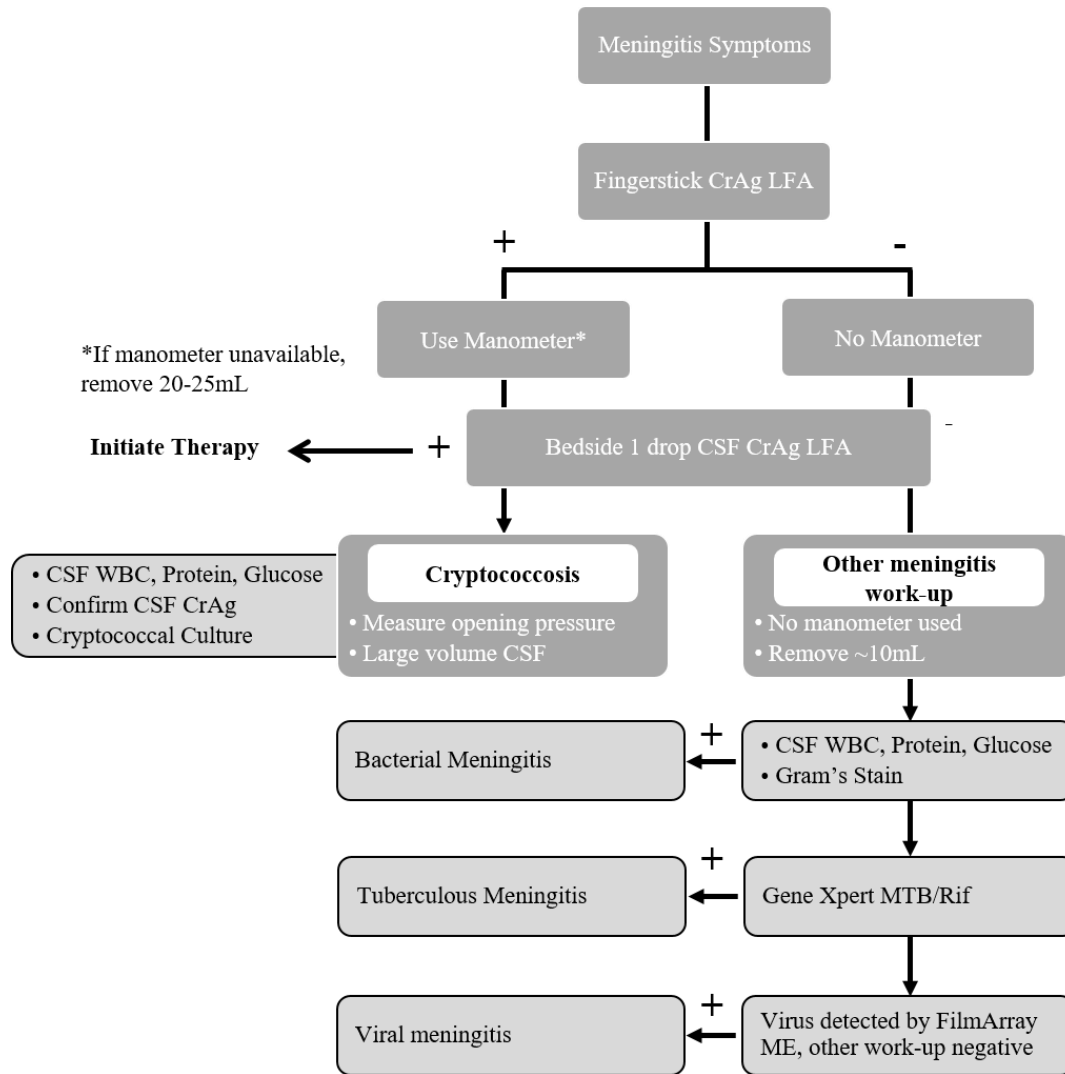


425 **Supplemental Figure 1. Stepwise Diagnostic Algorithm for Adult CSF Investigation.** In addition to
 426 BioFire ME, a CSF CrAg was obtained at bedside to direct further work-up. If CSF CrAg was positive,
 427 additional work-up included cryptococcal cultures with other testing at physician discretion. If CSF CrAg
 428 was negative, additional work-up included Gene Xpert MTB/Rif Ultra.

