

Evaluation of FilmArray and Verigene Systems for Rapid Identification of Positive Blood Cultures

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The Verigene tests for Gram-positive and Gram-negative organisms in blood culture and the FilmArray blood culture identification panel were assessed for their ability to identify pathogens from positive blood cultures. Both platforms correctly identified bacteria in 92% of monomicrobial cultures analyzed, with times to identification that were significantly shorter than those for identification from subcultures.

There are approximately 750,000 cases of sepsis per year in the United States, with a 25 to 70% mortality rate (1). The traditional subculturing, identification, and susceptibility testing of organisms from blood culture can be too slow to impact the management of sepsis (2). This study assessed two FDA-cleared systems designed to identify organisms directly from positive blood culture bottles: the FilmArray blood culture identification (BCID) panel (BioFire Diagnostics, Salt Lake City, UT) and the Verigene system (Nanosphere, Northbrook, IL) gram-positive blood culture (BC-GP) and gram-negative blood culture—research use only (BC-GN-RUO) nucleic acid tests.

The BCID panel detects 19 bacterial targets, two resistance genes, and five yeast targets and has a reported accuracy of 91 to 92% (3, 4). The Verigene system utilizes separate cartridges for identifying Gram-positive and Gram-negative bacteria. The BC-GP test contains 12 bacterial targets and three resistance markers with a stated accuracy of 90 to 96% (5–9). The BC-GN-RUO test has nine bacterial targets and six resistance markers and a recently published accuracy of 94 to 98% (10, 11). Our study is the first side-by-side assessment of these two platforms for identifying bacteria and resistance markers in positive blood cultures.

The study included 121 positive blood cultures from 121 patients obtained between March and June 2013 at the University of Chicago. Specimens were inoculated into Bactec culture bottles and incubated in the Bactec FX instrument (Becton Dickinson, Cockeysville, MD). When a culture signaled positive, a Gram stain was performed, and aliquots of broth medium were processed for detection by both platforms per the manufacturers' instructions. Subculturing was performed in parallel on appropriate agar plates. Following overnight incubation, bacterial colonies were identified by Vitek MS RUO (bioMérieux, Marcy l'Etoile, France) as previously described (12, 13). Susceptibility testing was performed per routine protocol with Vitek 2 (bioMérieux, Marcy l'Etoile, France) using the following cards: AST-GP67, AST-ST01, and AST-GN75. Time to identification (TTI) for both platforms was defined as the time between Gram staining of the positive blood culture bottle and organism identification. Subculturing TTI was defined as the time from reporting the Gram stain to recording the bacterial identification in the medical record. Because this was a workflow and accuracy study, none of the results from the two platforms under study were entered into the medical record or communicated to providers. Calculation of the mean TTIs and confidence intervals and two-sided *t* tests used to com-

pare mean TTIs were performed using QuickCalcs (www.graphpad.com/quickcalcs) by GraphPad Software, Inc.

Of the 118 monomicrobial cultures, 82 (69%) contained Gram-positive organisms (Table 1). Both systems accurately identified all 64 (100%) cultures containing staphylococci to the genus level. The only species of *Staphylococcus* that the BCID panel identifies is *Staphylococcus aureus*, and it identified all 32 (100%) isolates of *S. aureus* correctly. Of the 32 coagulase-negative staphylococci (CoNS), the BCID panel misidentified one (3%) as *S. aureus*. This error was considered minor, since it could lead to overtreatment, rather than undertreatment, of the patient. The Verigene BC-GP test correctly identified all cultures with *S. aureus* (32 [100%]), *Staphylococcus epidermidis* (23 [100%]), and *Staphylococcus lugdunensis* (1 [100%]); the remaining eight CoNS were all identified correctly as CoNS.

The BCID panel detected the *mecA* gene in 13 (100%) of the *S. aureus* isolates that were resistant to methicillin and in 18 (100%) of the CoNS isolates that were resistant to methicillin. Of the 19 isolates of *S. aureus* susceptible to methicillin, the *mecA* gene was detected in one (5%) sample. Of the 14 isolates of CoNS susceptible to methicillin, the *mecA* gene was detected in three (21%) samples. The false detection of *mecA* is cause for concern, as it might result in the use of vancomycin for the treatment of a methicillin-susceptible staphylococcal infection. While vancomycin is considered adequate therapy for methicillin-susceptible staphylococci, an appropriate beta-lactam agent has been shown to be superior, resulting in better outcomes than treatment with vancomycin (14).

