A mRNA host response signature accurately distinguishes bacterial and viral infections among Emergency Department patients

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Introduction

The rapid diagnosis of acute infections and sepsis is critical in Emergency Departments (EDs). Current tests have slow turnaround times, low sensitivities, and/or signals from contaminant or commensal organisms. Empirical antimicrobial treatment may result in severe adverse events and contributes to antimicrobial resistance. HostDx Sepsis (Inflammatix, Inc.) is a novel host response assay which aims to address this unmet need. HostDx Sepsis measures 29 human mRNA targets and employs advanced machine learning to predict the likelihoods of both bacterial and viral infections. We aimed to validate HostDx Sepsis on a cohort of 397 adults presenting to six Greece EDs with suspicion of acute infection.

Methods

n = 397
Patient Enrollment: Adults with suspected acute infection and ≥ 1 VS change at six EDs in Greece

n = 397
HostDx Sepsis
Predict likelihood of bacterial, viral infections.

Whole blood RNA quantified on NanoString nCounter. Predicted probabilities calculated with Inflammatix BVN-2 algorithm.

PCT (n=232), CRP (n=363), Resp. PCR Panel (n=165)
Assays performed outside of standard-of-care

n = 397
Clinical Data Collection
Generate case report form for each patient from EHR.

n = 397
3-Physician Chart Review
Determine ground truth for presence of bacterial, viral infections with clinical data and PCT, CRP, and resp. PCR panel results.

n = 102
Known Ground Truth
56 Bacterial, 45 Viral, and 1 Noninfected

n = 295
Indeterminant Ground Truth

n = 102
Assess HostDx Sepsis Performance
Compare HostDx Sepsis predictions against ground truths established through chart review.

Results

Patient Characteristics

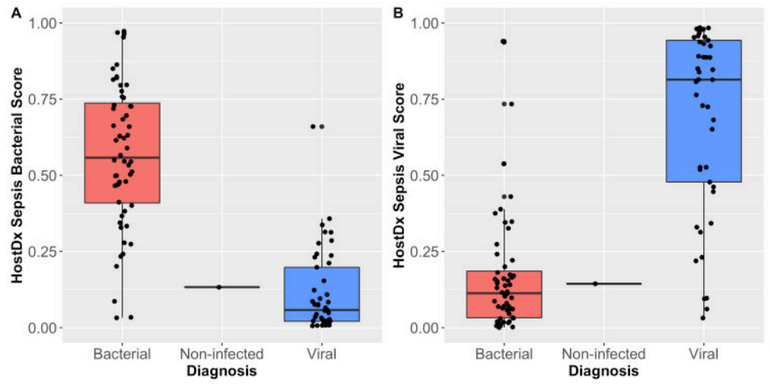
Characteristic	Number Patients (%)
Sex	
Female	203 (51%)
Male	194 (49%)
Mean Age	62.1 (SD 21.9)
Ethnicity	
White, Non-Hispanic	397 (100%)
Immune Status	
Immunocompetent	330 (83%)
Immunocompromised	63 (16%)
Unknown	4 (0.01%)

HostDx Sepsis and Procalcitonin Performance
Among Patients with Known Ground Truths (n=102)

	Bacterial AUROC[1]	Viral AUROC[2]
HostDx Sepsis	0.94 (95%CI 0.90-0.99)	0.89 (95% CI 0.83-0.96)
Procalcitonin[3]	0.88 (95% CI 0.79-0.96)	N/A

[1]Bacterial vs. Viral and Non-infected
[2]Viral vs. Bacterial and Non-infected
[3]Procalcitonin results available for only 69/102 patients with known ground truths

HostDx Sepsis Bacterial and Viral Scores
Among Patients with Known Ground Truths (n=102)



HostDx Sepsis Performance Segmented By Previously-Established Cutoffs (BVN-2)
Among Patients with Known Ground Truths (n=102)

		Ground Truth		Performance Per Band			
		Bacterial	Not Bacterial	% in Band	Sens.	Spec.	LR
HostDx Sepsis Predictions	Very Likely Bacterial	31	1	**31%**	55%	**98%**	**25**
	Possibly Bacterial	17	2	19%	30%	96%	7.0
	Unlikely Bacterial	5	13	18%	91%	28%	0.32
	Very Unlikely Bacterial	3	30	**32%**	**95%**	65%	**0.082**

PCT Performance Segmented by ProACT Study Cutoffs (Huang et al., *NEJM*, 2018)
Among Patients with Known Ground Truths (n=102)

		Ground Truth		Performance Per Band			
		Bacterial	Not Bacterial	% in Band	Sens.	Spec.	LR
Procalcitonin Predictions[1]	>0.5 µg/uL	22	2	**35%**	59%	**94%**	**9.5**
	0.25-0.5 µg/uL	7	0	10%	19%	100%	∞
	0.1-0.25 µg/uL	3	3	8.7%	92%	9.4%	0.86
	<0.1 µg/uL	5	27	**46%**	**86%**	84%	**0.16**

Discussion

Our results indicate that HostDx Sepsis identifies bacterial and viral infections with high accuracy. HostDx Sepsis is currently developed as a rapid point-of-care device with a turnaround-time of less than 30 minutes. HostDx Sepsis may therefore assist ED doctors in making appropriate treatment decisions earlier, towards the ultimate goal of antimicrobial stewardship.

Further Reading

1. Sweeney TE et al.. "Robust classification of bacterial and viral infections via integrated host gene expression diagnostics." *Science Translational Medicine.* 2016.
2. Mayhew MB et al. "A generalizable 29-mRNA neural-network classifier for acute bacterial and viral infections." *Nature Communications*. 2020
3. Gunsolus et al., "Diagnosing and Managing Sepsis by Probing the Host Response to Infection: Advances, Opportunities, and Challenges." *Journal of Clinical Microbiology*. 2019

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