Plasma Metagenomic Sequencing & BALF Metagenomic Sequencing

Leigh Furman, PharmD - Sr. Medical Science Liaison, Karius

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Background

Advantages and Limitations of Various Diagnostic Tools

	Culture	Antigen Tests	Serology	PCR
Advantages	• Traditional “gold standard” • Can isolate colonies • Can perform susceptibility	• Rapid • Inexpensive	• May detect non-culturable organisms	• Relatively higher sensitivity • Relatively higher specificity • May have shorter TAT (in-house v. send-out) • Multiplex PCR panels 4 to > 25 pathogens • Some are FDA-cleared
Limitations	• Can have prolonged TAT • Limited sensitivity • Limited species resolution • May require invasive sample	• Variable sensitivity • Variable specificity (subject to false-positives, or cross-reactivity between pathogens)	• Lower sensitivity in IC hosts • Subject to pathogen cross-reactivity • Weeks to months for antibody production (false negative in early infection) • Prone to false-positives and/or persistent positivity	• Fewer pathogens detected • Require a-priori hypothesis for suspected organism • May require send-out

TAT = turnaround time; PCR = polymerase chain reaction; IC = immunocompromised

Plasma Metagenomic Sequencing (mNGS) Test Overview

Liquid biopsy for infectious diseases

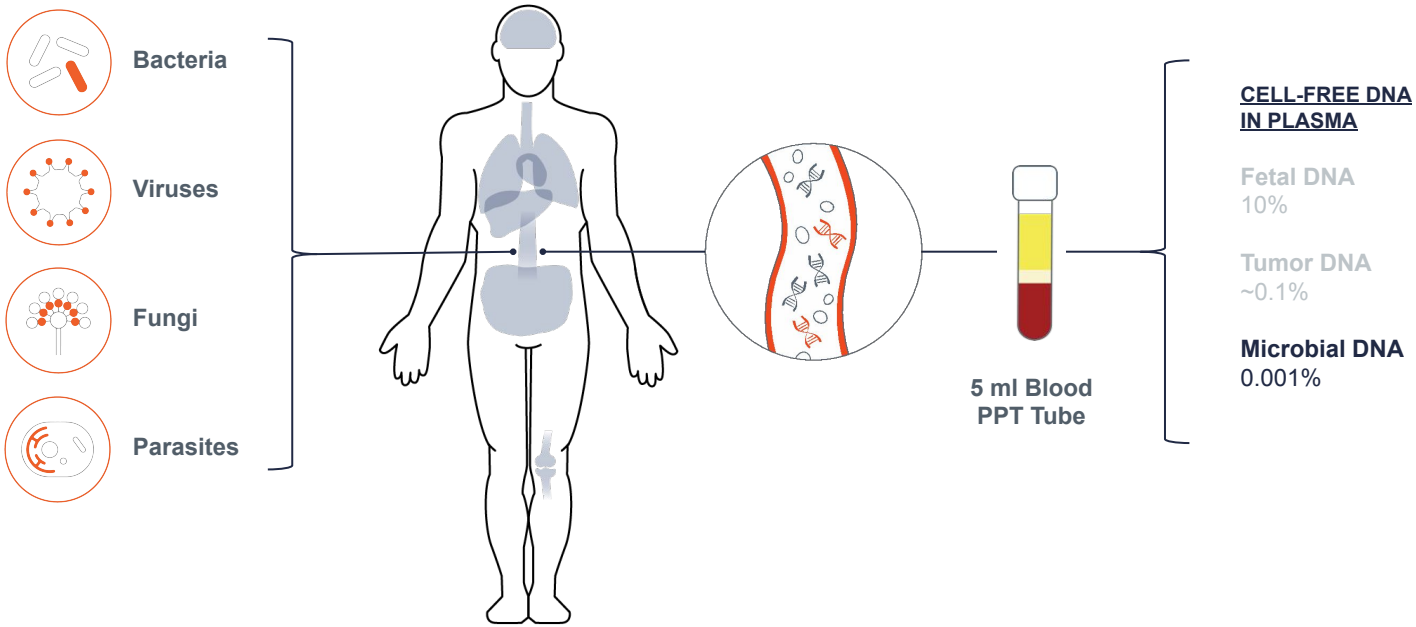
Plasma mNGS is a blood-based test using metagenomic next-generation sequencing (mNGS) of **microbial cell-free DNA (mcfDNA)**.

