RF IgM Plus Test System

REF A91101M

IVD

CE

Rx Only

INTENDED USE

The ZEUS **AtheNA Multi-Lyte®** Rheumatoid Factor (RF) IgM 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 only.

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 ASSAY

The ZEUS **AtheNA Multi-Lyte** RF IgM 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 Bead Suspension. The Bead Suspension contains a mixture of distinguishable sets of polystyrene microspheres (beads) each conjugated with a different antigen. If present in patient sera, RF IgM will bind to the immobilized antigen on one or more of the bead sets. The beads are rinsed to remove non-reactive serum proteins.
2. Phycoerythrin-conjugated goat anti-human IgM is added to the vessel and the plate is incubated. The Conjugate will react with 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).

TEST SYSTEM COMPONENTS

Materials Provided:

Each Test System contains the following components in sufficient quantities to perform the number of tests indicated on the packaging label. **NOTE: The following components contain Sodium Azide as a preservative at a concentration of <0.1% (w/v): Bead Suspension, Controls, Conjugate and SAVe Diluent®.**

SOLN	BEAD

1. Bead Suspension: Contains separate distinguishable 5.6 micron polystyrene beads that are conjugated with affinity purified human IgG. The Bead Suspension 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. One, amber bottle containing 5.5mL. Ready to use.

CONJ

2. Conjugate: Phycoerythrin conjugated goat anti-human IgM (µ chain specific). One, amber bottle containing 15mL. Ready to use.

CONTROL	+

3. Positive Control (Human Serum): One, red-capped vial containing 0.2mL.

CONTROL	-

4. Negative Control (Human Serum): One, green-capped vial containing 0.2mL..

DIL	SPE

5. SAVe Diluent®: One, green-capped bottle containing 50mL of phosphate-buffered-saline. Ready to use. **NOTE: The SAVe Diluent® will change color when combined with serum.**

WASHBUF	10X

6. Wash Buffer Concentrate (10X): Dilute 1 part concentrate + 9 parts deionized or distilled water. One, clear-capped bottle containing containing 50mL of 10X concentrated phosphate-buffered-saline.

NOTES:

1. **The following components are not Test System Lot Number dependent and may be used interchangeably with the ZEUS AtheNA Multi-Lyte Test Systems: Wash Buffer and SAVe Diluent®**
2. **Test System also contains:**
   a. **Component Label containing lot specific information inside the Test System box.**
   b. **Calibration CD containing lot specific kit calibration values required for specimen analysis and assay quality control, and Package Inserts.**
   c. **One 96-well dilution plate**.
   d. **One 96-well filter plate.**

PRECAUTIONS

1. For *In Vitro* diagnostic use.
2. Follow normal precautions exercised in handling laboratory reagents. 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.
3. The **AtheNA Multi-Lyte** Bead Suspension does not contain viable organisms. However, the reagent should be considered **potentially biohazardous materials** and handled accordingly.
4. 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, handle these products 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).
5. 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.
6. Improper washing could cause false positive or false negative results. Be sure to minimize the amount of any residual wash solution; (e.g., by blotting or aspiration) before adding Conjugate. Do not allow the wells to dry out between incubations.
7. The SAVe Diluent®, Bead Suspension, Controls, 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.

8. The Wash Buffer concentrate is an IRRITANT. It is irritating to eyes, respiratory system and skin.
9. Dilution or adulteration of these reagents may generate erroneous results.
10. Do not use reagents from other sources or manufacturers.
11. Never pipette by mouth. Avoid contact of reagents and patient specimens with skin and mucous membranes.
12. Avoid microbial contamination of reagents. Incorrect results may occur.
13. Cross contamination of reagents and/or samples could cause erroneous results.
14. Avoid splashing or generation of aerosols.
15. Do not expose reagents to strong light during storage or incubation. 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.
16. Collect the wash solution in a disposal basin. Treat the waste solution with disinfectant (i.e.: 10% household bleach - 0.5% Sodium Hypochlorite). Avoid exposure of reagents to bleach fumes.
17. Caution: Neutralize any liquid waste at an acidic pH before adding to a bleach solution.
18. Do not allow the Conjugate to come in contact with containers or instruments that may have previously contained a solution utilizing Sodium Azide as a preservative. Residual amounts of Sodium Azide may destroy the Conjugate's enzymatic activity.
19. 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 Test System.

