Multi-center Evaluation of the BioFire® FilmArray® Blood Culture Identification 2 Panel for the Detection of Microorganisms and Resistance Markers in Positive Blood Cultures

Y. Lu[1], J. Hatch[1], K. Holmberg[1], A. Hurlock[1], D. Drobysheva[1], U. Spaulding[1], S. Vourli[2], S. Pournaras[2], K. Everhart[3], A. Leber[3], B. Barr[4], J. Daly[4], T. Henry[5], A. Johnson[5], JM. Balada-Llasat[5], D. Rhoads[6], M. Jacobs[6], K. McKinley[7], A. Harrington[7], F. Zhang[8], G. Berry[8], M. Jeong[9], R. She[9], M. Fantini[10], G. Dirani[10], S. Zannoli[10], V. Sambri[10,11], K. Bourzac[1]

[1]BioFire Diagnostics, LLC, UT, USA. [2]National and Kapodistrian University of Athens, Athens, Greece. [3]Nationwide Children's Hospital, OH, USA. [4]Primary Children's Hospital, UT, USA. [5]The Ohio State University Wexner Medical Center, OH, USA. [6]University Hospitals Cleveland Medical Center, OH, USA. [7]Loyola University Medical Center, IL, USA. [8]Northwell Health Labs, NY, USA. [9]University of Southern California, CA, USA. [10]Unit of Microbiology, The Romagna Hub Laboratory, PIEVESESTINA - Cesena, Italy. [11]University of Bologna, Bologna, Italy.

Background

The BioFire® FilmArray® Blood Culture Identification 2 (BCID2) Panel is a diagnostic test that provides results for 26 bacterial pathogens, 7 fungal pathogens, and 10 antimicrobial resistance (AMR) genes from positive blood culture (PBC) specimens in about an hour. The BCID2 Panel builds upon the existing BioFire® FilmArray® Blood Culture Identification (BCID) Panel with several additional assays (highlighted in red in Table 3).

A prospective clinical evaluation was conducted between October 2018 – June 2019 at 7 US and 2 EU sites. A total of 1,074 valid specimens were enrolled in the study from unique, individual subjects. The enrolled population included adults and children. BCID2 Panel performance was compared to several reference methods including microbial culture and various molecular methods (Table 1). The data in this poster represent a preliminary analysis and are subject to change.

Summary

- **Overall 98.8% sensitivity and 99.6% specificity compared to reference methods using a multitude of common blood culture media and systems**
- **Broad panel menu allowed detection of at least one organism in >91% of PBC**
- **The BCID2 Panel was able to detect multiple types of organisms in a single sample (i.e. combinations of Gram+, Gram-, and yeast), some of which were not observed on the Gram stain**
- **Reduced detections of non-viable nucleic acid contained in blood culture media**
- **>99% of tests with valid results on first attempt using FilmArray 2.0 and Torch systems**

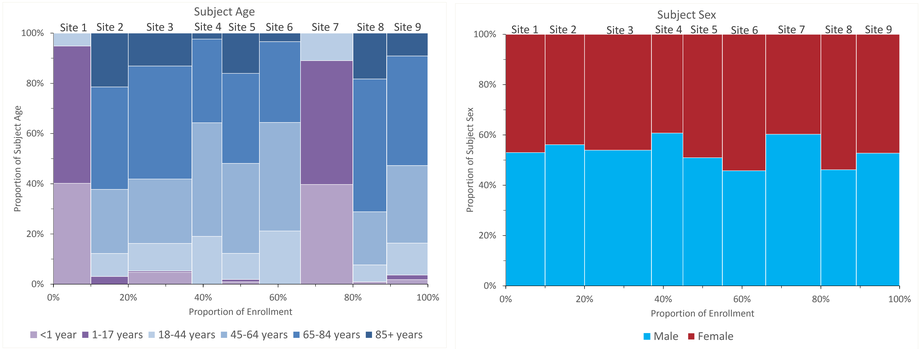
Table 1. Reference Methods

Analyte Type	Primary Reference Method
Bacterial analytes	Standard of Care (SoC) identification (performed at the source laboratory)
Cryptococcus neoformans/gattii	
***Candida* species**	SoC identification for genus level (performed at the source laboratory) followed by Sequencing of isolates for speciation
Antimicrobial Resistance Genes	BCID Panel for *mecA/C*, KPC, *vanA/B*; One PCR assay + Sequence for other antimicrobial resistance genes
***mecA/C* and MREJ (MRSA)**	Testing of blood culture aliquots with Cepheid Xpert MRSA/SA BC