1 blood sample (specifically, plasma)

1 day processing

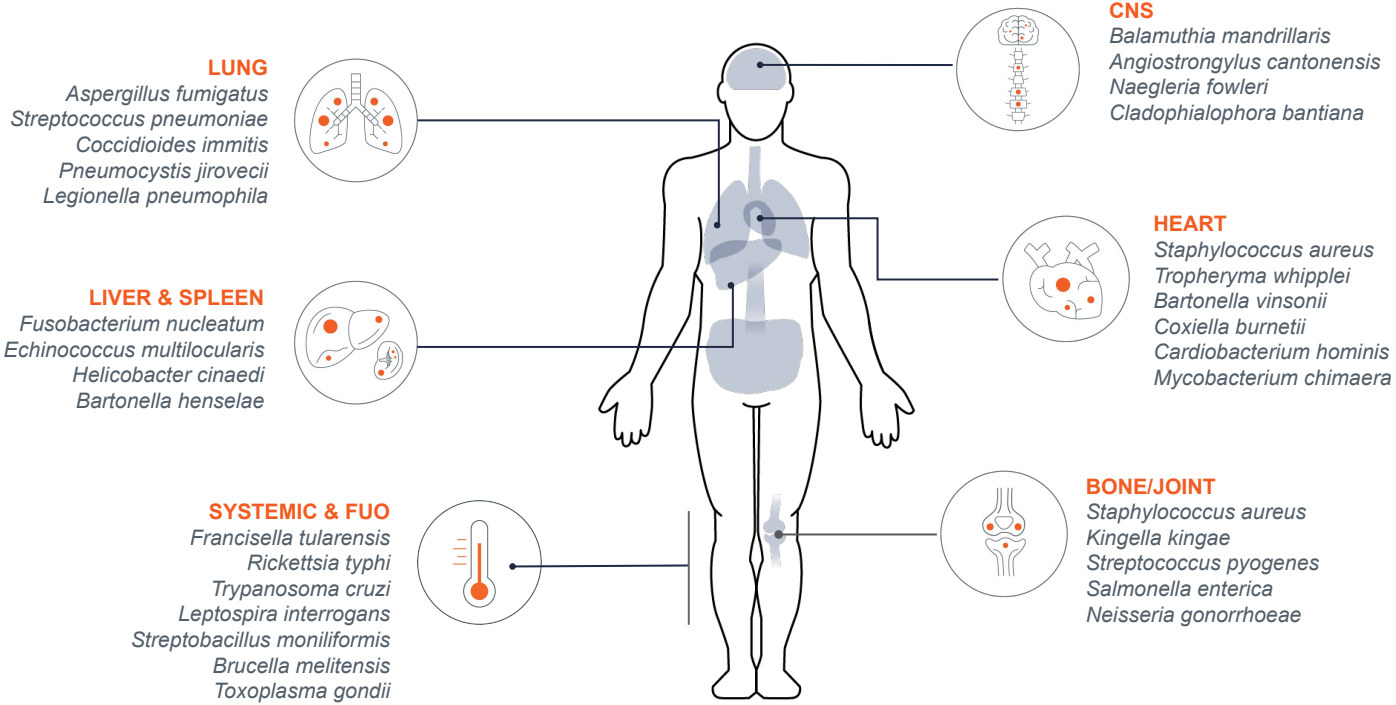
1000+ detectable pathogens

Microbial cell-free DNA (mcfDNA)