The BC-GP test reports *mecA* only for *S. aureus* and *S. epidermidis*; the *mecA* result was correct for all 54 (100%) cultures with these two species.

Both systems correctly identified all nine (100%) streptococci, with accurate identification of two *Streptococcus agalactiae* isolates

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TABLE 1 Results of two platforms for rapid identification of 118 mono-microbial blood cultures

Sample (n) ^a	No. (%) with result by test					
	FilmArray BCID panel			Verigene BC-GP and BC-GN-RUO		
	Correctly identified	Misidentified	Not identified	Correctly identified	Misidentified	Not identified
Total identifiable GP organisms (82)	77 (94)	5 (6)		82 (100)		
<i>Staphylococcus</i> spp. (64)	64 (100)			64 (100)		
<i>S. aureus</i> (32)	32 (100)			32 (100)		
<i>mecA</i> pos (13)	13 (100)			13 (100)		
<i>mecA</i> neg (19)	18 (95)	1 ^b (5)		19 (100)		
Coagulase negative (32)	31 (97)	1 ^c (3)		32 (100)		
<i>mecA</i> pos (18)	18 (100)					
<i>mecA</i> neg (14)	11 (79)	3 ^d (21)				
<i>S. epidermidis</i> (23)				23 (100)		
<i>mecA</i> pos (16)				16 (100)		
<i>mecA</i> neg (7)				7 (100)		
<i>S. lugdunensis</i> (1)				1 (100)		
Others ^e (8)				8 (100)		
<i>Streptococcus</i> spp. (9)	9 (100)			9 (100)		
<i>S. agalactiae</i> (2)	2 (100)			2 (100)		
<i>S. pyogenes</i> (1)	1 (100)			1 (100)		
<i>S. anginosus</i> group (1)				1 (100)		
<i>Enterococcus</i> spp. (9)	9 (100)					
<i>E. faecalis</i> (5)				5 (100)		
<i>vanA</i> neg (5)	5 (100)			5 (100)		
<i>E. faecium</i> (4)				4 (100)		
<i>vanA</i> pos (4)	4 (100)			4 (100)		
Nonidentifiable GP organisms ^f			5 (100)			5 (100)
Total identifiable GN organisms (27)	27 (100)			25 (96)		1 (4)
<i>Enterobacteriaceae</i> (23)	23 (100)					
<i>Enterobacter</i> spp. (1)				1 (100)		
<i>E. cloacae</i> complex (1)	1 (100)					
<i>E. coli</i> (11)	11 (100)			11 (100)		
<i>Klebsiella oxytoca</i> (1)	1 (100)			1 (100)		
<i>K. pneumoniae</i> (6)	6 (100)			6 (100)		
<i>S. marcescens</i> (2)	2 (100)			1 (50)		1 ^g (50)
<i>Citrobacter</i> spp. (1)				1 (100)		
Others ^h (2)	2 (100)					
<i>Pseudomonas aeruginosa</i> (4)	4 (100)			4 (100)		
GN resistance markers						
KPC (1)	1 (100)			1 (100)		
CTX-M (1)					1 (100)	
Nonidentifiable GN organisms ⁱ			4 (100)			5 (100)
Total identifiable isolates	104 (95)	5 (5)		107 (99)		1 (1)

^a GP, Gram-positive; GN, Gram-negative; pos, positive; neg, negative.

^b One culture positive for *S. aureus* was also positive for *mecA* but methicillin-sensitive by routine testing.

^c One culture identified as *S. aureus* grew *S. epidermidis* by routine identification.

^d Three cultures positive for coagulase negative staphylococci were positive for *mecA* but methicillin-sensitive by routine testing.

^e Included three *Staphylococcus capitis*, two *S. haemolyticus*, and three *S. hominis* strains.

^f Included one *Anaerococcus* sp., two *Corynebacterium* spp., one *Gemella* sp., and one anaerobic GP bacillus.

^g One culture reported as negative grew *S. marcescens* by routine identification.

^h Included one *Citrobacter amalonaticus* strain and one *Salmonella* sp.

