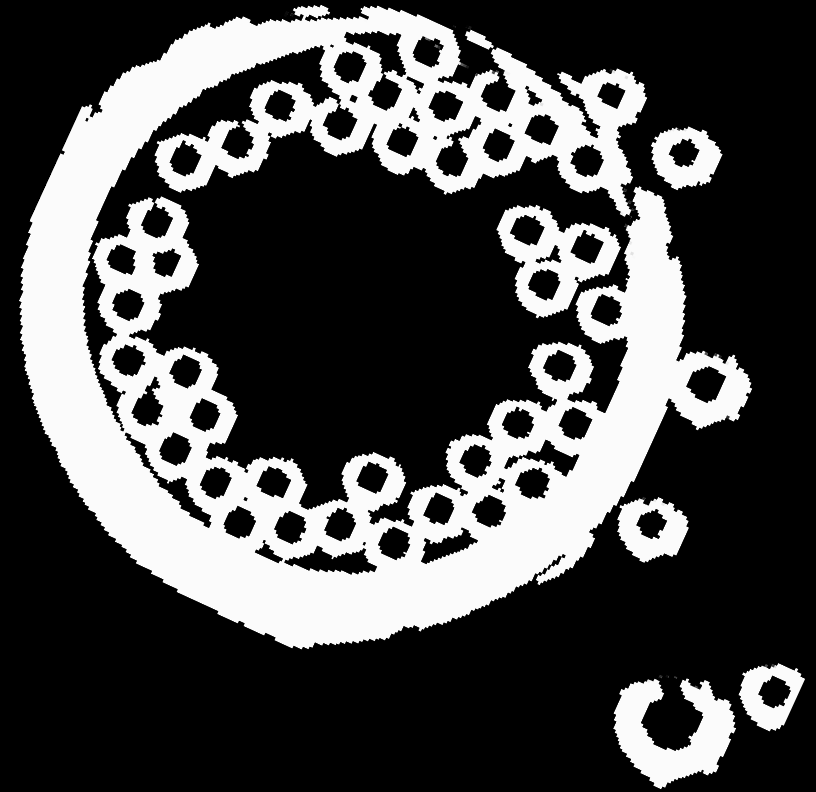


Future of Diagnostics: Metabolomics



Ian McHardy, PhD, D(ABMM)

Director, Clinical Microbiology & Core Laboratory

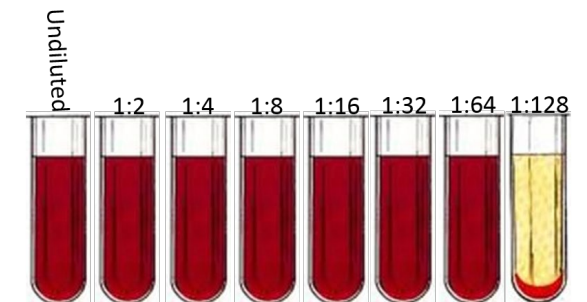
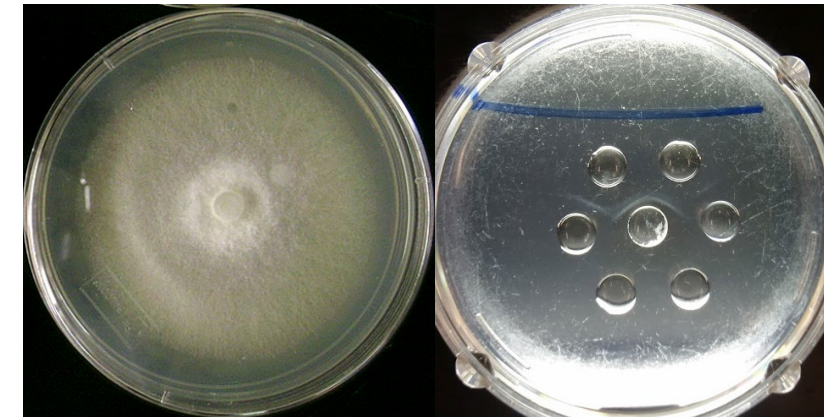
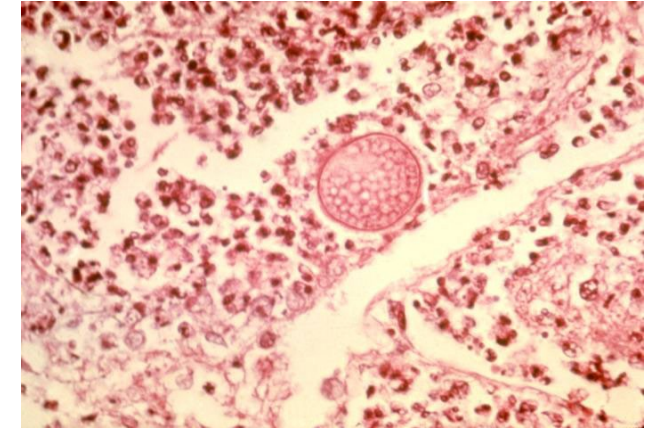
Scripps Health