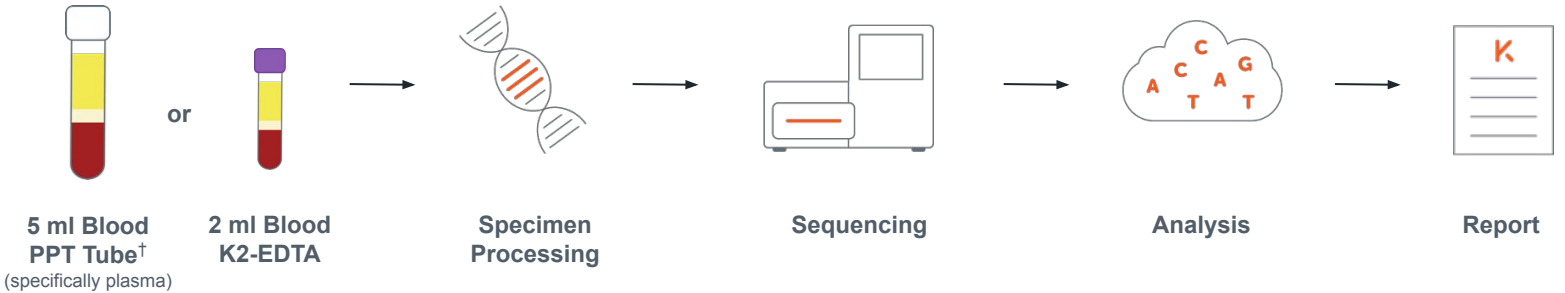


1. Blauwkamp, T. A. et al. *Nat.Microbiol.* 4, 663–674 (2019)
2. Hu, P., Liang, D., Chen, Y. et al. J. *TranslMed.* 17, 124 (2019)
3. Volik, S. et al. *Mol. Cancer Res.* 14, 898–908 (2016)

Plasma mNGS Provides Minimally-invasive Detection of Pathogens Associated with Deep-seated and Difficult-to-diagnose Systemic Infections



Plasma Metagenomic Sequencing – Test Process



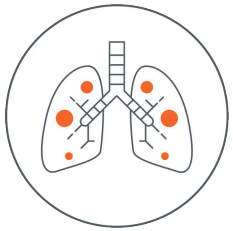
The Plasma Metagenomic Sequencing Test Can Detect Common AMR Markers for 4 Classes of Antimicrobials Across 18 Bacterial Pathogens

Gram-Negative Bacteria	AMR Marker						
	SCC*mec*	*mecA*	*mecC*	*vanA*	*vanB*	CTX-M	KPC
Carbapenem resistant and extended spectrum beta-lactamase (ESBL) producing bacteria							
E. cloacae						+	+
E. coli						+	+
K. aerogenes						+	+
K. pneumoniae						+	+
K. oxytoca						+	+
P. mirabilis						+	+
P. vulgaris						+	+
S. bongori						+	+
S. enterica						+	+
S. marcescens						+	+
P. aeruginosa						+	+
A. baumannii						+	+
A. calcoaceticus						+	+

Gram-Positive Bacteria	AMR Marker						
	SCC*mec*	*mecA*	*mecC*	*vanA*	*vanB*	CTX-M	KPC
Methicillin-resistant *Staphylococci*							
S. aureus	+	+	+				
S. epidermidis		+	+				
S. lugdunensis		+	+				
Vancomycin-resistant *Enterococci*							
E. faecalis				+	+		
E. faecium				+	+		

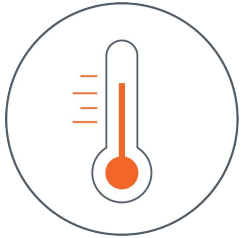
Plasma mNGS: Diagnostic Applications

Diagnostic Applications of Plasma mNGS



Complicated Pneumonia

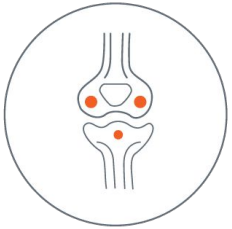
Invasive Fungal Infections



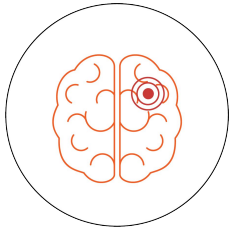
FUO

Endocarditis

Febrile Neutropenia



Osteomyelitis



Focal Abscess

Zoonoses

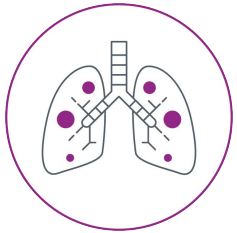
Diagnostic applications of plasma mNGS

Endocarditis

Eichenberger EM, et al. (Duke University)

