Cost-effectiveness model of a novel multi-mRNA assay for diagnosis and risk assessment of acute respiratory tract infections and sepsis in the emergency department

Inflammatix
Advanced Host-Response Diagnostics

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Background

Sepsis is a life threatening and high burden organ dysfunction caused by a dysregulated host response to infection. In the United States alone, over 15 million patient are assessed annually for acute infection and sepsis in the Emergency Department, with Acute Respiratory Tract Infections (ARTI) accounting for approximately 35% of testing burden. Early identification of acute infection and suspected sepsis and initiation of appropriate treatment saves lives. However, diagnosis and risk stratification remain challenging leading to overtreatment in many cases and undertreatment in some cases.

HostDx™ Sepsis, developed by Inflammatix, is a novel diagnostic that measures 30 host genes to accurately estimate the separately likelihoods of bacterial infection, viral infection, and severity (30-day mortality).

This study reports a United States cost-effectiveness model of how a test like HostDx Sepsis may impact clinical care compared to standard-of-care diagnostic accuracy.

Methods

To establish the cost per patient treated from a payer perspective, we first established a baseline model of how physicians may treat patients judged to be at low, moderate, or high risk of bacterial infections, viral infections, and 30-day mortality. We first combined each possible likelihood band for the three axes of bacterial infection, viral infection, and 30-day mortality, resulting in 18 diagnostic possibilities (Figure 1). Each diagnostic possibility was assigned a base action in ED (e.g. treatment vs. no treatment with antibiotics and anti-virals; Figure 1).

Figure 1. Model framework

Bacterial band	Viral band	Mortality	Bacterial action	Viral action	Mortality / Severity
Low	Low	Low	No abx	Nothing	Discharge
Low	Moderate / high	Low	No abx	Antiviral Treatment	Discharge
Low	Low	Moderate	No abx	Nothing	`Ward
Low	Moderate / high	Moderate	No abx	Viral PCR, Viral Treatment	Ward
Low	Low	High	IV abx - ward & blood culture	Nothing	ICU
Low	Moderate / high	High	IV abx - ward & blood culture	Viral PCR, Viral Treatment	ICU
Moderate	Low	Low	PO abx & blood culture	Nothing	Discharge
Moderate	Moderate / high	Low	PO abx & blood culture	Nothing	Discharge
Moderate	Low	Moderate	IV abx - ward & blood culture	Nothing	Ward
Moderate	Moderate / high	Moderate	IV abx - ward & blood culture	Viral PCR, Viral Treatment	Ward
Moderate	Low	High	IV abx -ICU & blood culture	Nothing	ICU
Moderate	Moderate / high	High	IV abx -ICU & blood culture	Viral PCR, Viral Treatment	ICU
High	Low	Low	PO abx & blood culture	Nothing	Discharge
High	Moderate / high	Low	PO abx & blood culture	Viral PCR, Viral Treatment	Discharge
High	Low	Moderate	IV abx - ward & blood culture	Nothing	Ward
High	Moderate / high	Moderate	IV abx - ward & blood culture	Viral PCR, Viral Treatment	Ward
High	Low	High	IV abx -ICU & blood culture	Nothing	ICU
High	Moderate / high	High	IV abx -ICU & blood culture	Viral PCR, Viral Treatment	ICU

For each combination of three diagnostic bands (bacterial/viral/severity), 2^3 = 8 true states are possible (for instance, a simulated patient could have a true state of non-bacterial, non-viral, and non-mortality). We thus evaluated 8*18 = 144 possible states within each version of the model, such that for each diagnostic combination, any of the 8 true states were possible. Each scenario of the 144 scenarios were thus given outcomes according to whether the action (based on the diagnostic) was right according to the true state (Table 1).

The costs and clinical parameters associated with each action were derived from literature (Table 2).

Proportions of patients assigned to each diagnostic band were based on ROC curves estimated from AUROCs. This yielded a vector of expected patient assignments per band for each of the 144 scenarios associated with a given ROC curve (in other words, how many of 1000 simulated patients ended up in each band). We then used a multinomial distribution to model thousands of possible patient assignment scenarios based on estimated probabilities.

The 30-day outcomes considered in the study for each of the 144 scenarios were expected total cost, incremental cost per life-year saved, antibiotics-free days, and hospital length of stay (HLOS). The cost per scenario was multiplied by the patient assignments (for each of 1000 models) to yield final estimates of costs and clinical outcomes.

Outcomes for standard of care and HostDx Sepsis were directly compared in the same model by varying estimated AUROCs for the three diagnostic axes (bacterial, viral, and mortality).