mchardy.ian@scrippshealth.org



Brief Overview of Diagnostics

Test	Utility
Immunodiffusion	Best serologic diagnostic
Complement Fixation	Most commonly used prognostic and disease monitoring tool
Enzyme immunoassays	Good for relatively fast serologic testing in endemic areas
Antigen testing	Helpful for diagnosis of immunocompromised patients
Culture	Helpful for diagnosis of acute and chronic infections
Histopathology	Helpful for diagnosis of acute and chronic infections
PCR/NGS etc	Helpful for diagnosis of acute infections



Diagnosis of coccidioidal meningitis:

- CSF abnormalities
- Clinical presentation
- CSF anti-coccidioidal complement fixing antibodies (poor sensitivity)
- Culture/microscopy (poor sensitivity)

Consequences of false negative: Coccidioidal meningitis is fatal if untreated

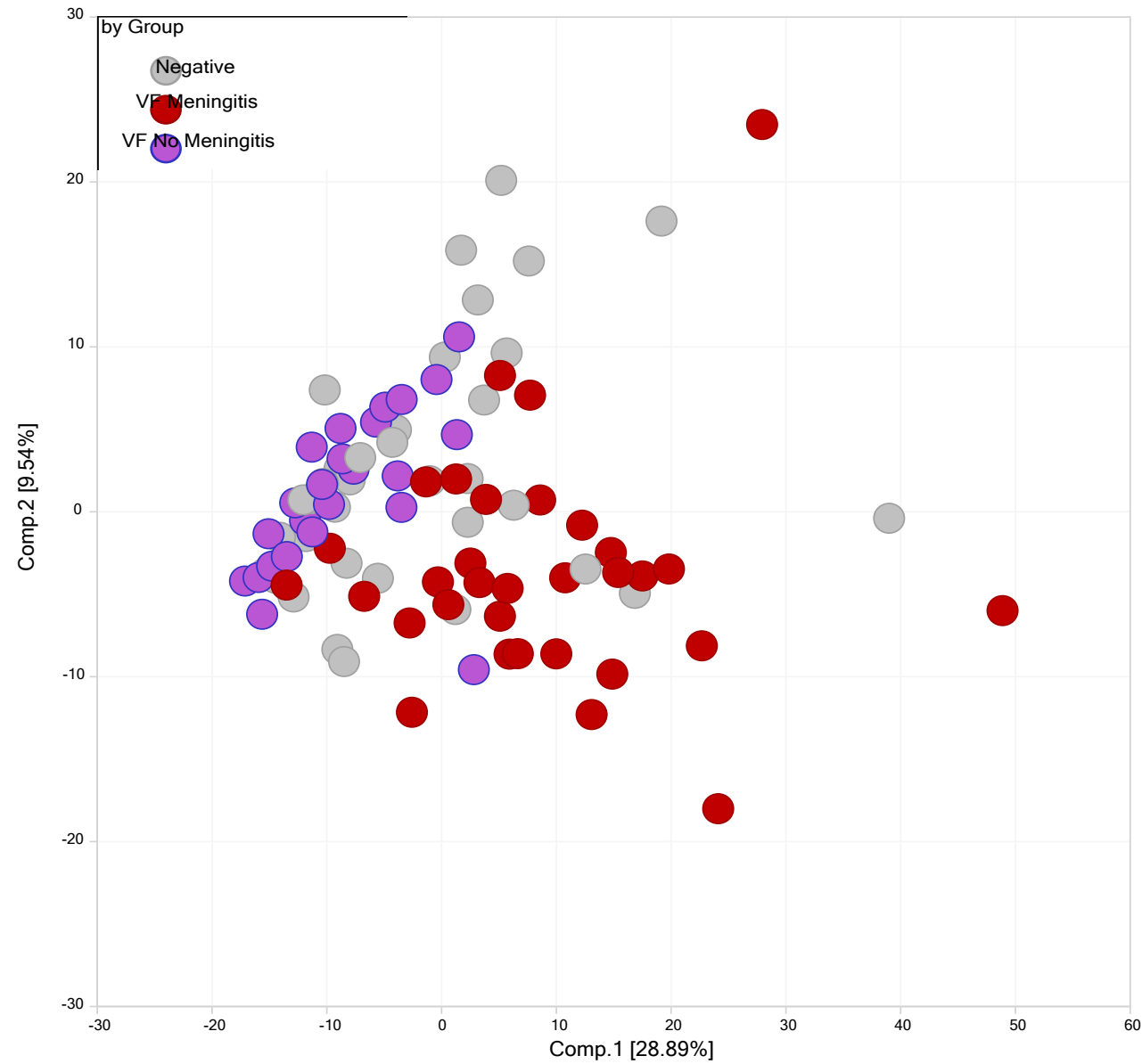
Consequences of false positive: Lifelong antifungal therapy
Many side-effects → decreased quality of life

