Test Definition: CLFA

Cryptococcus Antigen Screen with Titer, Spinal Fluid

Overview

Useful For

Aiding in the diagnosis of cryptococcosis

This test **should not be performed** as a screening procedure for the general population.

This test **should not be used** as a test of cure or to guide treatment decisions.

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CLFAT	Cryptococcus Ag Titer, LFA, CSF	Yes	No

Testing Algorithm

If result is positive, *Cryptococcus* titer will be performed at an additional charge.

For more information see Meningitis/Encephalitis Panel Algorithm

Special Instructions

- Meningitis/Encephalitis Panel Algorithm

Method Name

Lateral Flow Assay (LFA)

NY State Available

No

Specimen

Specimen Type

CSF

Specimen Required

Container/Tube: Sterile vial

Specimen Volume: 1 mL

Collection Instructions: Submit specimen from collection vial 2 (preferred), 3, or 4.

Forms

If not ordering electronically, complete, print, and send Infectious Disease Serology Test Request (T916) with the specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
CSF	Refrigerated (preferred)	14 days	
	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Cryptococcosis is an invasive fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. *C neoformans* has been isolated from several sites in nature, particularly weathered pigeon droppings. *C gattii* was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern United States and is associated with several different tree species.

Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of *C neoformans* infections occur in immunocompromised patient populations, *C gattii* has a higher predilection for infection of healthy individuals.(1,2)

In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Reference Values

Negative

Reference values apply to all ages.

Interpretation

The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid [CSF]) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the

same method utilizing dilutions to generate a titer value. CSF specimens submitted for initial diagnosis that test positive by LFA should also be submitted for routine fungal culture. Culture can aid in differentiating between the 2 common *Cryptococcus* species causing disease (*Cryptococcus neoformans* and *Cryptococcus gattii*) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured.

Disseminated infection is usually accompanied by a positive serum test.

Higher *Cryptococcus* antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

Cautions

A traumatic lumbar puncture and contamination of the cerebrospinal fluid (CSF) specimen with plasma may lead to a positive *Cryptococcus* antigen result from CSF in patients without neuroinvasive cryptococcosis.

A negative result does not preclude diagnosis of cryptococcosis, particularly if only a single specimen has been tested and the patient shows symptoms consistent with cryptococcosis.

A positive result is indicative of cryptococcosis; however, all test results should be reviewed considering other clinical findings.

Testing should not be performed as a screening procedure for the general populations and should only be performed when clinical evidence suggests the diagnosis of cryptococcal disease.

Although rare, extremely high concentrations of cryptococcal antigen can result in weak test lines and in extreme instances, yield false-negative test results.

This assay has not been evaluated for cross-reactivity in patients with trichosporonosis.

Supportive Data

Cerebrospinal fluid (CSF) retrospective specimens (111) were tested in a blinded fashion by the IMMY *Cryptococcus* Antigen Lateral Flow Assay (LFA; Normon, OK) and the Meridian Latex Agglutination (Meridian Bioscience Inc, Cincinnati, OH) assay within a 24-hour period. Of these 111 specimens, 45 were also tested by the Meridian *Cryptococcus* Antigen EIA also within a 24-hour period. Samples with discordant results after initial testing were repeated by both assays during the same freeze/thaw cycle. The results are summarized below in Table 1 and Table 2:

Table 1. Comparison of the IMMY LFA to the Meridian Latex Agglutination Assay in CSF

	Meridian Latex Agglutination			
LFA IMMY		Positive	Negative	Total
	Positive	18	0	18

	Negative	0	93	93
	Total	18	93	111

Sensitivity: 100% (18/18); 95% Confidence Interval (95% CI): 81.2%-100%
Specificity: 100% (93/93); 95% CI: 96.0%-100%
Overall Percent Agreement: 100% (111/111); 95% CI: 99.0%-100%

Table 2. Comparison of the IMMY LFA to the Meridian Cryptococcus Antigen EIA Assay in CSF

	Meridian EIA			
LFA IMMY		Positive	Negative	Total
	Positive	12	0	12
	Negative	0	33	33
	Total	12	33	45

Sensitivity: 100% (12/12); 95% CI: 72.2%-100%
Specificity: 100% (33/33); 95% CI: 87.8%-100%
Overall Percent Agreement: 100% (45/45); 95% CI: 90.8%-100%

Clinical Reference

1. Speed B, Dunt D: Clinical and host differences between infections with the two varieties of *Cryptococcus neoformans*. Clin Infect Dis. 1995;21(1):28-34
2. Chen S, Sorrell T, Nimmo G, et al: Epidemiology and host- and variety-dependent characteristics of infection due to *Cryptococcus neoformans* in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000 Aug;31(2):499-505. doi: 10.1086/313992
3. Perfect JR, Dismukes WE, Dromer F, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010 Feb 1;50(3):291-322
4. Perfect JR. Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161
5. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024;24(8):e4856. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

Performance

Method Description

The *Cryptococcus* antigen (CrAg) lateral flow assay is a sandwich immunochromatographic assay. Specimens and diluent are added to a test tube and the lateral flow device is added. The test uses specimen wicking to capture gold-conjugated, anticryptococcal antigen monoclonal antibodies and gold-conjugated control antibodies deposited on the test membrane. If cryptococcal antigen is present in the specimen, it binds to the gold-conjugated, anticryptococcal antigen antibodies. This complex wicks up the membrane and interacts with the test line, which has immobilized anticryptococcal antigen monoclonal antibodies. The antigen-antibody complex forms a sandwich at the test line causing a visible line to form. A valid test shows a visible line at the control line. Positive test results create 2 lines (control and

specimen), while negative results form only the control line.(Package insert: CrAg Lateral Flow Assay, IMMY, Norman, OK, Rev 2012)

PDF Report
No

Day(s) Performed
Monday through Sunday

Report Available
Same day/1 to 2 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Jacksonville Clinical Lab

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information
87899-*Cryptococcus* screen
87899-*Cryptococcus* titer (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CLFA	Cryptococcus Ag Screen w/Titer, CSF	29896-8

Result ID	Test Result Name	Result LOINC® Value
62074	Cryptococcus Ag Screen w/Titer, CSF	29896-8