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Prevalence of Antimicrobial Resistance Genes and Polymicrobial Bloodstream Infections Observed during a Prospective Pilot Evaluation of Research Use Only Prototypes of the BioFire® FilmArray® Blood Culture Identification 2 Panel

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Background

Rapid identification of polymicrobial bloodstream infections (pBSI) and timely intervention with targeted antibiotic therapy can positively impact patient outcomes and improve antimicrobial stewardship. The BioFire® FilmArray® Blood Culture Identification 2 (BCID2) Panel (BioFire Diagnostics, LLC) expands the pBSI and antimicrobial resistance (AMR) gene detection capabilities of the BioFire® FilmArray® Blood Culture Identification (BCID) Panel by addition of 14 novel assays targeting 6 bacterial, 2 fungal, and 6 AMR genes. The expanded AMR menu provides accurate methicillin-resistant *Staphylococcus aureus* (MRSA) results plus detection of *mcr-1*, bla_{CTX-M}, bla_{IMP}, bla_{NDM}, $bla_{OXA-48-like}$, and bla_{VIM} genes. pBSI and AMR gene detections by research-use-only (RUO) prototypes of BioFire BCID2 Panel from positive blood cultures (PBC) were compared to standard of care (SoC) and independent PCR results.

Methods

Prototypes of the BioFire BCID2 Panel were used to prospectively evaluate 649 de-identified residual PBCs with clinician-ordered SoC tests enrolled at 1 European and 4 US pilot sites; a subset was concurrently tested on the BioFire BCID Panel. Frozen PBC aliquots and isolates were used to verify AMR gene detection and discrepancies by independent PCR or by the BioFire BCID Panel.

The FilmArray BioFire Blood Culture Identification 2 Panel

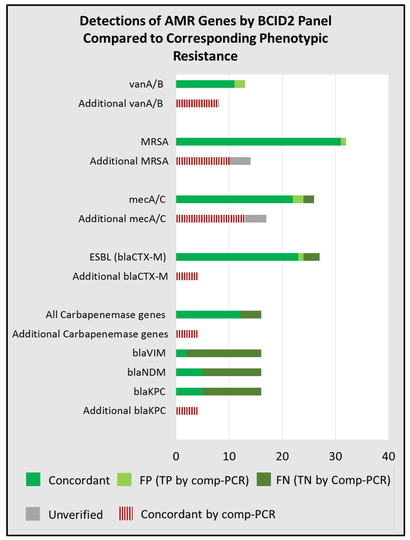
Gram-negative Bacteria
- *Acinetobacter calcoaceticus-baumannii* complex
- *Bacteroides fragilis*
- Enteric bacteria
  - *Enterobacter cloacae* complex
  - *Escherichia coli*
  - *Klebsiella aerogenes*
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae* group
  - *Proteus* spp.
  - *Salmonella* spp.
  - *Serratia marcescens*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*

Gram-positive Bacteria
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Listeria monocytogenes*
- *Staphylococcus* spp.
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Staphylococcus lugdunensis*
- *Streptococcus* spp.
  - *Streptococcus agalactiae* (Group B)
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes* (Group A)

Yeast
- *Candida albicans*
- *Candida auris*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*
- *Cryptococcus neoformans/gattii*

Antimicrobial Resistance Genes
- bla_{CTX-M}
- bla_{IMP}
- bla_{KPC}
- *mcr-1*
- *mec*A/C
- *mec*A/C and MREJ (MRSA)
- bla_{NDM}
- $bla_{OXA-48-like}$
- bla_{VIM}
- *van*A/B

BioFire BCID2 Panel Antimicrobial Resistance (AMR) Gene Detections and Concordance to SoC Antimicrobial Susceptibility Test (AST) Results



The BioFire BCID2 Panel detected a corresponding AMR gene in 88% (99/112) of cases with antimicrobial resistance by AST. Alternate PCR (comp-PCR) assays were used to confirm 41/49 additional detections, including 6 false positives.

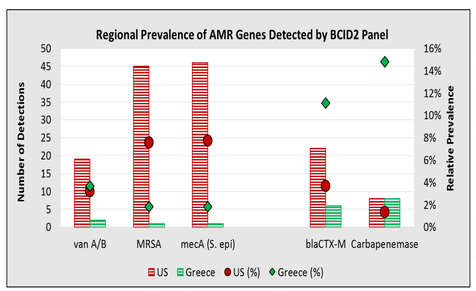
Vancomycin resistance in *E. faecium* and *E. faecalis:*
- All 11 PBC with vancomycin resistant PBC were detected by the Panel.

Methicillin resistance:
- MRSA accurately detected in all 31 cases where AST yielded a MRSA result; 4/14 additional detection remain unverified
- In 54/55 (98%) of methicillin susceptible cases, the Panel algorithm accurately identified absence of MRSA
- AST was not performed in 17/41 (41.5%) of detections of non-MRSA mecA/C gene (all detections in *S. epidermidis*)

bla_{CTX-M} identification in extended spectrum beta-lactamase (ESBL) producers:
- 23/26 ESBL producers identified by AST had the bla_{CTX-M} gene
- 3 were confirmed to be negative for bla_{CTX-M} gene by comp-PCR assay