ⁱ Included one *Moraxella* sp., two *Stenotrophomonas* spp., and one *Bacteroides* sp.; the BC-GN-RUO test was unable to identify one *Salmonella* sp.

and one *Streptococcus pyogenes* isolate. The BC-GP test also identified a culture of *Streptococcus anginosus* group. All nine (100%) enterococci were detected by both systems, with the BC-GP test correctly identifying five *Enterococcus faecalis* and four *Enterococcus faecium* isolates to the species level. Vancomycin resistance was correctly detected in all four isolates of *E. faecium* by both platforms. Five cultures contained organisms not detectable by either panel; all gave an expected negative result.

Thirty-one monomicrobial blood cultures containing Gram-negative organisms were studied (Table 1). The BCID panel accurately detected all 27 (100%) cultures containing identifiable Gram-negative organisms. The BC-GN-RUO test correctly identified 25 of 26 (96%) cultures with identifiable organisms; a *Serratia marcescens* isolate was not identified. A culture with a *Salmonella* isolate was undetectable by the BC-GN-RUO test but positive for the *Enterobacteriaceae* target on the BCID panel. Four cultures contained organisms undetectable by either system and gave negative results.

Both systems are capable of detecting the presence of resistance genes found in Gram-negative organisms. The BCID panel detects only the KPC resistance gene, while the BC-GN-RUO test identifies the KPC gene plus the CTX-M, IMP, NDM, OXA, and VIM genes. Only two resistance genes were detected in this study: a KPC gene by both platforms in a *Klebsiella pneumoniae* isolate and a CTX-M gene by the BC-GN-RUO test in a different *K. pneumoniae* isolate.

The time to identification (TTI) of monomicrobial blood cultures by subculture averaged 25.6 h (95% confidence interval [CI], 24.7 to 26.5). Both platforms provided significantly shorter TTIs ($P < 0.0001$). The BCID panel required 1.15 h (CI, 1.1 to 1.2). The BC-GP test averaged 2.5 h (CI, 2.4 to 2.5), and the BC-GN-RUO test, 2 h (CI, 1.9 to 2.1). The FilmArray TTI was significantly shorter than the Verigene TTI ($P < 0.0001$).

The goal of this study was to assess the accuracy and TTI of two systems capable of rapid bacterial identification from blood cultures. Both platforms were able to identify approximately 92% of the monomicrobial cultures studied, demonstrating that they have been appropriately devised to detect organisms commonly isolated from positive blood cultures and are significantly faster than subculture-based identification.

The major advantages of the BCID system include a shorter laboratory TTI, a single pouch for all specimens which does not rely on accuracy of Gram staining, and a target for *Enterobacteriaceae* family members.

The BCID panel detected *mecA* in four specimens that were susceptible to methicillin. Similar discordant results have been reported in previous assessments of the BCID panel (3), the Verigene BC-GP test (5, 8), and other staphylococcal detection systems (15, 16). Discordant *mecA*-positive staphylococci with methicillin-susceptible phenotypes have been demonstrated to possess an altered staphylococcal cassette chromosome *mec* (SCC*mec*) element which lacks a functional *mecA* gene (17). The presence of an altered SCC*mec* element is likely to account for the four false-positive *mecA* results.

The Verigene system utilizes different cartridges for bacterial identification and relies on accurate Gram staining to select the proper cartridge. The use of two cards allows a wider range of organisms and resistance markers. The BC-GP test can identify *S. lugdunensis*, which despite being a CoNS has a pathogenicity similar to that of *S. aureus* (18). The BC-GP test is capable of differ-

entiating *E. faecalis* from *E. faecium*. In this study, the BC-GP test correctly identified all Gram-positive organisms and correctly detected methicillin susceptibility and resistance in *S. aureus* and *S. epidermidis* cultures.

