Plasma cell free DNA (cfDNA) Test for Diagnosis of Infectious Diseases in Children: A Tertiary Care Children's Hospital Experience

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Introduction

Plasma cell free DNA (cfDNA) test (Karius Test®, KT) has emerged as an attractive diagnostic modality allowing noninvasive broad-range pathogen detection, and fast diagnosis. There are however few studies examining the impact of the KT in the diagnosis and management of infections in children. Our study aimed at evaluating the clinical impact of plasma cfDNA test since it was used at our institution.

Methods

Our retrospective study included children between 0 to 21 years of age who were admitted to Driscoll Children's Hospital, Corpus Christi, Texas between January 2019 and January 2022. Demographic and clinical course data were collected. KT and conventional tests (CT) results were analyzed to determine their agreement and clinical relevance of organisms. Clinical impact in diagnosis was assessed separately according to revised objective grading criteria.

Results

Among 182 patients identified, the median (SD) age was 9 (6.1) years, with 99 (54.4%) males and 150 (82.4%) Hispanic, 53 (29.1%) patients are immunocompromised, the median (SD) hospital length of stay was 17.2 (37.7) days. Among 186 Karius Test® ordered (Table 1), 97 (52.2%) tests were sent from general wards. 102 (54.8%) were positive for one or more organisms. Median (range) turn-around time for KT 2.8 (1.7-11.6) days. 59 (31.7%) KT results had positive clinical impact in diagnosis (Table 2 and 3), higher positive impact were found in the diagnosis of pneumonia (44.4%), bacteremia (42.9%), and musculoskeletal infection (41.2%). KT was the only diagnostic modality that provided the diagnosis in 41 (22%) cases (Table 3), including *Streptococcus pneumoniae*, *Pneumocystis jirovecii*, *Rickettsia typhi*, and *Bartonella henselae*. Among 41 cases, KT had shorter turnaround time than conventional tests in 31 (75.6%) cases.

Conclusions

In this retrospective cohort, we show that the plasma cell free DNA (cfDNA) test (Karius Test®) provided the only method of etiological diagnosis in 41 children. It was particularly useful in the diagnosis of pneumonia, musculoskeletal infection, bacteremia, Pneumocystis jirovecii and murine typhus with a relatively short turnaround time.

Table 1. Characteristics and Results of Plasma CfDNA Test (Karius Test®) Ordered

Category and Subcategory	Total tests (N=186)
Ordering teams, n (%)	
General wards	**97 (52.2)**
PICU	59 (31.7)
Subspecialty clinic	19 (10.2)
CICU	7 (3.8)
NICU	4 (2.2)
Indications for KT, n (%)	
Fever without a focus for < 7 days	**82 (44.1)**
Fever without a focus for ≥ 7 days	**38 (20.4)**
Pulmonary lesions identified on CXR or chest CT scan	**47 (25.3)**
Meningoencephalitis or brain lesions on head CT scan or brain MRI	21 (11.3)
Musculoskeletal lesions on extremities MRI	16 (8.3)
Cutaneous and facial lesion	16 (8.6)
Cervical lymphadenopathy	15 (8.1)
Liver or spleen lesions on abdominal ultrasound or CT scan	13 (7.0)
Cardiovascular insufficiency	12 (6.5)
Neutropenia	10 (5.4)
Positive KT results, n (%)	**102 (54.8)**
Turnaround time in days, mean (IQR)	**2.8 (1.7-11.6)**

KT: Karius Test®. CXR: chest X-ray. IQR: interquartile range.

Table 2. Objective Evaluation Criteria for Clinical Impact of Plasma CfDNA Test (Karius Test®) in Diagnosis

Clinical impact in diagnosis		
Details	Category	Total tests=186 n (%)
No change in diagnosis confirmed by only KT	**Positive**	4 (2.2)
New diagnosis confirmed by only KT		37 (19.9)
Earlier new diagnosis based on KT result, later confirmed by CT		18 (9.7)
Total		**59 (31.7)**
KT results led to additional unnecessary diagnostic investigations	Negative	1 (0.5)
KT result showed new organism, but results are not related to symptoms		21 (11.3)
Total		22 (11.8)
KT confirmed conventional microbiological diagnosis	No	19 (10.2)
Negative KT results	Indeterminate	84 (45.2)
KT results showed specimen doesn't meet the Karius quality standards for the testing protocol		2 (1.1)
Total		86 (46.2)

KT: Karius Test®. CT: conventional tests. Revised from Hogan et al.

Table 3. Rate of Positive Clinical Impact in Diagnosis and Pathogens Identified Only by Karius Test®

Final diagnosis	Rate of positive clinical impact in diagnosis, n/N*(%)	**Pathogens identified by only KT**	Number
Pneumonia	16/36 (44.4)	***Streptococcus pneumonia***	**5**
		Pneumocystis jirovecii	**3**
		Pseudomonas aeruginosa	3
		Haemophilus influenzae	2
		Fusobacterium nucleatum	1
		Prevotella melaninogenica	1
		Rhizopus microsporus	1
MSK infection	7/17 (41.2)	*Pseudomonas aeruginosa*	2
		Staphylococcus aureus	2
		Haemophilus influenzae	1
		Kingella kingae	1
		Proteus mirabilis	1
Cat scratch disease	4/11 (36.4)	*Bartonella henselae*	4
Murine typhus	4/14 (28.6)	*Rickettsia typhi*	4
Bacteremia	6/14 (42.9)	*Escherichia coli*	2
		Staphylococcus aureus	2
		Haemophilus influenzae	1
		Staphylococcus epidermidis	1
Viremia	3/5 (60)	HSV-1	1
		CMV	1
		HHV-6	1
Cervical lymphadenitis	1/9 (11.1)	*Streptococcus pyogenes*	1

KT: Karius Test®. MSK infection: Musculoskeletal infection, including osteomyelitis, septic arthritis, and myositis. HSV: herpes simplex virus. CMV: Cytomegalovirus. HHV-6: human herpesvirus.

*N: total number of each final diagnosis in 186 cases.