MATERIALS REQUIRED BUT NOT PROVIDED

1. Pipettes capable of accurately delivering 10 - 200µL.
2. Multichannel pipette capable of accurately delivering 10 - 200µL.
3. Reagent reservoirs for multichannel pipettes.
4. Serological pipettes.
5. Disposable pipette tips.
6. Paper towels.
7. Laboratory timer to monitor incubation steps.
8. Disposal basin and disinfectant (i.e.: 10% household bleach - 0.5% Sodium Hypochlorite).
9. **AtheNA Multi-Lyte** System (Luminex® Instrument) with Sheath Fluid (Product Number 40-50035).
10. Distilled or deionized water.
11. Vortex.
12. Small Bath Sonicator.
13. Plate shaker capable of shaking at 800 RPM (optional for mixing).
14. Vacuum aspirator and vacuum manifold for washing the microspheres.

STORAGE CONDITIONS

2°C – 8°C	Bead Suspension: Remove only the required amount to analyze the specimens to be tested and return the unused portion to storage.
	Conjugate: DO NOT FREEZE.
	Unopened Test System, Positive Control, Negative Control, SAVe Diluent®
2°C – 25°C	Wash Buffer (1X): 20 - 25°C for up to 7 days, 2 - 8°C for 30 days. Wash Buffer (10X): 2 - 25°C

SPECIMEN COLLECTION

1. ZEUS Scientific recommends that the user carry out specimen collection in accordance with CLSI document M29: Protection of Laboratory Workers from Infectious Disease (Current Edition).
2. No known test method can offer complete assurance that human blood samples will not transmit infection. Therefore, consider all blood derivatives potentially infectious.
3. Use only freshly drawn and properly refrigerated sera obtained by approved aseptic venipuncture procedures in this assay. Do not use if there are any added anticoagulants or preservatives. Avoid using hemolyzed, lipemic, or bacterially contaminated sera.
4. Store sample at room temperature for no longer than 8 hours. If testing is not performed within 8 hours, sera may be stored between 2 - 8°C, for no longer than 48 hours. If a 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. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine stability criteria for its laboratory (10).

ASSAY PROCEDURE

1. Remove the individual components from storage and allow them to warm to room temperature (20 - 25°C).
2. Determine the total number of Controls and samples to be tested. It is necessary to include the Negative and Positive Control with each run. The Negative Control should be tested in well A1 and Positive Control in well B1. Each Control and sample requires one microwell for processing.
   a. To optimize read times, the Bead Suspension must be thoroughly mixed just prior to use. The most effective for re-suspension is to first vortex for approximately 30 seconds followed by sonication for approximately 30 seconds in a small bath sonicator.
   b. 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 RPMs 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.

EXAMPLE PLATE SET-UP

	1	2
A	Negative Control	Etc.
B	Positive Control	
C	Patient 1	
D	Patient 2	
E	Patient 3	
F	Patient 4	
G	Patient 5	
H	Patient 6	

3. Prepare a 1:21 dilution (e.g.: 10µL of serum + 200µL of SAVe Diluent®) of the Negative Control, Positive Control, and each patient serum. **NOTE: The SAVe 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 according to 2b above.

4. After determining the total number of wells to process, use a multichannel or a repeating pipette to dispense 50µL of the Bead Suspension into each of the wells of the filtration plate.
5. 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 according to 2b above.
6. Incubate the plate at room temperature (20 - 25°C) for 30 ± 10 minutes.
7. After the incubation, rinse the Beads by vacuum filtration using the supplied Wash Buffer diluted to the 1X concentration.
   a. Place the filtration plate on the vacuum manifold and remove the solution, leaving the beads behind.
   b. Turn off the vacuum and add 200µL of 1X Wash Buffer.
   c. Apply the vacuum and remove the solution.
   d. Repeat steps 7b and 7c for a total of three rinses.
8. Following the final wash, gently blot the bottom of the filter plate and allow the plate to air dry for 3 - 5 minutes before proceeding to the next step.
9. Add 150µL of the Conjugate to each well, at the same rate and same order as the specimens. For proper performance, it is important that the Conjugate and Bead Suspension are thoroughly mixed according to 2b above. As an option, while mixing the Conjugate one may transfer the mixture to empty wells of a polystyrene reaction plate.
10. Incubate the plate at room temperature (20 - 25°C) for 30 ± 10 minutes.
11. Set the **AtheNA Multi-Lyte** instrument to analyze the reactions by selecting the RF IgM Plus template. Refer to the operators manual for details regarding the operation of the **AtheNA Multi-Lyte** instrument. Results may be read from the filter plate or a reaction plate. **NOTE: For proper specimen analysis, it is important that the instrument is set-up, calibrated and maintained according to the manufacturer's instructions.** Please review the instrument manual for instrument preparation prior to reading the assay results.
12. 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 prior to reading. This optional step may reduce the amount of time required to read the plate.