Fowler VG, et al. (2023 Duke-ISCVID Criteria)

Flurin L, et al. (Mayo Clinic)

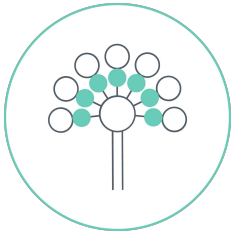


Pneumonia

Bergin SP, et al. (PICKUP-Multicentered)

Dworsky ZD, et al. (Rady's Children)

Foong KS, et al. (OSF St. Francis)



Invasive Fungal Infections

Armstrong AE, et al. (Lurie Children's)

Vissichelli NC, et al. (Virginia Commonwealth University)

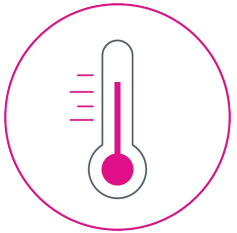
Gracia, M., et al. (Rady's Children)

Hoenigl M, et al

Febrile Neutropenia

Benamu E, et al. (Stanford)

Yu et al. (Advent Health Cancer Institute)



Fever of Unknown Origin

Francisco DMA, et al. (Baylor St. Luke)

Daher M, et al. (Baylor St. Luke)

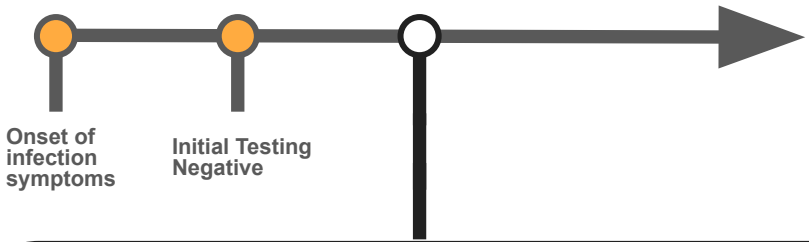
Shishido AA, et al. (University of Maryland Medical Center)

Note that the provided information and clinical evidence is not exhaustive.

Considerations for Time of Use of the Plasma mNGS

Optimizing Plasma mNGS Utilization in Diagnostic Applications

CLINICAL TIMELINE



When to Consider Plasma mNGS

- Initial rapid testing is nondiagnostic
- Persistent or worsening infectious symptoms
- Contraindication to invasive diagnostic procedures
- Imaging evidence of infection
- High-risk for opportunistic or fastidious pathogens
- Critical illness with suspected infection