429



430

431

432

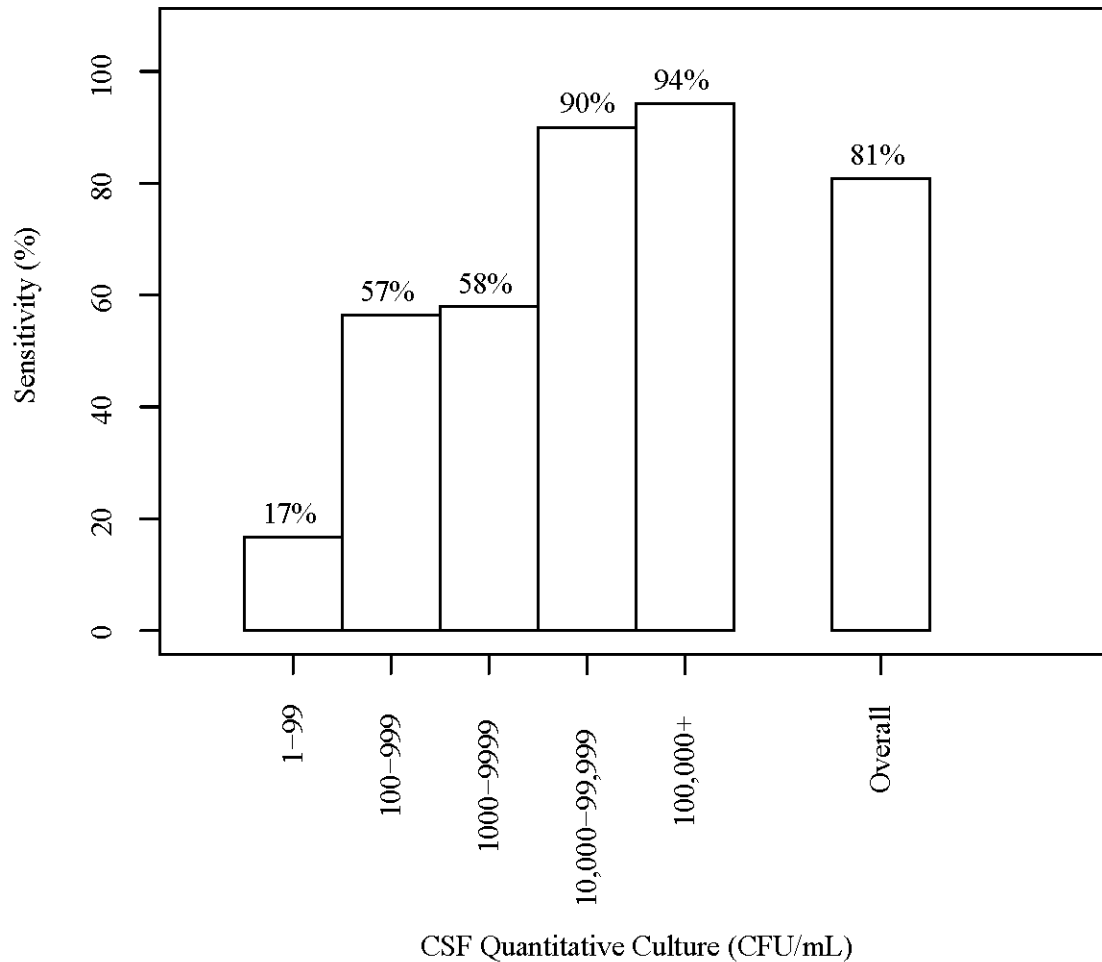
433

434

435

436

437 **Supplemental Figure 2. Sensitivity of BioFire ME among pooled (baseline and follow-up) CSF**
438 **samples, by *Cryptococcus* colony forming units/mL.** Figure includes analysis of all baseline CSF
439 samples in addition to follow-up CSF samples obtained from therapeutic lumbar punctures in participants
440 receiving antifungal therapy for cryptococcal meningitis. As with baseline samples, the sensitivity of
441 BioFire ME varied by fungal burden, with better sensitivity at higher fungal burdens.



N	12	23	19	40	105	199
---	----	----	----	----	-----	-----

442

443

444

445

446

447

448

449 **Supplemental Table 1:** Pooled diagnostic performance for *Cryptococcus* culture positivity in baseline
450 and follow-up tests.

451

Sensitivity P(T+ D+)	81% (161/199)
Specificity P(T- D-)	97% (98/101)
Positive Predictive Value P(D+ T+)	98% (161/164)
Negative Predictive Value P(D- T-)	72% (98/136)

¹CSF quantitative culture > 0 colony forming units used as gold standard for baseline and follow-up (days 2-28) specimens.

452

453 Of the 27 Biofire ME false negatives at baseline in comparison to CSF CrAg as the reference standard:

- 454
- 1 (3.7%) had a contaminated / invalid CSF quantitative culture.
 - 455 • 14 (51.9%) had sterile CSF cultures, CSF CrAg-positive only
 - 456 • 6 (22.2%) had 1-100 CFU/mL
 - 457 • 6 (22.2%) had >100 CFU/mL

458 All persons who were CSF CrAg positive were also positive for CrAg in blood, thus two false positive
459 CrAg tests in blood and in CSF are unlikely in this HIV-infected cohort with median CD4 = 15 cells/ μ L,
460 presenting with meningitis.

461 **Supplemental Table 2.** Pediatric Cohort Data.

	N=42
Demographics	
Median age, months	46 (1.0, 216)
Female sex	17 (40.5%)
Male sex	25 (59.5%)
Clinical Characteristics	
Mean Blantyre Coma Scale (1 - 5)	3.36
HIV-infected	6 (14.2%)
Malaria-positive (RDT or smear)	8 (19%)
Prior diagnosis of cerebral malaria	1 (2%)
Prior or current diagnosis of TB	5 (11%)
Taking antibiotics	15 (35.7%)
CSF Analysis Results	
CSF protein >40 mg/dL and >5 white cells/ μ L	2/42
Negative Xpert MTB/RIF Ultra result	5/10
Positive Xpert MTB/RIF Ultra result	0/10
CSF protein >40 mg/dL and >5 white cells/ μ L	5/42
Positive BioFire ME result	3/42

Data are N (%) or medians with [P25, [75].

Abbreviations: RDT, rapid diagnostic test; CSF, cerebrospinal fluid; WBC, white blood cell count.

462

463

464 **Supplemental Table 3.** Selected Pediatric Laboratory Data.

FilmArray ME result	Malaria status	HIV status	Xpert MTB/RIF Ultra result	Taking antibiotics	Elevated CSF protein and WBC
<i>C. neoformans</i>		+		Yes	
<i>S. pneumoniae</i>					
<i>S. pneumoniae</i>					
-	+			Yes	
-	+				
-	+			Yes	
-	+			Yes	
-	+				
-	+				
-	+		-	Yes	
-			-		
-			-	Yes	
-			-		
-			-	Yes	
-		+			
-		+			
-		+			
-		+			
-		+			
-					+
-					+

465