The BC-GN-RUO test correctly identified all identifiable Gram-negative organisms except one culture with *S. marcescens*. Issues with detection of *S. marcescens* have also been reported with the BCID panel (4). The FDA-cleared BC-GN does not contain a target for *S. marcescens*, and per the manufacturer, this is the only difference from the BC-GN-RUO test. The BC-GN-RUO test detects several resistance targets, a potentially major advantage. However, it failed to detect any markers in two strains of *P. aeruginosa*, one resistant to cefepime but susceptible to meropenem and the other resistant to meropenem but sensitive to cefepime. A recent assessment of the BC-GN-RUO test also reported an inability to detect resistance genes in *P. aeruginosa* with a carbapenem resistance phenotype (10). The mechanisms of antibiotic resistance in Gram-negative bacteria are complex, particular *P. aeruginosa*, which can harbor mutations resulting in reduced outer membrane permeability, express multidrug efflux systems, and/or possess beta-lactamases outside those detected by the BC-GN-RUO test (19). Therefore, the absence of known resistance genes does not equate to a susceptible organism, particularly for *P. aeruginosa*. Thus, the clinical utility of genotypic assays, such as the BC-GN-RUO test, to detect several resistance genes depends on local susceptibility patterns and prevalent mechanisms of resistance.

The study has a few limitations. A larger number of blood cultures would provide a more thorough assessment of the two platforms. Both systems can detect *S. pneumoniae*, *Listeria* spp., and *Acinetobacter*, and the BCID panel contains targets for *Haemophilus influenzae*, *Neisseria meningitidis*, and *Candida* spp., but no culture grew these organisms. Further studies with these organisms from clinical samples are needed. In addition, more studies with drug-resistant Gram-negative organisms are required to fully evaluate both platforms' ability to meaningfully detect antibiotic resistance.

This study demonstrates that the FilmArray BCID panel and Verigene BC-GP and BC-GN-RUO tests are capable of providing fast and reliable results in the detection of pathogens present in automated blood culture systems, but neither system can replace subculture. Growth of colonies is needed to identify organisms not included in the panels and to perform susceptibility testing. As the clinical microbiology laboratory continues to make advances in rapid identification of pathogens and resistance markers, the challenge will be working with clinicians and pharmacists to act quickly on these rapid results in order to improve patient outcomes.