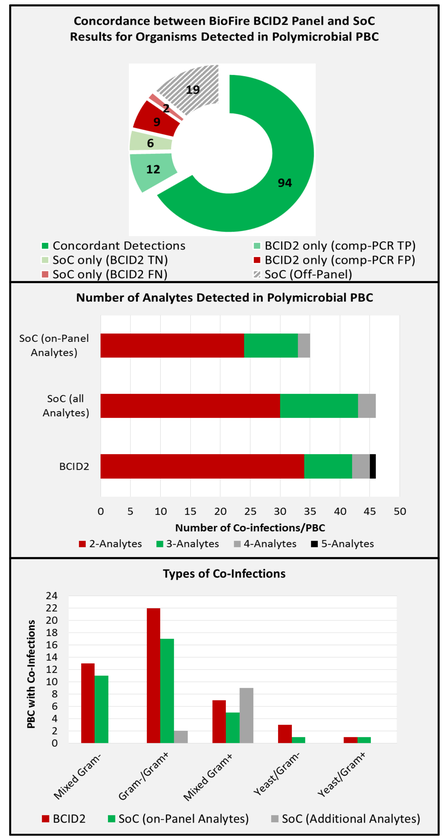
Carbapenemase gene detections:
- 12 carbapenemase genes (5 bla_{KPC}, 5 bla_{NDM}, and 2 bla_{VIM}) were detected in 11/16 PBC containing carbapenem resistant isolates and verified by comp-PCR
- Comp-PCR did not detect any on-panel carbapenemase genes in the 5 remaining PBC
- *K. pneumoniae* isolates yielded all bla_{KPC}, and bla_{NDM} detections

$bla_{OXA-48-like}$ and bla_{IMP} as well as the mobile colistin resistance gene, *mcr-1*, were not detected during this study by both the BioFire BCID2 Panel as well as alternate PCR assays.



Regional differences in prevalence of AMR genes detected by the BioFire BCID2 Panel:
- Higher prevalence of methicillin resistant *Staphylococci* in the US
- Although majority of bla_{CTX-M} were detected in the US (78% detections), the relative prevalence was greater in Greece
- Substantially higher prevalence (15%) was noted in samples from Greece for carbapenemase genes
- PBC samples from Greece yielded both bla_{VIM} detections

Comparison of Polymicrobial Bloodstream Infections (pBSI) Detected by BioFire BCID2 Panel and SoC Methods



56 samples were polymicrobial by either the SoC (46, 7.1%) or the BioFire BCID2 Panel (46, 7.1%).
- 36 of these samples were polymicrobial by both methods
- 10 additional pBSI samples by SoC contained organisms not included on the Panel
- 10 samples deemed monomicrobial by SoC, were pBSI for the Panel with 2 or more organisms detected

82% (94/115) of BCID2 organism detections were concordant with SoC results.
- 12 additional Panel detections were confirmed by alternate PCR assays
- 6/102 on-panel detections by SoC & 9/115 detections by the Panel could not be confirmed by alternate PCR assays

2-organism infections were the most frequent type of pBSI detected by both methods
- 10 PBC with monomicrobial SoC results were also identified as 2-organism pBSIs by the Panel
- Both methods had equivalent incidence of 3- & 4-organism pBSIs
- One instance of 5-organism infection was identified only by the BioFire BCID2 Panel

Mixed Gram+/Gram- infections were the most commonly identified type of pBSI by both methods.
- For all combinations of on-panel co-infections, the BioFire BCID2 Panel detected equal or more pBSI than SoC
- Majority of SoC results with off-panel organisms were found to be mixed Gram+ infections
- Neither method detected co-infections with more than one type of yeast/fungi
- Mixed yeast/Gram- infections were more frequently detected by the BioFire BCID2 Panel

Overall Performance of the RUO Prototype BioFire BCID2 Panel

Overall Performance BioFire BCID2 Panel	SoC Positive	SoC Negative
BCID2 Postive	626	26
BCID2 Negative	1	10937
Positive Percent Agreement	99.84%	
Negative Percent Agreement	99.76%	

347/649 samples were evaluated with the most recent prototype of the BioFire BCID2 Panel.

The overall percent agreement between SoC and the BioFire BCID2 Panel for pathogen detection was 99.77%

Study Sites And Demographics

Prospective Pilot Sites	Sample Contribution	Sex		Age					
		Female	Male	<1 y	1-17 ys	18-44 ys	45-64 ys	65-84 ys	85+ ys
Primary Children's Hospital	136 (21%)	68 (50%)	68 (50%)	70 (52%)	64 (47%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Loyola University Medical College	227 (35%)	98 (43%)	129 (57%)	0 (0%)	5 (2%)	37 (16%)	73 (32%)	97 (43%)	15 (7%)
Northwell Health Laboratories	63 (10%)	25 (40%)	38 (60%)	0 (0%)	0 (0%)	17 (26%)	23 (37%)	23 (37%)	0 (0%)
Ohio State University, Wexner Medical Center	169 (25%)	64 (38%)	105 (62%)	1 (1%)	2 (1%)	11 (7%)	39 (23%)	80 (47%)	36 (21%)
National and Kapodistrian University of Athens	54 (8%)	21 (39%)	33 (61%)	2 (4%)	0 (0%)	2 (4%)	12 (22%)	32 (59%)	6 (11%)
Overall	**649 (100%)**	276 (43%)	373 (57%)	73 (11%)	71 (11%)	69 (10%)	147 (23%)	232 (36%)	57 (9%)

Of 649 samples, 270 (42%) were anaerobic & 379 (58%) were aerobic PBC
- Only Becton Dickinson blood culture media were used at all sites
- 22% of enrolled samples were of pediatric origin (< 18 y)
- 45% of enrolled patients were geriatric (> 65 y)
- PBC collected from male patients represented 57% of samples
- Equal representation of males and females in pediatric samples

Conclusions

The BioFire BCID2 Panel exhibited >99% sensitivity and specificity, as well as pBSI and AMR gene detection capabilities comparable to SoC and should expedite implementation of appropriate therapy and improve antimicrobial stewardship.

All data presented were obtained with a development (RUO) version of the panel. The BioFire BCID2 Panel has not been evaluated by the FDA or other regulatory agencies for In Vitro *Diagnostic use.*