NACMID case presentation

There and back again

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History

- 70 something year old admitted with abdominal pain

- Pertinent PMH

  - Bladder cancer s/p TURBT with intravesicular BCG

  - Thoracic aortic aneurysm s/p TEVAR
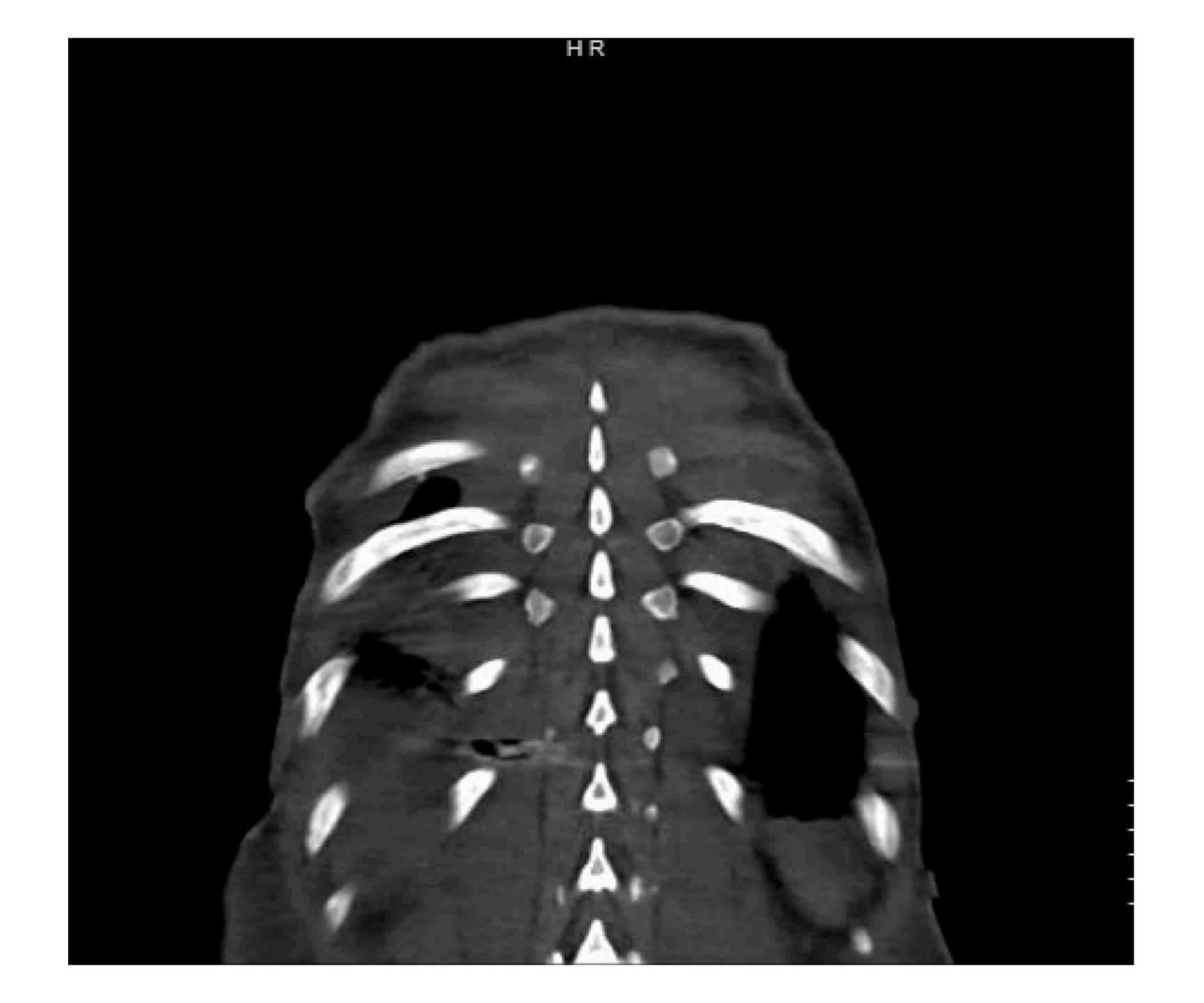
  - CAD, T2DM, COPD, CKD

Presentation

- Presented initially with abdominal pain with a negative workup

- Re-admitted 4 weeks later for persistent pain

  - Localized to the lower abdomen and radiating to the sides

- CT angiogram showed increase in the size of his endoleak (7cm → 10cm)

