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CLINICAL DIAGNOSIS

MiraVista *Histoplasma* Antigen Enzyme Immunoassay (EIA) for Diagnosis and Monitoring Treatment

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Background

Antigen detection is the most common method for diagnosis of severe and progressive forms of histoplasmosis [1]. The MiraVista *Histoplasma* antigen EIA is offered as a CAP and CLIA certified laboratory developed tests (LDT) performed only at MiraVista Diagnostics. Sensitivity is presented in table 1 [1]. Specificity was 99% but cross-reactivity occurred in 90% of patients with blastomycosis.

The MiraVista EIA has been modified to eliminate the "below the limit of quantification (BLQ)" classification and to extend the quantifiable range to reduce the "above the limit of quantification (ALQ)", addressing the most common requests of our customers. These modifications have been stringently validated in accordance with CLSI and CAP guidelines. The limit of detection in serum, urine, bronchoalveolar lavage fluid and cerebrospinal fluid is 0.2 ng/mL. Each specimen type was tested across five days, 10 different EIA runs, and four different robots. The standard deviations for a moderately positive specimen (1.4-1.8 ng/mL) ranged from 0.19-0.24 ng/mL and the coefficients of variation ranged from 11.5-16.9%. Standard curves for each of these specimen types exhibit excellent linearity between 0 and 20 ng/mL.

Comparison with other *Histoplasma* antigen EIAs.

FDA cleared *Histoplasma* antigen detection kits are available from ImmunoMycologics and as an analyte specific reagent (ASR) from Optimum Imaging Diagnostics (OIDx). Performance characteristics of these assays differ from the MiraVista EIA, table 2. MiraVista performs an average of 300 antigen test daily Monday-Saturday with a turnaround time of one day in 91% and 3 days in 99% of specimens. Commercial laboratories may not perform the test as frequently, increasing turnaround time. Consultation by experts in infectious disease and laboratory medicine are available to address questions from laboratory customers and clinicians.

Recommended Use of MVD EIA for Diagnosis

The test is most useful for diagnosing disseminated and moderate to severe acute pulmonary histoplasmosis [1]. Although detection of antigen in urine is most sensitive method for diagnosis of disseminated histoplasmosis, some cases will be missed by testing urine alone but detected by testing urine and serum [1]. The MiraVista antigen EIA is also useful for diagnosis of acute pulmonary histoplasmosis by detection of antigen in serum [2], meningitis by detection of antigen in cerebrospinal fluid [3] and pneumonia by detection of antigen in bronchoalveolar lavage fluid [4]. The MiraVista EIA may also be used for assessing clearance of antigen during treatment [5] and diagnosis of relapse [6].

Recommended Use for Monitoring Treatment

Both urine and serum should be tested to determine which is best for monitoring treatment. In many cases the urine is above the upper limit of the assay and may remain so for up to 6 months despite effective treatment. In such cases the serum is usually lower and is a better marker for monitoring treatment. Treatment should be continued until both the urine and serum antigen are negative. Once the serum has declined to below 5 ng/mL, urine antigen should be monitored until negative.

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Table 1. Sensitivity and specificity of the MiraVista Quantitative Galactomannan Antigen EIA

Histoplasmosis, sensitivity		Endemic mycoses, cross-reactivity [1]	Endemic controls, specificity	
Urine (N = 158)	Serum (N = 31)	Urine	Urine	Serum
91.8%	100%	70%	98%	100%

[1] Blastomycosis, 7/10; coccidioidomycosis, 6/10; paracoccidioidomycosis, 4/5; Talaromyces marneffei, 4/5

Table 2. Comparison of MiraVista *Histoplasma* antigen EIA with FDA cleared EIAs

Parameter	MVD LDT EIA	FDA-cleared EIA	ASR kit (OIDx) [1]
Quantification	Yes	No	Unknown
Monitoring treatment	Yes	No	Unknown
Diagnose relapse or treatment failure	Yes	Unknown	Unknown
Clinical sensitivity PDH	92% [1] to 100% [6]	Unknown	Unknown
Clinical specificity	99% [1, 6]	Unknown	Unknown
Specimens tested	Urine, Serum, BALF, CSF, other body fluids	Urine	Urine
Limit of detection	0.2 ng/mL	Unknown	Unknown
Turnaround time	1 day 91%, 2 days 96%, 3 days 99%	Unknown	Unknown
Expert clinical consultation	Yes	Unknown	Unknown
Publications	62	1	None

Analyte specific reagent (ASR) to be offered as a laboratory developed tests (LDT) at CAP and CLIA certified laboratories.

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