We performed sensitivity analysis over patient, test, and cost assumptions.

Table 1. Example of outcome of actions based on true latent class for the 'low/low/low' band

	Bacterial inf: Low Risk	Viral inf: Low Risk	Mortality: Low Risk	Outcome of acation
Scenario 1	TRUE	TRUE	TRUE	No Further action
Scenario 2	TRUE	TRUE	FALSE	Hospital readmission (7-days) due to high mortality risk
Scenario 3	TRUE	FALSE	TRUE	No Further action
Scenario 4	TRUE	FALSE	FALSE	Hospital readmission (7-days) due to high mortality risk
Scenario 5	FALSE	TRUE	TRUE	Hospital readmission (1 day) for failure to treat with antibiotics, continue antibiotics treatment outpatient
Scenario 6	FALSE	TRUE	FALSE	Hospital readmission (7 days) due to high mortality risk and failure to treat with antibiotics
Scenario 7	FALSE	FALSE	TRUE	Hospital readmission (1 day) for failure to treat with antibiotics, continue antibiotics treatment outpatient
Scenario 8	FALSE	FALSE	FALSE	Hospital readmission (7 days) due to high mortality risk and failure to treat with antibiotics

Table 2. Cost & clinical parameter inputs

Cost Parameters	Point Estimate	Resource
PCR viral testing	$ 129.00	Xu et al 2013
Blood culture testing	$ 290.00	Roque et al. 2013
Oseltamivir (episode of care treatment)	$ 82.00	Talbird et al 2009
Antibiotics cost (oral) outpatient	$ 52.28	Schuetz et al. 2015
Antibiotics cost (oral and IV) hospital setting	$ 128.62	Schuetz et al. 2015
Antibiotics cost (IV) a day (ICU setting)	$ 297.45	Schuetz et al. 2015
Abx Resistance cost attributable to every patient	$ 13.00	Michaelidis 2016
Hospital ward per day ARTIs cost	$ 2,285.00	Calculation
ICU cost per day	$ 4,300.00	Halpern 2015
Emergency room cost	$ 207.00	Assumption
Missed bact infection - no mort: assume 1 hosp day extra	$ 2,869.88	Assumption/Calculation
Missed bact infection - with mort	$ 51,680.76	Assumption/Calculation
Missed mort no bacterial	$ 37,730.51	Assumption/Calculation

Clinical Parameters	Point Estimate	Resource
Initial Diagnosis Admissions		
HostDx Sepsis		
Antibiotic days: ED	3.18	Assumption
Antibiotic days: Hospital ward	5.02	Assumption
Antibiotic days: ICU	6.86	Assumption
Length of stay: short hospital ward	1.771	HCUP 2015/assumption
Length of stay: ICU	4.851	HCUP 2015/assumption
Mortality for septic patients in ICU (viral infections)	23.0%	Crotty 2015
Mortality rate reduction if admitted to ICU on time	30.0%	Cardoso 2011
Mortality rate in ARTI patients	10.0%	Schuetz 2017
Mortality rate viral infection	6.7%	Kwon 2017
Standard of Care		
Outpatient admission/release	40.00%	Assumption
Hospital ward admission (short stay)	30.00%	Assumption
Hospital ward admission (ICU plus ward stay)	30.00%	Assumption
Mortality	10.00%	Schuetz 2017
Length of stay: short hospital ward	2.30	HCUP 2015
Length of stay: ICU	6.30	HCUP 2015
Rehospitalization Admissions		
ICU LOS	8.30	Alsolamy 2014
Nonsurvivors LOS	19.90	Angus 2001