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REFERENCES

1. Russell JA. 2006. Management of sepsis. *N. Engl. J. Med.* 355:1699–1713. <http://dx.doi.org/10.1056/NEJMra043632>.

2. Mancini N, Carletti S, Ghidoli N, Cichero P, Burioni R, Clementi M. 2010. The era of molecular and other non-culture-based methods in diagnosis of sepsis. *Clin. Microbiol. Rev.* 23:235–251. <http://dx.doi.org/10.1128/CMR.00043-09>.
3. Altun O, Almuhayawi M, Ullberg M, Ozenci V. 2013. Clinical evaluation of the FilmArray blood culture identification panel in identification of bacteria and yeasts from positive blood culture bottles. *J. Clin. Microbiol.* 51:4130–4136. <http://dx.doi.org/10.1128/JCM.01835-13>.
4. Blaschke AJ, Heyrend C, Byington CL, Fisher MA, Barker E, Garrone NF, Thatcher SA, Pavia AT, Barney T, Alger GD, Daly JA, Ririe KM, Ota I, Poritz MA. 2012. Rapid identification of pathogens from positive blood cultures by multiplex polymerase chain reaction using the FilmArray system. *Diagn. Microbiol. Infect. Dis.* 74:349–355. <http://dx.doi.org/10.1016/j.diagmicrobio.2012.08.013>.
5. Samuel LP, Tibbetts RJ, Agotesku A, Fey M, Hensley R, Meier FA. 2013. Evaluation of a microarray-based assay for rapid identification of Gram-positive organisms and resistance markers in positive blood cultures. *J. Clin. Microbiol.* 51:1188–1192. <http://dx.doi.org/10.1128/JCM.02982-12>.
6. Wojewoda CM, Sercia L, Navas M, Tuohy M, Wilson D, Hall GS, Procop GW, Richter SS. 2013. Evaluation of the Verigene Gram-positive blood culture nucleic acid test for rapid detection of bacteria and resistance determinants. *J. Clin. Microbiol.* 51:2072–2076. <http://dx.doi.org/10.1128/JCM.00831-13>.
7. Sullivan KV, Turner NN, Roundtree SS, Young S, Brock-Haag CA, Lacey D, Abuzaid S, Blecker-Shelly DL, Doern CD. 2013. Rapid detection of Gram-positive organisms by use of the Verigene gram-positive blood culture nucleic acid test and the BacT/Alert pediatric FAN system in a multicenter pediatric evaluation. *J. Clin. Microbiol.* 51:3579–3584. <http://dx.doi.org/10.1128/JCM.01224-13>.
8. Buchan BW, Ginocchio CC, Manii R, Cavagnolo R, Pancholi P, Swyers L, Thomson RB, Jr, Anderson C, Kaul K, Ledebroer NA. 2013. Multiplex identification of gram-positive bacteria and resistance determinants directly from positive blood culture broths: evaluation of an automated microarray-based nucleic acid test. *PLoS Med.* 10:e1001478. <http://dx.doi.org/10.1371/journal.pmed.1001478>.
9. Mestas J, Polanco CM, Felsenstein S, Dien Bard J. 2014. Performance of the Verigene Gram-positive blood culture assay for direct detection of Gram-positive organisms and resistance markers in a pediatric hospital. *J. Clin. Microbiol.* 52:283–287. <http://dx.doi.org/10.1128/JCM.02322-13>.
10. Mancini N, Infurnari L, Ghidoli N, Valzano G, Clementi N, Burioni R, Clementi M. 2014. Potential impact of a microarray-based nucleic acid assay for rapid detection of Gram-negative bacteria and resistance markers in positive blood cultures. *J. Clin. Microbiol.* 52:1242–1245. <http://dx.doi.org/10.1128/JCM.00142-14>.
11. Tojo M, Fujita T, Ainoda Y, Nagamatsu M, Hayakawa K, Mezaki K, Sakurai A, Masui Y, Yazaki H, Takahashi H, Miyoshi-Akiyama T, Totsuka K, Kirikae T, Ohmagari N. 2014. Evaluation of an automated rapid diagnostic assay for detection of gram-negative bacteria and their drug-resistance genes in positive blood cultures. *PLoS One* 9:e94064. <http://dx.doi.org/10.1371/journal.pone.0094064>.
12. Martiny D, Busson L, Wybo I, El Haj RA, Dediste A, Vandenberg O. 2012. Comparison of the Microflex LT and Vitek MS systems for routine identification of bacteria by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J. Clin. Microbiol.* 50:1313–1325. <http://dx.doi.org/10.1128/JCM.05971-11>.
13. Charnot-Katsikas A, Tesic V, Boonlayangoor S, Bethel C, Frank KM. 2014. Prospective evaluation of the VITEK MS for the routine identification of bacteria and yeast in the clinical microbiology laboratory: assessment of accuracy of identification and turnaround time. *J. Med. Microbiol.* 63:235–241. <http://dx.doi.org/10.1099/jmm.0.063636-0>.
14. Kim SH, Kim KH, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. 2008. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob. Agents Chemother.* 52:192–197. <http://dx.doi.org/10.1128/AAC.00700-07>.
15. Arbefeville SS, Zhang K, Kroeger JS, Howard WJ, Diekema DJ, Richter SS. 2011. Prevalence and genetic relatedness of methicillin-susceptible *Staphylococcus aureus* isolates detected by the Xpert MRSA nasal assay. *J. Clin. Microbiol.* 49:2996–2999. <http://dx.doi.org/10.1128/JCM.00046-11>.
16. Stamper PD, Louie L, Wong H, Simor AE, Farley JE, Carroll KC. 2011. Genotypic and phenotypic characterization of methicillin-susceptible *Staphylococcus aureus* isolates misidentified as methicillin-resistant *Staphylococcus aureus* by the BD GeneOhm MRSA assay. *J. Clin. Microbiol.* 49:1240–1244. <http://dx.doi.org/10.1128/JCM.02220-10>.
17. Wong H, Louie L, Lo RY, Simor AE. 2010. Characterization of *Staphylococcus aureus* isolates with a partial or complete absence of staphylococcal cassette chromosome elements. *J. Clin. Microbiol.* 48:3525–3531. <http://dx.doi.org/10.1128/JCM.00775-10>.
18. von Eiff C, Peters G, Heilmann C. 2002. Pathogenesis of infections due to coagulase-negative staphylococci. *Lancet Infect. Dis.* 2:677–685. [http://dx.doi.org/10.1016/S1473-3099\(02\)00438-3](http://dx.doi.org/10.1016/S1473-3099(02)00438-3).
19. Fournier D, Richardot C, Muller E, Robert-Nicoud M, Llanes C, Plesiat P, Jeannot K. 2013. Complexity of resistance mechanisms to imipenem in intensive care unit strains of *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* 68:1772–1780. <http://dx.doi.org/10.1093/jac/dkt098>.