Impact on Clinical Decision Making of Microbial Broad Range Metagenomic Cell-Free DNA at a Single Academic Medical Center, a Retrospective Study

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Introduction

- Conventional microbiologic testing (cultures, serology, antigenic markers, etc) may not always yield a diagnosis.
- Broad-range metagenomic cell-free DNA testing can identify a large variety of organisms from a single blood draw.[1]
- Concerns regarding metagenomic next generation sequencing (mNGS) include cost and difficulty in clinical interpretation of results.
- Few studies have evaluated the impact of mNGS testing on clinical decision making.[2,3]

Methods

- Retrospective cohort study:
  - Patients from the University of Iowa Hospitals and Clinics with blood samples sent to Karius® laboratory for mNGS.
  - Between 01/2020-06/2022.
- Reviewed:
  - Patient characteristics and clinical course.
  - Results of the mNGS and conventional tests were compared for concordance. Conventional tests included cultures, serology, antigen testing, targeted PCR.
  - Clinical impact and change in management were determined using previously established criteria outlined by Hogan et al.[3]

Table 1

Category of Clinical Impact	Change in Management	Clinical Impact Type
Positive	Yes	New diagnosis based on Karius result and not confirmed by conventional microbiological methods
		Earlier diagnosis based on Karius result and later confirmed by conventional microbiological methods
		Karius result enabled avoidance of invasive surgical biopsy
		Karius result enabled initiation of appropriate therapy
		Karius result enabled de-escalation of therapy
		Karius result enabled escalation of therapy
	No	Karius result confirmed clinical diagnosis
Negative	Yes	Karius result led to unnecessary treatment
		Karius result led to additional unnecessary diagnostic investigations
		Karius result led to longer length of stay
None	No	Karius result showed new organism but result not acted upon
		Karius result confirmed conventional microbiological diagnosis and not acted upon
		Karius test result was negative and not acted upon
		Patient died before Karius result available
Indeterminate	Yes	Could not determine clinical impact from chart review
	No	
	Indeterminate	

Hogan et al.(Clin Infect Dis. 2021 Jan 27;72(2):239-245)

Results

Table 2: Patient Demographics

Total Patients	N=37
Age (years), median (+/- SD)	54.3 (17.8)
Gender, n (%)	
Female	14 (42%)
Male	23 (58%)
Immunocompromising Condition, n (%)	29 (78%)
Bone Marrow Transplant	11 (30%)
Solid Organ Transplant	4 (11%)
Hematologic Malignancy	21 (58%)
Presence of Pulmonary Infiltrates/Nodules	30 (81%)
Infectious Disease Involvement	34 (92%)
Purpose of Testing, n (%)	
Diagnosis	30 (81%)
Rule Out	5 (14%)
Unknown	2 (5%)

Table 3: Concordance and Impact of mNGS

Total Patients	N=37
Concordance with Conventional Testing, n (%)	
Yes	11 (30%)
No	16 (43%)
NA (negative or deemed non-infectious)	10 (27%)
Clinical Impact, n (%)	
Positive	6 (16%)
Negative	0
None	30 (81%)
Indeterminant	1 (3%)

Discussion

Six cases with positive clinical impact:

- 2 cases with more rapid identification of mycobacterial pathogen (1 TB, 1 MAI) and earlier initiation of empiric therapy.
- 1 case with initiation of antifungal therapy for probable pulmonary aspergillosis.
- 1 case supported reduction of immunosuppression in a patient with a diffuse rash and pulmonary infiltrates; positive mNGS result for JCV, EBV, HPV.
- 1 case allowed for de-escalation of antifungal therapy based on negative results for more resistant organisms.
- 1 case provided reassurance to move forward with lung transplant in a patient with valvular echodensity on echocardiogram based on negative result.

Interesting false-negative result:

- Patient with renal and pulmonary lesions and a heart mass, prolonged positive beta D glucan, negative mGNS and negative blood cultures, with kidney biopsy demonstrating fungal forms on pathology review. Blood and right heart mass cultures eventually grew *Fusarium sp.*

Conclusions

- Overall clinical impact of mNGS appears limited.
- Although the criteria by Hogan et al. that we used in this study considered “de-escalation of therapy” as positive impact, a negative mNGS result should not be used to rule out any type of infection.
- There may be a niche for more rapid identification of mycobacterial pathogens over conventional AFB cultures.
- mNGS results may provide a useful additional piece of information in some cases, but must be interpreted in the context of the whole clinical picture and evaluation.
- Further studies are needed to identify patient populations or disease factors in which this test has clinical impact.

Citations

1. Miao Q, Ma Y, Wang Q, Pan J, Zhang Y, Jin W, Yao Y, Su Y, Huang Y, Wang M, Li B, Li H, Zhou C, Li C, Ye M, Xu X, Li Y, Hu B. Microbiological Diagnostic Performance of Metagenomic Next-generation Sequencing When Applied to Clinical Practice. Clin Infect Dis. 2018 Nov 13;67(suppl_2):S231-S240.
2. Shishido AA, Noe M, Saharia K, Luethy P. Clinical impact of a metagenomic microbial plasma cell-free DNA next-generation sequencing assay on treatment decisions: a single-center retrospective study. BMC Infect Dis. 2022 Apr 13;22(1):372
3. Hogan CA, Yang S, Garner OB, Green DA, Gomez CA, Dien Bard J, Pinsky BA, Banaei N. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2021 Jan 27;72(2):239-245.