beads behind.
    b. Turn off the vacuum and add 200 µL of Diluted Wash Buffer (1X).
    c. Apply the vacuum and remove the solution.
    d. Repeat steps 5.b and 5.c for a total of three rinses with the Diluted Wash Buffer (1X).
6. Following the final wash gently blot the bottom of the plate and allow plate to air dry for 3-5 minutes before proceeding to the next step.

Conjugate Incubation

1. Add 150µL of the Conjugate solution to each well at the same rate and in the same order as the specimens were added. For proper performance, it is important that the conjugate solution and bead suspension are thoroughly mixed. Mix according to **Note 2** above. As an option, while mixing the conjugate and beads, one may transfer the bead/conjugate mixture to empty wells of a polystyrene reaction plate.
2. Incubate the plate at room temperature (20-25°C) 30 +/- 10 minutes.

Specimen Analysis

NOTE: For proper specimen analysis, it is important that the instrument is installed, calibrated and maintained according to the manufacturer's instructions. Please review the instrument manual for instrument preparation prior to reading the assay results.

1. Set the **AtheNA Multi-Lyte** instrument to analyze the reactions by selecting the RF template. Refer to the operators manual for details regarding the operation of the **AtheNA Multi-Lyte** instrument.
2. The plate should be read within 60 minutes after the completion of the conjugate incubation. One may decide to shake the plate for approximately 15 seconds immediately prior to reading. This optional step may reduce the amount of time required to read the plate.

ABBREVIATED ASSAY PROTOCOL:

Step	Procedure
1	Dilute specimens 1:21 in Sample Diluent. Mix well.
2	Combine 50 µL of bead suspension and 10 µL of diluted specimen in an empty well of a filtration plate. Mix well.
3	Incubate at room temperature for 30 +/- 10 minutes.
4	Rinse the microspheres 3X with Diluted Wash Buffer (1X).
5	Gently blot the bottom of the plate and air dry for 3-5 minutes.
6	Add 150 µL of conjugate to each well. Mix well and transfer to a reaction plate (optional).
7	Incubate at room temperature for 30 +/- 10 minutes.
8	Shake plate (optional).
9	Read results within 60 minutes.

CONVERSION OF FLUORESCENCE TO UNIT VALUES

A. Calculations:

1. Assay Calibration

The **AtheNA Multi-Lyte** RF Plus Test System utilizes *Intra-Well Calibration Technology*™. *Intra-Well Calibration Technology*™ includes a multi-point standard curve within the bead suspension. With *Intra-Well Calibration Technology*™, each well of the assay is calibrated internally without any user intervention. The standard curve is designed to self-adjust based upon the unique characteristics of the patient or control serum. Calibrator values are assigned to the internal standards by Zeus Scientific, Inc. These values are lot specific and are encoded within the lot specific Calibration CD included in the kit box.

2. Analyte Cut Off Values

Each analyte of the **AtheNA Multi-Lyte** RF Plus Test system has an assigned cut off value. Cut off values are determined by Zeus Scientific, Inc. for each kit lot, and are encoded within the lot specific Calibration CD included in the kit box.

3. Calculations

Through *Intra-Well Calibration Technology*™, all calculations are performed automatically when using the AtheNA Multi-Lyte **system. *Intra-Well Calibration Technology*™ performs a regression analysis of the internal standards and then adjusts the calculated unit values based upon an additional standard and the characteristics of the serum sample.**

B. Interpretations:

1. **RF Interpretation**: The **AtheNA Multi-Lyte** RF assay results may be interpreted as follows:

	Unit Value
Negative Specimens	< 6 IU/mL
Positive Specimens	≥ 6 IU/mL
Strong Positive Specimens	>25 IU/mL

QUALITY CONTROL

1. Each time the assay is run it is necessary to include the Negative Control (in well A1) and the Positive Control (in well B1).
2. Run validity is determined through the performance of the positive and negative controls. These criteria are analyzed automatically through *Intra-Well Calibration Technology*™.
    a. The Negative Control and the Positive Control must all be negative on the non-specific or control antigen bead.
    b. The Negative Control must be negative for each and every analyte included in the multiplexed bead suspension.
    c. The Positive Control must be positive for a predetermined group of analytes included in the multiplexed bead suspension. The Positive Control must result in a positive RF outcome. In addition to the qualitative outcome, the Positive Control must meet the predetermined ranges for activity. These ranges are encoded within the Calibration CD.
    d. If any of the above criteria are not met, the entire run will be considered invalid and should be repeated.
3. Specimen validity is based upon the characteristics of the calibration beads and their interactions with the patient sera. There are various parameters monitored automatically through *Intra-Well Calibration Technology*™. If any of the criteria are found to be out of specification, the patient's results are considered invalid and should be repeated. Should this occur, the data report will indicate the particular specimen which has been invalidated as well as a trouble shooting code.
4. Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations. External controls must be representative of normal human serum since the **AtheNA**® calibration system is partially based upon the characteristics of the serum sample. If the specimen is pre-diluted or if the formulation is artificial (not human serum), erroneous results may occur.
5. Refer to NCCLS document C24: Statistical Quality Control for Quantitative Measurements for guidance on appropriate QC practices.