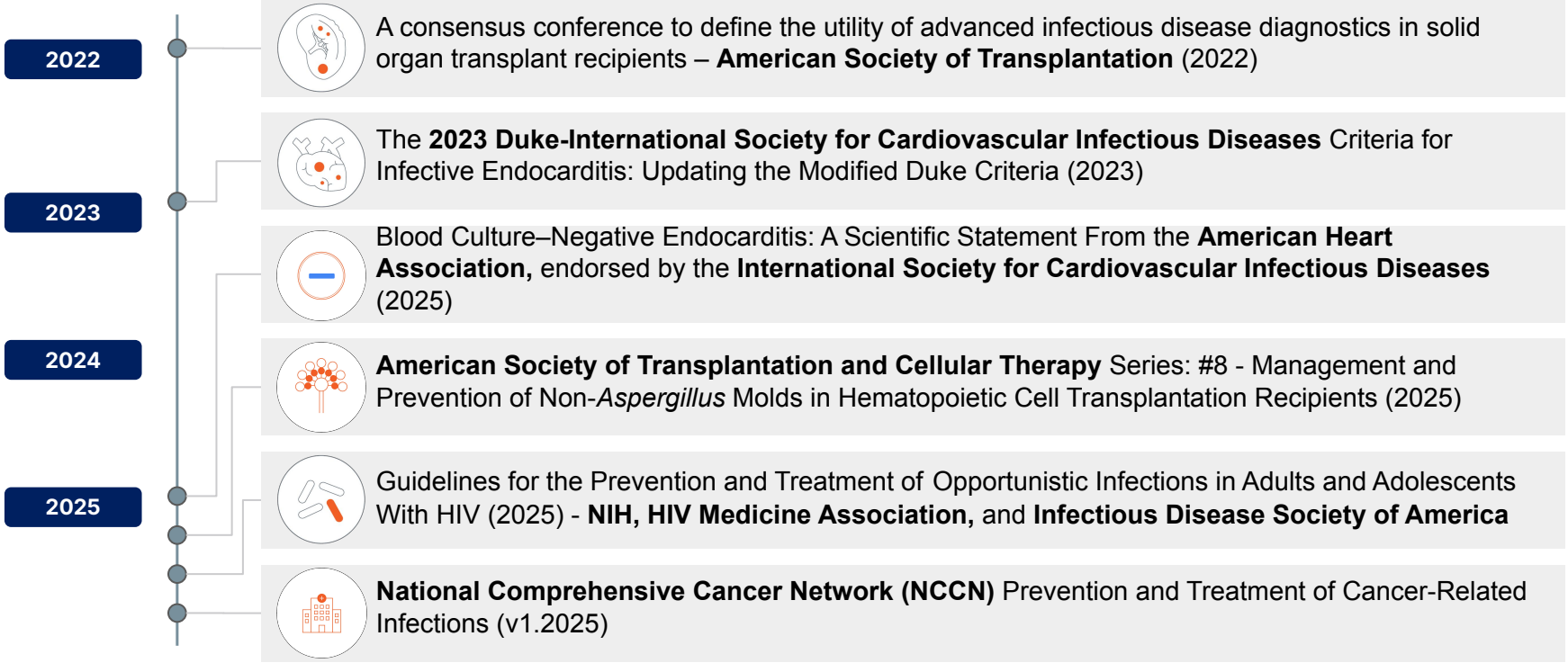
Results of Optimal Plasma mNGS Timing[1-5]

- **Highest Pathogen DNA Concentration**
  - Collect samples early in infection or during critical illness for highest DNA concentration
- **Avoid Low Diagnostic Yield**
  - Prolonged, active antimicrobial therapy and/or source control can reduce diagnostic yield
- **Achieving Positive Clinical Impact**
  - Early testing has shown positive outcomes in retrospective analyses

1. Gaston et al. *Clin Lab Med*. 2024 Mar;44(1):63-73
2. Solanky et al. *Front. Trop. Dis*. 3:842100
3. Eichenberger et al. *Clin Infect Dis*. 2022 Jun 10;74(11):2020-2027
4. Shishido et al. *BMC Infect Dis*. 2022 Apr 13;22(1):372
5. Francisco et al. *Antimicrob Steward Healthc Epidemiol*. 2023 Feb 17;3(1):e31