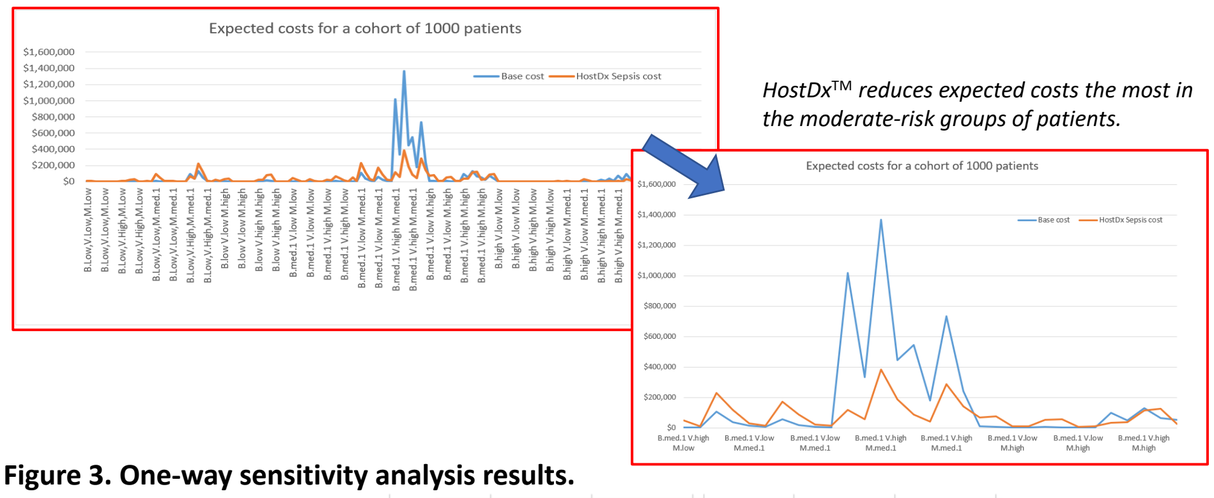
Results

We ran 1,000 versions of the model for standard-of-care and HostDx Sepsis arms. The primary effects of improved AUROCs in the HostDx Sepsis case were to move patients out of a non-informative 'moderate infection' band into informative bands (Figure 2). Compared to the base case, HostDx Sepsis resulted in 0.8 fewer hospital days, 1.5 more antibiotics-free days, a 1.6% reduction in mortality, and a cost savings of $1957 compared to standard of care assuming a $200 test price (Table 3). In sensitivity analysis, cost results were most sensitive to the HLOS and estimated hospital costs per day (Figure 3).

Table 3. Overall results for the model demonstrating effectiveness of HostDx Sepsis over base case

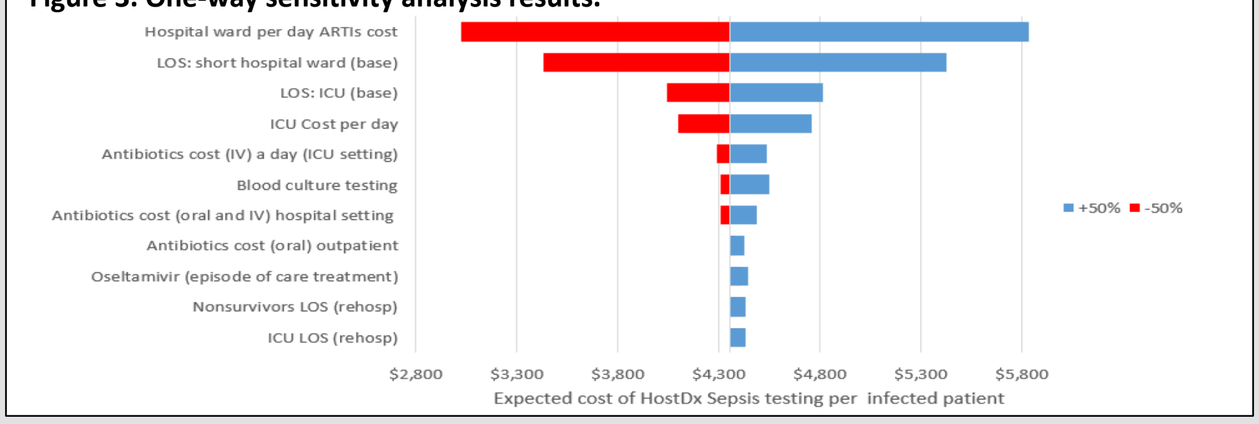
	Cost per person	Hospital days	Antibiotics-free days	Mortality (%)
Base case	$6,312	2.2	3.5	12.2%
HostDx	$4,353	1.4	5	10.6%
Difference	$1,959	0.8	1.5	1.6%

Figure 2. In-group proportions and expected costs of 1000 simulated patients for all 18 categories in the standard of care and HostDx Sepsis cases (sum of 8 scenarios for each band category).



HostDx™ reduces expected costs the most in the moderate-risk groups of patients.

Figure 3. One-way sensitivity analysis results.



Limitations

This model lacks interventional clinical trial data. Model assumptions are partially based on market research data. HostDx accuracy is based on retrospective data. Treatment assumptions based on a key-opinion-leader input only.

Conclusions

In our model, we compared HostDx Sepsis to standard of care in terms of improved ability to diagnose bacterial and viral infections and to appropriately judge level-of-care needs. The HostDx Sepsis arm demonstrated clinical utility and cost effectiveness versus the current standard of care arm. Improved care is reflected by fewer unnecessary antibiotic prescriptions and side effects and shorter HLOS. Interventional studies are necessary to evaluate the effects of HostDx Sepsis on clinical practice.

Key References

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