LIMITATIONS

1. The **AtheNA Multi-Lyte** RF Plus Test System is a diagnostic aid and by itself is not diagnostic. Test results should be interpreted in conjunction with the clinical evaluation and the results of other diagnostic procedures.
2. Due to the homogeneous nature of this assay, hemolytic, icteric, or lipemic samples may interfere with the outcome of this assay. Additionally, specimens with abnormal IgG concentrations may interfere with the outcome of this assay. Use of these types of specimens should be avoided.
3. A negative result does not exclude rheumatoid arthritis. Approximately 25% of patients with a diagnosed case of rheumatoid arthritis may present with a negative result for RF.

EXPECTED RESULTS

In the normal blood donor group, there were a total of 148 specimens. Of the 148 specimens, 128/148 (86.5%) were negative, 18/148 (12.2%) were positive and 2/148 (1.4%) were strong positive.
In the clinical specimens (those diagnosed with rheumatoid arthritis), 1/150 (0.7%) was negative, 149/150 (99.3%) were positive. Of the 149 positive specimens, 12/149 (8%) were positive and 137/149 (92%) were strong positive.
The AtheNA Multi-Lyte RF IgM test system has been calibrated to a standard provided by the World Health Organization (WHO). The assay has been calibrated to WHO 64/2 which has a defined value of 25 IU/mL. When analyzed using the AtheNA Multi-Lyte RF IgM test system a result of 24.25 IU/mL was obtained with this standard.

PERFORMANCE CHARACTERISTICS

Comparative Study:

An in-house comparative study was performed to demonstrate the equivalence of the Zeus Scientific, Inc., AtheNA Multi-Lyte RF IgM test system to a commercially available RF IgM ELISA test system. Performance was evaluated using 450 specimens; 150 normal donor sera, 150 specimens previously sent to a lab for routine RF testing, and 150 disease-state specimens from clinically diagnosed rheumatoid arthritis patients. The results of the investigation have been summarized in Table 1 below.

Table 1. Performance of the Qualitative ANA Outcome of the AtheNA Multi-Lyte RF IgM Test System:

		ELISA Results		
		Positive	Negative	Total:
AtheNA Results	Positive	308	11	319
	Negative	0	129	129
	Total:	308	140	448*
			95% confidence intervals	
	Relative Sensitivity	100%	98.21 to 99.99 %	
	Relative Specificity	92.1%	86.38 to 96.01%	
	Relative Agreement	97.5%	95.65 to 98.77 %	

*NOTE: There were originally 450 specimens included in the study. Two of the specimens yielded invalid results on the AtheNA RF assay and are therefore excluded from the data summary above.

Assessment of the clinical specificity of the AtheNA Multi-Lyte RF IgM Test System:

Clinical specificity of the AtheNA Multi-Lyte RF IgM test system was evaluated using 150 normal blood donors since it was presumed that such a group should be free of RF IgM antibody. Using this group, 128/148 were negative for RF IgM antibody. The

clinical specificity of the AtheNA Multi-Lyte RF IgM test system was therefore determined to be 128/148 or 86.5%. Expressed as a 95% confidence interval, the clinical specificity was determined to be 0.799 to 0.916

Assessment of the clinical sensitivity of the AtheNA Multi-Lyte RF IgM Test System:
Clinical sensitivity of the AtheNA Multi-Lyte RF IgM test system was evaluated using 150 clinically defined serum samples from patients diagnosed with rheumatoid arthritis. Using this group, 149/150 were positive for RF IgM antibody. The clinical sensitivity of the AtheNA Multi-Lyte RF IgM test system was therefore determined to be 149/150 or 99.3%. Expressed as a 95% confidence interval, the clinical specificity was determined to be 0.963 - 0.999

Reproducibility:
An in-house evaluation of both intra-assay and inter-assay reproducibility was conducted. Six specimens were tested. On each day of testing, each sample was diluted twice and then loaded for four replicates resulting in a total of eight wells of each of the six samples. This protocol was followed for three days. These results were then used to calculate mean IU/mL values, standard deviations, and percent CV. Specimens were selected in such a way that resulted in two of them being clearly negative, two being clearly positive and two were selected that were weakly positive.
The results of this study have been summarized in Table 2 below:

Table 2: Summary of Precision Testing.