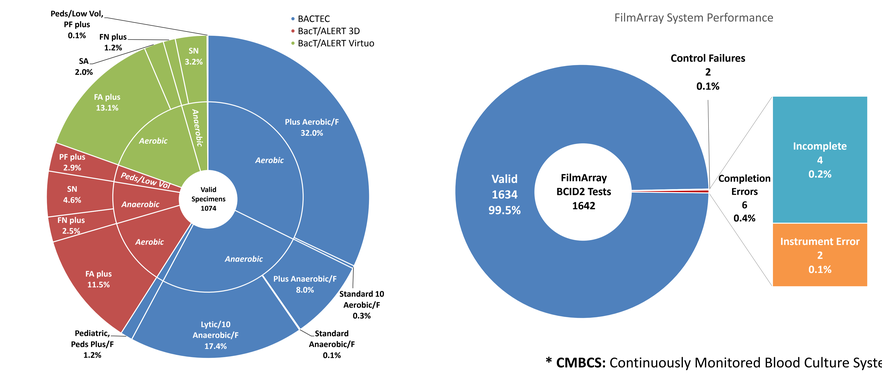
Table 2. Prospective Study Sites

Site	Site Name	City/State
1	Primary Children's Hospital	Salt Lake City, UT
2	Northwell Health Laboratories	Lake Success, NY
3	National and Kapodistrian University of Athens Hospital	Athens, Greece
4	Keck School of Medicine of USC	Los Angeles, CA
5	University Hospitals Cleveland Medical Center	Cleveland, OH
6	Ohio State University Wexner Medical Center	Columbus, OH
7	Nationwide Children's Hospital	Columbus, OH
8	The Greater Romagna Area Hub Laboratory	Cesena, Italy
9	Loyola University Medical Center	Chicago, IL