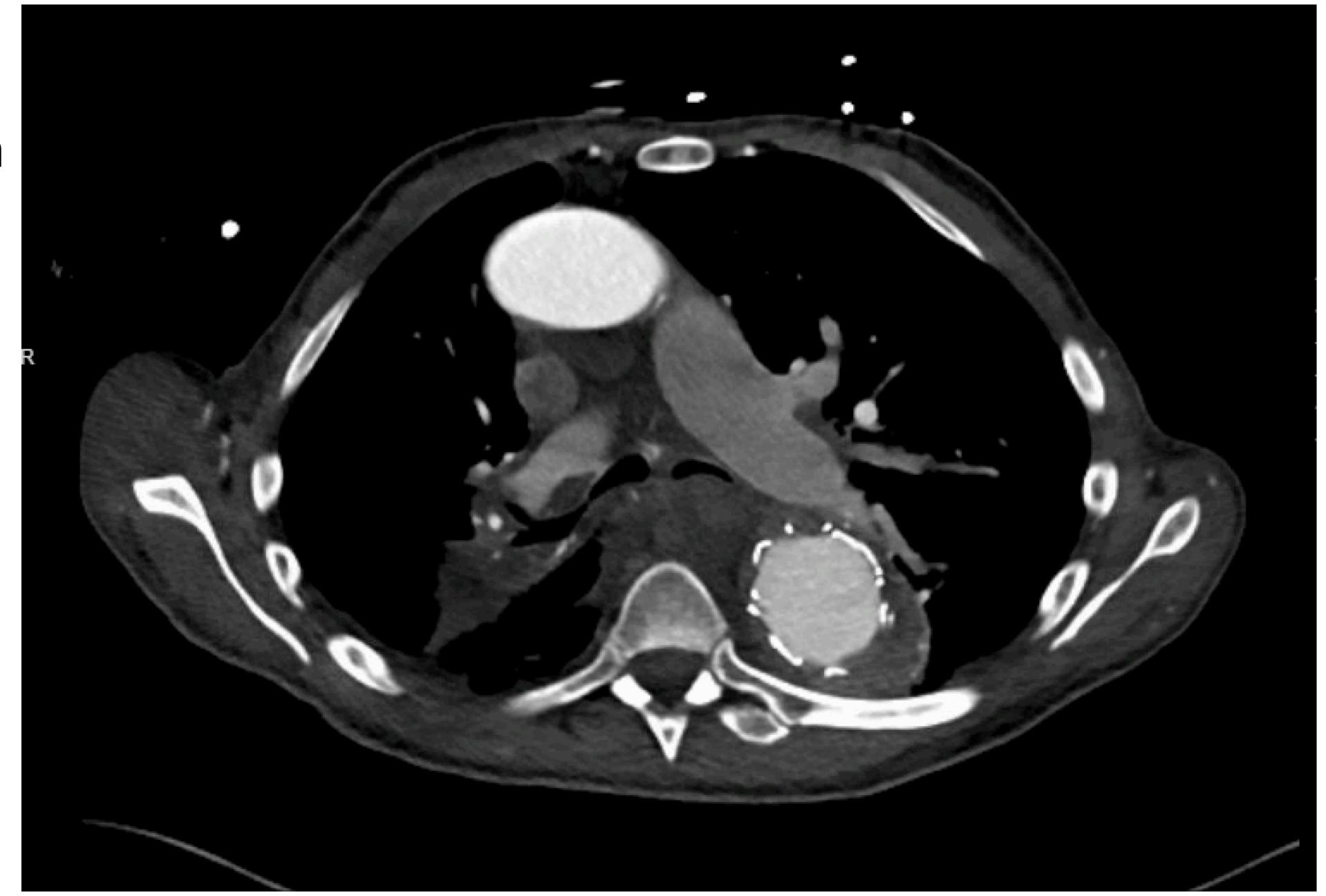- ID consulted for concern for graft infection and aortitis