Aims: Identify metabolomic changes associated with progression of coccidioidomycosis to coccidioidal meningitis and develop improved diagnostic(s).

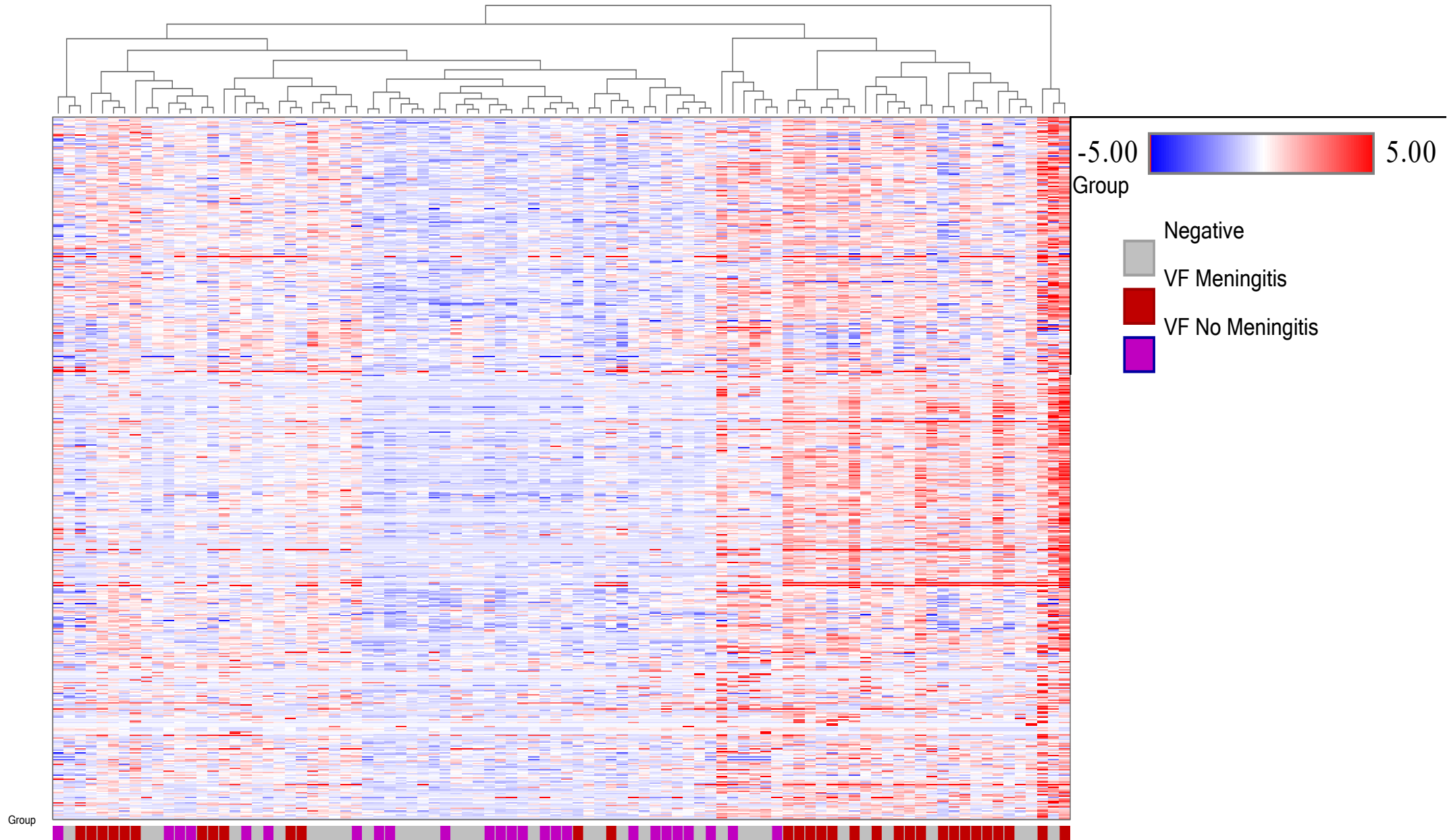
Study design:

Group Name	Group description	Patients
Negative	CSF specimens from patients without any serologic indication (in serum or CSF) of coccidioidomycosis	N=35
Valley Fever	CSF specimens from patients with serologic evidence of coccidioidomycosis in serum but not in CSF	N=26
VF Meningitis	CSF specimens from patients with serologic evidence of coccidioidomycosis in both serum AND CSF	N=33

Principal Component Analysis (PCA)



Hierarchical Cluster Analysis



Summary of Metabolomic Findings

Metabolites	Indication	Pilot cohort	Validation cohort	Merged Cohorts
Kynurenine metabolites	Altered Inflammatory status	↑	↑	↑
Lipid mediators	Inflammatory status	↑	↑	↑
Steroid metabolites	Altered steroid biosynthesis	↑	↑	↑
Bile acid metabolites	Altered bile acid biosynthesis	↑	↑	↑
Glycolysis/TCA cycle intermediates	Energy production	↑	↑	↑
Neuro-peptides	Neurological signaling	↑↓	↑↓	↑↓
Microbiome-derived Metabolites	Changes in gut microbial composition	↑	↑	↑

Open Forum Infectious Diseases

BRIEF REPORT

Sex Differences in Susceptibility to Coccidioidomycosis

Ian McHardy,^{1,2,3} Krystle L. Reagan,⁴ Jamie F. Sebastian,⁴ Bridget Barker,⁵ Derek J. Bays,^{2,6} Satya Dandekar,^{2,3} Stuart H. Cohen,^{2,3,6} Kathleen E. Jennings,⁷ Jane Sykes,^{2,5} and George R. Thompson III^{2,3,6}

¹Scripps Medical Laboratory, Scripps Health, San Diego, California, USA, ²University of California Davis Center for Valley Fever, Sacramento, California, USA, ³Department of Medical Microbiology and Immunology, University of California – Davis, Davis, California, USA, ⁴School of Veterinary Medicine, University of California – Davis, Davis, California, USA, ⁵Northern Arizona University, Flagstaff, Arizona, USA, ⁶Division of Infectious Diseases, Department of Internal Medicine, University of California Davis Medical Center, Sacramento, California, USA, and ⁷Born Free USA Primate Sanctuary, Cotulla, Texas, USA

Diagnostic potential?

Random Forest Confusion Matrix

RF Predicted Groups

Empirically established groups

CSF	Negative	VF Meningitis	VF No Meningitis	Class Error
Negative	17	4	14	0.514
VF Meningitis	2	28	2	0.125
VF No Meningitis	6	1	18	0.280
Predictive accuracy = 68.5%				

*Note that random segregation would give a predictive accuracy of **33%**.*

Questions?

Ian McHardy, PhD, D(ABMM)

Director, Microbiology Laboratory

Sorrento Mesa Core Laboratory | Scripps Health

mchardy.ian@scrippshealth.org