Study Sites and Demographics



CMBCS* Systems and BioFire® FilmArray® System Performance



*** CMBCS:** Continuously Monitored Blood Culture System

BCID2 Panel Co-Detections

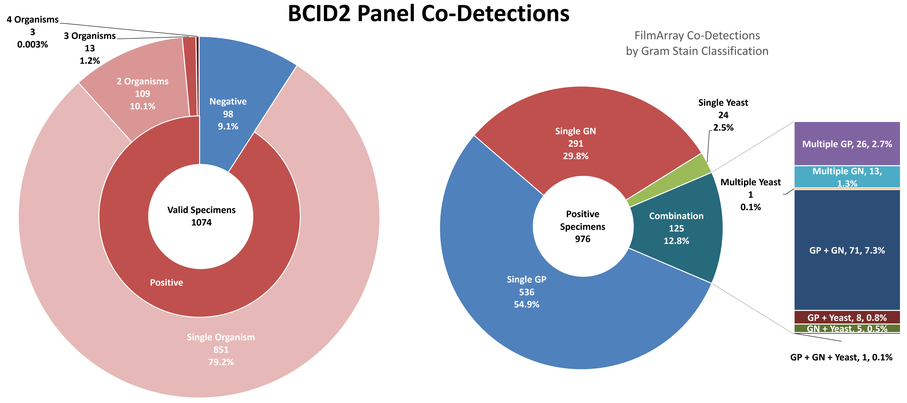


Table 3. Prospective Study Analytes Performance

Analyte	Sensitivity			Specificity		
	TP/(TP + FN)	%	95%CI	TN/(TN + FP)	%	95%CI
Gram-Positive Bacteria						
Enterococcus faecalis	31/33	93.9	80.4-98.3%	1040/1041	99.9	99.5-100%
Enterococcus faecium	27/27	100	87.5-100%	1044/1047	99.7	99.2-99.9%
Listeria monocytogenes	3/3	100	43.9-100%	1071/1071	100	99.6-100%
Staphylococcus spp.	471/472	99.8	98.8-100%	589/602	97.8	96.3-98.7%
Staphylococcus aureus	149/149	100	97.5-100%	923/925	99.8	99.2-99.9%
Staphylococcus epidermidis	221/229	96.5	93.3-98.2%	816/845	96.6	95.1-97.6%
Staphylococcus lugdunensis	4/4	100	51.0-100%	1067/1070	99.7	99.2-99.9%
Streptococcus spp.	121/123	98.4	94.3-99.6%	949/951	99.8	99.2-99.9%
Streptococcus agalactiae (Group B)	9/9	100	70.1-100%	1065/1065	100	99.6-100%
Streptococcus pneumoniae	26/26	100	87.1-100%	1048/1048	100	99.6-100%
Streptococcus pyogenes (Group A)	13/14	92.9	68.5-98.7%	1060/1060	100	99.6-100%
Gram-Negative Bacteria						
Acinetobacter calcoaceticus-baumannii complex	12/13	92.3	66.7-98.6%	1060/1061	99.9	99.5-100%
Bacteroides fragilis	6/7	85.7	48.7-97.4%	1064/1067	99.7	99.2-99.9%
Enteric bacteria	269/270	99.6	97.9-99.9%	750/804	93.3	91.3-94.8%
Enterobacter cloacae complex	16/16	100	80.6-100%	1058/1058	100	99.6-100%
Escherichia coli	158/159	99.4	96.5-99.9%	913/915	99.8	99.2-99.9%
Klebsiella aerogenes	2/2	100	34.2-100%	1072/1072	100	99.6-100%
Klebsiella oxytoca	8/8	100	67.6-100%	1066/1066	100	99.6-100%
Klebsiella pneumoniae group	55/56	98.2	90.6-99.7%	1018/1018	100	99.6-100%
Proteus spp.	14/14	100	78.5-100%	1059/1060	99.9	99.5-100%
Salmonella spp.	5/5	100	56.6-100%	1069/1069	100	99.6-100%
Serratia marcescens	11/11	100	74.1-100%	1063/1063	100	99.6-100%
Haemophilus influenza	8/8	100	67.6-100%	1066/1066	100	99.6-100%
Neisseria meningitidis	0/0	-	-	1074/1074	100	99.6-100%
Pseudomonas aeruginosa	29/29	100	88.3-100%	1043/1045	99.8	99.3-99.9%
Stenotrophomonas maltophilia	7/8	87.5	52.9-97.8%	1066/1066	100	99.6-100%
Antimicrobial Resistance Genes*						
CTX-M	46/47	97.9	88.9-99.6%	312/312	100	98.8-100%
IMP	0/0	-	-	359/359	100	98.9-100%
KPC	4/4	100	51.0-100%	328/328	100	98.8-100%
NDM	1/1	100	-	358/358	100	98.9-100%
OXA-48-like	0/0	-	-	323/323	100	98.8-100%
VIM	4/4	100	51.0-100%	355/355	100	98.9-100%
mecA/C	195/195	100	98.1-100%	60/60	100	94.0-100%
mecA/C and MREJ (MRSA)	52/57	91.2	81.1-96.2%	92/94	97.9	92.6-99.4%
mcr-1	0/0	-	-	240/240	100	98.4-100%
vanA/B	23/24	95.8	79.8-99.3%	38/38	100	90.8-100%
Yeast						
Candida albicans	12/12	100	75.8-100%	1061/1062	99.9	99.5-100%
Candida auris	0/0	-	-	1074/1074	100	99.6-100%
Candida glabrata	10/10	100	72.2-100%	1063/1064	99.9	99.5-100%
Candida krusei	2/2	100	34.2-100%	1072/1072	100	99.6-100%
Candida parapsilosis	8/8	100	67.6-100%	1065/1066	99.9	99.5-100%
Candida tropicalis	5/5	100	56.6-100%	1069/1069	100	99.6-100%
Cryptococcus neoformans/gattii	0/0	-	-	1074/1074	100	99.6-100%