Exam

- Denies fevers, chills, chest pain or back pain

- Noted to have some dyspnea on exertion

- Exam unremarkable

Imaging
CT angiogram

Imaging
CT angiogram

Laboratories

- Normal WBC and platelets, hemoglobin 7

- Remainder of labs unremarkable

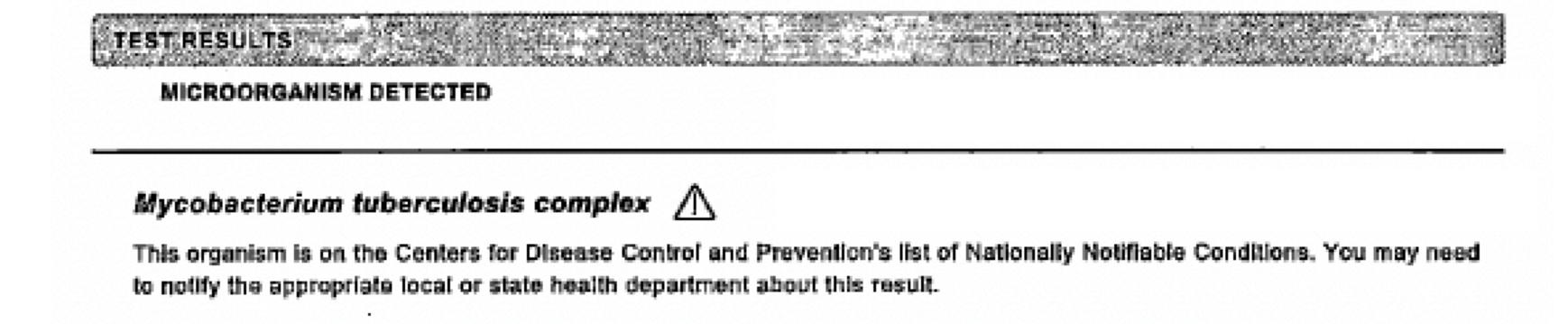- Multiple blood cultures from prior months and at present are negative

Discussion

- **What is your assessment of this patient?**

- **What types of organisms are you thinking about?**

- **What further tests would you send?**

S

- One week into his stay after a thorough negative infectious work up, a microbial cell free DNA assay (the Karius) returns with a positive result!

TEST RESULTS

MICROORGANISM DETECTED

Mycobacterium tuberculosis complex ⚠

This organism is on the Centers for Disease Control and Prevention's list of Nationally Notifiable Conditions. You may need to notify the appropriate local or state health department about this result.
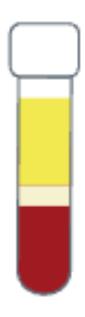
Discussion

