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Accuracy of the MVista® *Histoplasma* Antibody IgG, IgM Immunoassay to Evaluate Suspicious Lung Nodules

By Drs. Joseph Wheat, Chadi Hage, Deborah Blue, and Heather Largura

Endemic mycotic diseases (histoplasmosis, blastomycosis, coccidioidomycosis) are common causes of lung granulomas. They present diagnostic challenges when there is radiographic evidence of indeterminate pulmonary nodules (IPN) which are well defined nodules less than 1 centimeter in diameter, especially when found on a screening chest CT in residents of the endemic areas. Current guidelines recommend F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) in the presence of an IPN; however, specificity is reduced in regions of high endemicity[1-3] since fungal granulomas are usually FDG avid, necessitating biopsy of the IPNs to rule out infectious disease versus lung cancer. CT scans from endemic areas show three times the false positive rate compared to non-endemic areas, with granulomatous disease accounting for 50 to 75% of benign disease[1, 4, 5]. A non-invasive option to differentiate benign from malignant lesions would be very useful in this scenario. Studies have shown low sensitivity with immunodiffusion so current guidelines for IPNs suspicious for lung cancer do not recommend serologic testing to indicate infectious etiology[6, 7]. The MVista® *Histoplasma* Antibody IgG, IgM enzyme immunoassay (EIA), presents a novel means of diagnosing histoplasmosis as the cause of IPNs from endemic regions, potentially ruling out lung cancer.

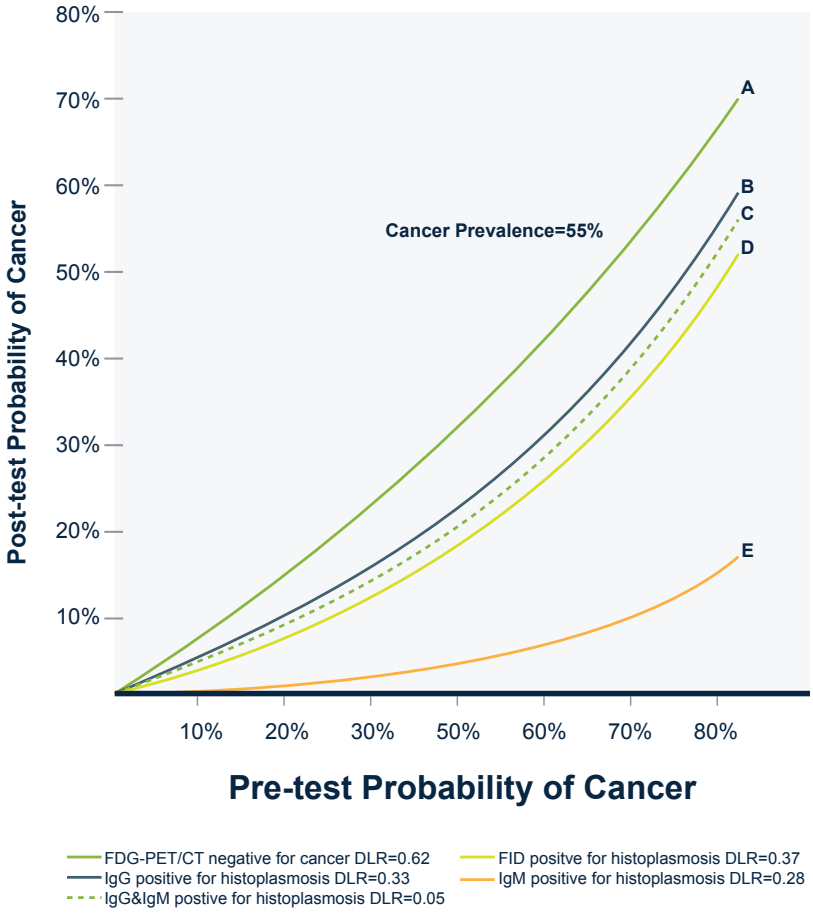
This pilot study performed at a tertiary referral research hospital in Nashville, TN compared immunodiffusion (ID) and the MVista® *Histoplasma* Antibody IgG, IgM EIA to FDG-PET/CT scans for IPNs in 152 patients from endemic areas who presented with an IPN of less than or equal to 30mm in diameter [8]. This study showed the MVista® *Histoplasma* Antibody IgG, IgM EIA to be superior to immunodiffusion (2.5-fold increase in detection) in detecting IgG antibodies to histoplasmosis. The study demonstrated a positive EIA IgG result was detected in eleven patients who also had malignancy; however, when both IgG and IgM antibodies to *Histoplasma* were present, no malignancy was detected.

For patients from endemic regions with IPN and positive *Histoplasma* IgG and IgM EIA results, 12% of granulomas were benign and etiology was attributed to histoplasmosis. The presence of IgG or IgM was associated with benign disease. The findings of this study suggest a potential non-invasive alternative to biopsy or expensive PET imaging in patients from regions of endemic mycoses who present with IPNs of ≤ 30mms and positive *Histoplasma* antibody EIA results, but further investigation is warranted with a larger study incorporating samples from endemic and non-endemic areas.

Table 1.

Cancer Prevalence 55% (83/152)	Number Positive (152 tested)	Sensitivity, CI = 95%	Specificity, CI = 95%	Negative diagnostic likelihood ratio	Negative Predictive Value
FDG-PET/CT	47 (32%)	76% (65-85)	39% (28-52)	.62 (0.38-1.00)	57 (42-72)NPV
Immunodiffusion	13 (8.5)	13% (6-23)	95% (88-99)	.37 (0.12-1.15)	69 (39-91)
Histo IgG positive	39 (26%)	41% (29-53)	87% (78-93)	.33 (0.18-0.61)	72 (55-85)
Histo IgM positive	12 (8%)	13% (6-23)	96% (90-99)	.28 (0.08-0.98)	75 (43-95)
Histo IgG and IgM positive	8 (5%)	12% (5-22)	100% (96-100)	.05 (0.003-0.83)	100 (63-100)
Histo IgG or IgM positive	43 (28%)	42% (30-55)	83% (73-91)	.40 (.23-.70)	63 (54-72)

Figure 2. Tissue acquisition test-treatment decision diagram [8]



Lines are the calculated diagnostic likelihood ratios (DLR) for 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET/CT) (A), Immunodiffusion (FID) (B), EIA IgG (C), EIA IgM (D) and combined EIA IgG and IgM serologies (E). The prevalence of cancer in the study was 55% with post-test probabilities estimated at those points. To determine the impact of fungal testing to rule out cancer and provide a comparison to FDG-PET scans, a positive histoplasmosis test was considered a negative test for cancer. Example: In a patient with a 55% pre-FDG-PET/CT probability of cancer, a negative FDG-PET scan gives a 43% post-test probability of cancer in our population (Point A). A serology test positive for only IgG antibodies (Point C) decreases the probability of cancer from 55% to 29%, a 26% point reduction in cancer risk. A positive serology for both IgG and IgM antibodies yields a 6% post-test probability of cancer (Point E). In this example using our data, a non-avid FDG-PET result does not change recommendation for resection. However, an enzyme immunoassay positive for both IgG and IgM antibodies would decrease even a 70% pre-test probability of cancer to 11% and to a surveillance strategy.

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