Red text indicates new targets on the BCID2 Panel

* antimicrobial resistance genes reported for applicable organisms

Table 4. Discrepancy Investigation

115 false positive (FP) and 27 false negative (FN) results were investigated. Among the 115 FPs, 54 were due to non-viable *E. coli* nucleic acid present in specific lots of BioMerieux blood culture bottles. Interestingly, *S. epidermidis* contributes to >50% of FP and >35% FN cases, some of which are associated with organism misidentification at the clinical sites. Regarding the discrepant MRSA results, the BCID2 Panel was in concordance with SoC phenotypic antibiotic susceptibility testing results in all cases. Major causes of discrepancies are summarized below.

Major Causes of Discrepancies	Discrepant Results from the BCID2 Panel
Organism present in PBC but sites failed to grow or report isolate	21 FP *S. epidermidis*, 1 FP *Acinetobacter calcoaceticus-baumannii* (ACB) complex, 1 FP *C. glabrata*, 1 FP *S. lugdunensis*, 1 FP *S. aureus*
Low number in polymicrobial PBC (below the BCID2 Panel Limit-of-Detection)	3 FN *S. epidermidis*, 1 FN *S. maltophilia*, 1 FN *Streptococcus* spp., 1 FN ACB complex
Organism misidentification by clinical sites	3 FP: *S. epidermidis* misidentified as *S. hominis* or *S. haemolyticus*
	4 FN *S. epidermidis*: *S. warneri*, *S. hominis*, *S. caprae* misidentified as *S. epidermidis*
	1 FN *B. fragilis*: *B. thetaiotaomicron* misidentified as *B. fragilis*
Non-viable *E. coli* nucleic acid present in specific lots of BacT/ALERT® blood culture bottles (3 sites)	52 FP Enteric and 2 Enteric/*E. coli*

Table 5. The BCID2 Panel Demonstrated Reduced Detections of Non-viable Nucleic Acid Contained in Blood Culture Media

The specificity of the *Proteus* spp. assay on the BCID Panel was affected by non-viable nucleic acid present in some BD BACTEC™ and BioMerieux BacT/ALERT® blood culture bottles. The BCID2 Panel *Proteus* spp. assay was optimized to reduce detection of the non-viable nucleic acid. However, non-viable *E. coli* nucleic acid present in specific lots of BioMerieux BacT/ALERT® blood culture bottles was detected by the Enteric assay (and to a lesser extent by the *E. coli* assay; see performance in Table 3).

Analyte	Sensitivity			Specificity		
	TP/(TP + FN)	%	95%CI	TN/(TN + FP)	%	95%CI
***Proteus* spp. – BCID**	14/14	100	78.5-100%	998/1060	94.2	92.6-95.4%
***Proteus* spp. – BCID2**	14/14	100	78.5-100%	1059/1060	99.9	99.5-100%

Table 6. The BCID2 Panel Detects Additional Organisms Not Observed on Gram Stain

BCID2 Gram Classification by Organisms Identified	SoC Gram Stain	
	Observed	Not Observed
Gram-Positive (N=642)	630 (98.1%)	12 (1.9%)
Gram-Negative (N=329)	320 (97.3%)	9 (2.7%)*
Yeast (N=39)	35 (89.7%)	4 (10.3%)

*** FPs due to non-viable *E. coli* nucleic acid are excluded from analysis**

Data presented are from assays that are Investigational Use Only (IUO) and have not been cleared or approved for diagnostic use.

Contact Information: Daisy.Lu@Biofiredx.com