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PICKUP: Pneumonia in the ImmunoCompromised - use of the Karius Test® for the detection of Undiagnosed Pathogens

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Background

Pneumonia is the most common infectious cause of morbidity and excess mortality complicating hematopoietic cell transplantation and treatment of hematologic malignancy (1, 2). Standard bronchoscopic and noninvasive microbiologic testing identifies a causative pathogen in less than half of cases. The Karius Test® (KT), a plasma microbial cell-free DNA (mcfDNA) sequencing test, may improve diagnostic yield.

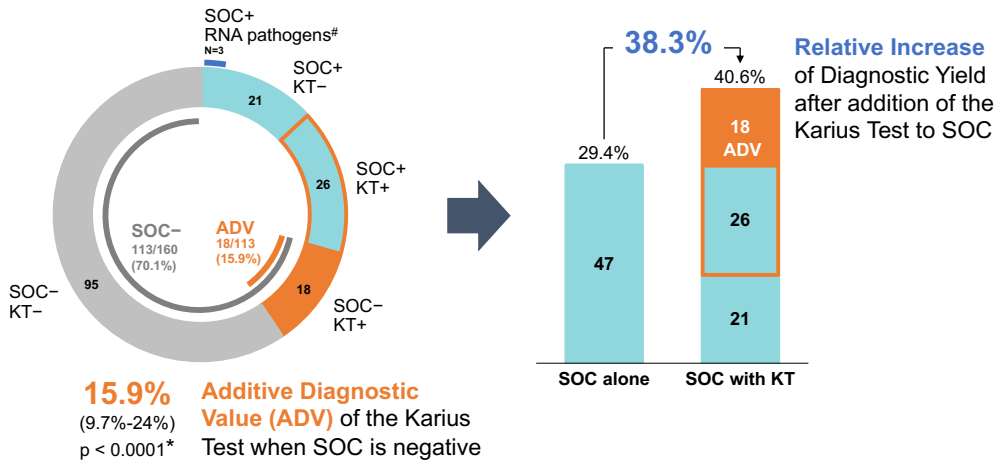
Study Design and Population

- Patients with hematologic malignancy or recent hematopoietic cell transplantation undergoing bronchoscopy for suspected pneumonia were prospectively enrolled in this observational study conducted at ten US medical centers.
- An independent committee of expert physicians blinded to the KT results reviewed a composite standard of microbiologic and molecular testing (**Table 1**), imaging results, clinical documentation, and any available additional Standard of Care (SOC) testing to adjudicate a probable cause of pneumonia.
- The composite standard included a prospectively defined Minimum Diagnostic Standard (MDS) encompassing a set of core microbiologic and molecular test results collected from SOC and completed by supplemental testing through a study reference laboratory, as necessary (**Table 1**).
- The committee then adjudicated whether a probable cause of pneumonia was identified by the KT.
- Per-protocol population - All subjects that met the study eligibility criteria AND had an enrollment KT collected within 24 hours after enrollment with valid test result AND met MDS for invasive and non-invasive SOC microbiologic testing results AND did not have protocol deviations that would invalidate SOC testing as an appropriate comparator were included in final analyses.
- Subjects positive for SARS-CoV-2 by any molecular testing within the 14 days prior to enrollment were excluded.
- Additive Diagnostic Value (ADV) was defined as the % of patients with an adjudicated probable cause of pneumonia identified by the KT when there was no adjudicated probable cause of pneumonia identified by SOC.
- The primary hypothesis for this study was that the ADV of the KT in the per-protocol population would be > 5%.

The Karius Test

- The KT was developed and validated in the Karius CLIA certified/CAP accredited lab (Redwood City, CA) to detect and quantify mcfDNA in plasma.
- Following mcfDNA enrichment, sequencing, and alignment to a curated database of reference genomic sequences, test results were generated using Karius versions 3.6 and 3.7 analytical pipelines, which were designed to detect and quantify 1,563 microbes across bacteria, DNA viruses, fungi, and other Eukaryotes.
- Plasma mcfDNA of microorganisms observed above background at statistically significant levels were reported and quantified in molecules per microliter (MPM).
- For >85% of tests, time to result reporting is the next day from sample receipt.