Summary of Guidelines Including Plasma mNGS

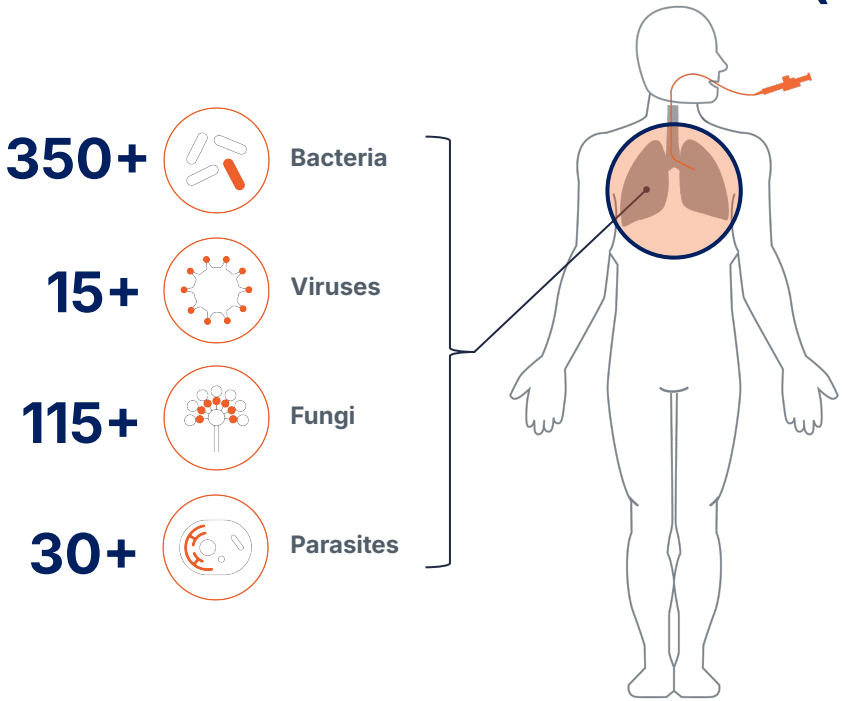
Metagenomic Sequencing has Increasingly Been Incorporated into Major Infectious Disease Guidelines and Definitions



References:
1. Azar MM et al. *Am J Transplant*. 2022 Dec;22(12):3150-3169 2. Fowler VG et al. *Clin Infect Dis*. 2023 Aug 22;77(4):518-526 3. DiSimone DC et al. *J Am Heart Assoc*. 2025;14:e040218 4. Douglas AP et al. *Transplant Cell Ther*. 2025;31(4):194-223 5. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Accessed June 6th, 2025 6. Prevention and Treatment of Cancer-Related Infections. Version 1.2025, 06/20/2025 © 2025 National Comprehensive Cancer Network® (NCCN®)

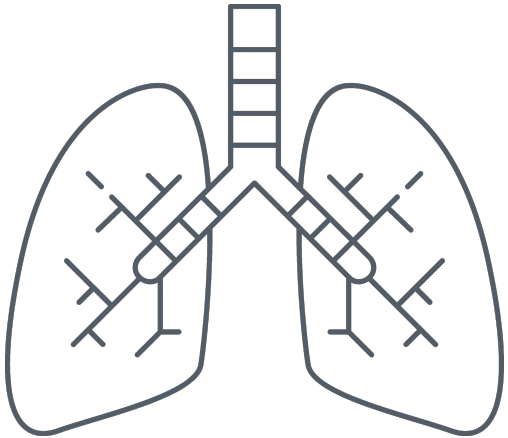
BALF Metagenomic Sequencing Product Overview

BALF Metagenomic Sequencing (mNGS) of microbial cell-free DNA (mcfDNA)



- Bronchoalveolar lavage fluid-based mcfDNA metagenomic sequencing test
- Designed for broad detection and classification of over 500 pathogens associated with lung infections

Patients who may be appropriate for BALF mNGS



- Suspected lung infection
- Immunocompromised
- Undergoing bronchoalveolar lavage (BAL)

mNGS's broad approach is optimized for adult & pediatric **immunocompromised** patients, are more likely to harbor difficult-to-diagnose pathogens.

Test Process Overview

Reports are typically available one day after specimen receipt

1 ml Streck CP Tube
(BALF)

Specimen Processing

Sequencing

Analysis

Report

BALF mNGS can rapidly identify the potential etiology of pneumonia and improve diagnostic yield over SOC testing

Harnessing mcfDNA from a low volume of BAL fluid sample (1 mL)

Convenient

>50% increased relative diagnostic yield compared to all SOC-BAL tests combined[1]

Comprehensive

Rapid identification of pathogens with results typically available within 1 day of sample receipt

Timely

1. Unpublished internal data from analysis performed on patients enrolled in PICKUP study; n=118; BALF mNGS identified adjudicated cause of pneumonia in 40 patients versus 29 with SOC alone

Questions?