- **How did this happen?**

Brief discussion on mcfDNA tests

Microbial cell free DNA sequencing

Step 1
Specimen Collection

5-mL standard blood draw in plasma preparation tube

Step 2
Specimen Processing

DNA extraction and library preparation

Step 3
Sequencing

Microbial cell–free DNA sequencing

Step 4
Analysis

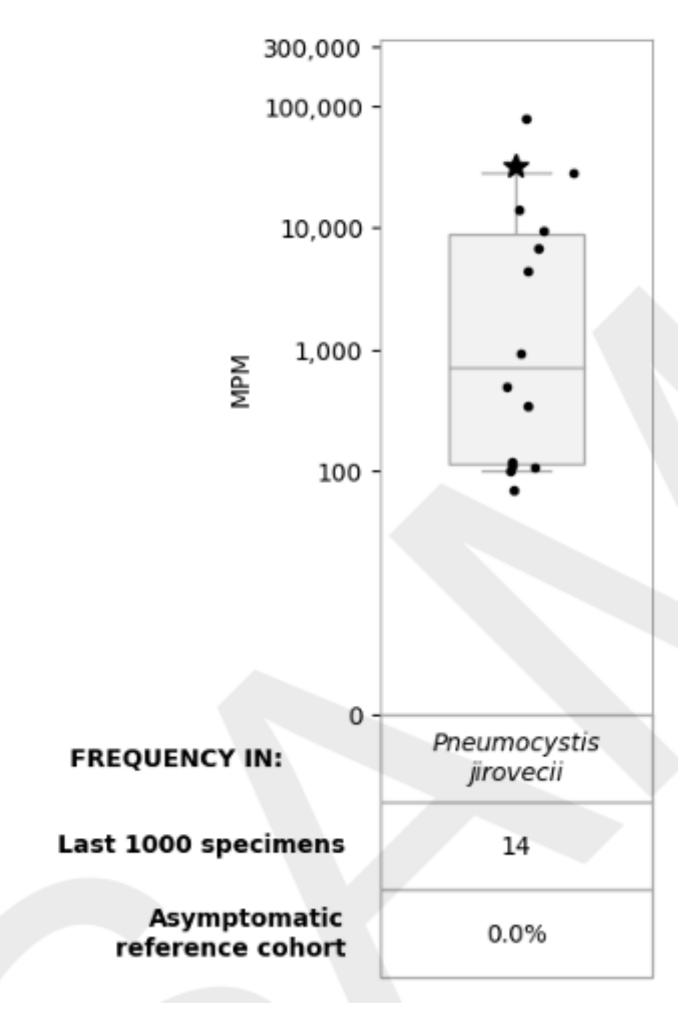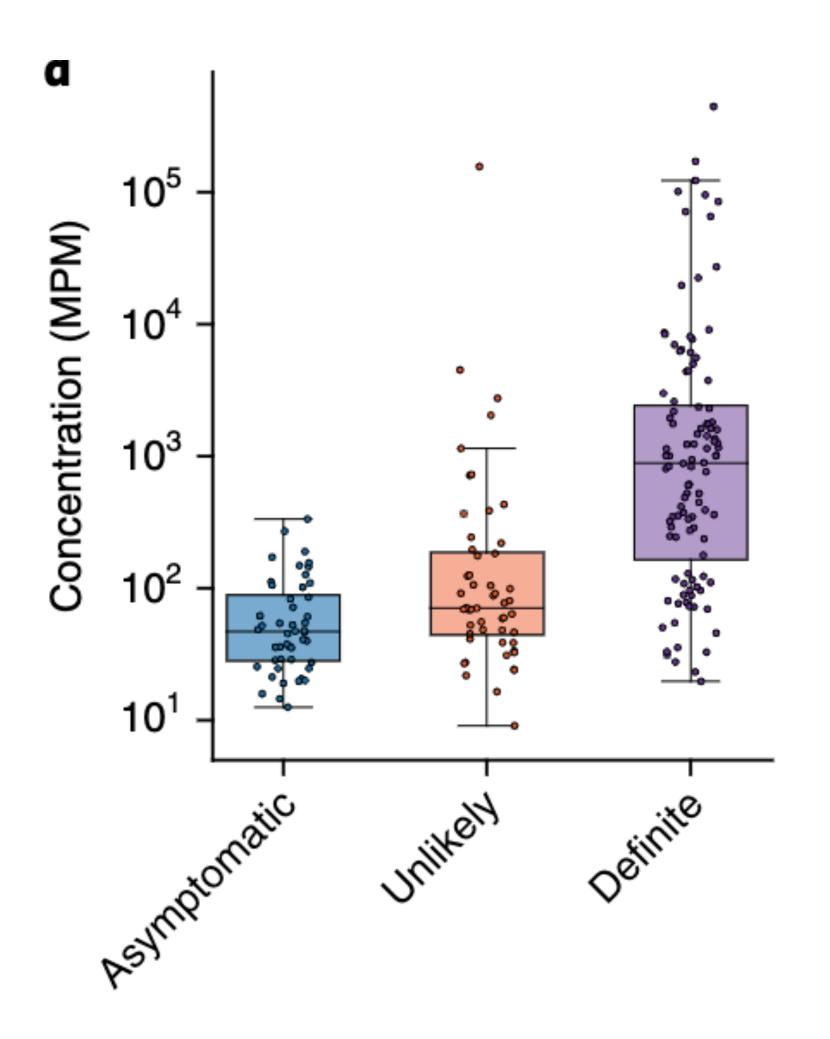Curated clinical-grade pathogen database

Step 5
Reporting

Quantitative amounts of clinically relevant pathogens

Sample report

MPM distribution for organism within Karius data

MPM distribution by symptoms in the validation paper

Blauwkamp, Nat Micro, 2019

Performance
Bloodstream infection

- Karius sent on 137 patients with known positive blood cultures from <u>typical</u> organisms