Step	Abbreviated Assay Procedure
1	Dilute specimens 1:21 in SAVe Diluent®. Mix well.
2	Combine 50µL of Bead Suspension and 10µL of diluted specimen in an empty well. Mix well.
3	Incubate at room temperature for 30 ± 10 minutes.
4	Rinse the microspheres 3 times with 200µL of 1X Wash Buffer.
5	Gently blot the bottom of the plate and air dry for 3 - 5 minutes.
6	Add 150µL of Conjugate to each well. Mix well.
7	Transfer to a reaction plate (optional).
8	Incubate at room temperature for 30 ± 10 minutes
9	Shake plate (optional).
10	Read results within 60 minutes.

QUALITY CONTROL

Caution: The Negative and Positive Controls are intended to monitor for substantial reagent failure. The Positive Control will not ensure precision at the assay cutoff.

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 and Positive Controls 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 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. **Do not report the patient results.**
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 **AtheNA Multi-Lyte's** calibration system is partially based upon the characteristics of the serum sample. If the specimen formulation is artificial (not human serum), erroneous results may occur.
5. Good laboratory practice recommends the use of positive and negative controls to assure functionality of reagents and proper performance of the assay procedure. Quality control requirements must be performed in conformance with local, state and/or federal regulations or accreditation requirements and the user's laboratory standard Quality Control procedures. It is recommended that the user refer to CLSI EP12-A and 42 CFR 493.1256 for guidance on appropriate QC practices.

INTERPRETATION OF RESULTS

1. **Calculations**
   a. Assay Calibration: The ZEUS **AtheNA Multi-Lyte** RF IgM 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, are lot specific and are encoded within the lot specific Calibration CD.
   b. Analyte Cutoff Values: Each analyte of the ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System has an assigned cutoff value. Cutoff values are determined by ZEUS for each test system lot, and are encoded within the lot specific Calibration CD.
   c. 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.
2. **Interpretations**

The ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System results may be interpreted as follows:

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

LIMITATIONS OF THE ASSAY

1. The ZEUS **AtheNA Multi-Lyte** RF IgM 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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus 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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System a result of 24.25 IU/mL was obtained with this standard.

PERFORMANCE CHARACTERISTICS

1. **Comparative Study**

An in-house comparative study was performed to demonstrate the equivalence of the ZEUS **AtheNA Multi-Lyte** RF IgM Plus 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: Qualitative ANA Performance Outcome of the ZEUS AtheNA Multi-Lyte RF IgM Plus Test System

		ELISA Results		
		Positive	Negative	Total
AtheNA Results	Positive	308	11	319
	Negative	0	129	129
	Total	308	140	448*

		95% Confidence Interval
Relative Sensitivity	100%	98.21 – 99.99
Relative Specificity	92.1%	86.38 – 96.01
Relative Agreement	97.5%	95.65 – 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 ZEUS AtheNA Multi-Lyte RF IgM Plus Test System:

Clinical specificity of the ZEUS **AtheNA Multi-Lyte** RF IgM Plus 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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System was therefore determined to be 86.5%. Expressed as a 95% confidence interval, the clinical specificity was determined to be 0.799 - 0.916.

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

Clinical sensitivity of the ZEUS **AtheNA Multi-Lyte** RF IgM Plus 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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System was therefore determined to be 99.3%. Expressed as a 95% confidence interval, the clinical specificity was determined to be 0.963 - 0.999.

2. **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 are shown in Tables 2 and 3 below.

Table 2: ZEUS AtheNA Multi-Lyte RF IgM Plus Precision Data

Sample ID	Characteristic	Day 1 Results		Day 2 Results		Day 3 Results	
		Dilution 1	Dilution 2	Dilution 1	Dilution 2	Dilution 1	Dilution 2
1	Negative	1	1	2	1	1	1
		1	1	1	2	1	1
		1	1	2	2	1	1
		1	1	1	1	1	1
2		1	1	4	1	1	1
		1	1	1	2	1	1
		1	1	2	2	1	1
		1	1	1	2	1	1
3	Strong Positive	226	197	193	185	209	219
		200	204	230	214	226	211
		224	226	196	202	217	213
		207	217	192	218	220	203
4		163	166	172	1744	162	158
		163	145	198	160	144	158
		152	162	191	174	165	151
		146	160	167	175	154	157
5	Positive	9	8	9	9	11	9
		9	8	8	9	10	8
		10	11	9	9	10	10
		9	8	10	10	10	9
6		8	8	10	9	10	9
		10	9	8	7	9	9
		8	8	10	7	11	10
		10	9	9	8	9	8

Table 3: ZEUS AtheNA Multi-Lyte RF IgM Plus Precision Testing Summary

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

3. **Cross Reactivity and Interfering Substances**
   The ZEUS **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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System. Of the 18 evaluated, two were reactive on the ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System. 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 ZEUS **AtheNA Multi-Lyte** RF IgM Plus Test System. One of the four was also positive by RF IgM ELISA.

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