Sample:	Characteristics:	Day One Results:		Day Two Results:		Day Three Results:	
		Dilution 1	Dilution 2	Dilution 1	Dilution 2	Dilution 1	Dilution 2
Sample 1	Negative	1	1	2	1	1	1
Sample 1	Negative	1	1	1	2	1	1
Sample 1	Negative	1	1	2	2	1	1
Sample 1	Negative	1	1	1	1	1	1
Sample 2	Negative	1	1	4	1	1	1
Sample 2	Negative	1	1	1	2	1	1
Sample 2	Negative	1	1	2	2	1	1
Sample 2	Negative	1	1	1	2	1	1
Sample 3	Strong Positive	226	197	193	185	209	219
Sample 3	Strong Positive	200	204	230	214	226	211
Sample 3	Strong Positive	224	226	196	202	217	213
Sample 3	Strong Positive	207	217	192	218	220	203
Sample 4	Strong Positive	163	166	172	174	162	158
Sample 4	Strong Positive	163	145	198	160	144	158
Sample 4	Strong Positive	152	162	191	174	165	151
Sample 4	Strong Positive	146	160	167	175	154	157
Sample 5	Positive	9	8	9	9	11	9
Sample 5	Positive	9	8	8	9	10	8
Sample 5	Positive	10	11	9	9	10	10
Sample 5	Positive	9	8	10	10	10	9
Sample 6	Positive	8	8	10	9	10	9
Sample 6	Positive	10	9	8	7	9	9
Sample 6	Positive	8	8	10	7	11	10
Sample 6	Positive	10	9	9	8	9	8

		Day 1 Intra-assay Precision:		Day 2 Intra-assay Precision:		Day 3 Intra-assay Precision:		Inter-assay Precision	
	Sample 1	mean	1	mean	2	mean	1	mean	1
		stdev	0	stdev	0.534522	stdev	0	stdev	0.38069
		%CV	0.0%	%CV	35.6%	%CV	0.0%	%CV	32.6%
	Sample 2	mean	1	mean	2	mean	1	mean	1
		stdev	0	stdev	0.991031	stdev	0	stdev	0.69025
		%CV	0.0%	%CV	52.9%	%CV	0.0%	%CV	53.4%
	Sample 3	mean	213	mean	204	mean	215	mean	210
		stdev	12.04678	stdev	15.42493	stdev	7.225945	stdev	12.49630
		%CV	5.7%	%CV	7.6%	%CV	3.4%	%CV	5.9%
	Sample 4	mean	157	mean	176	mean	156	mean	163
		stdev	8.253787	stdev	12.36282	stdev	6.53425	stdev	13.07164
		%CV	5.3%	%CV	7.0%	%CV	4.2%	%CV	8.0%
	Sample 5	mean	9	mean	9	mean	10	mean	9
		stdev	1.069045	stdev	0.64087	stdev	0.916125	stdev	0.89685
		%CV	11.9%	%CV	7.0%	%CV	9.5%	%CV	9.7%
	Sample 6	mean	9	mean	9	mean	9	mean	9
		stdev	0.886405	stdev	1.195229	stdev	0.916125	stdev	1.03472
		%CV	10.1%	%CV	14.1%	%CV	9.8%	%CV	11.7%

Cross Reactivity and Interfering Substances:

The AtheNA Multi-Lyte RF IgM Plus Test system was evaluated for potential cross reactivity to other antibodies and interference from serum components. For this study, a total of 38 specimens were evaluated., Eighteen specimens which were positive for various autoimmune and infectious disease antibodies were tested on the AtheNA Multi-Lyte RF IgM test system. Of the eighteen evaluated, two were reactive on the AtheNA Multi-Lyte RF IgM assay. One of the two was also reactive for RF IgM by ELISA.

There were a total of 20 specimens evaluated which contained potentially interfering substances. These 20 specimens contained either abnormal levels of hemolysis, (n=5), bilirubin (n=5), above normal IgG concentration (n=5) or above normal lipid levels (n=5). Four of the specimens were weakly positive using the AtheNA Multi-Lyte RF IgM test system. One of the four was also positive by RF IgM ELISA.

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