Microbial Cell-Free DNA Identifies Etiology of Bloodstream Infections, Persists Longer Than Conventional Blood Cultures, and Its Duration of Detection Is Associated With Metastatic Infection in Patients With *Staphylococcus aureus* and Gram-Negative Bacteremia
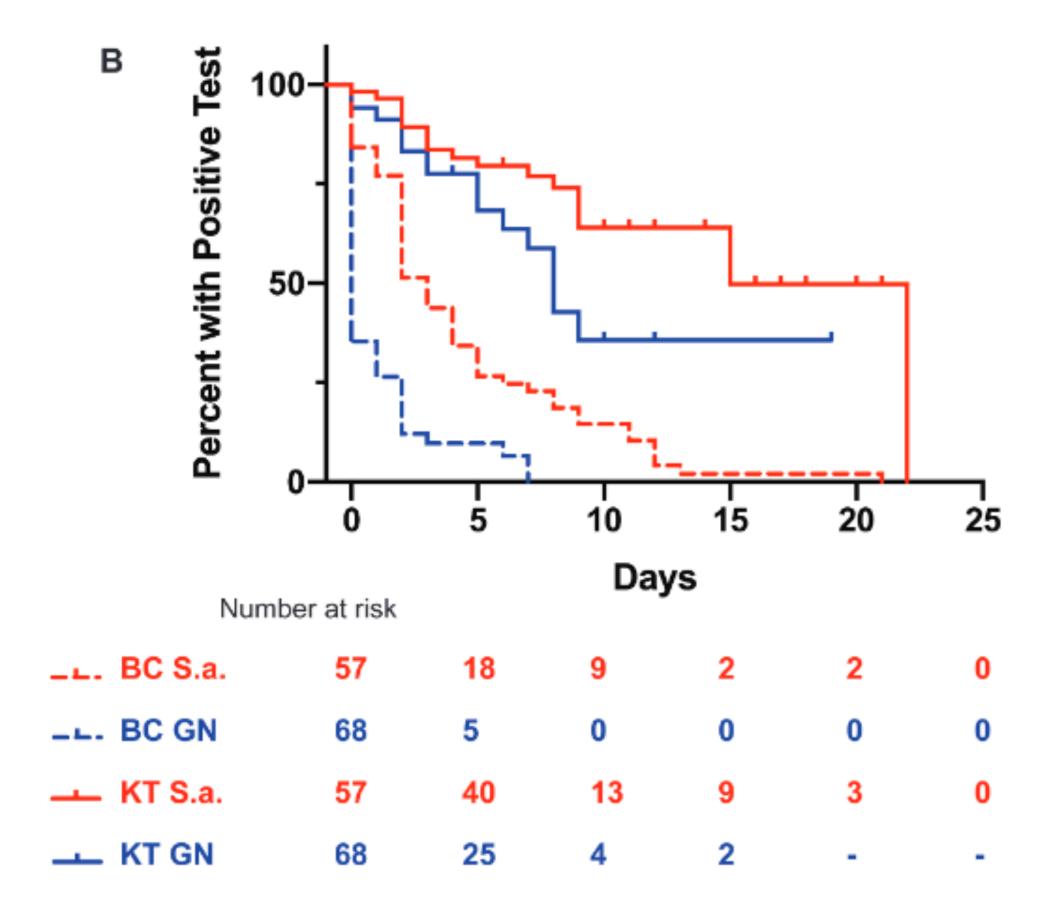
Emily M. Eichenberger,[1] Christiaan R. de Vries,[2] Felicia Ruffin,[1] Batu Sharma-Kuinkel,[1] Lawrence Park,[1] David Hong,[2] Erick R. Scott,[2] Lily Blair,[2] Nicholas Degner,[2] Desiree H. Hollemon,[2] Timothy A. Blauwkamp,[2] Carine Ho,[2] Hon Seng,[2] Pratik Shah,[3] Lisa Wanda,[4,5] Vance G. Fowler Jr,[1] and Asim A. Ahmed[2]

Organism	Karius positive	Karius negative	Agreement
Gram negatives	66	7	90.4%
S. aureus	50	14	78.1%
MRSA	28	4	87.5%
MSSA	22	10	68.8%
Total	116	21	84.7%
Negative	**9**	26	