Fig 1. Additive Diagnostic Value (ADV) of the Karius Test



15.9% (9.7%-24%) p < 0.0001*

Additive Diagnostic Value (ADV) of the Karius Test when SOC is negative

#The Karius Test only detects DNA pathogens; * When compared with an ADV of 5%

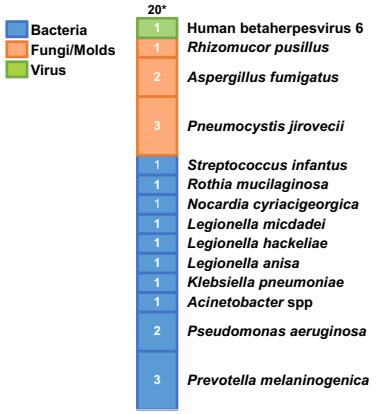
Table 1. Diagnostic Testing Utilized by Blinded Adjudication Committee Including the Required Minimum Diagnostic Standard

Standard of Care Adjudication						
Microbiological and Molecular Testing (Standard of Care and Study Reference Laboratory)						Narratives and Reports
Non-Invasive			Invasive			
Test	Primary sample type	Secondary sample type	Test	Primary sample type	Secondary sample type	Hospital Admission and Discharge Notes
Bacterial culture	Blood	N/A	PJP Testing (DFA Stain, GMS stain, PCR)	BAL	Bronchial Wash	Progress Notes within 48h of Enrollment, at Minimum
Galactomannan	Serum	BAL	Gram stain and bacterial culture			First Infectious Disease Consult
Respiratory Viral Panel	Nasopharyngeal Swab	Nasal Wash or BAL	Fungal stain and fungal culture			First Pulmonary Consult
			AFB smear and culture for mycobacteria			Bronchoscopy Report
All other testing collected for SOC						Radiology Reports

Minimum Diagnostic Standard Other Available Testing and Clinical Information BAL, Bronchoalveolar Lavage

1. Certan, M., et al., *Incidence and Predictors of Community-Acquired Pneumonia in Patients With Hematological Cancers Between 2016 and 2019.* Clinical Infectious Diseases, 2022.
2. Schuster, M.G., et al., *Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study.* Open Forum Infect Dis, 2017. 4(2): p. ofx050.

Fig 2. Adjudicated Probable Causes of Pneumonia Identified by the Karius Test Among Patients with no Pathogen Identified by SOC Testing



*Two patients had two adjudicated probable causes of pneumonia by KT

Results

- ✓ 160 patients meeting the pre-specified per-protocol population criteria were enrolled between Jan 3, 2020 and Feb 4, 2022
- ✓ An adjudicated probable cause of pneumonia was identified by SOC in 47/160 (29.4%) patients
- ✓ The KT identified an adjudicated probable cause of pneumonia in 18/113 (15.9%, [95% CI: 9.7%-24%]; p <0.0001) patients with no cause of pneumonia identified by SOC testing (**Fig. 1, Fig. 2**)
- ✓ The combination of SOC and the KT identified a probable cause of pneumonia in 65/160 (40.6%) patients

Conclusions

- ✓ KT identified an adjudicated probable cause of pneumonia in 15.9% of immunocompromised patients where no microbial etiology was identified by SOC, including bronchoscopy
- ✓ Compared to SOC testing performed within 7 days of enrollment, the KT increased the adjudicated diagnostic yield for pneumonia by 38.3%
- ✓ KT detected a broad spectrum of organisms not identified by SOC
- ✓ Despite an extensive required minimum diagnostic standard, SOC identified the microbial etiology of suspected pneumonia in only 29.4% of patients
- ✓ Collectively, these data suggest that the non-invasive KT can improve detection of the microbial etiology for suspected pneumonia in immunocompromised patients

These are preliminary results pending additional validation

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