- 5 unrelated organisms
- 4 from uncommon but theoretically plausible organisms

Eichenberger, Clin Inf Dis, 2022

Performance
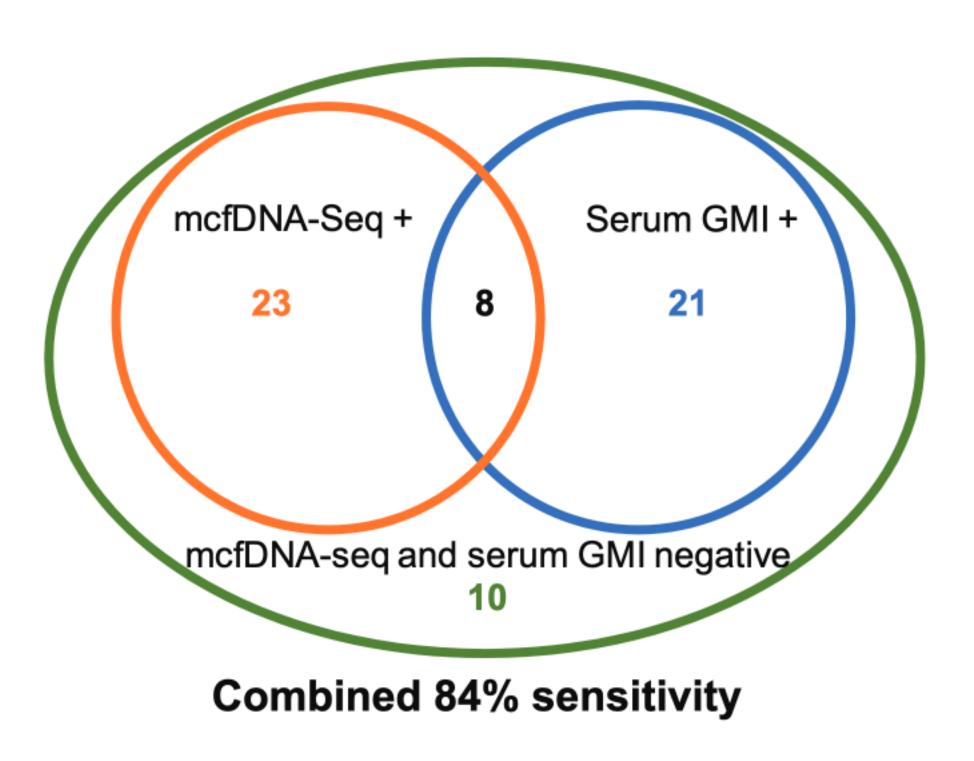## Bloodstream infection

- Karius positive up to 8 days (Gram negative) and 15 days (*S. aureus*) after index culture

- Trend towards longer positivity with metastatic infection

Eichenberger, Clin Inf Dis, 2022

Performance
Invasive mold infection

- Retrospective study using frozen samples from 75 patients with proven / probable invasive mold infection (IMI) between 1999 - 2018

- Sensitivity 51% (95% CI 39% - 62%)

  - *Aspergillus*: 31% (95% CI 19% - 46%)

  - Non-*Aspergillus*: 79% (95% CI 56% - 93%)

- Sensitivity improves when combined with serum GM

mcfDNA-Seq +   23   8   Serum GMI +   21

mcfDNA-seq and serum GMI negative   10

Combined 84% sensitivity

Hill, Clin Inf Dis, 2020

BWH experience
Overview

- Case series of 29 tests from 27 patients

- Focused on developing diagnostic stewardship testing criteria rather than evaluating testing accuracy

- All cases between January 2019 and January 2021

- 'Traditional' microbiology testing consists of

Cultures

Serologies

Targeted molecular assays (ie PCR)

Serum biomarkers

Histopathology

BWH experience
Definitions

- Infectious syndrome suspected
- Traditional testing negative

- Infectious syndrome suspected
- Organisms identified do not explain presentation or course

High pretest probability

Testing indication

- Signs and symptoms non-specific
- Treating teams desired to rule out infection

Low pretest probability

BWH experience

Definitions

Clinical impact

Positive
- New diagnosis made
- Earlier time to definitive diagnosis
- Avoidance of surgical procedure
- Optimization of antimicrobials

Negative
- Result led to unnecessary treatment
- Result led to unnecessary diagnostics

Unclear
- If neither of the above criteria are met

BWH experience
Results

Indication	N	Causative pathogen identified	Outcome		
			Positive	Negative	Unclear
1 - Suspicion for infection with negative workup	15	2 (13%)	5 (33%)	1 (7%)	11 (73%)
2 - Known infectious syndrome but continued suspicion for infection	9	7* (78%)	7 (78%)	0 (0%)	2 (22%)
3 - Non-specific signs and symptoms	5	0 (0%)	1 (20%)	2 (40%)	2 (40%)
Total	29	9 (7%)	**13 (45%)**	**3 (10%)**	**15 (52%)**

* All pathogens identified previously by traditional means

BWH experience
Conclusions

- Karius only worth sending when clinical suspicion for infection is the highest on the differential

- Highest yield for indication 1

- Reasonable for indication 2, but only if results can avert further diagnostics

- Not useful for indication 3

- Optimal time window to obtain sample not known

  - Need prospective data on utility and cost-effectiveness of preemptive collection and storage

Thank you!